1.0 Title Page

Clinical Study Protocol M12-914

A Phase 3 Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2-Negative Metastatic or Locally Advanced Unresectable *BRCA*-Associated Breast Cancer

Incorporating Administrative Changes 1, 2, 3, and 4 and Amendments 1, 2, 3, and 4

AbbVie Investigational Product:	Veliparib (ABT-888)
Date:	23 July 2020
Development Phase:	3
Study Design:	A Phase 3 Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel with or without the PARP Inhibitor Veliparib (ABT-888) in HER2-Negative Metastatic or Locally Advanced Unresectable *BRCA*-Associated Breast Cancer
EudraCT Number:	2014-000345-70
Investigator:	Multicenter Trial: Investigator information is on file at AbbVie.
Sponsor:	AbbVie*

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*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	17 March 2014
Amendment 1	12 June 2014
Amendment 2	11 February 2015
Administrative Change 1	24 July 2015
Administrative Change 2	16 October 2015
Amendment 3	17 June 2016
Administrative Change 3	29 September 2016
Administrative Change 4	07 November 2017

The purpose of this amendment is to:

- Add benefits and risks evaluation information and updated study procedures in the context of the ongoing COVID-19 pandemic (Section 3.5, Section 5.3.1.1, Section 5.4.1, Section 5.7, Section 6.1.6, Section 9.2, and Section 9.3).

  Rationale: *To confirm that the current pandemic situation does not change the benefit risk of study participation as COVID-19 related risks are not expected to differ substantially between trial participants and the broader population of subjects being treated for metastatic breast cancer, as well as allow for procedure modification in response to the COVID-19 pandemic (including local labs, study drug shipment from sites to patients, subject withdrawal, Adverse Event reporting and consent procedures).*
- Introduce the option of off-site phone visits every other cycle for subjects who have been receiving single-agent veliparib/placebo at a stable dose without adjustment for multiple cycles without uncontrolled adverse events, and to add table of assessments for these visits (Section 5.1, Section 5.3.1.1 and Appendix F).

  Rationale: *To add flexibility, with appropriate guidance, for subjects on study long term, while maintaining standard of care safety monitoring and tumor assessments.*

- Remove references to Blinded/Unblinded TA MD and study teams throughout protocol.

  Rationale: *Primary site monitors, investigators and subjects continue to be blinded to treatment assignment until disease progression, after which unblinding to determine eligibility for crossover can be requested. However, the sponsor was unblinded to treatment assignment at the time of the primary analysis (03 June 2019). Therefore, a separate unblinded Study management team within AbbVie is no longer responsible for study conduct and data monitoring for subjects who crossover to open-label veliparib.*

- Include language to indicate that AbbVie may remove the requirements for sites to send clinical laboratory samples to the central laboratory and radiology scans to the central reviewer, or discontinue the requirements for central review at any time during the course of the study (Section 5.3.1.1).

  Rationale: *Local laboratory evaluations and local review of radiology scans can support safety monitoring and tumor assessment evaluation. AbbVie may discontinue the requirements for the central laboratory and central radiology review, as the primary analysis has been completely.*

- Update tumor assessment schedule from every 9 weeks to allow every 12 weeks (or at longer intervals not to exceed 24 weeks per the investigator's discretion) from the prior scan (Section 5.3.1.1).

  Rationale: *To modify the tumor assessment schedule after completion of the primary analysis in order to allow the Investigators to follow standard of care for patients with disease control for several years and limit cumulative radiation exposure and associated risks.*

- Update IDMC review language according to current expectations (Section 5.3.5 and Section 8.1.8).

  Rationale: *As primary analysis has occurred, no additional IDMC reviews will occur.*

- Update the guidelines on when chemotherapy can begin based on hematologic blood counts (Section 5.7.1.1).

  Rationale: *The update aligns with other study guidance within the program for other veliparib studies, for which the primary analysis has been completed*

and the safety profile of veliparib in combination with carboplatin and paclitaxel was acceptable.

- Add language on the reporting of myelodysplastic syndrome, acute myeloid leukemia, or any secondary primary malignancy (Section 6.1.5).

  Rationale: *To clarify the time period of reporting of specific adverse events of special interest which may have a delayed onset.*

- Modify the Table of Study Procedures for Post Treatment Phase and for patients that are considered on study, off drug (Appendix E).

  Rationale: *To simplify procedures required for subjects who discontinue therapy without progressive disease (i.e., subjects who are on study, off drug), requiring only those procedures needed for safety monitoring and tumor assessment. Also, to ensure that survival follow-up is the same for all subjects who have discontinued therapy, and to remove the requirement of tumor assessment at Final Visit in subjects without a tumor assessment within 4 weeks as these were infrequently required and of lower priority after the primary analysis.*

- Clarify the timing/conduct of additional OS analyses before the final OS analysis, if needed (Section 8.1.3).

  Rationale: *Allow for additional interim analyses of study data if requested by regulatory agencies or otherwise warranted.*

- Change duration of response (DOR) from secondary to tertiary endpoint (Section 5.3.3 and Section 8.1).

  Rationale: *To align with most recent version of Statistical Analysis Plan which was finalized prior to primary analysis.*

- Include updates from Administrative Changes 3 and 4 throughout the protocol.
- Update contacts for safety reporting related questions or concerns and protocol deviations (Section 6.1.6 and Section 7.0).
- Correct grammatical errors and inconsistencies throughout the protocol.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix M.

1.2 Synopsis

AbbVie	**Protocol Number:** M12-914
Name of Study Drug: Veliparib (ABT-888)	**Phase of Development:** Phase 3
Name of Active Ingredient: Not applicable	**Date of Protocol Synopsis:** 23 July 2020
Protocol Title: A Phase 3 Randomized Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2-Negative Metastatic or Locally Advanced Unresectable *BRCA*-Associated Breast Cancer	
Objectives: The primary endpoint is to assess the progression-free survival (PFS) of veliparib in combination with carboplatin (C) and paclitaxel (P) compared to placebo with C/P in subjects with a *BRCA1* and/or *BRCA2* Mutation and HER2-Negative Metastatic or Locally Advanced Unresectable Breast Cancer. The secondary objectives of the study are to assess overall survival (OS), clinical benefit rate (CBR), objective response rate (ORR), and PFS2 in subjects treated with veliparib in combination with C/P versus subjects treated with placebo with C/P. The tertiary objectives are to assess duration of overall response (DOR), change in ECOG performance status, and change in Quality of Life (QoL).	
Study Sites: Multicenter; Approximately 200	
Study Population: Men and women ≥ 18 years of age with HER2-negative metastatic or locally advanced unresectable breast cancer and clinically significant (suspected deleterious or deleterious) *BRCA1* and/or *BRCA2* germline mutation. Patients with bone-only disease and/or hormone receptor positive (ER and/or PR) disease should be deemed appropriate candidates for combination chemotherapy.	
Number of Subjects to be Enrolled: Approximately 500	
Methodology: This is a Phase 3, randomized, double-blinded study to evaluate the efficacy and tolerability of veliparib in combination with C/P compared to placebo plus C/P in subjects with *BRCA1* or *BRCA2* germline mutation and with HER2-negative metastatic or locally advanced unresectable breast cancer who have received no more than 2 prior lines of cytotoxic therapy for metastatic disease. Veliparib/placebo will be dosed in combination with carboplatin AUC 6 with weekly paclitaxel (80 mg/m^2), on a 21-day cycle. Subject randomization will be in a 2:1 ratio to veliparib/C/P or placebo/C/P and stratified by estrogen receptor (ER) and/or progesterone receptor (PgR) positive versus ER/PgR negative, prior platinum therapy (yes versus no), and CNS metastases (yes versus no). Subjects with *BRCA1/BRCA2* mutation per local lab testing and who meet the remaining eligibility criteria may be randomized. Patients who meet NCCN guidelines for *BRCA1/BRCA2* testing are eligible for testing during the screening period. *BRCA* mutation status will be documented for all subjects by the central laboratory (Myriad). Subjects who discontinue carboplatin and paclitaxel and who have not progressed will continue veliparib/placebo as a single agent at the recommended Phase 2 single agent dose. Subjects will continue dosing until they meet the defined treatment discontinuation criteria. Subjects who discontinue carboplatin, paclitaxel, and veliparib/placebo for reasons other than progression should remain on study. At the time PD is documented according to RECIST 1.1, subjects randomized to placebo may be eligible to crossover to unblinded veliparib monotherapy.	

Methodology (Continued):

Tumor assessments (CT scan or MRI of the full chest, abdomen, pelvis and brain MRI or contrast CT) were performed at screening and then every 9 weeks from C1D-2 until tumor progression to determine the extent of tumor burden per RECIST 1.1. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks from last scan until tumor progression. At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control but must not exceed 24 weeks. Post-baseline brain MRI or contrast CT is only required in subjects with CNS lesions at baseline; in all other subjects, CNS imaging will be obtained as clinically indicated based upon symptoms indicative of CNS disease. Refer to Section 5.3.1.1 and Appendix C, Appendix D, and Appendix E for additional tumor assessment schedule details, including details for subjects on open-label crossover veliparib.

In addition to being reviewed by the investigator and/or site staff, radiographic scans will be sent to a central imaging center for review. Subjects who discontinue study treatment prior to disease progression should remain on study and continue to undergo a modified schedule of assessments until disease progression per RECIST 1.1. For these subjects who meet study treatment discontinuation criteria and who have not progressed (such as subjects who initiate another anti-cancer therapy), tumor assessment data per RECIST 1.1 will continue to be collected to document tumor status and the date of progression. Post treatment information (including dates and response to subsequent therapies) and survival information will be collected every two months beginning on the date the subject has discontinued study therapy until the endpoint of death, the subject is lost to follow-up or until the study termination by AbbVie.

QoL assessment via the EORTC QLQ-C30/BR23 and EQ-5D-5L questionnaires will be collected on C1D-2 pre-dose, Day 1 of Cycle 2 and every other cycle thereafter beginning with Cycle 4 (C6, C8, etc.), Final Visit, and 30-Day Follow-Up Visit. Subjects who crossover to the unblinded veliparib monotherapy arm will continue to have QoL assessments performed as per this schedule (Day 1 of the first and second cycle of unblinded monotherapy and every other cycle thereafter beginning with Cycle 4 until 2nd disease progression or until they meet the defined study treatment discontinuation criteria and at the Final Visit and 30-Day Follow-Up Visit). Pain assessment via the BPI-SF will be collected at every cycle.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Men and women ≥ 18 years of age.
2. Histologically or cytologically confirmed breast cancer that is either locally advanced or metastatic.
   - Locally advanced breast cancer must not be primarily amenable to surgical resection or radiation with curative intent.
   - Patients with bone-only disease and/or hormone receptor positive disease should be deemed by the investigator as appropriate candidates for combination chemotherapy.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

3. Suspected deleterious or deleterious *BRCA1* and/or *BRCA2* germline mutation.
   The investigator should ensure that the testing is consistent with local guidelines, and clinical practice, and that the test uses either 1) direct DNA sequencing/multiplex ligation-dependent probe amplification (MLPA) or 2) a well-characterized methodology previously validated by sequencing, such as that used to assess founder mutations. If testing has been performed prior to Study M12-914, subjects may be enrolled but must be re-tested by the Sponsor core laboratory for documentation of *BRCA1* or *BRCA2* germline mutations.
   Subjects with *BRCA* variants of uncertain significance or polymorphisms in *BRCA1* or *BRCA2* will not be eligible for the study.
4. Breast cancer must be HER2-negative, defined as IHC 0 – 1+ OR HER2-neu negative according to ASCO-CAP guideline recommendations.
5. Measurable or non-measurable (but radiologically evaluable) disease per RECIST version 1.1 on computed tomography (CT) scan (within 28 days of randomization) with at least one lesion outside previously irradiated areas.
6. ECOG Performance status of 0 to 2.
7. Subject is able to swallow and retain oral medication and does not have uncontrolled emesis.
8. Adequate hematologic, renal, and hepatic function as follows (within 28 days of randomization):
   - Bone Marrow: Absolute neutrophil count (ANC) $\geq 1500/mm^3$ ($1.5 \times 10^9/L$); Platelets $\geq 100{,}000/mm^3$ ($100 \times 10^9/L$); Hemoglobin ≥ 9.5 g/dL (5.89 mmol/L);
   - Renal Function: Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN) range OR creatinine clearance ≥ 50 mL/min/1.73 m^2 (according to local assessment method) for subjects with creatinine levels above institutional normal;
   - Hepatic Function: Aspartate aminotransferase (AST) $\leq 2.5 \times$ upper limit of normal; alanine transaminase (ALT) $\leq 2.5 \times$ upper limit of normal; bilirubin $\leq 1.5 \times$ the ULN range. For subjects with liver metastases, AST $< 5 \times$ ULN range; ALT $< 5 \times$ ULN range. Subjects with Gilbert's Syndrome may have a bilirubin $\geq 1.5 \times$ the ULN range if no evidence of biliary obstruction exists;
   - Activated Partial Thromboplastin Time (APTT) must be $\leq 1.5 \times$ the ULN range and international normalized ratio (INR) < 1.5. Subjects on anticoagulant therapy will have an appropriate APTT and INR as determined by the investigator.
9. Women of childbearing potential and men must agree to use adequate contraception (one of the following listed below) prior to study entry, for the duration of study participation, and for 6 months following completion of therapy. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to randomization. To be considered of non-childbearing potential, postmenopausal women must be amenorrheic for at least 12 months or subjects must be surgically sterile.
   - Total abstinence from sexual intercourse (abstinence is only acceptable as a contraceptive method if it is established as the subject's preferred and usual lifestyle);
   - Vasectomized male subjects or vasectomized partner of female subjects;

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or cream); or
- Intra-Uterine Device (IUD).
- Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms and refrain from sperm donation for the duration of the study and for 6 months following completion of therapy.

10. Capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to initiation of any screening or study-specific procedures.

Main Exclusion:

Subjects who meet any of the following exclusion criteria are not eligible:

1. Received anticancer agent(s) or an investigational agent within 21 days prior to C1D-2 or radiotherapy within 28 days prior to C1D-2.
   - Prior treatment with palliative local breast or bone lesion radiation (other than pelvis) can occur, if administered at least 14 days prior to C1D-2.
   - Anticancer hormonal therapy must be stopped 7 days before starting C1D-2.
   - Anti-cancer therapy should not be initiated by the site during the screening period, as a 21-day interval would be needed from the last dose and would lead to additional delays in therapy and potential exclusion of the subject.
2. Received more than 2 prior lines of cytotoxic chemotherapy (e.g., gemcitabine, doxorubicin, capecitabine) for metastatic disease.*
   - Regimens received in the adjuvant/neoadjuvant setting or for locally advanced breast cancer within the past 6 months will also be considered toward the maximum of 2 prior lines of therapy. Adjuvant/neoadjuvant chemotherapy for one cancer event will count as one prior line of therapy, if received within the past 6 months.
   - Previous treatments with hormonal therapy (tamoxifen, aromatase inhibitors) and signal transduction agents (e.g., erlotinib, gefitinib, everolimus, bevacizumab) are allowed and are not counted towards the prior line of therapy.
3. Progressed or recurred within 12 months of completing platinum therapy or received > 1 prior line of platinum therapy for breast cancer in any setting (adjuvant, neoadjuvant or metastatic).
4. Subjects experiencing a significant adverse effect or toxicity (Grade 3 or Grade 4) causally attributed to previous anticancer treatment that has not recovered to at least Grade 2.
5. Prior therapy with PARP inhibitors.*
6. Prior taxane therapy administered for the treatment of metastatic breast cancer with the below exceptions.*
   - Prior taxane therapy for metastatic breast cancer is allowed if the patient received ≤ 1 full cycle (i.e., therapy discontinued within 4 weeks for subjects receiving weekly paclitaxel or Abraxane; therapy discontinued within 3 weeks for subjects receiving paclitaxel or docetaxel every 3 weeks) in the absence of progression or if taxane therapy for metastatic disease was > 12 months prior to C1D-2.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

- Use of taxanes as adjuvant therapy or to treat locally advanced disease is permitted, if given more than 6 months prior to C1D-2.

7. Subjects with active brain metastases or leptomeningeal disease.
   - Subjects should have a brain MRI within 28 days of randomization to confirm the absence of CNS metastases. Contrast CT is acceptable for subjects who are unable to undergo a brain MRI.
   - Subjects with known brain metastases must have clinically controlled neurologic symptoms and have received previous adequate treatment, defined as surgical excision and/or radiation therapy with stable neurologic function and no evidence of Central Nervous System (CNS) disease progression as determined by comparing a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan performed during screening to a prior scan performed at least 4 weeks earlier and provided that the subject is asymptomatic, has no evidence of cavitation or hemorrhage, and does not require corticosteroids (must have discontinued steroids for management of neurological symptoms at least 3 months prior to study drug administration).
8. A history of uncontrolled seizure disorder; including focal or generalized seizure within the past year.
9. Pre-existing neuropathy in excess of Grade 1 (except focal neuropathy such as brachial plexopathy or carpal tunnel syndrome).
10. Major surgery within 3 weeks of randomization.
11. Known history of allergic reaction to cremophor-paclitaxel, carboplatin, Azo-Colourant Tartrazine (also known as FD&C Yellow 5 or E102), Azo-Colourant Orange Yellow-S (also known as FD&C Yellow 6 or E110) or known contraindications to any study supplied drug.
12. Clinically significant uncontrolled condition(s):
    - Active infection;
    - Symptomatic congestive heart failure;
    - Unstable angina pectoris or cardiac arrhythmia;
    - Myocardial infarction within last 6 months;
    - Known active hepatitis B or hepatitis C with abnormal liver function tests or organ dysfunction;
    - Uncontrolled hypertension (sustained systolic blood pressure > 150 mmHg or diastolic pressure > 100 mmHg despite optimal medical management);
    - Psychiatric illness/social situations that would limit compliance with study requirements; or
    - Any medical condition that, in the opinion of the investigator, places the subject at an unacceptably high risk for toxicities.
13. A previous or concurrent cancer that is distinct in primary site or histology from breast cancer, except cervical carcinoma in situ, non-melanoma carcinoma of the skin, or in situ carcinoma of the bladder or another in situ cancer that is considered cured by the Investigator. Any cancer curatively treated greater than 3 years prior to entry is permitted. For these subjects, metastases must be histologically or cytologically confirmed to be breast cancer.
14. Pregnant or breastfeeding.

*Note: For prior chemotherapy, treatment for 1 full cycle or less will not be considered as prior therapy unless the patient experienced progression of disease while on that therapy.

Investigational Product:	Veliparib or Placebo
Dose:	120 mg BID Days –2 through 5 of 21-day cycle in combination with carboplatin and paclitaxel
Mode of Administration:	Oral
Reference Therapy:	Carboplatin
Dose:	AUC 6 Day 1 of 21-day cycle
Mode of Administration:	Intravenously (IV)
Reference Therapy:	Paclitaxel
Dose:	80 mg/m^2 on Days 1, 8, 15 of 21-day cycle
Mode of Administration:	Intravenously (IV)
Investigational Product:	Veliparib or Placebo
Dose:	Starting dose of 300 mg BID Days 1 through 21 of 21-day cycle as single agent therapy, if tolerated, escalation to 400 mg BID will be allowed
Mode of Administration:	Oral
Interim Analyses:	To ensure subject safety, an IDMC reviewed unblinded safety data (which included all subjects enrolled in the study) when approximately 60 subjects met at least one of the following criteria: • Received 6 cycles of treatment • Reached an event of disease progression • Discontinued the study due to toxicity/adverse events Subsequent IDMC reviews of unblinded safety data prior to the primary analysis were carried out based on IDMC recommendations. No additional reviews by the IDMC will occur since the Sponsor management team was unblinded after completing the primary analysis.

Criteria for Evaluation:

Progression-free Survival (PFS): will be evaluated according to progression per RECIST (version 1.1) and survival information (death). Radiologic tumor response and disease progression will be assessed by CT scan utilizing RECIST (version 1.1). Assessments were be performed at Screening, at 9-week intervals (from C1D-2) thereafter until disease progression. Following the primary analysis and implementation of Protocol Amendment 4 the tumor assessment interval may be increased to every 12 weeks from last scan until tumor progression; at investigator discretion, the interval between scans may be longer than 12 weeks but must not exceed 24 weeks.

Clinical benefit rate (CBR), Objective Response Rate (ORR) and Duration of Overall Response (DOR): will be evaluated according to progression per RECIST (version 1.1). Radiologic tumor response and disease progression will be assessed by CT scan utilizing RECIST (version 1.1). Assessments were be performed at Screening, at 9-week intervals (from C1D-2) thereafter. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks from last scan until tumor progression; at investigator discretion, the interval between scans may be longer than 12 weeks but must not exceed 24 weeks.

Criteria for Evaluation (Continued):

Overall Survival (OS): will be evaluated according to survival information and post treatment information (including therapy, dates of therapy and response) collected at two month intervals beginning on the date the subject is registered off study and until the endpoint of death, the subject is lost to follow-up or until the study termination by AbbVie.

PFS2: will be evaluated according to survival information and post treatment information (includes dates of therapy and response per RECIST 1.1) collected at two-month intervals.

Statistical Methods: Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05 when rounded.

Sample Size Determination:

Assuming the true hazard ratio for PFS in favor of the veliparib + C/P group is 0.69, a total of 344 PFS events will be needed for the study to have 90% power at 2-sided α level of 0.05 to detect a statistically significant treatment effect for the veliparib + C/P group using the log-rank test for progression free survival. A total of approximately 500 subjects will be enrolled into the study.

Efficacy (Primary and Secondary Endpoints):

The analysis of the primary endpoint and secondary endpoints will include only the subjects who have been documented to have suspected deleterious or deleterious mutations by the Sponsor core lab. The primary and secondary analyses will be based upon the investigator's assessment of response and disease progression per RECIST 1.1. Sensitivity analyses of PFS, ORR, and CBR based on radiological and clinical assessment by the Central Imaging Center will be conducted.

Progression-Free Survival (PFS): will be defined as the number of days from the date the subject is randomized to the date the subject experiences disease progression, or to the date of death (all causes of mortality) if disease progression is not reached.

Clinical Benefit Rate (CBR): will be defined as the progression-free rate at 24 weeks from the Kaplan-Meier curve for time to progression (defined as from the date of randomization to the date of disease progression).

Overall Survival (OS): Time to death for a given subject will be defined as the number of days from the day the subject is randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurs while the subject is still taking study drug, or after the subject discontinues study drug. If a subject has not died, then the data will be censored at the date when the subject is last known to be alive.

Objective Response Rate (ORR): (CR and PR) will be defined as the proportion of subjects with a complete or partial objective response based on RECIST (version 1.1). All subjects who have had at least one measurable lesion at baseline will be included in the ORR calculation.

PFS2: will be defined as the number of days from the day the subject is randomized to the date that the subject has disease progression or death of any cause on the subsequent therapy, whichever occurs first.

Safety: Safety will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters. Subjects who are randomized but do not receive study drug (veliparib or placebo) will not be included in the analyses of safety. Safety analysis results will be presented by treatment group.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADP	Adenosine Diphosphate
AE	Adverse Event
AI	Aromatase Inhibitor
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
APTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BC	Breast Cancer
BCNU	Trade name for Carmustine
BID	Twice a Day
BSA	Body Surface Area
BPI-SF	Brief Pain Inventory – Short Form
BRCA	Breast Cancer Gene
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central Nervous System
CPT	Cell Preparation Tube
CR	Complete Response
CRF or eCRF	Case Report Form or Electronic Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTEP	Cancer Therapy Evaluation Program
CV	Cardiovascular

CYP	Cytochrome P450
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
EC	Effective Concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EDTA	Edetic Acid (ethylenediaminetetraacetic acid)
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
ER	Estrogen Receptor
EU	European Union
FDA	U.S. Food and Drug Administration
FFPE	Formalin fixed, paraffin embedded
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GOG	Gynecologic Oncology Group
HE	Hematoxylin and Eosin
HER2	Human Epidermal Growth Factor Receptor 2
IC	Informed Consent
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDMS	Isotope Dilution Mass Spectroscopy
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent To Treat

IUD	Intra-Uterine Device
IV	Intravenously
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MLPA	Multiplex Ligation Dependent Probe Amplification
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria For Adverse Events
NCI CTEP	National Cancer Institute Cancer Therapy Evaluation Program
NE	Not Evaluable
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PAR	Poly(ADP-ribose)
PARP	Poly(ADP-ribose)-Polymerase
PCP	Pneumocystis carinii Pneumonia
PD	Pharmacodynamic
PD	Progressive Disease
PFS	Progression-Free Survival
PG	Pharmacogenetic
PgR	Progesterone Receptor
PK	Pharmacokinetic
PO	Oral Route of Administration
POR	Proof of Receipt
PR	Partial Response
PRO	Patient Reported Outcome
QA	Quality Assurance
QC	Quality Control
QD	Once Daily

QoL	Quality of Life
q PCR	Quantitative Polymerase Chain Reaction
QTc	QT interval corrected for heart rate
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Stable Disease
SERM	Selective Estrogen Receptor Modulator
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOD	Sum of Diameter
TA MD	Therapeutic Area Medical Director
TNBC	Triple-Negative Breast Cancer
ULN	Upper Limit of Normal
U.S.	United States
US	Ultrasound
WBC	White Blood Cell

Definition of Terms

AUC	Area under the concentration-time curve
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
C_{max}	Maximum observed concentration
T_{max}	Time to maximum observed plasma concentration

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3.0 Introduction

3.1 Breast Cancer

Breast cancer (BC) is diagnosed in over 1.3 million women worldwide each year and accounts for over 500,000 deaths, making it the leading cause of cancer-related death in women. Internationally, the incidence of breast cancer varies dramatically with North America, Australia, and Northern and Western Europe having the highest incidence and Eastern Europe having intermediate levels.[1] In the United States (US) and Europe, breast cancer is the most common cancer in women, with over 180,000 new cases in the US and 332,000 new cases in the countries of the European Union (EU-27) in 2008.[2,3] Although the number of agents approved for the treatment of advanced breast cancer continues to increase, overall survival has changed relatively little and median survival remains unchanged, in the range of 2 to 3 years from initial diagnosis of metastatic disease.

With the development of gene expression array technology, the heterogeneity of breast cancer has become clearer and the identification of novel cancer subtypes has reinvigorated the search for more specific and effective therapies. Additionally, identification of genetic characteristics has helped in identifying risk factors. One of these genetic characteristics includes mutations or alterations in the breast cancer susceptibility genes, *BRCA1* and *BRCA2*. It is estimated that at least 5% of breast cancer cases result from inherited mutations or alterations in *BRCA1* and *BRCA*.[2,4] Furthermore, women with these mutations have a lifetime risk of 40% to 85% of developing breast cancer.[5] Males with *BRCA2* mutations also carry an increased risk of breast cancer. Malignancies with deficiencies in homologous repair, such as *BRCA1*- and *BRCA2* deficient tumors, are more susceptible to cytotoxicity induced by DNA damaging agents and are more dependent on PARP for DNA repair than normal cells. This explains why *BRCA1/2* mutated cells, which are defective in homologous recombination, are selectively more sensitive to a PARP inhibitor than wild-type cells.[6,7]

Hierarchical clustering of genomic expression data from breast cancer specimens has demonstrated several distinct tumor subgroups with unique expression profiles, including

a HER2-positive subgroup, an estrogen receptor (ER)-positive subgroup, and a subgroup termed "basal-like" or "triple-negative." A common feature of tumors in the basal-like subgroup is the lack of expression of ER, PgR, and HER2, resulting in the description "triple-negative breast cancer" (TNBC). Although not all triple-negative breast cancers are basal-like, the classification of triple-negative tumors based on immunohistochemical staining is a clinically useful surrogate for the majority of basal-like breast cancer. The majority of breast cancers with germline *BRCA1* mutations are of the triple-negative phenotype, and chemotherapy is the only current treatment option for these patients.[8] Little progress has been made in identifying specific molecular pathways associated with TNBC that may be effectively targeted for therapeutic purposes and, consequently, this is an area of active research.[9,10] There is particular interest in the role of PARP inhibitors as well as alkylating agents and platinum-based chemotherapy as treatment for *BRCA*-associated TNBC.

In contrast to the *BRCA*1 carcinomas that often have the basal cell phenotype, the *BRCA2* carcinomas are more similar to sporadic breast cancer and tend to be ER- and PgR-positive. Treatment of hormone receptor-positive (HR+) breast cancer often involves sequencing of successive lines of endocrine therapy with either aromatase inhibitors (AI) or the selective estrogen receptor modulator (SERM) tamoxifen. In addition, exemestane with everolimus has demonstrated benefit in endocrine refractory patients. However, up to one-third of subjects are primarily resistant to endocrine therapy and most subjects who initially respond to endocrine therapy will eventually become resistant. Therefore, the vast majority of HR+ advanced breast cancer subjects will receive chemotherapy during the course of their disease.

A minority of *BRCA*-deficient tumors also express HER2 receptors (approximately 3%).[11] The development of HER2-directed targeted therapy has changed the natural history of this subtype of breast cancer. Adjuvant therapy with trastuzumab has consistently shown up to 50% reductions in risk of recurrence compared to non-trastuzumab–based therapy.[12] In metastatic HER2 positive breast cancer, trastuzumab therapy results in improved survival when used in combination with paclitaxel chemotherapy compared to paclitaxel

alone.[13] Pertuzumab, a monoclonal antibody that inhibits the ligand-dependent dimerization of HER2 and its downstream signaling, was recently approved for the treatment of first-line HER2-positive metastatic BC and has become a standard first-line therapy. An antibody drug conjugate, ado-trastuzumab emtansine, has also recently demonstrated an increase in PFS and OS in women with HER2-positive metastatic breast cancer who had progressed following trastuzumab and taxane chemotherapy. Despite these important advances, many patients eventually progress, and additional treatment options are needed for HER2-refractory patients.

3.2 Carboplatin and Paclitaxel

Carboplatin is a commonly used platinum compound that acts by producing interstrand deoxyribonucleic acid (DNA) cross-links and, thus, interrupting cell division. It is approved by the Food Drug Administration (FDA) for the treatment of ovarian cancer and by the European Medicines Agency (EMA) for ovarian cancer of epithelial origin and small cell lung carcinoma. It is also used for the treatment of non-small cell lung cancer (NSCLC), head and neck cancer, endometrial cancer, metastatic seminoma, and more recently in breast cancer, with reported response rates of 20% to 50% in previously untreated patients with metastatic breast cancer.[14] Carboplatin is eliminated by renal excretion and the clearance is related to the glomerular filtration rate (GFR). Therefore, it is dosed on the basis of GFR and the target area under the concentration versus time curve (AUC). Myelosuppression is the dose limiting toxicity of carboplatin and is dose dependent. Anemia may be cumulative and require transfusion support with prolonged therapy. Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. The risk of allergic reactions is increased in patients previously exposed to platinum therapy. Other toxicities include nausea, vomiting, renal toxicity, and neurotoxicity.

Paclitaxel promotes the assembly of microtubule formation and stabilizes them by preventing depolymerization. It is insoluble in water and, therefore, is formulated in cremophor. Paclitaxel is approved by the FDA for the treatment of breast cancer and is widely used in the adjuvant and metastatic setting. It is also approved by the FDA for the

treatment of ovarian cancer, NSCLC, and Kaposi's sarcoma. It is administered as an intravenous (IV) infusion and can be used either on a 3-weekly schedule or a weekly schedule. Main toxicities associated with the use of paclitaxel are myelosuppression and neuropathy. Hypersensitivity reactions requiring treatment have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials; thus, patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists.

Emerging data suggest that *BRCA1/2*-mutated tumors may be more sensitive to DNA damaging agents, including carboplatin. Specifically, two studies by Bryski et al are relevant to the use of platinum agents for *BRCA*-associated breast cancer. The first was a small prospective trial of single-agent neoadjuvant cisplatin in patients with *BRCA1*- and *BRCA2*-associated breast cancer and demonstrated a high pathologic complete response rate (9 of 10 patients; 90%).[15] The data were recently updated to include 25 patients in the expanded cohort, and it was found that the pathological complete response rate to be 72%.[16] The second study evaluated a cohort of 12 patients from the first study in comparison to retrospective data in patients with *BRCA1*-associated breast cancer who were treated with non-platinum regimens. The pathological complete response rate across all regimens was 24% in the 102 patients with *BRCA*-deficient breast cancer; in contrast, the pathological complete response rate in the cisplatin-treated cohort was 83% (10 of 12 patients; 95% CI = 54% – 96%) and was far lower in the other aggregated regimens (14 of 90 patients; 16%, CI = 9% – 25%).[17] The results from the TNT trial in metastatic or recurrent locally advanced triple negative breast cancer indicated greater sensitivity to carboplatin than docetaxel in germline BRCA mutation carriers (68% [17/25; 95%CI 46.5 – 85.1] versus 33.3% [6/18, 95%CI 13.3 – 59.0] p = 0.03).[18] Thus, the use of platinum-based regimens may be particularly appealing in this population.

The combination of carboplatin and paclitaxel is widely used for the treatment of patients with advanced NSCLC, ovarian cancer, and other solid tumors. Paclitaxel in combination with carboplatin is also highly active in breast cancer, with response rates of approximately 39% to 62% in first-line metastatic breast cancer.[14] Notably, data suggest that the administration of carboplatin in combination with paclitaxel results in less

thrombocytopenia than is expected from the use of carboplatin alone.[19] Because of the increased sensitivity of *BRCA*-mutated tumors to DNA-damaging agents such as carboplatin, and the activity and potential platelet-sparing effects of paclitaxel, the combination of carboplatin and paclitaxel may have particular utility in patients with *BRCA*-mutated tumors.

3.3 Poly(ADP-ribose)-Polymerase (PARP) Mechanism of Action

Poly(ADP-ribose)-polymerase (PARP) is a nuclear enzyme that recognizes deoxyribonucleic acid (DNA) damage and facilitates DNA repair.[20,21] Inactive PARPs 1 and 2 bind to damaged DNA, which leads to their auto-activation. The resulting activated PARP then poly(ADP-ribosyl)ates many nuclear target proteins, including those that facilitate DNA repair of both single-stranded or double-stranded DNA breaks. Thus, PARP inhibition will result in less efficient DNA repair following a DNA damage insult.

DNA-damaging agents, including cytotoxic chemotherapy and radiation therapy, remain a mainstay of treatment for many subjects with cancer. Since cancer cells are genetically unstable, often exhibiting complex karyotypes that include large deletions, insertions, and unbalanced translocations of chromosomal fragment, these cells are more susceptible than normal tissues to cytotoxicity induced by DNA-damaging agents.[22] Of these, deficiencies in mismatch repair and homologous recombination are associated with the largest number of malignancies. These deficiencies render cells more dependent on PARP for DNA repair and, hence, are more prone to cytotoxicity induced by PARP inhibition.[23] In particular, tumor cells with *BRCA1* or *BRCA2* deficiencies are exquisitely sensitive to PARP inhibition, even in the absence of any other insults.[6,24]

3.4 Veliparib

Veliparib is a potent inhibitor of PARP-1 and PARP-2. When DNA-damaging cytotoxic agents are coadministered, veliparib inhibits the repair of DNA damage induced by these cytotoxic agents. In addition, veliparib demonstrates single agent activity in tumors defective in DNA damage repair, such as *BRCA1*- and *BRCA2*-mutated tumors. A

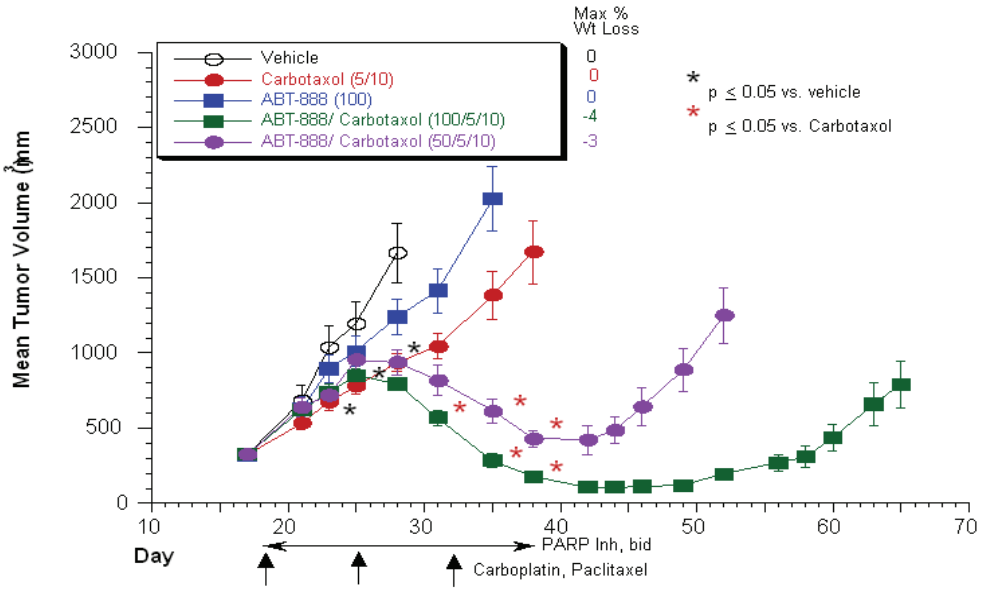
detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[38]

3.4.1 Preclinical Experience

Veliparib is a novel small molecule that is a potent inhibitor of both PARP-1 and PARP-2 with K_is of 5 nM and 3 nM, respectively. In cells under oxidative stress, veliparib inhibits the PARP induced formation of poly(ADP-ribose) (PAR) with an EC_{50} of 2.4 nM. Consistent with the conclusion of mechanism-based efficacy, significant inhibition of PAR levels was observed with doses of veliparib capable of delivering significant antitumor efficacy in preclinical models.

Veliparib has been shown to enhance the efficacy of the combination of carboplatin and paclitaxel in several xenograft tumor models. As a single agent, carboplatin produces a dose-dependent tumor growth inhibition in the MX-1 breast carcinoma xenograft model. Veliparib administered at 50 and 100 mg/kg/day in combination with carboplatin given at 50 mg/kg/day (intraperitoneally [IP], QD Days 18, 25, 32) and with paclitaxel given at 10 mg/kg/day (IV, QD Days 18, 25, 32) also regressed tumor volumes, whereas veliparib alone or carboplatin + paclitaxel did not (Figure 1).

Figure 1. Veliparib in Combination with Carboplatin in the MX-1 Breast Carcinoma Xenograft Model in SCID Mice



3.4.1.1 Pharmacokinetics/Pharmacodynamics

Preliminary clinical pharmacokinetic (PK) data available from 6 studies indicate that exposure of veliparib is approximately dose-proportional over 10 through 500 mg BID dose range. The absorption of veliparib after oral dosing is relatively fast where veliparib plasma concentrations peak at approximately 1 to 2 hours after dosing across dose levels. The terminal half-life of veliparib is about 6 hours, with minimal accumulation following multiple BID dosing. Food does not have a significant effect on veliparib bioavailability. The mean total urinary recovery of veliparib (as parent compound and M8 metabolite) is 86%, which indicates that renal excretion is an important pathway in veliparib elimination.

Potential drug-drug interactions (DDI) of veliparib are being evaluated in veliparib combination studies. Veliparib is not a potent inhibitor, nor an inducer, of the major human cytochrome P450s (CYPs), suggesting a minimal potential for DDIs at the anticipated therapeutic concentrations.

In Phase 0 Study A10-161, substantial inhibition of PARP activity was observed in tumor biopsies collected 3 to 6 hours after dosing in all 3 subjects who received a single dose of 25 mg veliparib (92%, 95%, and 100%). Complete inhibition of PARP activity in PBMCs, maintained through 24 hours after dosing, was achieved in 3 of the subjects who received 50 mg veliparib. For the 50 mg dose group, PARP activity inhibition in tumor biopsies averaged 75% 3 to 6 hours after dosing (N = 3) and averaged 74% 24 hours after dosing (N = 3). Therefore, both 25 mg and 50 mg veliparib were found to be biologically active.

3.4.1.2 Toxicology

The toxicological profile of veliparib has been characterized in general toxicology studies of up to 6 months' duration in rats and 9 months' duration in dogs, in genotoxic studies (Ames assay, in vitro cytogenetics assay, in vivo micronucleus study), and in embryofetal development studies. The primary target organs of veliparib exposure are the central nervous system (convulsions and other CNS-related signs), the hematologic system (decreased red and white blood cells), the bone marrow (hypocellularity), the lymphoid tissues (lymphocyte depletion), and the male (germ cell depletion) and the female (corpora lutea decrease and minimal degeneration of granulosa cells in follicles) reproductive tissues, with lesser effects on the cardiovascular system (10% QTc prolongation) and the gastrointestinal tract (single cell necrosis). Convulsions and other CNS-related signs were considered exposure-dependent and were generally self-limiting, ameliorated by dose reduction or cessation of dosing, or respondent to treatment. All other findings were dose-dependent and reversible upon discontinuation of veliparib administration. Veliparib was genotoxic (induced chromosomal aberrations in vitro and increased micronuclei formation in vivo) and was toxic to the developing fetus (increased incidence of fetal, visceral, skeletal malformations and/or variations).

3.4.2 Clinical Experience

In combination with cytotoxic chemotherapy, the mechanism of action of PARP inhibitors is to block repair of DNA that has been damaged by the cytotoxic agent, such as

carboplatin. By a similar mechanism, PARP inhibitors may potentiate the toxicities of cytotoxic chemotherapies. Thus, each veliparib combination regimen will have a unique set of toxicities that is predominately similar to that anticipated for the backbone regimen, and also, a unique recommended Phase 2 dose. Due to this, multiple Phase 1 studies of veliparib in combination with various chemotherapeutic agents are being conducted.

The combination of veliparib with carboplatin and paclitaxel has been investigated in ongoing Phase 1 studies conducted in collaboration with the NCI CTEP. In CTEP Study 7967 the maximum dose administered in subjects with advanced or metastatic solid tumors was veliparib 120 mg BID for 7 days in addition to carboplatin AUC 6 and paclitaxel 200 mg/m^2 administered on Day 3 of a 21-day cycle with 2 out of 6 subjects developing protocol-defined dose limiting toxicities (DLTs) at this dose. The first DLT was grade 3 nausea lasting more than 48 hours after standard anti-emetic therapy; this event resolved with additional treatment. The second DLT was grade 3 febrile neutropenia in a subject who previously received multiple cycles of dacarbazine (an alkylating agent which may cause cumulative bone marrow damage). Both of these DLTs were reversible and manageable and did not lead to study treatment discontinuation due to toxicity. Both febrile neutropenia and nausea are known toxicities of carboplatin + paclitaxel therapy and are known to resolve after standard therapies such as G-CSF, antibiotic therapy, anti-emetics, and well-defined dose reductions. Preliminary data from CTEP 7967 indicate that 8 out of 14 subjects with metastatic breast cancer had confirmed responses (3 CR, 5 PR).[25] In CTEP Study 8620, veliparib was escalated beginning at 50 mg PO BID to a maximum of 200 mg PO BID in combination with carboplatin (AUC 2) and weekly paclitaxel (80 mg/m^2) in subjects with advanced solid tumors, and the study is currently enrolling the expansion cohort of 6 to 12 patients with TNBC at the MTD (150 mg BID). Dose-limiting toxicities included thrombocytopenia (veliparib 150 mg BID) and febrile neutropenia (veliparib 200 mg BID).[25] In a subsequent analysis of preliminary data in refractory triple negative breast cancer subjects receiving veliparib in combination with carboplatin and paclitaxel on either a q-3week regimen (CTEP 7967) or a weekly regimen (CTEP 8620), an objective response rate of 50% was observed with the weekly regimen (2 CR, 3 PR, n = 10) and an objective

response rate of 55% was observed with the q-3week regimen (2 CR, 4 PR).[25] In the ongoing randomized, placebo-controlled Study M12-895 Phase 2 study, numerical increases in PFS and OS and increased ORR were observed with the addition of veliparib to carboplatin and paclitaxel compared to placebo with carboplatin and paclitaxel in patients with BRCA-mutated advanced breast cancer, supporting further evaluation in a larger Phase 3 trial.

Study GOG 9923 is an ongoing Phase 1 dose escalation study evaluating the safety and MTD of the combination of carboplatin (AUC 6, q-3week), paclitaxel (175 mg/m^2 q-3weeks or 80 mg/m^2 weekly), bevacizumab (15 mg/kg, q-3week, initiated in Cycle 2) with escalating doses of veliparib on both an intermittent and continuous schedule in subjects with newly diagnosed ovarian cancer. Intermittent veliparib treatment is given for the first week of each cycle. Preliminary safety data communicated by the investigator indicate Grade 3 febrile neutropenia and Grade 4 thrombocytopenia were DLT's in Cycle 1 at a dose of veliparib 300 mg PO BID (intermittent schedule) with carboplatin AUC 6 and paclitaxel 175 mg/m^2 q-3week, with no DLTs observed in the 200 mg BID or 250 mg BID cohorts. For subjects receiving intermittent veliparib in combination with carboplatin AUC 6 and weekly paclitaxel 80 mg/m^2, no DLTs were observed at the 100 mg, 150 mg, and 200 mg BID dose levels; at both the 250 mg BID and 300 mg BID dose levels, 1 of 6 subjects experienced a DLT (Grade 4 thrombocytopenia).

Study Rationale

The therapeutic potential of PARP inhibitors was suggested by two clinical trials evaluating PARP inhibition in breast cancer and one clinical trial in ovarian cancer. In subjects with metastatic breast cancer, the addition of a PARP inhibitor (veliparib) to carboplatin resulted in responses in subjects with deleterious germline mutations in *BRCA1/2*, with an objective response rate of 54% (14/26), with four complete responses. A single-arm trial evaluated a PARP inhibitor in metastatic breast cancer subjects with *BRCA1/2* mutations and demonstrated single-agent activity, with an ORR of 38% in heavily pretreated subjects.[26] A similar trial in *BRCA1/2* mutation carriers with metastatic ovarian cancer showed a response rate of 33%.[27] Together, these results validate the

proof of concept that PARP inhibition is an attractive therapeutic target in breast and other cancers.

Therapeutic potential in breast cancer has also been observed with veliparib in combination with carboplatin + paclitaxel. In Study CTEP 7967, the combination of veliparib with carboplatin + paclitaxel was well tolerated with a similar incidence of most toxicities, including hematological toxicities to the Eastern Cooperative Oncology Group (ECOG) carboplatin + paclitaxel study.[28] Preliminary data from this study indicate that 8 out of 14 subjects with metastatic breast cancer had responses (3 CR, 5 PR).[28] In a subsequent analysis of preliminary data in refractory triple negative breast cancer subjects receiving veliparib in combination with carboplatin and paclitaxel on either a q-3week regimen (Study CTEP 7967) or a weekly regimen (carboplatin AUC 2, paclitaxel 80 mg/m^2; Study CTEP 8620), an objective response rate of 50% was observed with the weekly regimen (2 CR, 3 PR, n = 10) and an objective response rate of 55% was observed with the q-3week regimen (2 CR, 4 PR).[30] The I-SPY 2 adaptive Phase 2 study explored 5 experimental agents (neratinib, veliparib, granitumumab, AMG 386, and MK-2206) in combination with weekly paclitaxel administration (+ trastuzumab if indicated) for 12 weeks followed by standard 4 cycles of Adriamycin/cyclophosphamide given every 3 weeks in the neoadjuvant setting. Results reported for Study I-SPY 2 on 13 December 2013 at the San Antonio Breast Cancer Symposium showed an increase of 26% in the pCR rate in subjects with triple negative breast cancer that had veliparib and carboplatin added to standard of care (SoC) [pCR of 52% for veliparib + carboplatin + SoC versus 26% for SoC].

3.5 Benefits and Risks

This study proposes to establish improved clinical outcomes for patients with HER2-negative metastatic or locally advanced unresectable breast cancer with a suspected deleterious/deleterious germline mutation of BRCA1 or BRCA2 through the addition of veliparib to therapy with carboplatin and paclitaxel. Preclinical data demonstrate that veliparib potentiates the anti-tumor activity of platinums, and data from early-phase clinical studies (completed or preliminary) are consistent with these observations.

Veliparib in combination with carboplatin and paclitaxel has been investigated in three Phase 1 studies, an adaptive Phase 2 study, and two randomized blinded Phase 2 studies. Of these studies, preliminary efficacy data is available from the Phase 1 study conducted in advanced solid tumors (Study CTEP 7967) with durable responses observed in breast cancer (5 PR, 3 CR, n = 14), non-small cell lung cancer (4 PR, 1 CR with an additional PR in a patient with SCLC, n = 16), and other advanced solid tumors (gastric, head and neck, melanoma, urothelial). The most common treatment-emergent serious adverse event in studies with veliparib in combination with carboplatin and paclitaxel has been neutropenia (4.5% of subjects) and the most common treatment-emergent adverse events (> 30% of subjects) have been neutropenia, leucopenia, fatigue, thrombocytopenia, nausea, anemia, and peripheral sensory neuropathy. These events have been similar in severity and nature to that anticipated for the backbone regimen of carboplatin/paclitaxel alone.

Gastrointestinal toxicities such as nausea and vomiting are the most common toxicities with veliparib single-agent therapy and have occurred in some subjects following a single dose. Antiemetics may be used as per standard of care for nausea during the course of the study. Anemia and decreased lymphocyte count have been observed in clinical studies with continuously dosed single agent PARP inhibitors, including veliparib.

Other potential risks of veliparib administration, identified in preclinical studies or based on pharmacological mechanism, but not confirmed in clinical studies must also be considered. These risks include seizures, changes in testes/ovaries, toxicity to the developing fetus and secondary malignancies.

In summary, veliparib is an orally available PARP inhibitor that has been shown to significantly potentiate the effects of carboplatin/paclitaxel in multiple preclinical models of tumor progression. Anti-tumor activities also were observed in early clinical studies. Potential risks, as identified above, will be minimized by careful patient selection and monitoring. The potential clinical benefit and the mitigation of potential risks to metastatic breast cancer patients support the evaluation of veliparib in combination with carboplatin and paclitaxel in this Phase 3 study.

The benefits and risks of study participation have been evaluated in the context of the ongoing COVID-19 pandemic. No data are available to characterize the risk of participation in this trial specific to COVID-19. COVID-19-related risks are not expected to differ substantially between trial participants and the broader population of individuals receiving treatment for advanced breast cancer. In consideration of the life-threatening nature of the disease under study, the benefit/risk balance for participation in this trial is not changed.

3.6 Differences Statement

This is the first randomized, Phase 3 study of veliparib in HER2-negative metastatic or locally advanced unresectable breast cancer in patients with clinically significant (suspected deleterious or deleterious) germline mutation of *BRCA*1 or *BRCA*2.

4.0 Study Objectives

The primary objective of the study is to assess the PFS of veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with a *BRCA*1 or *BRCA*2 mutation in HER2-negative metastatic or locally advanced unresectable breast cancer.

The secondary objectives of the study are to assess overall survival (OS), clinical benefit rate (CBR) through the end of Week 24, objective response rate (ORR) and PFS2 in subjects treated with veliparib in combination with carboplatin and paclitaxel versus placebo in combination with carboplatin and paclitaxel.

The tertiary objectives are to assess ECOG performance status, QoL, duration of overall response, and exploratory correlative endpoints.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3 randomized, double-blind, multinational, multicenter study to evaluate the efficacy and tolerability of veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with *BRCA*1 or *BRCA*2 mutation as documented by the Sponsor core laboratory with HER2-negative metastatic or locally advanced unresectable breast cancer who have received no more than two prior lines of DNA-damaging cytotoxic therapy for metastatic disease. For the purposes of eligibility, HER2-negativity status will be based on the most recent tumor biopsy. Approximately 200 research sites will participate. Subjects will be randomized in a 2:1 ratio to one of the two treatment arms with a total of approximately 500 subjects randomized. Veliparib 120 mg/placebo BID will be dosed Days –2 through 5 with carboplatin AUC 6 administered on Day 1 and Paclitaxel 80 mg/m^2 administered weekly on Days 1, 8 and 15 of each 21-day cycle.

Subject randomization will be stratified by estrogen receptor (ER) and/or progesterone receptor (PgR) positive versus ER/PgR negative, prior platinum therapy (yes versus no), and CNS metastases (yes versus no). Tumors with any detectable (≥ 1%) expression of ER and/or PgR by IHC are considered hormone-receptor positive. Tumors with no detectable expression of ER and PgR are considered hormone receptor negative or endocrine non-responsive. For subjects with heterogeneity between primary tumor and metastases, the biopsy most proximal to C1D-2 will be used for the purposes of stratification. For subjects with de novo Stage IV disease, the receptor status of the primary tumor will be used for the purposes of stratification.

Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel)

Dosing of oral veliparib/placebo will begin 2 days prior to the start of the carboplatin/paclitaxel infusion on C1D-2 and will continue twice a day (BID) through C1D5 (7 consecutive days). All subjects will receive carboplatin and paclitaxel IV infusion of Day 1. In addition, subjects receive paclitaxel IV infusion on Days 8 and 15.

Carboplatin and paclitaxel are to be given only after veliparib/placebo dosing on Day –2 and Day –1 are confirmed.

Table 1. Treatment Schema for Each Cycle

			Week 1				
Days	**–2**	**–1**	**1**	**2**	**3**	**4**	**5**
Veliparib/Placebo	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day
Paclitaxel			Once				
Carboplatin			Once				
			Week 2				
	6	**7**	**8**	**9**	**10**	**11**	**12**
Veliparib/Placebo							
Paclitaxel			Once				
Carboplatin							
			Week 3				
	13	**14**	**15**	**16**	**17**	**18**	**19**
Veliparib/Placebo							
Paclitaxel			Once				
Carboplatin							

Subjects will continue to receive veliparib/placebo in combination with carboplatin/paclitaxel until unacceptable toxicity occurs or radiographic progression occurs. Subjects who experience toxicities due to carboplatin/paclitaxel or veliparib may require a delay in dosing or dose modification as described in Section 5.7.

Subjects who discontinue carboplatin and paclitaxel and who have not progressed will receive single-agent, blinded veliparib/placebo starting at 300 mg BID. If the subject tolerates 300 mg BID for 2 weeks, veliparib/placebo may be increased to 400 mg BID at the investigator's discretion. Dosing with veliparib/placebo will begin on Day 1 and continue through Day 21 of a 21-day cycle. For subjects who have been receiving single-agent veliparib/placebo at a stable dose without adjustment for multiple cycles and who have no ongoing study drug related uncontrolled AEs (Adverse Events), it is possible to

alternate on-site visits and phone visits every other cycle. At a minimum, these subjects should have an on-site visit every other cycle. If an on-site visit is not possible for 2 consecutive cycles, or if the subject is not on a stable dose or has ongoing study drug-related uncontrolled AEs but wishes to alternate on-site and phone visits every other cycle, the plan for the subject's visits should be discussed with the AbbVie TA MD (see Section 7.0 for contact information). Subjects will continue to follow the schedule of assessments as outlined in Appendix C and Appendix F.

Subjects who have discontinued blinded study treatment due to unmanageable toxicity or for reasons other than progression will remain on study, off drug and follow a reduced schedule of study assessments which will include tumor assessments per RECIST 1.1 and survival status assessments, until disease progression as outlined in Appendix E.

Once a subject discontinues blinded study treatment (including subjects that discontinued treatment due to unmanageable toxicity or for reasons other than progression), a Final Visit will be conducted. All subjects will have a 30-Day Follow-Up Visit approximately 30 days after the last dose of study treatment. Follow-Up Visit procedures should be completed prior to starting any new anti-cancer therapy. Subjects who have progressed on blinded study treatment may be eligible for unblinded veliparib monotherapy treatment as described below.

Optional Unblinded Veliparib Monotherapy Treatment (Crossover)

Subjects will be eligible to receive unblinded veliparib monotherapy treatment upon confirmation of the following:

- Documented disease progression in EDC per RECIST 1.1;

  Note: Discussion with the AbbVie TA MD (see Section 7.0 for contact information) may be needed prior to unblinding and crossover to verify that criteria for unequivocal PD are met.
- Confirmation subject was receiving placebo during blinded portion of the study;

Transition to crossover treatment should occur within approximately 60 days following a confirmed event of progressive disease. Transitions that occur after 60 days should be discussed with the AbbVie TA MD.

Unblinded veliparib monotherapy will start at 300 mg BID on Cycle 1 Day 1. If the subject tolerates 300 mg BID for approximately 2 weeks, veliparib may be increased to 400 mg BID at the investigator's discretion. For subjects who have been receiving veliparib monotherapy at a stable dose without adjustment for multiple cycles and who have no ongoing study drug related uncontrolled AEs, it is possible to alternate on-site visits and phone visits every other cycle. At a minimum, subjects should have an on-site visit every other cycle. If an on-site visit is not possible for 2 consecutive cycles, or if the subject is not on a stable dose or has ongoing study drug-related uncontrolled AEs but wishes to alternate on-site and phone visits every other cycle, the plan for the subject's visits should be discussed with the AbbVie TA MD (see Section 7.0 for contact information). Subjects will follow the schedule of assessments as outlined in Appendix D and Appendix F. Subjects will continue on unblinded study treatment until a second disease progression event or unacceptable toxicity occurs.

Subjects who have discontinued unblinded study treatment due to unmanageable toxicity or for reasons other than progression will remain on study, off drug and follow a reduced schedule of study assessments, which will include tumor assessments per RECIST 1.1 and survival status until disease progression as outlined in Appendix E.

Once a subject discontinues the unblinded study treatment (including subjects that discontinued treatment due to unmanageable toxicity or for reasons other than progression), a Final Visit will be conducted. All subjects will have a 30-Day Follow-Up Visit approximately 30 days after the last dose of study treatment. Follow-Up Visit procedures should be completed prior to starting any new anti-cancer therapy.

Survival and Post Blinded and Unblinded Study Treatment Information

Once a subject meets study treatment discontinuation criteria, subjects will be followed for survival and post study treatment information as outlined in Section 5.3.1.1 will be collected every two months (unless requested by sponsor more frequently to support data analysis) beginning on the date the subject is discontinued from therapy. All randomized subjects should be followed for disease progression (PFS) and for the second progression (PFS2), until the endpoint of death (OS), until the subject has become lost to follow-up or until study termination by AbbVie.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

Subjects will be adult men and women with HER2-negative metastatic or locally advanced unresectable breast cancer and a documented deleterious or suspected deleterious *BRCA1* or *BRCA2* germline mutation.

Subjects must meet all of the following inclusion criteria to be eligible:

1. ≥ 18 years of age.
2. Histologically or cytologically confirmed breast cancer that is either locally advanced or metastatic.
    - Locally advanced breast cancer must not be primarily amenable to surgical resection or radiation with curative intent.
    - Patients with bone-only disease and/or hormone receptor positive disease should be deemed by the investigator as appropriate candidates for combination chemotherapy.
3. Suspected deleterious or deleterious *BRCA1* or *BRCA2* germline mutation.

    The investigator should ensure that the testing is consistent with local guidelines, and clinical practice, and that the test uses either 1) direct DNA sequencing/multiplex ligation-dependent probe amplification (MLPA) or 2) a

well-characterized methodology previously validated by sequencing, such as that used to assess founder mutations. If testing has been performed prior to Study M12-914, subjects may be enrolled but must be re-tested by the Sponsor core laboratory for documentation of *BRCA1* or *BRCA2* germline mutations. Subjects with *BRCA* variants of uncertain significance or polymorphisms in *BRCA1* or *BRCA2* will not be eligible for the study.

4. Breast cancer must be HER2-negative defined as IHC 0 – 1+ OR HER2-neu negative according to ASCO-CAP[41] guideline recommendations (Appendix K).
5. Measurable or non-measurable (but radiologically evaluable) disease per RECIST (version 1.1) on CT scan (within 28 days of randomization) with at least one lesion outside previously irradiated areas.
6. ECOG performance status of 0 to 2.
7. Subject is able to swallow and retain oral medication and does not have uncontrolled emesis.
8. Adequate hematologic, renal, and hepatic function as follows (within 28 days of randomization):
   - Bone Marrow: Absolute neutrophil count (ANC) $\geq 1500/mm^3$ ($1.5 \times 10^9/L$); Platelets $\geq 100{,}000/mm^3$ ($100 \times 10^9/L$); Hemoglobin ≥ 9.5 g/dL (5.89 mmol/L);
   - Renal Function: Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN) range **OR** creatinine clearance ≥ 50 mL/min/1.73 m^2 (according to local assessment method) for subjects with creatinine levels above institutional normal;
   - Hepatic Function: AST $\leq 2.5 \times$ upper limit of normal; ALT $\leq 2.5 \times$ upper limit of normal, bilirubin $\leq 1.5 \times$ the ULN range. For subjects with liver metastases, AST $< 5 \times$ ULN range; ALT $< 5 \times$ ULN range. Subjects with Gilbert's syndrome may have a bilirubin $\geq 1.5 \times$ the ULN range, if no evidence of biliary obstruction exists;
   - Activated Partial Thromboplastin Time (APTT) must be $\leq 1.5 \times$ the ULN range and INR < 1.5. Subjects on anticoagulant therapy will have an appropriate APTT and INR as determined by the investigator.

9. Women of childbearing potential and men must agree to use adequate contraception (one of the following listed below) prior to study entry, for the duration of study participation, and for 6 months following completion of therapy. If male, subjects and subject's female partner(s) of childbearing potential should practice at least one of the following methods of birth control. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to randomization (within 24 hours). To be considered of non-childbearing potential, postmenopausal women must be amenorrheic for at least 12 months or subjects must be surgically sterile.
    - Total abstinence from sexual intercourse (abstinence is only acceptable as a contraceptive method if it is established as the subject's preferred and usual lifestyle);
    - Vasectomized male subjects or vasectomized partner of female subjects;
    - Double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or cream); or
    - Intra-Uterine Device (IUD).
    - Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms and refrain from sperm donation for the duration of the study and for 6 months following completion of therapy.
10. Capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by an IEC/IRB, prior to initiation of any screening or study-specific procedures.

Rationale for Inclusion Criteria

(1 – 7) To select the appropriate subject population with sufficient disease severity for evaluation.

(8) For the safety of the subjects.

(9) The impact of veliparib, carboplatin, and paclitaxel on the unborn fetus is unknown; therefore, these criteria ensure that adequate precautions are taken to avoid pregnancy.

(10) In accordance with harmonized Good Clinical Practice (GCP).

5.2.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not eligible:

1. Received anticancer agent(s) or an investigational agent within 21 days prior to C1D-2 or radiotherapy within 28 days prior to C1D-2.
   - Prior treatment with palliative local breast or bone lesion radiation (other than pelvis) can occur, if administered at least 14 days prior to C1D-2.
   - Anticancer hormonal therapy must be stopped 7 days before starting C1D-2.
   - Anticancer therapy should not be initiated by the site during the screening period, as a 21-day interval would be needed from the last dose and would lead to additional delays in therapy and potential exclusion of the subject.
2. Received more than 2 prior lines of cytotoxic chemotherapy (e.g., gemcitabine, doxorubicin, capecitabine) for metastatic disease.*
   - Regimens received in the adjuvant/neoadjuvant setting or for locally advanced breast cancer within the past 6 months will also be considered toward the maximum of 2 prior lines of therapy. Adjuvant/neoadjuvant chemotherapy for one cancer event will count as one prior line of therapy, if received within the past 6 months.
   - Previous treatments with hormonal therapy (tamoxifen, aromatase inhibitors) and signal transduction agents (e.g., erlotinib, gefitinib, everolimus, bevacizumab) are allowed and are not counted towards the prior line of therapy if not given in combination with cytotoxic chemotherapy.
3. Progressed or recurred within 12 months of completing platinum therapy or received > 1 prior line of platinum therapy for breast cancer in any setting (adjuvant, neoadjuvant or metastatic).

4. Subjects experiencing a significant adverse effect or toxicity (Grade 3 or Grade 4), causally attributed to previous anticancer treatment that has not recovered to at least Grade 2.
5. Prior therapy with PARP inhibitors.*
6. Prior taxane therapy administered for the treatment of metastatic breast cancer with the below exceptions.*
    - Prior taxane therapy for metastatic breast cancer is allowed if the patient received ≤ 1 full cycle (i.e., therapy discontinued within 4 weeks for subjects receiving weekly paclitaxel or Abraxane; therapy discontinued within 3 weeks for subjects receiving paclitaxel or docetaxel every 3 weeks) in the absence of progression or if taxane therapy for metastatic disease was > 12 months prior to C1D-2.
    - Use of taxanes as adjuvant therapy or to treat locally advanced disease is permitted, if given more than 6 months prior to C1D-2.
7. Subjects with active brain metastases or leptomeningeal disease.
    - Subjects should have a brain MRI within 28 days of randomization to confirm the absence of CNS metastases. Contrast CT is acceptable for subjects who are unable to undergo a brain MRI.
    - Subjects with known brain metastases must have clinically controlled neurologic symptoms and have received previous adequate treatment, defined as surgical excision and/or radiation therapy with stable neurologic function and no evidence of Central Nervous System (CNS) disease progression as determined by comparing a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan performed during screening to a prior scan performed at least 4 weeks earlier and provided that the subject is asymptomatic, has no evidence of cavitation or hemorrhage, and does not require corticosteroids (must have discontinued steroids for management of neurological symptoms at least 3 months prior to study drug administration).
8. A history of uncontrolled seizure disorder, including focal or generalized seizure within the past year.

9. Pre-existing neuropathy from any cause in excess of Grade 1 (except focal neuropathy such as brachial plexopathy or carpal tunnel syndrome).

10. Major surgery within 3 weeks of randomization.

11. Known history of allergic reaction to cremophor/paclitaxel, carboplatin, Azo-Colourant Tartrazine (also known as FD&C Yellow 5 or E102), Azo-Colourant Orange Yellow-S (also known as FD&C Yellow 6 or E110) or known contraindications to any study supplied drugs.

12. Clinically significant uncontrolled condition(s) including, but not limited to:

    - Active infection;
    - Symptomatic congestive heart failure;
    - Unstable angina pectoris or cardiac arrhythmia;
    - Myocardial infarction within last 6 months;
    - Known active hepatitis B or hepatitis C with abnormal liver function tests or organ dysfunction;
    - Uncontrolled hypertension (sustained systolic blood pressure > 150 mmHg or diastolic pressure > 100 mmHg despite optimal medical management);
    - Psychiatric illness/social situations that would limit compliance with study requirements; or
    - Any medical condition that, in the opinion of the investigator, places the subject at an unacceptably high risk for toxicities.

13. A previous or concurrent cancer that is distinct in primary site or histology from breast cancer, except cervical carcinoma in situ, non-melanoma carcinoma of the skin, or in situ carcinoma of the bladder or another in situ cancer that is considered cured by the Investigator. Any cancer curatively treated more than 3 years prior to entry is permitted. For these subjects, metastases must be histologically or cytologically confirmed to be breast cancer.

14. Pregnant or breastfeeding.

* Note: For prior chemotherapy, treatment for 1 full cycle or less will not be considered as prior therapy unless the patient experienced progression of disease while on that therapy.

Rationale for Exclusion Criteria

(1 – 12) For the safety of the subjects.

(13) To select the appropriate subject population with sufficient disease severity for evaluation.

(14) The impact of veliparib and carboplatin or paclitaxel on pregnancies or breastfeeding is unknown.

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at Screening, receives during the study, and up to 30 days following the last dose of study treatment must be recorded in source documents and the eCRFs. The reason for use, dates of administration (including start and end dates), and dosage information (including dose and frequency) must be recorded.

For the purposes of this protocol, antitumor treatment may be defined as, but is not limited to, anticancer agents (cytotoxic chemotherapy, hormonal therapy, immunotherapy, biologic therapy), radiotherapy, and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans.

The AbbVie TA MD identified in Section 6.1.6 should be contacted if there are any questions regarding prior or concomitant therapy(ies).

5.2.3.1 Prior Therapy

Anticancer Agents:	Subject must have received no more than two prior lines of cytotoxic therapy for metastatic breast cancer. Regimens received in the adjuvant/neoadjuvant setting or for locally advanced disease within the past 6 months will also be considered towards the maximum of two prior lines of therapy. If received within the past 6 months, adjuvant/neoadjuvant chemotherapy for one cancer event will count as one prior line of therapy. Prior therapy with biologic agents including vaccines and immunostimulants are allowed. Prior therapy with signal transduction agents such as EGFR/HER2-direct agents (e.g., erlotinib, gefitinib, bevacizumab) are allowed and will not count toward prior lines of therapy if not given in combination with cytotoxic chemotherapy. Anticancer hormonal therapy is not permitted within 7 days prior to C1D-2 or during the study.
Radiation:	Prior treatment with radiation is allowed as long as the last treatment was at least 28 days prior to C1D-2. Prior treatment with palliative local breast or bone lesion radiation (other than pelvis) is allowed if the last treatment was at least 14 days prior to C1D-2.

5.2.3.2 Concomitant Therapy

The locally approved product label, institutional guidelines, local practice, or applicable Summary of Product Characteristics (SmPC) for carboplatin, and paclitaxel should be referenced for any concomitant therapy guidelines.

Premedication:	To reduce the severity of hypersensitivity reactions due to treatment with paclitaxel, please manage according to institutional guidelines, the locally approved product label, local practice, or applicable SmPC (i.e., premedication with corticosteroids, diphenhydramine, and H_2 antagonists).

Anticancer Agents:	Anticancer agents (including anticancer hormonal agents such as tamoxifen or aromatase inhibitors) are not permitted during the treatment portion of the study. All subjects will receive carboplatin + paclitaxel with veliparib/placebo during the treatment portion of the study. A subject receiving maintenance GnRH antagonists for ovarian suppression prior to the screening period may be allowed to remain on therapy. This should be discussed with the AbbVie TA MD. The locally approved carboplatin and paclitaxel product labels or SmPCs should be referenced to determine if there are any contraindications associated with concomitant medications (e.g., yellow fever vaccine, phenytoin, etc.). Caution must be exercised when a subject receives concomitant treatment with carboplatin and aminoglycosides due to increased renal and/or audiologic toxicity. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Supportive Care:	Best supportive care and treatment will be given as appropriate to each subject (antiemetics, antibiotics, transfusions, nutritional support, non-radiation palliative treatment for pain) according to institutional guidelines or American Society of Clinical Oncology (ASCO) guidelines. Bisphosphonate therapy for the treatment of osteoporosis and bisphosphonate or denosumab therapy for the management of bone metastases is allowed as per standard of care. Bisphosphonate therapy intended for an anti-cancer effect is not allowed during the study. If bisphosphonates or denosumab are initiated after randomization, the reason for its use must be clearly documented. When possible, initiation of bisphosphonates or denosumab should be avoided during Cycle 1. ASCO guidelines recommend a two drug combination of palonosetron and dexamethasone for moderately emetogenic therapies, such as carboplatin. If palonosetron is not available, any of the first generation 5-HT^3 receptor antagonists may be used, preferably ondansetron or granisetron. ASCO dosing guidelines are as follows: • Palonosetron 0.25 g IV OR 0.50 mg oral, Day 1 only • Dexamethasone 8 mg (IV or oral), Days 1 to 3 Aprepitant is not recommended, though clinicians may consider its use. If clinicians opt to use aprepitant, dosing guidelines are as follows: • Aprepitant: 125 mg Day 1, 80 mg Day 2 and Day 3 • 5-HT^3 receptor antagonist dosing • Dexamethasone: 12 mg on Day 1 only.[31]
Growth Factors:	Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) and colony stimulating factors (e.g., G-CSF, GM-CSF, etc.) may be administered as supportive care or to maintain dose intensity or to avoid dose delays according to standard practice, institutional or clinical practice guidelines (e.g., ASCO, ESMO). In the case of a dose modification in the treatment regimen due to WBC discrepancies growth factors (G-CSF) can be used to correct these discrepancies before a second dose modification.
Radiation:	Palliative radiotherapy is only allowed during the study treatment period for a symptomatic bone lesion present at baseline and for which no radiographic progression is visible on radiographic assessments. If a patient requires radiation therapy to a new lesion, that new lesion would, per RECIST 1.1, qualify as progressive disease. Subjects should not be randomized with the intent to receive local therapy for breast cancer (i.e., not initially a locally advanced patient appropriate for neoadjuvant therapy or other therapy with curative intent). If a subject becomes a candidate for local treatment with radiation therapy, this should be discussed with the AbbVie TA MD and should be consistent with standard or institutional guidelines (a subject with multiple metastases is unlikely to benefit from local therapy).

Surgery:	If the subject requires surgery during the study, timing of the procedure, study drug interruption, and resuming the study drug needs to be discussed with AbbVie TA MD. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded including the dates, description of the procedure(s), and any clinical findings. As a precautionary measure, it is recommended, but not strictly required, that if subjects require placement of a central venous access device (CVAD), that procedure should be done 7 days prior to first study treatment start. Subjects should not be randomized with the intent to receive local therapy for breast cancer (i.e., not initially a locally advanced patient appropriate for neoadjuvant therapy or other therapy with curative intent). If a subject becomes a candidate for surgical resection, this should be discussed with the AbbVie TA MD and should be consistent with standard or institutional guidelines (a subject with multiple metastases is unlikely to benefit from local therapy).
Alternate Therapy	No anti-cancer medicine/herbal (e.g., Chinese medicine/herbals) remedies may be taken concurrently with veliparib (a 14-day washout period must be documented).

5.3 Efficacy Pharmacokinetic, Biomarker, Exploratory Research and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

A schedule of study activities is presented in Appendix C, Appendix D, Appendix E, and Appendix F. Biomarker and Exploratory Research assessments will be performed as summarized in Table 2. Pharmacokinetic (PK) assessments will be performed as summarized in Table 3.

Table 2. Schedule Biomarker and Exploratory Research Assessments (Blinded Study Treatment)

Procedure	Visit Schedule	Before Drug Administration	Sampling Plan Specimen Matrix
PD Blood Sampling Plasma Markers[a,b]	C1D-2, C3D1	Pre-dose	Blood → Plasma Frozen –70°C or colder
	Final Visit	At the time of the clinic visit	
BRCA Sequencing: Bridging Sample	C1D-2	Pre-dose	Blood Frozen –20°C or colder
Optional with Consent Pretreatment Tissue Biopsy	C1D-2	Pre-dose	Formalin fixed, paraffin embedded (FFPE) tissue blocks or FFPE slides ambient
Optional with Consent Post treatment Tissue Biopsy	Final Visit	At the time of clinic visit	Formalin fixed, paraffin embedded (FFPE) tissue blocks or FFPE slides ambient
Optional with Consent PG Blood Sampling Genetic (DNA)	C1D-2	Pre-dose	Blood Frozen –20°C or colder

a. An additional sample may be collected at the time of study treatment discontinuation due to unmanageable toxicity.

b. Based on a discussion between AbbVie and the investigator, samples for an individual subject may be collected at an alternate time point.

Note: PD/PG sample collection will not be collected during unblinded veliparib monotherapy treatment. The post-treatment tissue biopsy can be collected after the subject completes blinded study treatment.

Table 3. Schedule of Pharmacokinetic Assessments (Blinded Study Treatment)

Procedure	Visit Schedule	Before Drug Administration	After Veliparib AM Dose	Sampling Plan Specimen Matrix
Veliparib/placebo PK Sampling[a]	C1D1	0 h[a]	1, 3 h	Blood → Plasma Frozen –20°C or colder
Veliparib/placebo PK Sampling[a]	C2D1	0 h[a]	--	Blood → Plasma Frozen –20°C or colder

a. Before the administration of the morning dose of veliparib/placebo, which should be dosed in the clinic prior to carboplatin + paclitaxel on C1D1 and C2D1.

The date and time of the sample collection and the date and time of the last two doses of veliparib/placebo will be captured on the eCRF.

Note: PK samples will not be collected during unblinded veliparib monotherapy treatment.

5.3.1.1 Study Procedures

The study procedures outlined in Appendix C, Appendix D, Appendix E, and Appendix F are discussed in detail in this section, with the exception of the monitoring of treatment compliance (Section 5.5.6) and the collection of concomitant medication (Section 5.2.3) and adverse event information (Section 6.1). All study data will be recorded within the EDC system.

For procedures performed at Screening and repeated, the later procedure performed prior to dosing will serve as a baseline for clinical assessment. Subsequent study procedures (excluding labs) should be performed within four (4) days surrounding the scheduled study visit date.

Study visits may be impacted by changes in local regulations due to the COVID-19 pandemic. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted as outlined per the protocol due to travel restrictions or other pandemic-related reasons, the site should contact the Sponsor for further guidance.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative in order to participate in this study. The IRB/IEC-approved informed consent must be signed and dated by each subject prior to undergoing any study procedures or before any prohibited medications are withheld from the subject in order for the subject to participate in this study. Informed consent will be required for the optional exploratory research. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Subjects will be considered screen failures if the informed consent has been signed and after a study-specific procedure has been done (e.g., central laboratories drawn), but the subject does not meet eligibility criteria. The reason for screen failure will be documented in the source document and will be captured in the eCRF.

Medical History

The following information will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical condition;
- History of tobacco and alcohol use;
- Presence and severity of any symptoms/conditions associated with metastatic breast cancer; and
- Detailed oncology history, including:
  - Previous testing for BRCA1/BRCA2 germline testing and results of tumor profiling/molecular markers (if applicable)
  - Date of primary cancer diagnosis;
  - Pathology (histology or cytology) of primary tumor
  - Surgical history;
  - Anticancer and radiation treatments administered (including dates and type of modality);
  - Metastasis information (including the location and histological markers), if applicable.

On C1D-2 any changes from the screening assessments, observed prior to dosing, will be recorded in the subject's medical history. At each subsequent visit, the subject's medical history will be reviewed and any clinically significant changes from baseline will be recorded in the source documents and on the adverse event eCRF.

Physical Examination

A complete physical examination (PE), including height, will be performed at Screening. A symptom-directed PE, including weight, will be performed at all other visits, unless indicated otherwise. Height will be measured at Screening only. For height and weight assessments, the subject should not wear shoes. If the Screening PE is performed within 7 days of C1D-2, PE is not required on C1D-2, unless clinically indicated. Clinically significant changes from baseline will be documented in the source documentation and

eCRF as adverse events. Physical exams should include clinical evaluation for progression with subsequent confirmation by CT.

12-lead Electrocardiogram (ECG)

A resting 12 lead ECG will be performed at the Screening Visit within 28 days of C1D-2 (prior to the first dose of veliparib/placebo to document the baseline status of the subject) C1D1 and at each blinded and unblinded study treatment Final Visit if not performed within the last 4 weeks. The C1D1 ECG must be obtained one hour after dosing with veliparib/placebo and prior to the paclitaxel or carboplatin infusions. For subjects in the crossover treatment, the C1D1 ECG must be obtained one hour after dosing with veliparib. A qualified physician will sign and date the ECGs, determine whether any findings outside normal physiological variation are clinically significant (in consultation with a cardiologist if necessary), and document this on the ECG report. The original ECG tracing or copy with physician's assessment will be retained in the subject's records at the study site.

Vital Signs

Vital sign determinations of heart rate, sitting blood pressure, and body temperature will be measured at all visits, unless indicated otherwise. If possible, blood pressure and heart rate measurements should not take place immediately after scheduled blood collections.

Pregnancy Test (In Women of Childbearing Potential)

For female subjects of childbearing potential, a serum pregnancy test will be done at screening and a urine pregnancy test will be done prior to randomization (within 24 hours). A serum pregnancy test can be performed at C1D-2 and analyzed locally prior to randomization. If a serum pregnancy test is performed on C1D-2, a urine pregnancy test does not need to be completed. Pregnancy tests may also be repeated during the study according country requirements. Subjects considered not of childbearing potential must be documented as being surgically sterile or postmenopausal (amenorrheic for at least 12 months).

If pregnancy results are equivocal (e.g., false positive due to B-hCG being a tumor marker) in subjects with evidence to support lack of pregnancy (e.g., surgically sterile), the results should be discussed with the AbbVie TA MD and the investigator's interpretation along with supporting information documented in the source documents.

The C1D-2 urine pregnancy test results must be reviewed and determined to be negative prior to randomization. If the urine pregnancy test is positive at C1D-2, it should be confirmed by a serum pregnancy test and dosing should be delayed.

For female subjects of childbearing potential, who have prolonged interruption of therapy (> 3 months), a pregnancy test (urine or serum) must be performed and confirmed to be negative prior resuming therapy. In situations of suspected pregnancy, pregnancy testing will be performed as soon as possible. In addition, pregnancy testing may be repeated at the discretion of the investigator and according to country requirements at any time during the study.

Clinical Laboratory Tests

All subjects will undergo the laboratory assessments outlined in Table 4.

All laboratory samples will be assessed using a certified central laboratory and these data will be used for all data analysis. The central laboratory will provide instructions regarding the collection, processing, and shipping of samples. All laboratory samples will be shipped to the central laboratory.

A certified local reference laboratory may perform complete blood count (CBC) and chemistry tests prior to dosing in each cycle to allow for immediate subject management; however, split or concurrent samples will be drawn and sent to the central laboratory for analysis. When necessary, local labs can be split and used to determine subject eligibility upon discussion with the AbbVie TA MD. The appropriate certifications will be collected from both the central and local laboratories, as needed.

Due to travel restrictions and other changes in local regulations in cases of state of emergency or pandemic or other special situations that prevent the site from collecting a Central Laboratory sample, if possible, sites should arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained per the protocol, the site should discuss with the AbbVie TA MD prior to continuing dosing.

AbbVie may discontinue the requirement for concurrent samples to be sent to the central laboratory, and require instead local laboratory results only at protocol-specified timepoints, at any time during the course of the study.

Samples for chemistry, hematology, and urinalysis will be collected at all visits, unless otherwise indicated, as detailed below. For Screening labs performed greater than 7 days prior to C1D-2, hematology/chemistry should be split at C1D-2 (with a 24 hour window) and local labs reviewed prior to dosing. For Day 1 visits of each cycle after Cycle 1, study samples for central laboratory analysis may be performed within 72 hours prior to dosing. For visits conducted by phone as outlined in Appendix F, lab tests do not need to be performed and are to be collected at a minimum at the on-site visits (every other cycle). For Day 8 and Day 15 visits (during blinded study treatment), study samples for central laboratory analysis may be performed within 24 hours from the scheduled day. There is no visit window for C1D-2 as any sample prior to randomization is still considered to be screening. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions and should be entered into EDC, but this cannot replace the central laboratory analysis on a protocol defined visit.

- Urinalysis samples will be collected at Screening, C1D-2 and at each blinded and unblinded study treatment Final Visit.
- APTT/INR will be collected at Screening.

- *BRCA*1 and *BRCA*2 germline mutation testing will be collected on all subjects by the Sponsor core laboratory.

Qualified medical staff at the site will review, initial, and date all local and central laboratory results. Any laboratory value outside the reference range that the investigator considers clinically significant will be followed, as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.1.

Table 4. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands (if indicated) Lymphocytes Monocytes Basophils (if indicated) Eosinophils (if indicated) Platelet count (estimate not acceptable) Mean corpuscular volume Mean corpuscular hemoglobin concentration RBC distribution width	Sodium Potassium Chloride Bicarbonate Blood Urea Nitrogen (BUN) Serum creatinine Glucose Calcium Inorganic phosphorus Magnesium Total protein Albumin Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Uric acid Lactate dehydrogenase (LDH) Serum or urine β-HCG*	Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin
Coagulation	**Special Chemistry**	
Activated partial thromboplastin time (APTT)* International normalized ratio (INR)*	*BRCA1* and *BRCA2* germline mutation**	

* Collected at Screening. Serum or urine β-HCG will also be collected prior to randomization (within 24 hours).

** Collected prior to C1D-2.

***BRCA1*/*BRCA2* Testing**

***BRCA1* and *BRCA2* Germline Mutation Testing**

The diagnosis of a suspected deleterious or deleterious *BRCA1* or *BRCA2* mutation must be documented prior to randomization and genetic risk assessment and counseling should proceed per NCCN guidelines or the standard policy of the institution. A copy of the results (including non-Sponsor testing) will be needed for the site study file. Subjects with *BRCA* variants of uncertain significance or polymorphisms in *BRCA1* or *BRCA2* will not be eligible for the study.

Documentation of *BRCA* mutation status must occur by one of the following mechanisms prior to randomization:

- Previous diagnosis of a *BRCA*1 or *BRCA*2 mutation.

  If the diagnostic testing for *BRCA*1/*BRCA*2 was not conducted by the Sponsor core laboratory, the investigator should ensure that the testing and classification is consistent with local guidelines and clinical practice and that the test employs either 1) direct DNA sequencing/MLPA or 2) a well-characterized methodology previously validated by sequencing, such as that used to assess founder mutations. These subjects must also undergo Sponsor core laboratory *BRCA* gene sequencing during Screening or on C1D–2.

  Subjects with local labs indicating a suspected deleterious or deleterious mutation and who meet all of the eligibility criteria may be randomized prior to receiving results from the Sponsor core laboratory.
- Subjects considered high risk for carrying a *BRCA1*/*BRCA*2 mutation are eligible for Sponsor core *BRCA* testing. Subjects may be considered high risk if they meet one of the following criteria (per the most current NCCN guidelines):[32]
  - Individual from a family with a known deleterious *BRCA1/BRCA2* gene mutation;
  - Personal history of breast cancer and one or more of the following:
    - Diagnosed at age ≤ 45;

- Diagnosed at age ≤ 50 with:
  - An additional breast cancer primary (i.e., bilateral disease or two or more clearly separate ipsilateral primary tumors);
  - ≥ 1 close blood relative with breast cancer at any age;
  - ≥ 1 close relative with pancreatic cancer;
  - ≥ 1 relative with prostate cancer (Gleason score ≥ 7);
  - An unknown or limited family history;
- Diagnosed at age ≤ 60 with a triple negative breast cancer;
- Diagnosed at any age with:
  - ≥ 1 close blood relative with breast cancer diagnosed at age ≤ 50;
  - ≥ 2 close blood relatives with breast cancer at any age;
  - ≥ 1 close blood relative with ovarian carcinoma;
  - ≥ 2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥ 7) at any age;
  - A close male blood relative with breast cancer;
  - For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required;
- Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer;
- Personal history of male breast cancer;
- Personal history of prostate cancer (Gleason score ≥ 7) at any age with ≥ 1 close blood relative with breast and/or ovarian cancer and/or pancreatic cancer or prostate cancer (Gleason score ≥ 7) at any age;
- Personal history of pancreatic cancer with ≥ 1 close blood relative with breast and/or ovarian cancer and/or pancreatic cancer or prostate cancer (Gleason score ≥ 7) at any age.

Note: Patients who pre-qualify with one or more of these criteria will be eligible to screen for *BRCA*1/*BRCA*2 mutation by the Sponsor core laboratory. These subjects may be eligible for randomization upon receipt of documentation of a suspected deleterious or

deleterious germline *BRCA*1/*BRCA*2 mutation by the Sponsor core laboratory. Germline mutation testing obtained greater than 28 days prior to Cycle 1 Day –2 will not preclude a subject from randomization.

BRCA Bridging Sample

In order to permit future bridging studies to other potential *BRCA* assays, in addition to the sample collected for the Sponsor core laboratory *BRCA* test, two tubes of blood must be obtained from all subjects per Table 2 to be tested at a future date.

Tumor Assessments (Radiologic)

Appropriate diagnostic CT assessments using modified RECIST version 1.1[33] for solid tumor response will be used in the evaluation of cases, as appropriate. If the subject is unable to undergo a CT scan with IV contrast due to allergy or renal insufficiency, a non-contrast CT may be performed if the disease, especially potentially measurable lesions as present, can be appropriately evaluated. Magnetic resonance imaging (MRI) may replace the CT imaging in cases where local laws or requirements mandate, but should have sponsor or central imaging center approval prior to performing the MRI.

Axial plane CT scans of the full chest, abdomen, pelvis (or MRI), and brain MRI or contrast CT to determine the extent of tumor burden were performed for all tumor assessments at Screening (within 28 days of randomization), and every 9 weeks from C1D-2 (tumor assessments could be conducted 5 days prior or 5 days following the scheduled assessment) until progression. For subjects in the blinded treatment period, following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks from last scan (tumor assessments may be conducted 10 business days prior or 10 business days following the scheduled assessment). At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control but must not exceed 24 weeks.

For subjects on open-label crossover veliparib, tumor assessments will be conducted every 9 weeks (± 5 business days) from C1D1. Following the primary analysis and implementation of Protocol Amendment 4, if a crossover subject has disease control after 6 scans while following the 9 week scan interval schedule, the tumor assessment frequency can be increased to every 12 weeks (± 10 business days) from the last scan. At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control, but must not exceed 24 weeks.

Subjects who have discontinued study treatment due to unmanageable toxicity or reasons other than progression will remain on study but off drug and continue to complete scheduled tumor assessments until unequivocal progression per RECIST 1.1 is documented as per Appendix E.

Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study, unless evidence of tumor metastasis warrants otherwise.

Post baseline brain MRI or contrast CT is only required in subjects with CNS lesions at baseline; in all other subjects, CNS imaging will be obtained as clinically indicated based upon symptoms indicative of CNS disease. Coronal or sagittal plane imaging may be acquired for paraspinal findings and other lesions that may be better appreciated in that plane. Measurements should only be performed on axial imaging and lesions followed in non-axial planes should be assessed qualitatively only.

Baseline full body bone scan is required for study entry. Subsequent bone scans will be performed, as clinically indicated or per the institution's standard of care. A new bone lesion requires detection of new area of lysis, cortical destruction, or increasing soft tissue component. New bone scan lesions will not be considered as PD, unless confirmed as increasing destruction/lytic on CT/MRI. Increasing sclerosis will not be considered PD. New lesions or increasing sclerosis of existing bone lesions (flare) must be evaluated by CT/MRI.

Subject treatment management will be based on the tumor assessment review by the local investigator and/or site staff. If the investigator's assessment of progression is equivocal, the subject should remain on study until subsequent assessment demonstrates unequivocal PD per RECIST 1.1 is documented.

In addition to being reviewed by the investigator and/or site staff, radiology scans will be sent to a central imaging center (PAREXEL Informatics) within 1 week during the course of the study and in cases of suspected PD, within 2 days of collection for review. The central imaging center will provide instructions regarding the preparation and shipment of the images. Imaging sent to the central imaging center should also include any unscheduled bone scan, PET-FDG or X-ray acquired by the sites for study purposes. Radiology scans will be assessed by the central imaging center according to RECIST (version 1.1) as outlined in Section 5.3.4.1. Interpretations from the central imaging center will not be sent to the site. It is recommended that subjects remain on study until the investigator and/or site staff receives notification from AbbVie that the assessment of PD has been completed. AbbVie may discontinue the requirement for radiology scans to be sent to the central imaging center or the requirement for completing central reviews at any time during the course of the study.

ECOG Performance Status

ECOG performance status will be assessed as outlined in Appendix C, Appendix D, Appendix E, and Appendix F.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Patient Reported Outcomes (PRO) Questionnaires

To assess the subject's health-related quality of life and symptoms, the EORTC QLQ C30, the EORTC BR23, and the European Quality of Life-5 Dimensions (EQ 5D 5L) (Appendix G, Appendix H and Appendix I, respectively) will be administered pre-dose at, C1D-2, C1D1 (unblinded veliparib monotherapy treatment only), every other cycle thereafter beginning with Cycle 2 (C2, C4, C6, etc.), each blinded and unblinded study treatment Final Visit and at each blinded and unblinded study treatment 30-Day Follow-Up Visit. In addition, to assess pain more specifically, the Brief Pain Inventory Short Form (BPI-SF) questionnaire (Appendix J) will be administered pre-dose at C1D-2, C1D1 (unblinded veliparib monotherapy treatment only), Day 1 of every cycle, each blinded and unblinded study treatment Final Visit and each blinded and unblinded study treatment Follow-Up Visit. To minimize response bias, all PRO questionnaires will be administered before subjects are informed of their tumor assessment. Subjects must complete the questionnaires on paper forms, which are then entered into EDC by the investigator or designee. The Investigator or a designee will need to check the form returned by the subject for completeness before the subject leaves the clinic. For subjects who are eligible to alternate on-site visits and phone visits, the PRO questionnaires should still be completed at the phone visits. PRO questionnaires to be completed for the cycle during which the phone visit occurs should be provided to the subject by the investigator or

designee during the preceding on-site visit, so these can be completed at home as outlined in the schedule of assessments in Appendix F.

The EORTC QLQ-C30 is a 30-item questionnaire that consists of a global health status/QoL scale, a financial difficulties scale, five functional scales (cognitive functioning, social functioning, physical functioning, emotional functioning, and role functioning), and eight symptom scales/items (fatigue, insomnia, appetite loss, pain, constipation, diarrhea, dyspnea, and nausea and vomiting). The EORTC BR-23 is a breast cancer–specific questionnaire and is meant for use complementary to the generic EORTC QLQ-C30 for patients with different disease stages and treatment modalities.[34] It comprises of 23 items divided in four functioning scales (body image, sexual functioning, sexual satisfaction, and future perspective) and four symptom scales (side effects of systemic therapy, breast symptoms, arm symptoms, and upset by hair loss). The questionnaire has been validated in an international study.

The EuroQol 5 Dimensions 5 Level (EQ-5D 5L)[35] is a generic preference instrument that has been validated in numerous populations. The EQ-5D 5L is composed of 5 questions and a visual analog scale (VAS) assessing overall health that can be converted into a single health status or "utility" score for use in an economic evaluation to adjust life-years gained by the subject's health-related quality of life.

The Brief Pain Inventory-Short Form (BPI-SF), originally developed to assess cancer related pain in clinical trials, is one of the most widely used measurement tools for assessing clinical pain.[39] The BPI-SF allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function.

Due to the COVID-19 pandemic and any local restrictions, sites may administer PRO questionnaires over the phone as needed. Sites may read the PRO questions and response options to the subject and record the subject's responses. Sites may send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date

and time of PRO data collection should be recorded along with who collected the information.

Randomization and Subject Number Assignment

The site will contact the IVRS/IWRS to obtain a screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., central labs drawn). Once the screening number is assigned, if the subject is not randomized into the study, the reason for screen failure will be documented in the source document and will be captured in the eCRF.

Subjects who complete all Screening procedures and meet the eligibility criteria in Section 5.2 and none of the exclusion criteria in Section 5.2.2 will proceed to randomization.

A bottle number randomization schedule and a subject randomization schedule will be generated by the Clinical Statistics Department at AbbVie prior to the start of the study. A copy of all randomization schedules will be kept by the Clinical Statistics Department at AbbVie and a copy will be forwarded to the IVRS/IWRS vendor.

Dispensing Study Drug

The IVRS/IWRS will assign bottles of veliparib or placebo and vials of carboplatin and paclitaxel that are supplied by AbbVie to be dispensed to a subject during the study from the available supply at the site. Prior to each scheduled drug dispensation visit (per Appendix C and Appendix D), site personnel must contact the IVRS/IWRS for the bottle number assignments no more than 5 days before Day 1 of each cycle. Study medication cannot be dispensed unless the IVRS/IWRS is contacted. AbbVie or the designee will provide specific instructions on the use of the IVRS/IWRS.

Subjects will be provided with self-administration instructions and subject dosing cards. Subjects will be instructed to store veliparib or placebo according to specific directions included in Section 5.5.2.2. Subjects should return bottles of veliparib or placebo (empty,

partially filled, or full) to the study site prior to each cycle and each blinded and unblinded study treatment Final Visit.

Depending on local regulations due to the COVID-19 pandemic, provision of study drug for direct-to-patient (DTP) and direct-from patient (DFP) transfer will be available upon request. AbbVie has contracted with third party vendors for sites to ship study drug DTP and DFP. Sites will be able to use the third party vendor and/or another local courier for drug shipment, as needed. If necessary, notify AbbVie if DTP and/or DFP shipping will be used.

Sites will be responsible to:

- Meet IRB/IEC reporting requirements and submit the booking form (which will be provided to site by the courier) to the local IRB/IEC, as applicable.
- Submit the booking form at least 72 business hours before the drug needs to be picked up, or as per the requirements of the courier.
- Discuss the DTP and DFP process with the subject including:
  - Obtain consent to provide delivery information to the courier and document this in the source.
  - Obtain results of required safety procedures before registering subject dispensation of study drug in IRT.
  - Confirm the subject will be available to accept delivery.
  - Confirm the subject will maintain the drug containers, as well as any unused drug for return to site.
- Follow up with the subject after shipment is received.
- Retain documentation of the shipment for IP accountability and monitoring.

Blinded Study Treatment

Subjects will receive sufficient quantities of veliparib/placebo for 7 days of administration in each 21-day cycle. Subjects should start treatment with veliparib/placebo within approximately 48 hours of randomization. At C1D-2, subjects will be given

veliparib/placebo for dosing through Day –1. At C1D1, subjects will be given veliparib/placebo for dosing through Day 5 and additional study drug for Cycle 2 Days –2 and –1. For subsequent cycles, subjects will receive veliparib/placebo for Days 1 – 5 of the current cycle and a separate bottle for Days –2 and –1 of the following cycle. This dispensing schedule will allow subjects to begin veliparib/placebo dosing prior to receiving carboplatin and paclitaxel infusions without requiring a return to the investigative site on Day –2.

Trained site personnel will administer the carboplatin + paclitaxel intravenously on Day 1 and paclitaxel on Days 8 and 15 of each 21-day cycle. Subjects will be supervised at the time of the infusion.

If carboplatin or paclitaxel is obtained commercially via the site pharmacy, the site will be responsible for tracking the lot numbers for all carboplatin and paclitaxel dispensed and include the information in the trial master file (TMF).

On Day 1, subjects on blinded single-agent veliparib/placebo will be given study drug for dosing through Day 21.

For subjects who are eligible to alternate on-site visits and phone visits every other cycle, during the on-site visits, the investigator or designee should dispense blinded study drug via IRT and subject dosing cards for 2 consecutive cycles, as outlined in the schedule of assessments in Appendix F.

Unblinded Study Treatment

Subjects will receive sufficient quantities of unblinded veliparib for 21 days of administration in 21-day cycle. At C1D1, subjects will be given unblinded veliparib for dosing through Day 21. For subsequent cycles, subjects will receive unblinded veliparib monotherapy for Days 1 – 21 of the current cycle.

For subjects who are eligible to alternate on-site visits and phone visits every other cycle, during the on-site visits, the investigator or designee should dispense unblinded study

drug via IRT and subject dosing cards for 2 consecutive cycles, as outlined in the schedule of assessments in Appendix F.

Post-Progression/Survival Follow-Up Information

Once a subject meets study treatment discontinuation criteria, subjects will continue to be followed during the Post Treatment Follow-Up Phase for survival (i.e., the date and cause of death) and post-therapy information, including date of progression to the first post-study therapy. These data will be collected on the appropriate eCRF at 2 month intervals (or as requested by Sponsor to support data analysis), beginning on the date the subject discontinued from study therapy until the endpoint of death, the subject has become lost-to follow-up, or AbbVie terminates the study.

The following will be collected for post-therapy information:

- Name(s) of post-therapy regimens;
- Post-therapy dates of initiation and completion;
- Date of progression on the first post-study therapy (PFS2);
- Response to subsequent therapies and reason for discontinuation.

The investigator must report the withdrawal to the IVRS/IWRS system within 3 days of the subject's discontinuation. Following entry into the Post Treatment Follow-Up Phase, the subject will be treated in accordance with the investigator's best clinical judgment.

Subjects who have discontinued study treatment due to unmanageable toxicity or reasons other than progression will remain on study, off drug and continue to be followed for survival and post-treatment therapy information at 2 months intervals (or as requested by Sponsor to support data analysis) as outlined in the schedule of assessments in Appendix E.

Subjects who wish to withdraw specifically from survival follow-up must have the request documented in the subject's medical record and signed by the investigator. If the subject withdraws from the Post Treatment Follow-Up, the study staff may use public

information source (such as county records) to obtain information about survival status only per local regulations, as appropriate.

5.3.1.2 Collection and Handling of Biomarker and Exploratory Research Samples

Blood and tissue samples will be collected for biomarker and optional exploratory research. Subjects may still participate in the main study even if they decide not to participate in optional exploratory research.

All biomarker and exploratory research samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store the biomarker and exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on Veliparib (or drugs of this class), this disease and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

Biomarker Samples

Plasma and blood for BRCA bridging will be collected at time points as outlined in Table 2 and may be utilized to evaluate known and/or novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status, related conditions or to evaluate the association with pharmacokinetics, safety or efficacy. The biomarker rationale will be discussed in the Biomarker Research Variables Section (Section 5.3.8).

Collection of Optional Exploratory Research Samples

Pharmacogenetic Sample (Optional) for Exploratory Research

One 4-mL whole blood sample for DNA isolation will be collected at C1D-2 (during the blinded study portion) from each subject who consents to provide samples for exploratory research. If the sample is not collected at C1D-2, the sample may be collected at any time

throughout the study. PG samples will not be collected during unblinded veliparib monotherapy treatment.

Pretreatment Tissue Biopsy-Archived or Fresh Tissue Biopsy for Exploratory Research (Optional)

If available, fixed samples from most recent pathological analysis will be collected from subjects (with consent) at C1D-2. Only one of the following forms of pre-treatment tumor tissue (archived tissue or fresh biopsy) is required:

- Pretreatment Biopsy-Archived
- Fresh Tumor Tissue Biopsy

The most recent archived biopsy is preferred and should be obtained during Screening if possible. If no archived material is available, a fresh biopsy may be collected from subjects who consent according to Institutional procedures for subjects. If a fresh biopsy is collected, it should be fixed in formalin and embedded in paraffin according to Institutional procedures. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study specific laboratory manual. Tumor samples should be stored according to Institutional procedures until shipment to AbbVie or an AbbVie-designated contract research organization (CRO).

Included with each shipment should be a copy of the pathology report with all subject-identifying information redacted and completed shipment inventory form. Tissue slides will be shipped in slide boxes. Slide boxes should be packaged using suitable shipping materials and sent to AbbVie at ambient temperature.

Post Treatment Tumor Biopsy for Exploratory Research (Optional)

An optional post treatment tumor tissue biopsy should be collected at the blinded study treatment Final Visit. Institutional procedures should be followed to fix and embed the collected biopsy in paraffin. While tissue blocks are preferred, slides prepared by the

local pathology lab are acceptable and should be prepared as described in the subject specific laboratory manual.

Included with each shipment should be a copy of the pathology report with all subject-identifying information redacted and completed shipment inventory form. Tissue slides will be shipped in slide boxes. Slide boxes should be packaged using suitable shipping materials and sent to AbbVie at ambient temperature.

5.3.2 Drug Concentration Measurements

Pharmacokinetic variables are discussed in Section 5.3.6.

5.3.2.1 Collection of Samples for Analysis

Blood samples for determination of plasma concentration of veliparib will be collected at time points as outlined in Table 3. The date and time of sample collection and the date and time of the last 2 doses of veliparib will be captured on the eCRF. Approximately 3 mL of blood will be collected by venipuncture into one 3-mL potassium (K_2) EDTA (purple cap) tube in conjunction with clinical lab blood draws (if possible). Sufficient blood will be collected to produce approximately 1 mL of plasma for each sample. The date and time of collection for each sample will be recorded. Plasma should be transferred into one 2 mL Greiner tube.

If an indwelling catheter of any type is used, approximately 3 mL volume of blood must be collected and discarded prior to collection of the veliparib sample. The use of indwelling catheter for the collection of pharmacokinetic samples is discouraged unless it is absolutely necessary.

Samples should not be collected when subjects are on a dose interruption.

5.3.2.2 Handling/Processing of Samples

The complete process of centrifugation, transfer to polypropylene tubes, and freezing should be accomplished within 120 minutes from blood draw. The processing of pharmacokinetic samples should be performed, as described below:

- Collect the blood sample in a 3-mL EDTA (purple top) tube.
- Immediately invert the collection tubes 8 to 10 times.
- Within 60 minutes from blood draw, centrifuge sample at 1100 to 1300 × g for 10 minutes at 2° to 8°C. If a refrigerated centrifuge is not available, samples can be centrifuged under room temperature conditions.
- Transfer plasma into an appropriately labeled (drug name, type of sample, protocol number, subject number, treatment cycle and day, and the planned time of sample collection relative to dosing, and the sample collection date) screw-capped polypropylene tube and freeze at –20°C or colder.
- Plasma samples must be frozen upright at –20°C or colder within 2 hours after collection and must remain frozen until shipped frozen to the central laboratory. Samples should not be allowed to thaw prior to arrival at the central laboratory.

5.3.2.3 Disposition of Samples

Samples and inventory sheet should be batch shipped frozen to a designated laboratory on dry ice sufficient for 3 days. Samples should not be allowed to thaw prior to arrival at the designated laboratory. Shipment information will be provided in the laboratory manual.

5.3.2.4 Measurement Methods

Plasma concentrations of veliparib will be determined under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

The primary efficacy endpoint will be PFS. The secondary efficacy endpoints will be OS, CBR, ORR, and PFS2. The tertiary endpoints will include DOR, change in ECOG performance status, and change in QoL indices.

5.3.4 RECIST (Version 1.1) for Tumor Response

Response criteria will be assessed using RECIST (version 1.1). Changes in the target and non-target lesions over the course of therapy must be evaluated using the criteria listed below.

Eligibility

Subjects with measurable or non-measurable (but radiologically evaluable) disease with at least one lesion outside previously irradiated areas at baseline can have objective tumor response evaluated by RECIST (version 1.1). Measurable disease is defined by the presence of at least one measurable (target) lesion in at least one site which has not received prior radiotherapy. Lesions that have been previously irradiated will be considered non-target lesions. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology, if possible.

Measurability

Measurable Lesions	Lesions accurately measured in at least one dimension with a minimum size of: Longest diameter ≥ 10 mm (CT scan slice thickness no greater than 5 mm) 10-mm caliper measurement by clinical exam
Non-Measurable Lesions	All other lesions, including small lesions (longest diameter < 10 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, and abdominal masses that are not confirmed and followed by imaging techniques.
Measurable Malignant Lymph Nodes	To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At Baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Malignant Lymph Nodes	Pathological lymph nodes with ≥ 10 to < 15 mm short axis.
Special Considerations Regarding Lesion Measurability	Bone lesions Bone lesions are considered non-target/non-measurable lesions. Cystic lesions Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. "Cystic lesions" thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions. Lesions with prior local treatment Tumor lesions situated in a previously irradiated area will be considered non-target lesions.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days prior to randomization.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers. In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. All measurements should be taken using calipers and recorded in metric notation, if clinically assessed. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken, since it is more objective and may also be reviewed at the end of the study.

Methods of Measurement

Conventional CT should be performed with contiguous axial cuts of 5 mm or less in slice thickness for tumors of the chest, abdomen and pelvis. A scale should be incorporated into all radiographic measurements. MRI can be performed if required by local law, but must have sponsor/central imaging center approval. Non-axial slices may be of value in the interpretation of paraspinal lesions findings and other lesions that are better appreciated in non-axial planes. Lesions followed on non-axial imaging should be assessed qualitatively (i.e., as CR, Non-CR/Non-PD, unequivocal PD, unequivocal new, NE). Lesions only visible on non-axial imaging are not considered suitable as target lesions.

For accurate objective response evaluation, ultrasound or bone scan should not be used to measure tumor lesions.

The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology can be used to differentiate between benign and malignant fluid collections in cases of new and/or enlarging pleural effusion and/or ascites in which the response will be based on other target or non-target lesions. New effusions or ascites should be considered unknown until cytology confirms whether they are benign or malignant. If cytology is available and suggesting malignancy, the data must be entered into the eCRF and will be considered in the determination of progression. While fluid collections are present, the response determination cannot be considered CR.

Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at Baseline. Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are considered non-target lesions.

Lymph nodes merit special mention, since they are normal anatomical structures, which may be visible by imaging, even if not involved by tumor. Pathological nodes, which are defined as measurable and may be identified as target lesions (no more than 2 may be selected), must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge whether a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane). The smaller of these measures is the short axis. For example, an abdominal node, which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (SOD) for all target lesions will be calculated and reported as the baseline sum SOD. If lymph nodes are to be included in the sum, then, as noted above,

only the short axis is added into the sum. The baseline SOD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease), including pathological lymph nodes, CNS metastases and skin lesions, should be identified as non-target lesions and should also be recorded at Baseline. Measurements of these lesions are not required, but the presence (stable, increasing, or decreasing) or absence of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR)

The disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD)

At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest SOD recorded since the treatment started (baseline or after) or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SOD since the treatment started (baseline or after).

Assessment of Target Lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero, even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

All lesions (nodal and non-nodal) recorded at Baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (< 5 mm). However, sometimes target lesions or lymph nodes become too small to measure. If it is in the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the radiologist believes that the lesion is present, but too small to measure, a default value of 5 mm should be assigned (as derived from the 5-mm CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progression based upon measurement error.

If interventions occur during the study that affect disease burden, such as surgery, the lesion(s) affected will typically be considered non-evaluable (NE) from that point forward and subsequent time points will be either NE or PD (if evidence of progression is available).

Evaluation of Non-Target Lesions

Complete Response (CR)

The disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD

Persistence of one or more non-target lesion(s).

Progressive Disease (PD)

Unequivocal progression of existing non-target lesions.

In this setting, to achieve "unequivocal progression" on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease, therefore, will be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression. While there are no specific criteria for the identification of new radiographic lesions, the findings of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique, timing of scanning, phase of contrast administration, change in imaging modality, or possibly representing something other than tumor (e.g., some "new" bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up study in an anatomical location that was not scanned at Baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal (e.g., too small to measure), continued therapy and follow-up evaluation will clarify whether it truly represents new disease. If repeat scans confirm there is a new lesion, then progression should be declared using the date of the initial scan.

Calculating Final Response:

Response of Combined Lesion Type			
Target Lesion	**Non-Target Lesion**	**Unequivocal New Lesion***	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* Equivocal new lesions will not allow for CR but will otherwise not impact the overall response.

Calculating Final Response for Non-Measurable Disease:

Non-Target Lesion	**New Lesion**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

5.3.4.1 Definition of Disease Progression

Disease progression will be defined as progression of disease by RECIST (version 1.1).

If the subject experiences symptomatic deterioration and clinical progression is determined by the investigator, every effort will be made to document radiographic or clinical evidence of progression for analysis of the primary endpoint, even after discontinuation of treatment. Thus, all randomized subjects should be followed for disease progression and for the second progression (PFS2), death, or withdrawal of consent for follow up until PD.

Clinical data that support progression will be collected and submitted for central review, including the following:

- Data on palliative radiotherapy and/or surgery/resection while on study, including specific location, date and results, as applicable;
- Biopsy or cytology, including reason, date and pathology result (additional assessment eCRF);
- Redacted reports on any lesions on off-protocol modalities, such as x-ray or FDG-PET, including specific locations, dates and status; redacted reports should only include data on imaging not submitted for review;
- Skin lesion reports (using the study approved form) will be provided by investigative sites for any lesions assessed by physical exam.

Clinical data provided to the central independent reviewers (additional assessment eCRF and Lesions Assessed by Physical Exam form) will not include information on images submitted for central review or information indicative of the site's assessment of tumor status (PD).

5.3.5 Safety Variables

AbbVie will assess adverse events, laboratory data, and vital signs throughout the study. Adverse events will be assessed according to NCI CTCAE version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).

During the conduct of the study, the AbbVie medical and safety team will be monitoring subject laboratory results, adverse event and serious adverse event data, as it is reported. Medically significant changes in vital signs and ECGs will be reviewed, as available.

An IDMC reviewed unblinded safety data intermittently prior to the primary analysis. No additional reviews by the IDMC will occur since the Sponsor management team was unblinded after completing the primary analysis.

Please refer to Section 8.1.8 for further details pertaining to the IDMC review.

5.3.6 Pharmacokinetic Variables

Collection and shipment of PK samples is discussed in Section 5.3.2.

Values for compartmental pharmacokinetic parameters of veliparib such as rate of absorption (Ka), apparent volume of distribution (V/F) and oral clearance (CL/F) may be estimated using a nonlinear mixed-effect population modeling approach with NONMEM software and reported in a separate pharmacokinetic report. Additional analyses may be performed, if useful in the interpretation of the data.

AbbVie or a designated laboratory will store the PK samples in a secure storage space with adequate measures to protect confidentiality. To increase confidence in trends, remaining sample aliquots may be used to perform replicate tests or sample analysis may be performed at additional time points for tests currently identified in the protocol. Upon completion of this research, AbbVie or a designated laboratory will destroy the samples.

5.3.7 Exploratory Research Variables

Optional blood and tissue samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. The results from these analyses are exploratory in nature and may not be included with the study report. Samples will be collected to conduct exploratory analyses to investigate biomarkers.

5.3.8 Biomarker Variables

Several putative biomarkers of efficacy and response may be evaluated in this protocol with the goal of exploring the relationship between tumor response and/or disease status.

Biospecimens collected may be evaluated for genetic lesions whether they occur by amplification, chromosomal loss and/or mutational/methylation with the intent of identifying potential associations with subject outcome or to better characterize the disease. These characterizations may be included, but are not limited, characterization of gene methylation/mutational status or copy number changes of genes, particularly those involved in DNA repair pathways.

Biospecimens may be evaluated for levels of biomarkers including nucleic acids, proteins/peptides and metabolites. For example, protein analysis of relevant proteins, including but not limited to, DNA repair proteins, such as ERCC1 and XPF, may be performed on tumor tissue obtained from each consented subject.

Samples collected during the course of this study may be banked and used in the future to investigate new scientific questions related to this study. Additionally, the samples may be anonymized and used for diagnostic test development. AbbVie (or a designated laboratory) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on veliparib (or drugs of this class) continues for up to but no longer than 20 years.

***BRCA* Bridging Sample**

In order to permit future bridging studies, additional samples will be collected to allow testing using additional assays to assess assay performance compared to other potential *BRCA* assays to be tested in the future.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will receive therapy until disease progression according to Section 5.3.4, RECIST 1.1, unmanageable toxicity (per discussion with the AbbVie TA MD), or they meet the study treatment discontinuation criteria as outlined below. Subjects who discontinue therapy for reasons other than disease progression will continue to be followed as per a modified scheduled of assessments per Appendix E.

Each subject has the right to withdraw from study treatment at any time. In addition, the investigator may discontinue a subject from the study treatment at any time for any reason if the investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol. Each subject will discontinue study treatment, if any of the following occur:

- The subject experiences disease progression as defined by RECIST (version 1.1).
- Clinically significant deterioration of the subject's medical status, as determined by the investigator.
- The investigator believes it is in the best interest of the subject;
- The subject requires alternative anticancer agents for primary or metastatic disease;
- The subject becomes pregnant or begins breastfeeding during the treatment portion of the study;
- The subject or subject's legally acceptable representative decides to withdraw consent for any reason; or
- Any other medical reason that AbbVie or the investigator deems appropriate.

Criteria for study discontinuation include:

- The subject experiences unequivocal disease progression as defined by RECIST (version 1.1) on blinded therapy and does not meet criteria for proceeding to the unblinded portion of the study, or experiences unequivocal disease progression as defined by RECIST (version 1.1) on unblinded therapy;
- The subject becomes pregnant or begins breastfeeding during the treatment portion of the study; or
- The subject or subject's legally acceptable representative decides to withdraw consent for any reason.

In cases of state of emergency or pandemic situations, if subjects withdraw consent from study treatment, they should be considered as on study, off drug and follow the schedule of assessments per Appendix E, if the subject consents to continued follow up.

When a subject discontinues either the blinded or unblinded study treatment, a Final Visit will be conducted. During a Final Visit, the reasons for the discontinuation from the study treatment will be recorded and a physical examination, vital signs measurement, laboratory analyses, performance status, ECG (if not performed within the last 4 weeks), QoL assessment, collection of unused study drug, and an assessment of adverse events will be performed. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition.

All subjects will have a 30-Day Follow-Up Visit approximately 30 days after the last dose of study treatment. Follow-Up Visits should not precede a Final Visit. Subjects starting any new cancer therapy within 30 days after the last dose of study treatment should complete the 1 month follow-up assessments in advance of starting any anti-cancer therapy. Assessments performed within the 7 days prior to the 30-Day Follow-up Visit do not need to be repeated, unless further study treatment was administered or a test result was abnormal. The 30-Day Follow-Up Visit does not need to be performed for subjects who have had a Final Visit conducted ≥ 30 days after the last dose of study treatment.

When a subject discontinuation is planned without the subject reaching a protocol-defined endpoint, the investigator will notify the AbbVie TA MD or the clinical team representative (Section 6.1.6) via telephone, as soon as possible (provided, in each case, subject care and safety are not compromised). If not notified prior to discontinuation, the AbbVie TA MD may contact the site to discuss the reason for withdrawal from the study.

If a subject is discontinued from study treatment with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

In the event that a subject becomes pregnant during the study, the administration of study treatment to that subject must be discontinued immediately. The site must report the pregnancy by telephone within 24 hours to one of the AbbVie representatives listed in Section 7.0. Discontinued subjects will not be replaced.

5.4.1.1 Discontinuation of Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel)

Subjects will receive veliparib/placebo + carboplatin + paclitaxel until reaching a protocol defined event of disease progression or they experience unmanageable toxicity. Dose reductions of carboplatin and paclitaxel will occur on the basis of the toxicity observed and may result in discontinuation of either agent (e.g., discontinuation of paclitaxel for neurotoxicity). The subject may continue on therapy with the remaining agent in combination with veliparib/placebo. Discontinuation of carboplatin and paclitaxel in the absence of toxicity requiring dose modification should be discussed with the AbbVie TA MD. Subjects who discontinue carboplatin and paclitaxel and who have not progressed will receive blinded veliparib/placebo as a single agent starting at 300 mg BID.

Carboplatin and paclitaxel administration will continue after veliparib/placebo has been discontinued.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his or her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped for reasons of safety. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

The following procedures for discontinuation must be followed:

- If the Sponsor has decided to prematurely discontinue the study, the Sponsor will promptly notify in writing the investigator, as well as regulatory authorities of the decision and give detailed reasons for the discontinuation;
- The investigator must promptly notify the IRB/IEC and give detailed reasons for the discontinuation; and
- The investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments, such as replacement of the treatment regimen by other appropriate regimens, if applicable.

5.5 Treatments

5.5.1 Treatments Administered

Subjects will be randomized in a 2:1 ratio to receive one of the following blinded treatments:

- Veliparib + Carboplatin and Paclitaxel
- Placebo + Carboplatin and Paclitaxel

General chemotherapy guidelines are found in Appendix L.

Veliparib/Placebo

Subjects will self-administer veliparib/placebo twice daily (with the morning and the evening doses approximately 8 – 12 hours apart) with or without food in the same calendar day for Days –2 through 5 of the 21-day cycle during the blinded study treatment portion. Dosing of veliparib/placebo on Day 1 of every cycle should be done before carboplatin + paclitaxel infusion.

Subjects who discontinue chemotherapy will self-administer veliparib/placebo twice daily (with the morning and the evening doses approximately 8 – 12 hours apart) with or without food in the same calendar day for Days 1 through 21 of the 21-day cycle.

Subjects in the unblinded veliparib monotherapy treatment will self-administer twice daily (with the morning and the evening doses approximately 8 – 12 hours apart) with or without food in the same calendar day for Days 1 through 21 of the 21-day cycle.

If the subject vomits within 15 minutes of taking veliparib/placebo, another dose should be administered. It is recommended that if a subject misses a scheduled dose of veliparib and less than 6 hours have passed since the scheduled dosing time, the dose should be taken immediately. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose, but should wait and take the next regularly scheduled dose.

Paclitaxel

All subjects should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists according to institutional guidelines, the locally approved product label, local practice, or applicable SmPC.

Paclitaxel will be administered intravenously over approximately 1 hour at a dose of 80 mg/m^2 on Day 1, 8 and 15 of every cycle. Paclitaxel will be infused prior to carboplatin on Day 1. Dosing of veliparib/placebo should always be done before the carboplatin or paclitaxel infusion.

If needed per dose modifications guidelines, it is recommended that growth factors (i.e., filgrastim, peg-filgrastim) dosed according to institutional standard will be administered daily subcutaneously starting 24 – 72 hours after the last dose of carboplatin/paclitaxel or after last dose of weekly paclitaxel. Pegfilgrastim should not be used for subjects receiving Day 15 paclitaxel as they do not have a 2-week chemotherapy-free interval.

Carboplatin

Carboplatin will be administered intravenously over approximately 15 to 30 minutes at (AUC 6 mg/mL/min) immediately following paclitaxel infusion on Day 1 of every cycle. The duration of carboplatin infusion may be lengthened according to institutional

guidelines. Dosing of veliparib/placebo should always be done before the carboplatin or paclitaxel infusion.

Maximum carboplatin dose will be capped as follows:

Carboplatin dose (mg) = target AUC (mg/mL/min) × (150 mL/min)

- For a target AUC = 6, the maximum dose is 6 × 150 = 900 mg
- For a target AUC = 5, the maximum dose is 5 × 150 = 750 mg*
- For a target AUC = 4, the maximum dose is 4 × 150 = 600 mg*

* Only for subjects who have had dose modifications.

Serum creatinine as provided by the central laboratory is based upon the IDMS method. Use of the central laboratory creatinine result for the calculation of estimated GFR and the Calvert formula for carboplatin dosing is strongly encouraged, with the maximum carboplatin dose capped as above. If the central laboratory value of plasma creatinine is not available at the time of carboplatin dose calculation, the local value may be used.

Similarly, when the GFR is estimated using isotopic/EDTA clearance, maximum carboplatin dosing should be based upon standard guidelines and institutional practices (e.g., AUC – 1). In subjects with a low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a minimum value of 0.7 mg/dl.

eGFR determined according to local practice will be capped at a maximum of 125 mL/min/1.73m^2. If a subject experiences toxicity that would lead to dose reduction of carboplatin to an AUC of < 4, carboplatin will be discontinued. Note that carboplatin dose will be recalculated if the subject has a weight change of greater than or equal to 10% from baseline; adjustments for weight change of < 10% are allowed per institutional guidance. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine > 1.5 × ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

If needed per dose modifications guidelines, it is recommended that growth factors (i.e., filgrastim, peg-filgrastim) dosed according to institutional standard will be administered daily subcutaneously starting 24 – 72 hours after the last dose of carboplatin/paclitaxel or after last dose of weekly paclitaxel.

5.5.2 Identity of Investigational Product

Information about veliparib, placebo, carboplatin, and paclitaxel formulations to be used in this study is presented in Table 5.

Table 5. Identity of Investigational Products

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Veliparib (ABT-888)	Capsule	40 mg active 50 mg active 100 mg active	Oral	AbbVie
Veliparib (ABT-888) Placebo	Capsule	40 mg placebo 50 mg placebo 100 mg placebo	Oral	AbbVie
Carboplatin (commercially available)*	Vial*	150 mg /15 mL aqueous solution* 450 mg/45 mL aqueous solution*	Intravenously	Generic manufacturer
Paclitaxel (commercially available)*	Vial*	100 mg/16.7 mL non-aqueous solution*	Intravenously	Generic manufacturer

* Carboplatin and paclitaxel formulations may vary based on the source.

AbbVie will supply veliparib capsules and a matching placebo for veliparib. Veliparib will be tested for stability and relabeled and/or replaced as necessary. Instructions for relabeling supplies will be provided by AbbVie. Carboplatin and paclitaxel will either be obtained commercially by the site or AbbVie will supply carboplatin and paclitaxel to sites depending on local regulations and availability of supplies.

5.5.2.1 Packaging and Labeling

Veliparib and placebo will be packaged in bottles containing the required number of capsules of 40 mg active, 50 mg active or 100 mg active or placebo. Each bottle label will include all information, as required by local regulations and must remain affixed to the bottle. The site staff must complete all blank spaces on the label prior to dispensing drug to the subject.

If carboplatin and/or paclitaxel are provided by AbbVie, the label will include all information as required by local regulations and must remain affixed to the primary and secondary packaging material. The site staff must complete all blank spaces on the label prior to dispensing drug to the subject.

AbbVie will provide the study site with detailed instructions and training for the handling of study supplies.

5.5.2.2 Storage and Disposition of Study Drug

All clinical supplies provided by AbbVie must be stored in a secure place at the proper storage conditions as presented in Table 6, until they are dispensed for subject use or are returned to AbbVie.

Investigational products are for investigational use only and are to be used only within the context of this study. The clinical supplies supplied for this study must be maintained under adequate security and stored under conditions specified on the label. If pre-arranged between AbbVie and the site, destruction of used and unused study drug will be performed at the site.

Table 6. Study Drug Storage Conditions

Study Drug	Country**	Storage Conditions
Veliparib or placebo	All countries, except Australia	Store at 15° to 25°C (59° to 77°F).
	Australia	Store below 25°C.
Carboplatin	All countries, except Australia	Store at 15° to 25°C (59° to 77°F). Protect from light.
	Australia	Store below 25°C. Protect from light.
Paclitaxel	All countries, except Australia	Store at 15° to 25°C (59° to 77°F). Protect from light.
	Australia	Store below 25°C. Protect from light.

** Study drug must be stored according to the labeled storage conditions or local labeling instructions.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects in study will be randomized to the blinded portion of the study by an IVRS/IWRS. Before the study is initiated, each site will be provided with directions for the IVRS/IWRS. The site will contact the IVRS/IWRS to obtain a Screening (subject) number once the subject has signed the informed consent **and** a study-specific procedure has been performed (i.e., central labs drawn). Once the screening number is assigned, if the subject is not randomized into the study, the reason for screen failure will be documented in the source document and in the eCRF.

Subjects who complete all Screening procedures and meet the inclusion criteria in Section 5.2, and none of the exclusion criteria in Section 5.2.2 will proceed to randomization. The site should access the system on or within 2 days prior to the subject's C1D-2 visit to randomize the subject.

The IVRS/IWRS will randomize subjects in a 2:1 ratio, between the veliparib BID + carboplatin + paclitaxel arm and the placebo BID + carboplatin + paclitaxel arm. Subject randomization will be stratified by estrogen receptor (ER) and/or progesterone receptor (PgR) positive versus ER/PgR negative, prior platinum therapy (yes versus no), and CNS metastases (yes versus no). Tumors with any detectable (≥ 1%) expression of

ER and/or PgR by IHC are considered hormone-receptor positive. Tumors with no detectable expression of ER and PgR are considered hormone receptor negative or endocrine non-responsive. For subjects with heterogeneity between primary tumor and metastases, the biopsy most proximal to C1D-2 will be used for the purposes of stratification. For subjects with de novo Stage IV disease, the receptor status of the primary tumor will be used for the purposes of stratification.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects will be randomized into 1 of 2 treatment arms.

Subjects will self-administer veliparib/placebo twice daily (with the morning and the evening doses approximately 8 – 12 hours apart) with or without food in the same calendar day.

Subjects will return to the site on Day 1 of each cycle to have carboplatin and paclitaxel administered intravenously. In addition subjects will return to the site on Days 8 and 15 of each cycle to have paclitaxel administered intravenously.

5.5.5 Blinding

This is a double-blind study. AbbVie, the investigator, the study site personnel, and the subject will remain blinded to each subject's treatment with veliparib/placebo until progression of disease. Subjects who discontinue study treatment because of disease progression as defined by Section 5.3.4 have the option to be unblinded to determine eligibility for unblinded veliparib monotherapy (crossover). Following progression of disease, a separate unblinded study team was responsible for study conduct and data monitoring for subjects who crossed over to veliparib monotherapy.

After completion of the primary analysis the sponsor was unblinded to treatment assignment. A separate unblinded study team is no longer responsible for study conduct and data monitoring for subjects who crossover to veliparib monotherapy. Primary site monitors, investigators and subjects continue to be blinded to treatment assignment until

disease progression, after which unblinding to determine eligibility for crossover can be requested.

5.5.5.1 Blinding of Investigational Product

The IVRS/IWRS will provide access to blinded subject treatment information for an individual during the double-blind period. The AbbVie TA MD (listed in Section 6.1.6) must be notified before the blind is broken unless identification of the study drug is required for medical emergency, i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF. In the event the AbbVie Clinical Project Team should break the blind, the reason will be documented in a note to study file and on the appropriate eCRF.

5.5.6 Treatment Compliance

The investigator or his or her designated and qualified representatives will administer and dispense veliparib/placebo, carboplatin, and paclitaxel only to subjects enrolled in the study in accordance with the protocol. Veliparib, placebo, carboplatin, and paclitaxel must not be used for reasons other than those described in the protocol.

Veliparib/placebo should be taken as directed by the investigator.

Carboplatin and paclitaxel will be administered intravenously by trained site personnel.

Subjects will be instructed to return all veliparib/placebo bottles (empty, partially filled, or full) to the study site personnel prior to each cycle and at each blinded and unblinded study treatment Final Visit. The study site personnel will document the bottles/cartons of veliparib/placebo returned and the number of capsules per bottle/carton on the appropriate form. The bottles/cartons will be retained until the site monitor performs accountability

of veliparib/placebo, carboplatin (when supplied by AbbVie), and paclitaxel (when supplied by AbbVie).

The study coordinator will document subject study drug administration details on the appropriate eCRF. If the number of capsules taken and the number of capsules returned do not add up to the number of capsules dispensed, an explanation will be provided.

Unless otherwise directed by the investigator at the site, a subject will be considered compliant with veliparib/placebo if 80% of the assigned dose is taken during a cycle. Compliance below 80% will require counseling of the subject by study site personnel.

5.5.7 Drug Accountability

Upon receipt of a shipment, the representative at each site will 1) open and inspect the shipment; 2) verify that the veliparib, placebo, carboplatin, and paclitaxel has been received intact, in the correct amounts, and at the correct address; 3) sign and date the Proof of Receipt (POR) or similar documentation accompanying the shipment; and 4) register the shipment as received via the IVRS/IWRS. All study drugs must be retained in the designated secure area under proper storage conditions. This will be documented by signing and dating the POR or similar document or via direct recording in the IVRS/IWRS.

An overall accountability of veliparib, placebo, carboplatin, and paclitaxel supplied by AbbVie will be performed and verified by the site monitor via IWRS throughout the study and at the study site closeout visit. An accurate running inventory of veliparib, placebo, carboplatin, and paclitaxel supplied by AbbVie will be kept by the site in the IWRS and will include the lot number, POR numbers, the bottle/carton numbers, and the date veliparib, placebo, carboplatin, and paclitaxel were dispensed for each subject.

Upon completion or termination of the study, all original bottles/cartons containing unused veliparib, placebo, carboplatin, paclitaxel (empty containers will be defaced and discarded on site) will be returned to AbbVie according to AbbVie's instructions, or if

pre-arranged between the sponsor and site, destruction of used and unused veliparib, placebo, carboplatin, and paclitaxel in bottles/cartons will be performed at the site.

The investigator or his or her designated representative agrees not to supply veliparib, placebo, carboplatin, or paclitaxel to any persons not enrolled in the study or not named as a sub-investigator listed on the FDA 1572 or IIA form.

The site will record the bottle number and dose of veliparib, placebo and the bottle/carton number and dose of carboplatin and paclitaxel given to each subject in the source documents and on the eCRF.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is a Phase 3, randomized, double-blind study to evaluate the efficacy and tolerability of veliparib in combination with carboplatin + paclitaxel compared to an active, placebo controlled arm of carboplatin + paclitaxel in subjects with HER2-negative locally advanced unresectable or metastatic BRCA-Associated breast cancer. The choice of the control group allowed for a blinded assessment of the contribution of veliparib to the safety and efficacy of the backbone regimen of carboplatin + paclitaxel. In addition to paclitaxel being an approved agent for breast cancer, emerging data indicate enhanced sensitivity of *BRCA* mutated cells to platinums; thus, there is potential for increased activity of this regimen in this population.

The randomization will be 2:1. Randomization will be stratified by estrogen receptor (ER) and/or progesterone receptor (PgR) positive versus ER/PgR negative, prior platinum therapy (yes versus no), and CNS metastases (yes versus no). Tumors with any detectable ($\geq$ 1%) expression of ER and/or PgR by IHC are considered hormone-receptor positive. Tumors with no detectable expression of ER and PgR are considered hormone receptor negative or endocrine non-responsive.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. The efficacy measurements in this study are standard and validated.

5.6.3 Suitability of Subject Population

Documented *BRCA*1 or *BRCA*2 mutation carriers with histologically (or cytologically) confirmed HER2-negative locally advanced unresectable or metastatic breast cancer will be enrolled into the study. Subjects must have had no more than two prior DNA-damaging cytotoxic chemotherapy agents for metastatic disease. Subjects must have measurable or non-measurable (but radiologically evaluable) disease as defined by modified RECIST (version 1.1).

5.6.4 Selection of Doses in the Study

The combination of veliparib with carboplatin and paclitaxel has been investigated in ongoing Phase 1 studies conducted in collaboration with the NCI CTEP. CTEP 7967 enrolled subjects who are chemotherapy-naive as well as subjects who received previous DNA damaging chemotherapy including platinum compounds. In this study, the maximum dose administered is veliparib 120 mg BID for 7 days in addition to carboplatin AUC 6 and paclitaxel 200 mg/m^2 administered on Day 3 of a 21-day cycle (regimen based upon standard of care for non-small cell lung cancer). Chemotherapy is administered on the third day of veliparib treatment to ensure steady state levels of veliparib (and thus maximal inhibition of PARP for given dose) at the start of chemotherapy treatment. Toxicities were as expected with carboplatin and paclitaxel chemotherapy, including neutropenia, thrombocytopenia, and peripheral neuropathy.[29] Weekly paclitaxel is standard therapy for breast cancer. The safety and tolerability of veliparib in combination with paclitaxel and carboplatin has been evaluated in study GOG 9923; current dose levels for intermittent veliparib are 300 mg BID with both q-3week carboplatin/paclitaxel (1/7 DLT at 300 mg BID, febrile neutropenia) and weekly carboplatin/paclitaxel (1/6 DLT at 250 mg BID; G4 thrombocytopenia), further supporting the tolerability of the 120 mg BID dose. The proposed study will allow subjects who discontinue chemotherapy to

continue with single agent veliparib starting at 300 mg BID and if tolerated, escalate to 400 mg BID administered continuously. This dose has been selected based upon the recommended Phase 2 dose (CTEP 8282) and additional safety and efficacy data in Phase 2 studies in *BRCA*-mutation carriers with breast cancer (CTEP 8264) or ovarian cancer (GOG 280), in which durable responses were observed to single agent therapy.

The maximum dose of veliparib for any subject under this protocol is 120 mg BID in combination with carboplatin and paclitaxel and 400 mg BID as monotherapy.

5.7 Dose Reductions or Delays

The intention is for veliparib/placebo to be administered concurrently with carboplatin + paclitaxel. Thus, if a delay in any component of the regimen is required for any reason, all drugs within the regimen should be delayed until the subject is eligible to receive all drugs. All toxicities, with the exception of anemia, alopecia, and non-treatment related clinically insignificant laboratory abnormalities, should be resolved to Grade 1 or lower or to baseline if Grade 2 is present at the time of study entry prior to initiation of a new cycle of therapy. Neuropathy should be resolved to Grade 1 or lower to initiate a new cycle of therapy, unless paclitaxel has been previously discontinued.

If chemotherapy must be withheld because of hematological toxicity, CBC should be obtained at least weekly until the counts reach the lower limits for treatment as outlined.

The AbbVie TA MD is to be contacted for subjects who require cycle delays of > 28 days due to toxicity.

Study drug interruptions for events that are clearly not related to the study drug, e.g., underlying cancer, planned surgical procedures, or acute viral illnesses, do not necessitate a dose reduction. The timing of dose resumption should be at the investigator's discretion.

Dose reduction for fatigue will only be done if the fatigue is deemed to be study drug-related in the investigator's opinion.

In the case of delays, interruptions or study treatment discontinuation, tumor assessments should have continued at intervals of 9 weeks from C1D-2. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks (or not to exceed 24 weeks for subjects with durable disease control, at investigator discretion) from last scan.

Due to the COVID-19 pandemic, temporary study drug interruption may occur. The AbbVie TA MD is to be contacted for subjects who require cycle interruptions of > 28 days.

5.7.1.1 Carboplatin + Paclitaxel Dose Reduction and Delays

If a dose reduction or delay is required for carboplatin and/or paclitaxel, the investigator should follow procedures according to institutional guidelines, the locally approved product label, local practice, or applicable SmPC. The dose levels and guidelines for dose modifications based on prior studies with veliparib, carboplatin, and paclitaxel appear in Table 7, Table 8, Table 9, and Table 10, respectively.

Table 7. Dose Levels for Veliparib/Placebo + Carboplatin/Paclitaxel

Dose Level	Carboplatin	Paclitaxel*	Veliparib/Placebo
Starting Dose Level	AUC 6	80 mg/m^2	120 mg BID
Dose Level –1	AUC 5	70 mg/m^2	80 mg BID
Dose Level –2	AUC 4	60 mg/m^2	40 mg BID

* Discontinuation of the Day 15 paclitaxel infusion for hematological toxicities (per Table 8) will be considered a dose reduction and will be maintained in subsequent cycles.

It is recommended that treatment on Day 1 of each cycle proceeds only if ANC is ≥ 1500 cells/mm^3 and the platelet count is ≥ 100,000/mm^3. Recommended dose modifications/delays based on hematologic toxicities on Day 1 are outlined in Table 8. For subjects with an ANC of 1000 – 1499/mm^3 or platelet count 75,000 – 99,999/mm^3 on Day 1, dosing may continue without modification or delay until recovery, at investigator discretion, if drug-related toxicity has been ruled out. If ANC is below 1000/mm^3 or the platelet count is below 75,000/mm^3, treatment should be delayed until recovery.

For subjects receiving paclitaxel on the second and third week of the cycle, ANC must be ≥ 1000/mm3 and platelets ≥ 75,000/mm^3 on Day 8 and Day 15 of the cycle. If counts are lower than this, treatment for that day will be omitted with reassessment of hematological counts 1 week later. Dose reductions as outlined in the tables will be used in the following cycle. Within a given cycle, if the Day 8 dose is omitted and the counts recover by Day 15, the Day 15 dose may be given. If the ANC and platelet counts have not recovered sufficiently for the Day 15 paclitaxel infusion to be administered, therapy may be resumed with the subsequent cycle once the hematological counts have recovered (the intent is to maintain a 21-day cycle).

Carboplatin and paclitaxel are to be delayed if veliparib/placebo was not taken by the subject on Day –2 and Day –1. In such a case, a new supply of veliparib/placebo is to be dispensed, and Day –2 and Day –1 are to be repeated for that cycle.

For any Grade 3 or 4 toxicities not mentioned in Table 8, Table 9 and Table 10 treatment will be withheld until the patient recovers to Grade 1 or baseline, and the dose of the drug(s) most likely to have caused the toxicity will be reduced. Re-escalation of therapy on combination chemotherapy is not permitted.

Table 8. Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel) Dose Reduction and Delays for Hematologic Toxicities on Day 1

	Adverse Event		Dose Reduction/Delay for Weekly Paclitaxel Dosing		
			Paclitaxel	**Carboplatin**	**Veliparib or Placebo**
Hematological toxicity attributable to any or all treatment	ANC 1000 – 1499/mm^3 and/or Platelets 75000 – 99999/mm^3		Resume at the same dose level after recovery.	Resume at the same dose level after recovery.	Resume at the same dose level after recovery.
			For repeated occurrences or delays > 2 weeks, consider reducing paclitaxel, carboplatin or veliparib/placebo by one dose level.		
	ANC < 1000/mm^3	First Occurrence	Reduce paclitaxel by one dose level after recovery.	Reduce carboplatin one dose level and it is recommended to use G-CSF.	Resume at the same dose level after recovery.
		Second Occurrence	Discontinue Day 15 paclitaxel.[b]	Resume at the same dose level after recovery.	
	Platelets 25000 – 74999/mm^3	First Occurrence	Resume at the same dose level after recovery.	Reduce carboplatin by one dose level.	
		Second Occurrence	Resume at the same dose level after recovery.	Reduce carboplatin by one dose level.	
	ANC < 1000/mm^3 AND Platelets 25000 – 74999/mm^3	First Occurrence	Reduce paclitaxel by one dose level after recovery.	Reduce carboplatin by one dose level and it is recommended to use G-CSF.	
		Second Occurrence	Discontinue Day 15 paclitaxel.[b]	Reduce carboplatin by one dose level.	

Table 8. Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel) Dose Reduction and Delays for Hematologic Toxicities on Day 1 (Continued)

	Adverse Event		Dose Reduction/Delay for Weekly Paclitaxel Dosing		
			Paclitaxel	**Carboplatin**	**Veliparib or Placebo**
Hematological toxicity attributable to any or all treatment (continued)	ANC < 500/mm^3 for ≥ 7 days		Hold until recovery to ANC ≥ 1500/mm^3. Reduce paclitaxel by one dose level. It is recommended to use G-CSF.	Reduce carboplatin by one dose level.	Resume at the same dose level after recovery.
	Febrile neutropenia (ANC ≤ 1000/mm^3 with temperature of > 38.5°C[a])	First Occurrence	Hold until recovery to ANC ≥ 1500/mm^3. Reduce paclitaxel by one dose level. It is recommended to use G-CSF.	Resume at the same dose level after recovery.	Resume at the same dose level after recovery.
		Second Occurrence	Hold until recovery to ANC ≥ 1500/mm^3. Discontinue Day 15 paclitaxel.[b] It is recommended to use G-CSF.	Reduce carboplatin by one dose level.	Resume at the same dose level after recovery.
	Anemia[a]		No reduction or delay.	No reduction or delay.	No reduction or delay.

a. For clinically significant anemia consider treatment with erythrocyte growth factor and RBC transfusion according to local institutional guidelines.

b. For subjects who have already discontinued Day 15 paclitaxel, reduce paclitaxel by one additional dose level.

Note: If needed per dose modifications guidelines, it is recommended that growth factors (i.e., filgrastim, peg-filgrastim) dosed according to institutional standard will be administered daily subcutaneously starting 24 – 72 hours after the last dose of carboplatin/paclitaxel or after last dose of weekly paclitaxel. Pegfilgrastim should not be used for subjects receiving Day 15 paclitaxel as they do not have a 2-week chemotherapy-free interval.

Table 9. Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel) Dose Reduction and Delays for Hematologic Toxicities on Day 8 or 15

	Adverse Event		Dose Reduction/Delay for Weekly Paclitaxel Dosing		
			Paclitaxel	**Carboplatin**	**Veliparib or Placebo**
Hematological toxicity attributable to any or all treatment	ANC 500 – 999/mm^3 and Platelets 50,000 – 74,999/mm^3		Resume at the same dose level after recovery.	Resume at the same dose level after recovery.	Resume at the same dose level after recovery.
	ANC <500/mm^3	First Occurrence	Resume at the same dose level after recovery.	Reduce carboplatin by one dose level and it is recommended to use G-CSF with next cycle.	Resume at the same dose level after recovery.
		Second Occurrence	Discontinue Day 15 paclitaxel.[b]	Resume at the same dose level after recovery.	
	Platelets <50,000/mm^3	First Occurrence	Resume at the same dose level after recovery.	Reduce carboplatin by one dose level with the next cycle.	
		Second Occurrence	Discontinue Day 15 paclitaxel.[b]	Reduce carboplatin an additional dose level with the next cycle.	
	ANC < 500/mm^3 AND Platelets < 50,000/mm^3	First Occurrence	Resume at the same dose level after recovery.	Reduce carboplatin by one dose level and it is recommended to use G-CSF with the next cycle.	
		Second Occurrence	Discontinue Day 15 paclitaxel.[b]	Reduce carboplatin by one dose level.	

Table 9. Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel) Dose Reduction and Delays for Hematologic Toxicities on Day 8 or 15 (Continued)

	Adverse Event		Dose Reduction/Delay for Weekly Paclitaxel Dosing		
			Paclitaxel	Carboplatin	Veliparib or Placebo
Hematological toxicity attributable to any or all treatment (continued)	ANC < 500/mm^3 for ≥ 7 days		Hold until recovery. Reduce paclitaxel by one dose level. It is recommended to use G-CSF.	Hold until recovery. Reduce carboplatin by one dose level.	Resume at the same dose level after recovery.
	Febrile neutropenia (ANC ≤ 1000/mm^3 with temperature of > 38.5°C[a])		Hold until recovery. Reduce paclitaxel by one dose level. It is recommended to use G-CSF.	Resume at the same dose level after recovery.	Resume at the same dose level after recovery.
	Anemia[a]		No reduction or delay.	No reduction or delay.	No reduction or delay.

a. For clinically significant anemia consider treatment with erythrocyte growth factor and RBC transfusion according to local institutional guidelines.

b. For subjects who have already discontinued Day 15 paclitaxel, reduce paclitaxel by one additional dose level.

Note: If needed per dose modification guidelines, it is recommended that growth factors (i.e., filgrastim, peg-filgastrim) dosed according to institutional standard will be administered daily subcutaneously starting 24 – 72 hours after the last dose of carboplatin/paclitaxel or after last dose of weekly paclitaxel. Pegfilgrastim should not be used for subjects receiving Day 15 paclitaxel as they do not have a 2-week chemotherapy-free interval.

Table 10. Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel) Dose Reduction and Delays for Other Toxicities

		Dose Reduction/Delay		
	Adverse Event	**Paclitaxel**	**Carboplatin**	**Veliparib or Placebo**
Hepatic Toxicity[a]	Grade 3 or greater AST (SGOT), ALT (SGPT), Total Bilirubin, or Alkaline Phosphatase	Hold until recovery to Grade 1 or baseline. Reduce by one dose level.	Hold until recovery to Grade 1 or baseline. Resume at previous dose.	Hold until recovered to Grade 1 or baseline. Resume at previous dose.
	Total Bilirubin > 5 × ULN or AST or ALT > 10 × ULN	Discontinue	Hold until AST/ALT < 3 × ULN. Resume at previous dose.	Hold until AST/ALT < 3 × ULN. Resume at previous dose.
Non-hematologic Grade 3 or 4 toxicity attributable to any or all treatment	Grade 3 or 4 nausea/vomiting despite optimal antiemetic treatment[b]	Hold until nausea/vomiting have resolved to ≤ Grade 1. Reduce by one dose level.	Hold until nausea/vomiting have resolved to ≤ Grade 1. Resume at 1 dose level below current dose level.	Hold until nausea/vomiting have resolved to ≤ Grade 1. Resume at previous dose.
	≥ Grade 2 stomatitis	Hold until stomatitis has resolved to ≤ Grade 1. Reduce by one dose level.	Hold until stomatitis has resolved to ≤ Grade 1. Reduce by one dose level.	Hold until stomatitis has resolved to ≤ Grade 1. Resume at previous dose.
	≥ Grade 2 neuropathy[c]	Hold until recovery to Grade 1 or less. Reduce dose by one dose level. If peripheral neuropathy fails to recover to Grade 1 within 3 weeks, paclitaxel should be discontinued.	Resume at the same dose level after recovery.	Resume at the same dose level after recovery.
Toxicity attributable to veliparib and not carboplatin or paclitaxel, nor underlying disease	Any Grade 3 or 4 toxicity	Resume at the same dose level after recovery to ≤ Grade 1 or to baseline.	Resume at the same dose level after recovery to ≤ Grade 1 or to baseline.	Hold until recovery to ≤ Grade 1 or to baseline. After recovery, reduce by one dose level.
Any other Grade 3 or 4 toxicity not attributable to underlying disease		Hold until recovery to ≤ Grade 1 or to baseline and reduce the dose of the drug(s) most likely to have caused the toxicity by one dose level.		

Table 10. Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel) Dose Reduction and Delays for Other Toxicities (Continued)

a. A subject will be allowed a maximum of 2 dose reductions. If a third reduction is required, the subject should discontinue paclitaxel. If paclitaxel is withheld because of hepatic toxicity, carboplatin should also be withheld and administered when the paclitaxel is resumed. If paclitaxel is withheld, hepatic values must recover to ≤ Grade 1 within 3 weeks or paclitaxel will be discontinued.

b. Prophylactic anti-emetic therapy (e.g., aprepitant, ondansetron, palonosetron, dexamethasone) should be administered to all subjects per institutional guidelines; specific agents are at the discretion of the treating physician.

c. Dose reductions of paclitaxel for Grade 1 neuropathy will also be allowed, per the investigator's standard practice. For neurologic toxicity, the subject will be allowed a maximum of 2 dose reductions. If a third dose reduction is required, the subject should discontinue paclitaxel. If the subject continues to receive carboplatin, veliparib may also be continued.

5.7.1.2 Veliparib or Placebo Dose Reductions and Delays in Combination with Carboplatin + Paclitaxel

The following are guidelines for dose reduction, delay, and discontinuation of veliparib/placebo in combination with carboplatin and paclitaxel. Dose reductions are outlined below and subjects will continue to follow the schedule of assessments as outlined in Appendix C.

1. For any subject who experiences Grade 3/4 toxicity which is not attributable to carboplatin/paclitaxel or the underlying disease, the veliparib/placebo dose is to be held until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 is present at the time of study entry. Upon resuming veliparib/placebo treatment, the dose is to be reduced one dose level. Any dose reduction below 40 mg BID is to result in veliparib/placebo discontinuation.
2. Carboplatin and/or paclitaxel administration will continue after veliparib/placebo has been discontinued.
3. Veliparib/placebo administration will continue after carboplatin and paclitaxel discontinuation (Section 5.7.1.3). Subjects who discontinue carboplatin and paclitaxel due to toxicity and protocol-defined dose modifications and who have not progressed will receive single-agent, blinded veliparib/placebo starting at 300 mg BID. The treatment plan for subjects who experience a robust and durable response (such as a confirmed CR following 10 or more cycles of therapy) and for whom the investigator considers the potential risks of continued cytotoxic chemotherapy outweigh the benefits should be discussed with the AbbVie TA MD prior to initiating single-agent blinded veliparib/placebo.
4. If a subject begins veliparib/placebo on Day –2, but subsequently experiences an event requiring the delay of the carboplatin/paclitaxel dosing on Day 1, the subject is to stop veliparib/placebo dosing immediately. Upon resolution of the event, the subject may restart the current cycle by repeating Day –2 and Day –1. For such delays, a new veliparib supply will be dispensed to restart the cycle at Day –2.

5. For any ≥ Grade 2 event of seizure attributed to veliparib/placebo, veliparib/placebo is to be interrupted, brain CT or MRI obtained, and the event should be discussed with the AbbVie TA MD.

5.7.1.3 Blinded Veliparib/Placebo and Unblinded Veliparib Monotherapy Dose Reductions and Delays

Subjects who discontinue carboplatin and paclitaxel and who have not progressed may receive single-agent, blinded veliparib/placebo starting at 300 mg BID. Subjects will continue to follow the schedule of assessments as outlined in Appendix C. In addition, subjects who progressed while on placebo may crossover to unblinded veliparib monotherapy and will follow the schedule of assessment as outlined in Appendix D. If veliparib was discontinued previously in combination with carboplatin and paclitaxel, the subject can resume veliparib/placebo monotherapy dosing if symptoms resolve to ≤ Grade 1. If veliparib/placebo monotherapy is initiated, the starting dose should be 300 mg BID for 2 weeks followed by an increase to 400 mg BID, if well tolerated.

The following are guidelines for dose reductions, delays and discontinuation of blinded veliparib/placebo or unblinded veliparib monotherapy. Dose reductions are outlined in Table 11.

It is recommended that treatment on Day 1 of each cycle proceeds only if ANC is ≥ 1500 cells/mm^3 and the platelet count is ≥ 100,000/mm^3. Dosing may continue in subjects with ANC and/or platelet counts ranges of ANC of 1000 – 1499/mm^3 or platelet count 75,000 – 99,999/mm^3 without modification at investigator discretion if drug-related toxicity has been ruled out.

For any subject who experiences Grade 3 or 4 toxicity despite optimal supportive care and the toxicity is not attributable to underlying disease, the veliparib/placebo dose will be held until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 is present at the time of study entry.

The dose of veliparib/placebo will be reduced by one dose level for subjects experiencing the following toxicities if attributed to veliparib/placebo:

Hematological toxicities:

- Grade 3 or 4 neutropenia persisting ≥ 7 days
- Grade 3 or 4 ANC with fever (ANC < 1.0×10^9/L, fever ≥ 38.5°C)
- Grade 3 or 4 thrombocytopenia

Non-hematological toxicities

- Any CTCAE ≥ Grade 3 toxicity that represents at least 2 grade increase from baseline with the following clarifications
  - Excludes nausea, vomiting, diarrhea, and tumor pain that have not received optimal treatment with antiemetics, antidiarrheals, or analgesics.
  - A rise in creatinine to Grade 3, only if not corrected to Grade 1 or baseline within 24 hours with IV fluids.
  - Metabolic toxicities, only if not corrected to Grade 2 or less within 24 hours (such as glucose changes, hypokalemia, hypomagnesemia, hyperuricemia, hypophosphatemia, and hyponatremia). Grade 4 metabolic toxicities that are symptomatic will result in dose reduction regardless of duration or ability to correct.
  - For any > Grade 2 event of seizure attributed to veliparib/placebo, veliparib/placebo is to be interrupted, brain CT or MRI obtained, and the event should be discussed with the AbbVie TA MD.

Re-escalation may be permitted on the veliparib monotherapy arm only if toxicity resolved to Grade 1 or lower and can be maintained with optimal supportive care. This should be discussed with the appropriate AbbVie TA MD.

Table 11. Blinded Veliparib/Placebo and Unblinded Veliparib Monotherapy Dose Levels

Dose Level	Veliparib	
Starting Dose Level	300 mg BID (if unable to escalate dose due to toxicity by C1D15 then continue current dose)	400 mg BID (if acceptable toxicity then escalate dose on C1D15)
Dose Level –1	200 mg BID	300 mg BID
Dose Level –2	150 mg BID	200 mg BID

5.7.1.4 Allergic Reaction/Hypersensitivity

Paclitaxel:

Severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria, require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Subjects who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

Carboplatin:

Severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria, require immediate discontinuation of carboplatin and aggressive symptomatic therapy. Subjects who have developed hypersensitivity reactions may undergo desensitization per institutional protocol as determined by the investigator. This should be discussed with the AbbVie TA MD.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor. For adverse events, please refer to Sections 6.1 through 6.1.8. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study treatment, and any action(s) taken. For serious and nonserious adverse events considered as having "no reasonable possibility" of being associated with study treatment, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events

only if they result in discontinuation from the study, necessitate therapeutic medical intervention, [meets protocol specific criteria (see Section 6.1.8 regarding toxicity management)] and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry or is due to an improvement in the underlying disease. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie, as appropriate, as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility, hospitalization for respite care, or hospitalization due solely to progression of the underlying cancer.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A toxicity is deemed "clinically significant" on the basis of the investigator's medical judgment. Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The study Investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0).[36]

For adverse events not captured by the NCI CTCAE Version 4.0, the Investigator will use the following definitions to rate the severity of each adverse event:

Mild (Grade 1)	The adverse event is transient and easily tolerated by the subject.

Moderate (Grade 2)	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe (Grade 3 or 4)	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.
Death (Grade 5)	The adverse event resulted in death of the subject (severe).

If a reported adverse event **increases** in severity, the initial adverse event should be given an outcome date and a new adverse event should be reported to reflect the change in severity.

For all reported serious adverse events that increase in severity, the supplemental CRFs also need to be updated and need to include the new AE serial number.

6.1.2.1 Adverse Events Expected Due to Breast Cancer or Progression of Breast Cancer

Adverse events that may be expected from primary breast cancers or progression of breast cancer include skin erythema, skin edema, skin erosion, non-cardiac chest pain, metastases to bone, metastases to brain, metastases to central nervous system, metastases to liver, and tumor pain.

These events may occur alone or in various combinations and are considered expected adverse events in breast cancer subjects.

6.1.3 Adverse Events Expected Due to Study Related Endpoints

6.1.3.1 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event collection period (Section 6.1.5) that are more likely related to disease progression will therefore be an expected adverse event and will not be an expedited report.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

6.1.3.2 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be subject to expedited reporting. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

6.1.4 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study treatment: For the purpose of this section, study treatment is considered veliparib or placebo, carboplatin and or paclitaxel.

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study treatment will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not

associated." In addition, when the investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study treatment is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.5 Adverse Event Collection Period

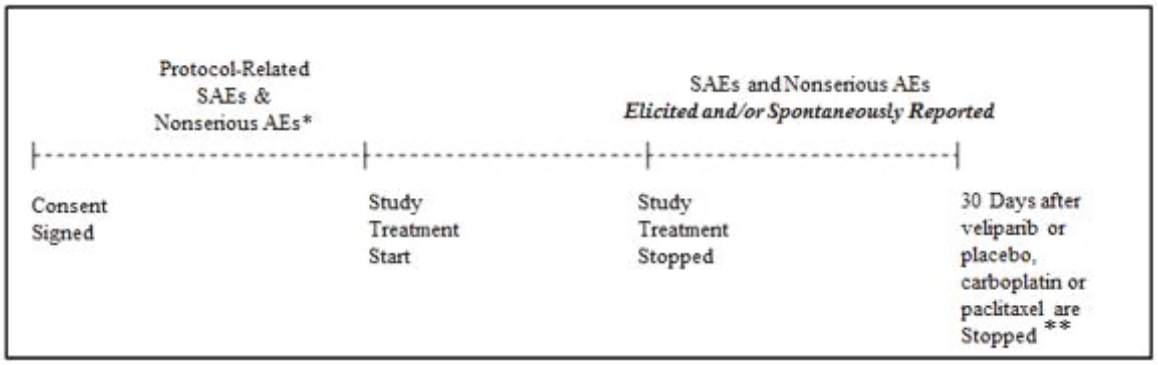
All protocol-related serious and nonserious adverse events must be collected from the signing of the study specific informed consent until study treatment administration.

In addition, all adverse events reported from the time of study treatment administration until 30 days following discontinuation of study treatment administration have elapsed will be collected, whether solicited or spontaneously reported by the subject.

Serious and nonserious adverse events occurring after the study-specific informed consent is signed but prior to the initial dose of veliparib/placebo, carboplatin or paclitaxel will be collected **only** if they are considered by the Investigator to be causally related to study required procedures.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



* Only if considered by the Investigator to be causally related to study-required procedures.

** Adverse events of myelodysplastic syndrome, acute myeloid leukemia or any second primary malignancy should be reported throughout the entire duration of follow-up phase even if the onset is > 30 days following discontinuation of study treatment.

6.1.6 Adverse Event Reporting

In the event of a serious adverse event, whether related to AbbVie study medication or not, the Investigator will notify AbbVie Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the Electronic Data Capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be faxed to AbbVie Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

FAX to: +1 (847)-938-0660 or
Email to: PPDINDPharmacovigilance@abbvie.com

For safety reporting related questions or concerns, contact the Oncology Safety Team at:

AbbVie Oncology Safety Team
Bldg. AP51
1 North Waukegan Road
North Chicago, IL 60064
Office: + 1 847 935-2609
Email: SafetyManagement_Oncology@abbvie.com

For any emergent safety concerns for the blinded study treatment arm or unblinded veliparib monotherapy (crossover) treatment arm, please contact the AbbVie TA MD.

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Office: [redacted]
Cell:
Email:

Should in case of subject safety concerns or medical emergencies the TA MD is unavailable, please call the following central back-up number:

Phone: +1 (973) 784-6402

In the EU, AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The safety reference material used for SUSAR reporting will be the most current version of the Investigator's Brochure for veliparib or SmPC for carboplatin, and paclitaxel.

Due to the COVID-19 pandemic and evolving local regulations, urgent safety measures may need to be employed in order to protect participating subjects from any immediate hazard. Such events and measures should be reported to the sponsor emergency medical contact listed above immediately.

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. If a subject has a confirmed or suspected COVID-19 infection, the investigator should contact the AbbVie TA MD before reintroducing study drug.

6.1.7 Pregnancy

As there is a potential risk of birth or early development defects with study treatment(s), subjects will consent to avoid pregnancy and/or breastfeeding for a minimum of 6 months (or longer per local labels of carboplatin and paclitaxel, if applicable) following completion of therapy. Pregnancy in a study subject must be reported to AbbVie within 24 hours of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected within the EDC system. Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Male subjects should be informed that contraceptive measures should be taken by their female partners. If the subject's partner should become pregnant during the study, this should also be reported and data may be collected. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

6.1.8 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the Investigator. The table of clinical toxicity grades modified from the NCI CTCAE Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010) (available on the CTEP home page http://ctep.info.nih.gov) is to

be used in the grading of adverse events and laboratory abnormalities that are reported as adverse events, each of which will be followed to satisfactory clinical resolution.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the Investigator or AbbVie as a "reasonable possibility" to be related to the study treatment (Section 6.1.1.1).

A toxicity is deemed "clinically significant" on the basis of the investigator's medical judgment.

All adverse events will be followed to a satisfactory conclusion.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol eligibility criteria. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and his or her assigned clinical monitor or the following AbbVie representatives:

Primary Contact:

[redacted]
AbbVie
Ing. E. Butty 240 [redacted]
C1001AFB, Buenos Aires, Argentina
Cell:
Email:

Alternate Contact:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Office:
Cell:
Email:

Alternate Contact:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Phone:
Fax:
Mobile:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a 2-sided P value ≤ 0.05. The date of randomization (enrollment) is defined as the date that the IVRS/IWRS issued a randomization number.

The analysis of all efficacy endpoints will include only subjects who have been documented to have suspected deleterious or deleterious mutations by the sponsor core lab. Sensitivity analyses will be conducted using all randomized subjects' data to evaluate

the impact of any discrepancies between results from the local laboratory and from the Sponsor core laboratory.

All subjects who receive at least one dose of the study treatment (veliparib or placebo) will be included in the safety analysis.

Comparisons will be performed between the two treatments as assigned by the IVRS/IWR (veliparib 120 mg BID + carboplatin + paclitaxel versus placebo BID + carboplatin + paclitaxel).

8.1 Statistical and Analytical Plans

8.1.1 Baseline Characteristics

All baseline summary statistics and analyses will be based on characteristics prior to the initiation of study treatment (or randomization for non-treated subjects). Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to the first dose of study treatment.

Baseline characteristic data will be summarized for all subjects who are randomized to veliparib 120 mg BID + carboplatin + paclitaxel and placebo BID + carboplatin + paclitaxel.

8.1.1.1 Demographics

Continuous demographic data (e.g., age, height, and weight) will be summarized with means, standard deviation, and range. Frequencies and percentages will be computed for the following parameters: gender, race, *BRCA*1, *BRCA*2, ER/PgR status, number and sites of metastases, prior platinum therapy (yes versus no), CNS metastases (yes versus no), and baseline ECOG performance status.

8.1.1.2 Medical Histories

Frequencies and percentages will be computed for each medical history parameter.

8.1.2 Efficacy Endpoints

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy analysis will be a comparison of progression-free survival (PFS) between veliparib 120 mg BID + carboplatin + paclitaxel and placebo BID + carboplatin + paclitaxel.

For a given subject, time to PFS will be defined as the number of days from the date the subject was randomized to the date the subject experiences disease progression (as determined by the investigators), or death, whichever occurs first (all causes of mortality). All events of disease progression will be included, regardless of whether the event occurred while the subject was still taking study treatment or had previously discontinued study treatment. Events of death will be included for subjects who had not experienced an event of disease progression, provided the death occurred within 9 weeks of the last evaluable disease progression assessment. If the subject does not have an event of disease progression and the subject has not died as defined above, the subject's data will be censored at the date of the subject's last evaluable disease progression assessment. Every effort should be made to document radiographic progression for analysis of the primary endpoint, even after discontinuation of treatment or initiation of subsequent anti-cancer therapy.

8.1.2.2 Secondary Efficacy Endpoints

Secondary efficacy analyses comparing the effects of veliparib 120 mg BID + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel on the following set of endpoints will be performed: overall survival (OS), clinical benefit rate (CBR) through the end of Week 24, objective response rate (ORR) and progression-free survival on subsequent therapy (PFS2).

Time to death (overall survival) for a given subject will be defined as the number of days from the date the subject was randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurred while the subject was still

taking study treatment or after the subject discontinued study treatment. If a subject has not died, the data will be censored at the date last known to be alive.

Clinical Benefit Rate (CBR) is defined as the progression-free rate at 24 weeks from the Kaplan-Meier curve for time to progression (defined as from the date of randomization to the date of disease progression as determined by the investigators).

Objective Response Rate (ORR) is calculated as the proportion of subjects who have PR or CR based on assessment by the investigators. All subjects who have had at least one measurable lesion at baseline will be included in the ORR calculation.

Progression Free Survival 2 (PFS2) will be defined as the number of days from the day the subject is randomized to the date that the subject has disease progression or death of any cause on the subsequent therapy, whichever occurs first. If the subject does not have an event of PFS2 (as determined by the Investigator), the subject's data will be censored at the subject's last known date of follow-up.

8.1.2.3 Tertiary Efficacy Endpoints

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses will be performed comparing the effects of veliparib 120 mg BID + carboplatin + paclitaxel versus placebo + carboplatin + paclitaxel on duration of response (DOR), quality of life, and performance status.

Duration of response will be defined as the number of days from the day that the criteria are met for CR or PR, whichever is recorded first, to the date that progressive disease is documented. If a subject's response is ongoing at the analysis cutoff date then the subjects data will be censored at the date of the last disease progression assessment performed prior to the cutoff. Subjects who never experience a confirmed PR or CR will not be included in the analysis.

8.1.3 Timing of Efficacy Analyses and Safety Evaluations

When the 344th PFS (determined by the investigators) event occurs, there will be a final review of the eCRF data. When the data are reviewed for completeness and all data management quality assurance (QA) and quality control (QC) procedures are performed, the randomization schedule will be released and clinical database data will be extracted for documentation and statistical analyses of the efficacy and safety data.

The data cutoff date for the primary PFS analyses will be specified in the statistical analysis plan (SAP) prior to database lock. All imaging related efficacy analyses (PFS, CBR, ORR, DOR) will include data up to the cutoff date.

OS will be analyzed at the time of 'Primary PFS Analysis' as an interim analysis. The Lan DeMets alpha spending function with an O'Brien-Fleming boundary will be used to ensure that the one-sided false positive rate will be 0.025 or less for overall survival. If OS is not statistically significant at the interim analysis, a 'Final OS Analysis' will be performed after observing approximately 357 death events. Additional OS analyses may be performed before the 'Final OS analysis,' if requested by regulatory agencies or otherwise warranted. For each additional interim analysis of OS, a small amount of alpha (0.00001) will be spent.

The clinical study report (CSR) will summarize the results from the above analyses.

8.1.4 Primary Analysis of Efficacy

The distribution of PFS (PFS as determined by the investigators, as detailed in Section 5.3.3) will be estimated for each treatment group using Kaplan-Meier methodology and compared between veliparib 120 mg BID + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel treatment groups using the log-rank test, stratified by ER and/or PgR positive versus ER/PgR negative and prior platinum therapy (yes versus no).

8.1.5 Secondary Analyses of Efficacy

If the veliparib treatment group is not statistically significantly better than the placebo treatment group for the primary endpoint of PFS, then none of the secondary endpoints will be tested and statistical significance will not be declared for any secondary endpoints regardless of the observed *P* values. *P* values for secondary efficacy analyses will be subject to multiple comparison adjustments using the fixed sequence testing method, with analyses performed in the following order: OS, CBR, ORR, and PFS2.

8.1.5.1 Overall Survival

The distribution of overall survival will be estimated for each treatment group using Kaplan-Meier methodology and compared between veliparib 120 mg BID + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel using the log-rank test, stratified by ER and/or PgR positive versus ER/PgR negative and prior platinum therapy (yes versus no).

8.1.5.2 Clinical Benefit Rate

Clinical benefit rate (CR, PR, SD or Non-CR/Non-PD) at Week 24 will be defined as the progression-free rate at 24 weeks from the Kaplan-Meier curve for time to progression (defined as from the date of randomization to the date of disease progression as determined by investigators). A test statistic based on Kaplan-Meier estimates of the progression-free probability at 24 weeks and the estimated variance will be constructed to test the null hypothesis that the clinical benefit rate at Week 24 for the two treatment groups are the same.

8.1.5.3 Objective Response Rate

The objective response rate (CR and PR) will be computed for all subjects with measurable disease at baseline. The proportion of subjects with a complete or partial objective response based on the RECIST (version 1.1) criteria in Section 5.3.3 will be estimated for each treatment group and compared between veliparib 120 mg BID + carboplatin + paclitaxel and placebo BID + carboplatin + paclitaxel using CMH test,

stratified by ER/PgR positive versus ER/PgR negative and prior platinum therapy (yes versus no).

8.1.5.4 PFS2

The distribution of PFS2 will be estimated for each treatment group using Kaplan-Meier methodology and compared between veliparib 120 mg BID + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel treatment groups using the log-rank test, stratified by ER and/or PgR positive versus ER/PgR negative and prior platinum therapy (yes versus no).

8.1.6 Tertiary Analyses of Efficacy

8.1.6.1 Duration of Overall Response

The distribution of the duration of overall response for responders (CR or PR) will be estimated for each treatment group using Kaplan-Meier methodology.

8.1.6.2 Patient Reported Outcomes (PRO)

The EORTC scoring manual will be used to transform the raw scores into the domain scores (global heath, functional scales, symptom scales/items). The EQ-5D manual and the published weights will be used to convert the individual items to the utility scores. The BPI-SF user guide will be used to convert the raw responses to pain severity and pain interference scores.

Descriptive statistics will be used to summarize the individual item and scored domain/sub-scale QoL and pain scores at each scheduled assessment time point. Change from baseline in the domain scores at the time of each assessment will be summarized. Subjects with a baseline score and at least one post baseline score during the treatment period will be included in the change from baseline analyses.

The PRO variables will include the global health status/QoL and the functional and symptom domain scores from the EORTC questionnaires, the utility score from EQ-5-D

questionnaire, and the pain severity and pain interference scores from the BPI-SF questionnaires.

Analyses of the above PRO variables and the corresponding endpoints will be specified in the Statistical Analysis Plan (SAP) to answer the following primary questions:

- Is there a statistically significant difference between treatment arms in the longitudinal changes in overall quality of life and specific symptoms from baseline to pre-specified time points (details will be specified in SAP);
- Are the longitudinal changes meaningful?

Change from baseline to post-baseline assessment visit between two treatment arms will be compared using ANCOVA model with treatment and corresponding baseline value as covariates. Additional statistical analyses may be performed if deemed necessary and helpful in understanding the drug effect, such as an analysis of repeated measure may be used to compare overall change from baseline between two treatment groups by including baseline value, treatment, and time of visit as covariates. Clinical meaningful changes from baseline to assessment points will be based on minimum important difference (MID) derived from the data using published distribution and anchor based methods.[40] Time to the first deterioration in overall QoL may also be assessed using survival analysis based on pre-specified MID for deterioration based on published information.

8.1.6.3 Performance Status

Analyses of changes from baseline will be performed for each scheduled post-baseline visit for ECOG performance status using an analysis of covariance (ANCOVA) model with treatment group as the factor and baseline value as a covariate. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included.

8.1.7 Additional Efficacy Analyses

The primary and secondary efficacy endpoints will also be analyzed using all randomized subjects' data, regardless whether or not the subject has suspected deleterious or deleterious mutation confirmed by the Sponsor core lab.

In addition to the stratified log-rank test for the primary and secondary efficacy endpoints, the unstratified log-rank test, Wilcoxon test, and the Cox proportional hazards model may be used for the comparison of PFS and overall survival between veliparib 120 mg BID + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel.

PFS, ORR, CBR, and duration of overall response based on radiological and clinical assessment by the central imaging center will also be analyzed using the same statistical methodology as that for the corresponding primary and secondary efficacy endpoints.

For those subjects who take other anti-cancer therapies after discontinuation of the study treatment, the primary efficacy and secondary efficacy endpoints of PFS, and overall survival will be censored at the date of subject's initiation of other anti-cancer therapies. These modified primary and secondary efficacy endpoints will be analyzed using the same methodology as detailed in previous sections.

For PFS and OS, additional analyses may also be performed, such as 1) including only data and events occurring on treatment or within 30 days of the last dose of study treatment, 2) using a Cox proportional hazard model to explore the effect of baseline factors including (but not limited to) the following: ER/PgR status, *BRCA*1/2 status, prior platinum therapy (yes versus no), ECOG performance status, stage of the disease, and others, 3) subgroup analysis by ER/PgR status, *BRCA*1/2 status, prior platinum therapy (yes versus no), CNS metastases (yes versus no), ECOG performance status, stage of the disease, and others, 4) stratified log-rank test by region (US versus non-US), and ECOG performance status (0 to 1 versus 2), and 5) using interval censoring methods to analyze PFS.

Alternative statistical analyses may be performed if deemed necessary and helpful in understanding the drug effect.

8.1.8 Interim Analysis

An independent data monitoring committee (IDMC) reviewed the unblinded safety data for this veliparib Phase 3 study (including all subjects enrolled in the study) when approximately 60 subjects met at least one of the following criteria:

- Received 6 cycles of treatment
- Reached an event of disease progression
- Discontinued the study due to toxicity/adverse events

BRCA status discordances between Sponsor core laboratory and local labs were assessed internally at the time of the interim analysis. Subsequent IDMC reviews of unblinded safety data prior to the primary analysis were carried out based on IDMC recommendations. No additional reviews by the IDMC will occur since the Sponsor management team was unblinded after completing the primary analysis.

An alpha of 0.0001 (the Haybittle-Peto stopping boundary) will be allocated for PFS at the interim analysis, although there is no intention to stop the study early for efficacy. The final PFS analysis will be tested at one-sided alpha of 0.025. With this stopping boundary, the overall Type 1 error rate is controlled at 0.025 or less.

8.1.9 Safety Assessments

The safety of veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel will be assessed by evaluating study treatment exposure, adverse events, serious adverse events, and all deaths, as well as changes in laboratory determinations and vital sign parameters. Subjects who were randomized but did not receive study treatment (veliparib or placebo) will not be included in the analyses of safety.

8.1.10 Statistical Analyses of Safety

8.1.10.1 Duration of Study Treatment

A summary of the number of days and/or cycles subjects were exposed to study treatment will be provided.

8.1.10.2 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug (veliparib or placebo). Analyses will not include those that have an onset greater than 30 days after the last dose of study treatment.

Treatment-emergent adverse events will be coded and summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA)[37] adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE version 4.0 grade, and relationship to study treatment will be provided. Comparisons of the percentages of subjects experiencing an adverse event between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel will be performed using Fisher's exact test.

8.1.10.3 Serious Adverse Events

Serious adverse events will be summarized using the same methods as adverse events described above in Section 8.1.10.2.

8.1.10.4 Deaths

The number of subject deaths will be summarized 1) for deaths occurring while the subject was still receiving study treatment in this study, 2) for deaths occurring off treatment within 30 days after the last dose of study treatment, and 3) for all deaths in this study regardless of the number of days after the last dose of study treatment.

8.1.10.5 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of randomized study treatment will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. Comparisons of the differences in mean changes from baseline between veliparib + carboplatin + paclitaxel and placebo BID + carboplatin + paclitaxel will be made using ANOVA with treatment group as the factor.

8.1.10.6 Analyses of Laboratory Data Using NCI CTCAE

Where applicable, blood chemistry and hematology determinations will be categorized according to NCI CTCAE version 4.0 grades, and shifts from baseline NCI CTCAE version 4.0 grades to maximum and final post-baseline grades will be assessed. The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of study treatment, and as the grade of the last post-baseline measurement collected no more than 30 days after the last dose of study treatment. If multiple values are available for a post baseline measurement, then the value with the highest NCI CTCAE grade will be used in the assessment of shift. Comparisons of the number of subjects experiencing a shift from baseline grades of 0 to 2 to maximum postbaseline grades of 3 to 4, and from baseline grades of 0 to 2 to final postbaseline grades of 3 to 4 between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel will be performed using Fisher's exact tests.

Detailed listings of data for subjects experiencing NCI CTCAE Grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study treatment, will be included in these listings.

8.1.10.7 Analyses of Vital Signs Using Criteria for Potentially Clinically Significant Vital Sign Values

Detailed listings of data for subjects experiencing potentially clinically significant vital sign values according to the AbbVie-defined criteria for vital sign values will be provided. All measurements collected, regardless of the number of days after the last dose of study treatment, will be included in these listings.

8.1.10.8 Multiplicity Adjustments

If the veliparib treatment group demonstrates statistically significantly better PFS than the placebo group, then the secondary endpoints will be tested using the fixed sequence testing procedure with the following testing order: OS, CBR, ORR, and PFS2.

A multiplicity issue is introduced through the multiple testing of the OS endpoint. It is anticipated that, at the analysis time of the primary efficacy endpoint PFS, there will be too few death events to support an adequately powered OS analysis. Therefore, two OS analyses are planned, the first one based on the "Primary PFS Analysis" database, and the second one based on the "OS Analysis" database with a total of 357 death events. Statistical significance for OS will be declared if a significant result is obtained for either analysis, consistent with group sequential testing methods.

The Lan DeMets alpha spending function with an O'Brien-Fleming boundary will be used to ensure that the one-sided false positive rate will be 0.025 or less for overall survival. The exact α level to be used at the first OS analysis will be dependent on the information fraction for OS at the time of the 'Primary PFS Analysis'. This approach is being taken so that the majority of the α- level will be withheld until a total of 357 death events have occurred.

8.1.10.9 Censoring Dates for Subjects that had the Prematurely Blind Broken

For progression free survival analysis, if the subjects does not experience an event of disease progression or death (as defined above for PFS endpoint) on or before the date of

blind break, the subject's data will be censored at the date of the subject's last available disease progression assessment on or before the blind break.

For duration of overall response and clinical benefit rate through the end of Week 24 (CBR) analyses, if the subject does not experience an event of disease progression on or before the date of blind break, the subject's data will be censored at the date of the subject's last available disease progression assessment on or before the blind break.

For objective response rate (ORR) analysis, disease progression assessment data after the blind break date will not be included.

A blind break performed by AbbVie pharmacovigilance will not be considered a premature blind break.

8.2 Determination of Sample Size

Assuming the true hazard ratio in favor of the veliparib + carboplatin + paclitaxel treatment group is 0.69 for PFS, a total of 344 PFS events will be needed for the study to have at least 90% power at 2-sided α level of 0.05 to detect a statistically significant treatment effect for the veliparib + carboplatin + paclitaxel treatment group using the log-rank test for PFS. Assuming the median PFS of 12 months in the placebo arm, a hazard ratio of 0.69 would correspond approximately to an increase in median PFS of 5.5 months under the exponential model assumption.

In addition, assuming the true hazard ratio in favor of the veliparib 120 mg BID + carboplatin + paclitaxel treatment group is 0.714 for OS, a total of 357 death events will be needed for the study to have at least 85% power at 2-sided α level of 0.05 to detect a statistically significant treatment effect for the veliparib + carboplatin + paclitaxel treatment group using the log-rank test for OS.

A total of approximately 500 subjects with a BRCA mutation as documented by the Sponsor core laboratory will be enrolled into the study to accrue the anticipated 344 PFS

events and 357 death events. The required number of PFS events has been increased to ensure 90% power if true HR is 0.69.

8.3 Randomization Methods

IVRS/IWRS will be utilized to randomize subjects. Before the study is initiated directions for the IVRS/IWRS will be provided to each site. The investigational site will contact the IVRS/IWRS on or within 2 days prior to the subject's Study Day 1 (C1D-2). The randomization numbers will assign subjects in 2:1 ratio to either veliparib + carboplatin + paclitaxel, or placebo + carboplatin + paclitaxel. Subject randomization will be stratified by ER and/or PgR positive versus ER/PgR negative, prior platinum therapy (yes versus no), and CNS metastases (yes versus no).

One set of subject randomization schedule will be generated by the Clinical Statistics Department at AbbVie prior to the start of the study. A copy of all randomization schedules will be kept by the Clinical Statistics Department at AbbVie and a copy will be forwarded to the IVRS/IWRS vendor.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Investigator will be required to submit,

maintain and archive study essential documents according to International Conferences on Harmonization (ICH) GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix A.

In the event that the COVID-19 pandemic leads to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related

screening procedures being performed on the subject, the informed consent statement will be reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

In the event a subject withdraws consent to participate from the study, stored biomarker and exploratory research samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker and exploratory research samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

An informed consent, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected for optional exploratory research. The nature of the testing should be explained and the subject given an opportunity to ask questions. The informed consent must be signed before the samples are collected and any testing is performed. If the subject does not consent to provide samples for the optional exploratory research, it will not impact their participation in the study.

Due to the COVID-19 pandemic, modifications to the protocol may be necessary. Subjects should be informed of the changes to the conduct of the study relevant to their participation (e.g., cancellation of visits, change in laboratory testing site, drug delivery method, etc.). Documentation of this notification and verbal consent should be maintained at the site. A signed and dated informed consent form should be obtained from the subject afterwards as soon as possible, if required by local regulations.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The QoL questionnaires (EORTC QLQ-C30/BR23, EQ-5D-5L) will be completed by the subject on worksheets and will be considered source data.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from Investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Prior to enrolling any subject in the study, a Site Initiation Visit will be held with AbbVie personnel (**and/or** their representatives), the Investigators, and the appropriate site personnel. This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, eCRF completion, and specimen collection methods. The personnel at the study site will be trained on the study procedures, when applicable, by an AbbVie monitor or designee.

The AbbVie monitor or designee will monitor the study site throughout the study. A source document review will be performed against entries on the eCRFs and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, ongoing review of the data will be conducted by a physician or representative at AbbVie.

Data entered into eCRFs will be electronically transferred to AbbVie and imported into the database using validated software throughout the study. Computer logic checks will be run to identify such items as inconsistent study dates. Any necessary corrections will be made to the eCRF.

If applicable, data hand-entered directly in the database from paper CRFs or reports will be verified by a double-key entry procedure at AbbVie. Any discrepancies will be reviewed against the hard-copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to identify such items as inconsistent study dates. Any necessary corrections will be made to the database in the same manner via the appropriate change form.

Routine hematology, serum chemistry and serology, and urinalysis will be conducted using a central laboratory. The data from these analyses will be electronically transferred from the central laboratory to the study database.

A review of all laboratory results will be conducted by a physician and clinical review team at AbbVie, the AbbVie monitors (or their representatives), the Investigator, and other appropriate personnel from AbbVie.

12.0 Use of Information

Any research that may be done using optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision-making or subject management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Data from optional exploratory research may be provided to investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

12.1 Publication

The Investigators have the right to publish the results of the study, but with due regard to the protection of confidential information. Accordingly, AbbVie shall have the right to review and approve any paper for publication, including oral presentation and abstracts, which utilize data generated from this study. At least 60 days before any such paper or abstract is presented or submitted for publication, a complete copy shall be given to AbbVie for review. AbbVie shall review any such paper or abstract and give its comments to the author(s) promptly. The Investigator shall comply with AbbVie's confidential information in any such paper and agrees to withhold publication of same for an additional 60 days in order to permit AbbVie to obtain patent or other proprietary rights protection, if AbbVie deems it necessary.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for veliparib (ABT-888).
2. I have received and reviewed the locally approved product label or applicable Summary of Product Characteristics for carboplatin, and paclitaxel.
3. I have read this protocol and agree that the study is ethical.
4. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
5. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title:	A Phase 3 Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2-Negative Metastatic or Locally Advanced Unresectable *BRCA*-Associated Breast Cancer
Protocol Date:	23 July 2020

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees [e.g., independent ethics committee (IEC) or institutional review board (IRB)] review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Statistics
		Clinical
		Clinical
		Clinical
		Pharmacokinetics

Appendix C. Study Activities for Blinded Study Treatment (Veliparib/Placebo + Paclitaxel + Carboplatin)

Activity	Screening	C1D-2	C1D1	C1D8[a]	C1D15[a]	Day 1 of Subsequent Cycles[t]	Days 8 and 15 of Subsequent Cycles[a]	Every 12 Weeks[l]
Informed Consent[b]	X							
Medical and Cancer History	X							
Physical Exam (including weight)	X[c]	X[d]			X	X		
12-lead ECG	X		X[e]					
Vital Signs	X	X	X	X	X	X	X	
Pregnancy Test (women of childbearing potential)[f]	X	X						
Hematology/Chemistry[g,h]	X	X[i]	X	X	X	X	X	
Urinalysis[g]	X	X						
APTT/INR[j]	X							
BRCA1 and 2 germline mutation testing	X[k]							
Tumor Assessment[l]	X[m]							X
Full Body Bone Scan	X[n]							
Performance Status (ECOG)	X	X				X		
QLQ C30, BR23, EQ 5D 5L Questionnaires		X[o]				X[p]		
BPI-SF Questionnaire		X[o]				X		
AE Assessment		X	X	X	X	X	X	
Randomization		X						
Dispense veliparib or placebo		X[q]	X			X[q]		

Activity	Screening	C1D-2	C1D1	C1D8[a]	C1D15[a]	Day 1 of Subsequent Cycles[t]	Days 8 and 15 of Subsequent Cycles[a]	Every 12 Weeks[l]
Administer paclitaxel premedication[r]			X	X	X	X	X	
Administer carboplatin			X[s]			X[s]		
Administer paclitaxel			X[s]	X	X	X[s]	X	

a. If a subject discontinues paclitaxel on Day 8 and/or Day 15, the study visit and assessments for that specific day can be omitted.

b. Must be performed prior to the initiation of any screening or study-specific procedures.

c. Height will be recorded at Screening Visit only.

d. Physical exam not required, if performed within 7 days prior to C1D-2, unless clinically indicated.

e. ECG must be obtained one hour after dosing with veliparib/placebo and prior to the paclitaxel or carboplatin infusions.

f. Pregnancy tests must be completed and confirmed as not indicative of pregnancy prior to randomization (within 24 hours) and may be repeated during the study according country requirements.

g. Refer to Table 4 for detailed list of tests to be performed and frequency.

h. For Day 1 visits, study samples for central laboratory analysis may be performed within 72 hours prior to dosing. For Day 8 and Day 15 visits, study samples for central laboratory analysis may be performed within 24 hours of the scheduled day. There is no visit window for C1D-2 as any sample prior to randomization is still considered to be screening. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions but this cannot replace the central laboratory analysis on a protocol defined visit, unless AbbVie removes the requirements for sites to send clinical laboratory samples to the central laboratory or under special situations (i.e., pandemic) that are approved by the Sponsor and allowed as per local regulation.

i. For Screening labs performed greater than 7 days prior to C1D-2, hematology/chemistry should be split (and sent to central lab) at C1D-2 and local labs reviewed prior to dosing.

j. For subjects on prophylactic or therapeutic anticoagulation with warfarin, INR should be monitored before each treatment. Treatment should be held for INR of > 1.5 × ULN on prophylactic warfarin or > therapeutic range if on full dose warfarin.

k. *BRCA1 and BRCA2* germline mutation testing will be collected on all subjects even if Sponsor core laboratory testing was performed prior to screening.

l. Tumor assessments to support evidence of PD for PFS endpoint were conducted every 9 weeks until PD, death or withdrawal of consent for follow-up until PD. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks (tumor assessments may be conducted ± 10 business days following the scheduled assessment from last scan). At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control but must not exceed 24 weeks.

m. The baseline tumor assessment, including diagnostic CT scans of the chest, abdomen, and pelvis, and brain MRI or contrast CT will be obtained no more than 28 days prior to randomization.

n. Full body bone scan will be obtained no more than 28 days prior to randomization with subsequent bone scans to be obtained as clinically indicated.

o. Should be completed on C1D-2 prior to dosing.

p. QLQ C30, BR23, EQ 5D 5L questionnaires will be administered every other cycle prior to dosing beginning with Cycle 2 (C2, C4, C6, etc.).

q. Sufficient medication will be dispensed to cover the entire cycle. The site is advised to contact the subject on the morning of Day –2 to reiterate the dosing instructions of veliparib/placebo. It is recommended the site contact the subject on Day 5 to instruct about ceasing dosing.

r. The US paclitaxel package insert recommends a premedication regimen, such as dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

s. Carboplatin and paclitaxel are to be given only after veliparib/placebo dosing on cycle Day –2 and Day –1 are confirmed.

t. For subjects who have been receiving single-agent veliparib/placebo at a stable dose without adjustments for multiple cycles and who have no ongoing study drug related uncontrolled AEs, it is possible to alternate on-site visits and phone visits every other cycle. Study procedures for phone visits are detailed in the Appendix F.

Note: Study procedures (excluding labs and tumor assessments) may be performed four (4) business days prior to the scheduled study visit date. C1D1 procedures may be performed within 24 hours surrounding the scheduled study visit.

Appendix D. Study Activities for Unblinded Veliparib Monotherapy (Crossover Treatment)

Note: The following schedule of assessments should be followed for subjects who crossed over (were previously randomized to placebo, discontinued study treatment because of disease progression and received Sponsor approval for crossover treatment).

Activity	C1D1	C1D15[g]	Day 1 of Each Cycle Starting with C2[i]	Every 9 Weeks from C1D1[c]
Physical Exam (including weight)	X	X	X	
12-lead ECG	X[f]			
Vital Signs	X	X	X	
Pregnancy Test (women of childbearing potential)[h]				
Hematology/Chemistry[a,b]	X	X	X	
Urinalysis[a]	X			
Tumor Assessment[c]	X[d]			X
Performance Status (ECOG)	X		X	
QLQ C30, BR23, EQ 5D 5L Questionnaires	X		X[e]	
BPI-SF Questionnaire	X		X	
AE Assessment	X	X	X	
Dispense veliparib	X		X	

a. Refer to Table 4 for detailed list of tests to be performed and frequency.

b. Study samples for central laboratory analysis may be performed within 72 hours of the scheduled day. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions but this cannot replace the central laboratory analysis on a protocol defined visit, unless AbbVie removes the requirements for sites to send clinical laboratory samples to the central laboratory or under special situations (i.e., pandemic) that are approved by the Sponsor and allowed as per local regulation.

c. Tumor assessments will be conducted every 9 weeks (± 5 business days from the scheduled C1D1 assessment. Following the primary analysis and implementation of Protocol Amendment 4, if a crossover subject has disease control after 6 scans while following the 9 week scan interval schedule, the tumor assessment frequency can be changed to every 12 weeks from last scan (± 10 business days). At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control but must not exceed 24 weeks.

d. To be performed if a tumor assessment has not been performed within 4 weeks.

e. QLQ C30, BR23, EQ 5D 5L questionnaires will be administered every other cycle prior to dosing beginning with Cycle 2 (C2, C4, C6 etc.).

f. ECG must be obtained 1 hour after dosing with veliparib.

g. If the subject tolerates 300 mg BID for 2 weeks veliparib may be increased to 400 mg BID at the investigator's discretion.

h. Pregnancy tests may be repeated during the study according country requirements.

i. For subjects who have been receiving veliparib monotherapy at a stable dose without adjustments for multiple cycles and who have no ongoing study drug related uncontrolled AEs, it is possible to alternate on-site visits and phone visits every other cycle. Study procedures for phone visits are detailed in the Appendix F.

Notes: Study procedures (excluding labs and tumor assessments) may be performed four (4) business days prior to the scheduled study visit date. C1D1 procedures may be performed within 24 hours surrounding the scheduled study visit.

Appendix E. Study Activities for Post Treatment Phase

Activity	Discontinuation of Therapy (all subjects)			Discontinuation of therapy without disease progression (on study, off drug)[a,b,d]
	Final Visit[a]	30-Day Follow-Up Visit[b]	Post Treatment Follow-Up	Every 12 weeks from last scan[e]
Physical Exam (including weight)[d]	X	X		
12-lead ECG	X			
Vital Signs[d]	X	X		
Hematology/Chemistry[d]	X	X		
Urinalysis[d]	X			
Tumor Assessment				X[e]
Performance Status (ECOG)	X	X		
QLQ C30, BR23, EQ 5D 5L, BPI-SF Questionnaires	X	X		
AE Assessment[d]	X	X		
Survival[c]			X	X

a. When a subject discontinues the blinded or unblinded study treatment, a Final Visit will be conducted.

b. All subjects will have one Follow-up Visit approximately 30 days after the last dose of study drug. This Follow-up Visit does not need to be performed for subjects who have had a Final Visit conducted ≥ 30 days after the last dose of study drug or for subjects who are entering unblinded veliparib monotherapy treatment. Follow-up visits should not precede a Final Visit.

c. If a subject meets criteria for discontinuation of therapy, survival and post treatment therapy will be collected every two months (unless requested by sponsor more frequently to support data analysis) beginning on the date the subject discontinues therapy. All randomized subjects should be followed for disease progression (PFS) and for the second progression (PFS2), until the endpoint of death (OS), until the subject has become lost to follow-up, or until study termination by AbbVie.

d. Refer to Table 4 for detailed list of tests to be performed and frequency. Laboratory assessments, physical examinations and vital signs will only be completed for AE follow-up or reported SAEs after the 30-day follow-up visit per Section 6.1.5.

e. Tumor assessments to support evidence of PD for PFS endpoint were conducted every 9 weeks until PD, death or withdrawal of consent for follow-up until PD. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks (tumor assessments may be conducted ± 10 business days following the scheduled assessment from last scan). At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control, but must not exceed 24 weeks.

Note: Study procedures (excluding labs and tumor assessments) may be performed four (4) business days prior to the scheduled study visit date.

Appendix F. Study Activities for Blinded or Unblinded Study Treatment Phone Visit

Activity	Day 1 Phone Visit[a]
Performance Status (ECOG)	X
QLQ C30, BR23, EQ 5D 5L Questionnaires[b]	X[c]
BPI-SF Questionnaire[b]	X
AE and Concomitant Medication Assessment	X[d]
Treatment Compliance Assessment	X[d]
Disease Progression Assessment	X[d]
Dispense Veliparib or Placebo[e]	X

a. For subjects who have been receiving single-agent veliparib/placebo at a stable dose without adjustments for multiple cycles and who have no ongoing study drug related uncontrolled AEs, it is possible to alternate on-site visits and phone visits by the investigator or designee every other cycle. At a minimum, subjects should have an on-site visit every other cycle. If an on-site visit is not possible for 2 consecutive cycles, or if the subject is not on a stable dose or has ongoing study drug related uncontrolled AEs but wishes to alternate on-site and phone visits, the plan for the subject's visits should be discussed with the AbbVie TA MD (see Section 7.0 for contact information).

b. During the on-site visits the Investigator or designee will provide the PRO Questionnaires (QLQ C30, BR23, EQ 5D 5L and BPI-SF) for the next cycle to the subject, so these can be completed at home.

c. QLQ C30, BR23, EQ 5D 5L questionnaires will be administered every other cycle prior to dosing beginning with Cycle 2 (C2, C4, C6, etc.). If questionnaires were completed during an on-site visit, they may not be required at the subsequent phone visit.

d. In addition to assessing AEs and Concomitant Therapies, the investigator or designee should assess treatment compliance and to the extent possible, assess for any clinical evidence of disease progression. If there are concerns about new or worsening AEs or if there is suspicion of disease progression, an unscheduled on-site visit, local labs, and/or tumor assessment should be scheduled.

e. During the on-site visits, the Investigator or designee will dispense medication for 2 cycles via IRT and the double amount of Dosing Cards, so subjects can complete them for both cycles.

Note: Phone visit may be performed four (4) business days prior or after the scheduled study visit date.

Appendix G. EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling 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): 31 ____

	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 on to the next page

ENGLISH

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 circle 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 H. 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

During the past four weeks:		Not at All	A Little	Quite a Bit	Very Much
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

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

Appendix I. EQ-5D 5L Health Questionnaire

EQ-5D-5L

Health Questionnaire

(English version for the US)

Under each heading, please check the ONE box that best describes your health TODAY

Mobility

I have no problems walking ☐
I have slight problems walking ☐
I have moderate problems walking ☐
I have severe problems walking ☐
I am unable to walk ☐

Self-Care

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (e.g., work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

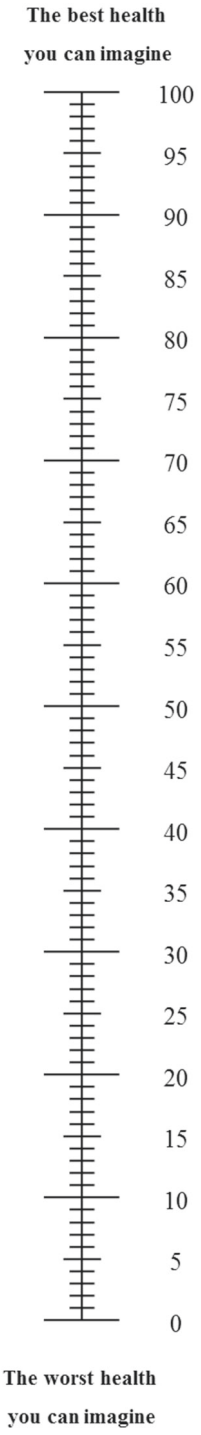
Pain/Discomfort

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.



YOUR HEALTH TODAY = ☐

Appendix J. Brief Pain Inventory – Short Form

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

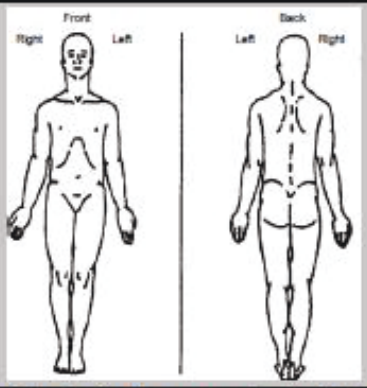
Date: ___/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ___/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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Appendix K. ASCO-CAP HER2 Test Guideline Recommendations

ASCO-CAP HER2 Test Guideline Recommendations[41]	
Topic	**2013 Recommendations**
Optimal algorithm for HER2 testing	Must report a HER2 test result as negative if a single test (or both tests) performed show: 1. IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cells 2. IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells 3. ISH negative based on: o Single-probe average HER2 copy number < 4.0 signals/cell o Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell

Source: American Society of Clinical Oncology; College of American Pathologists. ASCO-CAP HER2 Test Guideline Recommendations. Summary of Guideline 2007 and 2013 Recommendations. 2013.

Appendix L. General Chemotherapy Guidelines

- A patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a 24-hour window before and after the protocol-defined date for Day 1 treatment. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (Day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window" for scheduling conflicts; for example: "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately ± 5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Subjects are permitted to have chemotherapy doses recalculated for < 10% weight changes.

Appendix M. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency Contact:

Emergency Contact:
[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Phone:
Fax:
Mobile: [redacted]

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Phone:
Fax:
Mobile: [redacted]

Has been changed to read:

Sponsor/Emergency Contact:

Emergency Contact:
[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Phone:
Mobile: [redacted]

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Phone:
Fax:
Mobile: [redacted]

Section 1.2 Synopsis
Previously read:

AbbVie	**Protocol Number:** M12-914
Name of Study Drug: Veliparib (ABT-888)	**Phase of Development:** Phase 3
Name of Active Ingredient: Not applicable	**Date of Protocol Synopsis:** 17 June 2016

Protocol Title: A Phase 3 Randomized Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2-Negative Metastatic or Locally Advanced Unresectable *BRCA*-Associated Breast Cancer
Objectives: The primary endpoint is to assess the progression-free survival (PFS) of veliparib in combination with carboplatin (C) and paclitaxel (P) compared to placebo with C/P in subjects with a *BRCA1* and/or *BRCA2* Mutation and HER2-Negative Metastatic or Locally Advanced Unresectable Breast Cancer. The secondary objectives of the study are to assess overall survival (OS), clinical benefit rate (CBR), objective response rate (ORR), PFS2 and duration of overall response (DOR) in subjects treated with veliparib in combination with C/P versus subjects treated with placebo with C/P. The tertiary objectives are to assess change in ECOG performance status, change in Quality of Life (QoL).
Study Sites: Multicenter; Approximately 200
Study Population: Men and women ≥ 18 years of age with HER2-negative metastatic or locally advanced unresectable breast cancer and clinically significant (suspected deleterious or deleterious) *BRCA1* and/or *BRCA2* germline mutation. Patients with bone-only disease and/or hormone receptor positive (ER and/or PR) disease should be deemed appropriate candidates for combination chemotherapy.
Number of Subjects to be Enrolled: Approximately 500
Methodology: This is a Phase 3, randomized, double-blinded study to evaluate the efficacy and tolerability of veliparib in combination with C/P compared to placebo plus C/P in subjects with *BRCA1* or *BRCA2* germline mutation and with HER2-negative metastatic or locally advanced unresectable breast cancer who have received no more than 2 prior lines of cytotoxic therapy for metastatic disease. Veliparib/placebo will be dosed in combination with carboplatin AUC 6 with weekly paclitaxel (80 mg/m^2), on a 21-day cycle. Subject randomization will be in a 2:1 ratio to veliparib/C/P or placebo/C/P and stratified by estrogen receptor (ER) and/or progesterone receptor (PgR) positive versus ER/PgR negative, prior platinum therapy (yes versus no), and CNS metastases (yes versus no). Subjects with *BRCA1/BRCA2* mutation per local lab testing and who meet the remaining eligibility criteria may be randomized. Patients who meet NCCN guidelines for *BRCA1/BRCA2* testing are eligible for testing during the screening period. *BRCA* mutation status will be documented for all patients by the central laboratory (Myriad). Subjects who discontinue carboplatin and paclitaxel and who have not progressed will continue veliparib/placebo as a single agent at the recommended Phase 2 single agent dose. Subjects will continue dosing until they meet the defined treatment discontinuation criteria. Subjects who discontinue carboplatin, paclitaxel, and veliparib/placebo for reasons other than progression should remain on study. At the time PD is documented according to RECIST 1.1, subjects randomized to placebo may be eligible to crossover to unblinded veliparib monotherapy.

Methodology (Continued):

Tumor assessments (CT scan or MRI of the full chest, abdomen, pelvis and brain MRI or contrast CT) will be performed at screening and then every 9 weeks from C1D-2 until tumor progression to determine the extent of tumor burden per RECIST 1.1 (post-baseline brain MRI or contrast CT is only required in subjects with CNS lesions at baseline; in all other subjects, CNS imaging will be obtained as clinically indicated based upon symptoms indicative of CNS disease). In addition to being reviewed by the investigator and/or site staff, radiographic scans will be sent to a central imaging center for review. Subjects who discontinue study treatment prior to disease progression should remain on study and continue to undergo a modified schedule of assessments until disease progression per RECIST 1.1. For subjects who meet study discontinuation criteria and who have not progressed (such as patients who initiate another anti-cancer therapy), tumor assessment data per RECIST 1.1 will continue to be collected to document tumor status and the date of progression. Post treatment information (including dates and response to subsequent therapies) and survival information will be collected every two months beginning on the date the subject is registered as off study until the endpoint of death, the subject is lost to follow-up or until the study termination by AbbVie.

QoL assessment via the EORTC QLQ-C30/BR23 and EQ-5D-5L questionnaires will be collected on C1D-2 pre-dose, Day 1 of Cycle 2 and every other cycle thereafter beginning with Cycle 4 (C6, C8, etc.), Final Visit, and 30-Day Follow-Up Visit. Subjects who crossover to the unblinded veliparib monotherapy arm will continue to have QoL assessments performed as per this schedule (Day 1 of the first and second cycle of unblinded monotherapy and every other cycle thereafter beginning with Cycle 4 until 2nd disease progression or until they meet the defined study treatment discontinuation criteria and at the Final Visit and 30-Day Follow-Up Visit). Pain assessment via the BPI-SF will be collected at every cycle.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Men and women ≥ 18 years of age.
2. Histologically or cytologically confirmed breast cancer that is either locally advanced or metastatic.
   - Locally advanced breast cancer must not be primarily amenable to surgical resection or radiation with curative intent.
   - Patients with bone-only disease and/or hormone receptor positive disease should be deemed by the investigator as appropriate candidates for combination chemotherapy.
3. Suspected deleterious or deleterious *BRCA1* and/or *BRCA2* germline mutation.
   The investigator should ensure that the testing is consistent with local guidelines, and clinical practice, and that the test uses either 1) direct DNA sequencing/multiplex ligation-dependent probe amplification (MLPA) or 2) a well-characterized methodology previously validated by sequencing, such as that used to assess founder mutations. If testing has been performed prior to Study M12-914, subjects may be enrolled but must be re-tested by the Sponsor core laboratory for documentation of *BRCA1* or *BRCA2* germline mutations.
   Subjects with *BRCA* variants of uncertain significance or polymorphisms in *BRCA1* or *BRCA2* will not be eligible for the study.
4. Breast cancer must be HER2-negative, defined as IHC 0 – 1+ OR HER2-neu negative according to ASCO-CAP guideline recommendations.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

5. Measurable or non-measurable (but radiologically evaluable) disease per RECIST version 1.1 on computed tomography (CT) scan (within 28 days of randomization) with at least one lesion outside previously irradiated areas.
6. ECOG Performance status of 0 to 2.
7. Subject is able to swallow and retain oral medication and does not have uncontrolled emesis.
8. Adequate hematologic, renal, and hepatic function as follows (within 28 days of randomization):
   - Bone Marrow: Absolute neutrophil count (ANC) $\geq 1500/mm^3$ ($1.5 \times 10^9/L$); Platelets $\geq 100{,}000/mm^3$ ($100 \times 10^9/L$); Hemoglobin ≥ 9.5 g/dL (5.89 mmol/L);
   - Renal Function: Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN) range OR creatinine clearance ≥ 50 mL/min/1.73 m^2 (according to local assessment method) for subjects with creatinine levels above institutional normal;
   - Hepatic Function: Aspartate aminotransferase (AST) $\leq 2.5 \times$ upper limit of normal; alanine transaminase (ALT) $\leq 2.5 \times$ upper limit of normal; bilirubin $\leq 1.5 \times$ the ULN range. For subjects with liver metastases, AST $< 5 \times$ ULN range; ALT $< 5 \times$ ULN range. Subjects with Gilbert's Syndrome may have a bilirubin $\geq 1.5 \times$ the ULN range if no evidence of biliary obstruction exists;
   - Activated Partial Thromboplastin Time (APTT) must be $\leq 1.5 \times$ the ULN range and international normalized ratio (INR) < 1.5. Subjects on anticoagulant therapy will have an appropriate APTT and INR as determined by the investigator.
9. Women of childbearing potential and men must agree to use adequate contraception (one of the following listed below) prior to study entry, for the duration of study participation, and for 6 months following completion of therapy. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to randomization. To be considered of non-childbearing potential, postmenopausal women must be amenorrheic for at least 12 months or subjects must be surgically sterile.
   - Total abstinence from sexual intercourse (abstinence is only acceptable as a contraceptive method if it is established as the subject's preferred and usual lifestyle);
   - Vasectomized male subjects or vasectomized partner of female subjects;
   - Double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or cream); or
   - Intra-Uterine Device (IUD).
   - Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms and refrain from sperm donation for the duration of the study and for 6 months following completion of therapy.
10. Capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to initiation of any screening or study-specific procedures.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

Subjects who meet any of the following exclusion criteria are not eligible:

1. Received anticancer agent(s) or an investigational agent within 21 days prior to C1D-2 or radiotherapy within 28 days prior to C1D-2.
   - Prior treatment with palliative local breast or bone lesion radiation (other than pelvis) can occur, if administered at least 14 days prior to C1D-2.
   - Anticancer hormonal therapy must be stopped 7 days before starting C1D-2.
   - Anti-cancer therapy should not be initiated by the site during the screening period, as a 21-day interval would be needed from the last dose and would lead to additional delays in therapy and potential exclusion of the subject.
2. Received more than 2 prior lines of cytotoxic chemotherapy (e.g., gemcitabine, doxorubicin, capecitabine) for metastatic disease.*
   - Regimens received in the adjuvant/neoadjuvant setting or for locally advanced breast cancer within the past 6 months will also be considered toward the maximum of 2 prior lines of therapy. Adjuvant/neoadjuvant chemotherapy for one cancer event will count as one prior line of therapy, if received within the past 6 months.
   - Previous treatments with hormonal therapy (tamoxifen, aromatase inhibitors) and signal transduction agents (e.g., erlotinib, gefitinib, everolimus, bevacizumab) are allowed and are not counted towards the prior line of therapy.
3. Progressed or recurred within 12 months of completing platinum therapy or received > 1 prior line of platinum therapy for breast cancer in any setting (adjuvant, neoadjuvant or metastatic).
4. Subjects experiencing a significant adverse effect or toxicity (Grade 3 or Grade 4) causally attributed to previous anticancer treatment that has not recovered to at least Grade 2.
5. Prior therapy with PARP inhibitors.*
6. Prior taxane therapy administered for the treatment of metastatic breast cancer with the below exceptions.*
   - Prior taxane therapy for metastatic breast cancer is allowed if the patient received ≤ 1 full cycle (i.e., therapy discontinued within 4 weeks for subjects receiving weekly paclitaxel or Abraxane; therapy discontinued within 3 weeks for subjects receiving paclitaxel or docetaxel every 3 weeks) in the absence of progression or if taxane therapy for metastatic disease was > 12 months prior to C1D-2.
   - Use of taxanes as adjuvant therapy or to treat locally advanced disease is permitted, if given more than 6 months prior to C1D-2.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

7. Subjects with active brain metastases or leptomeningeal disease.
   - Subjects should have a brain MRI within 28 days of randomization to confirm the absence of CNS metastases. Contrast CT is acceptable for subjects who are unable to undergo a brain MRI.
   - Subjects with known brain metastases must have clinically controlled neurologic symptoms and have received previous adequate treatment, defined as surgical excision and/or radiation therapy with stable neurologic function and no evidence of Central Nervous System (CNS) disease progression as determined by comparing a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan performed during screening to a prior scan performed at least 4 weeks earlier and provided that the subject is asymptomatic, has no evidence of cavitation or hemorrhage, and does not require corticosteroids (must have discontinued steroids for management of neurological symptoms at least 3 months prior to study drug administration).
8. A history of uncontrolled seizure disorder; including focal or generalized seizure within the past year.
9. Pre-existing neuropathy in excess of Grade 1 (except focal neuropathy such as brachial plexopathy or carpal tunnel syndrome).
10. Major surgery within 3 weeks of randomization.
11. Known history of allergic reaction to cremophor-paclitaxel, carboplatin, Azo-Colourant Tartrazine (also known as FD&C Yellow 5 or E102), Azo-Colourant Orange Yellow-S (also known as FD&C Yellow 6 or E110) or known contraindications to any study supplied drug.
12. Clinically significant uncontrolled condition(s):
    - Active infection;
    - Symptomatic congestive heart failure;
    - Unstable angina pectoris or cardiac arrhythmia;
    - Myocardial infarction within last 6 months;
    - Known active hepatitis B or hepatitis C with abnormal liver function tests or organ dysfunction;
    - Uncontrolled hypertension (sustained systolic blood pressure > 150 mmHg or diastolic pressure > 100 mmHg despite optimal medical management);
    - Psychiatric illness/social situations that would limit compliance with study requirements; or
    - Any medical condition that, in the opinion of the investigator, places the subject at an unacceptably high risk for toxicities.
13. A previous or concurrent cancer that is distinct in primary site or histology from breast cancer, except cervical carcinoma in situ, non-melanoma carcinoma of the skin, or in situ carcinoma of the bladder or another in situ cancer that is considered cured by the Investigator. Any cancer curatively treated greater than 3 years prior to entry is permitted. For these subjects, metastases must be histologically or cytologically confirmed to be breast cancer.
14. Pregnant or breastfeeding.

* Note: For prior chemotherapy, treatment for 1 full cycle or less will not be considered as prior therapy unless the patient experienced progression of disease while on that therapy.

Investigational Product:	Veliparib or Placebo
Dose:	120 mg BID Days –2 through 5 of 21-day cycle in combination with carboplatin and paclitaxel
Mode of Administration:	Oral
Reference Therapy:	Carboplatin
Dose:	AUC 6 Day 1 of 21-day cycle
Mode of Administration:	Intravenously (IV)
Reference Therapy:	Paclitaxel
Dose:	80 mg/m^2 on Days 1, 8, 15 of 21-day cycle
Mode of Administration:	Intravenously (IV)
Investigational Product:	Veliparib or Placebo
Dose:	Starting dose of 300 mg BID Days 1 through 21 of 21-day cycle as single agent therapy, if tolerated, escalation to 400 mg BID will be allowed
Mode of Administration:	Oral
Interim Analyses:	To ensure subject safety, an IDMC will review unblinded safety data (which will include all subjects enrolled in the study) when approximately 60 subjects have met at least one of the following criteria: • Received 6 cycles of treatment • Reached an event of disease progression • Discontinued the study due to toxicity/adverse events Subsequent reviews will be based on recommendations from the IDMC.

Criteria for Evaluation:

Progression-free Survival (PFS): will be evaluated according to progression per RECIST (version 1.1) and survival information (death). Radiologic tumor response and disease progression will be assessed by CT scan utilizing RECIST (version 1.1). Assessments will be performed at Screening, at 9-week intervals (from C1D-2) thereafter until disease progression and at each blinded and unblinded study treatment Final Visit, if not performed within the last 4 weeks.

Clinical benefit rate (CBR), Objective Response Rate (ORR) and Duration of Overall Response (DOR): will be evaluated according to progression per RECIST (version 1.1). Radiologic tumor response and disease progression will be assessed by CT scan utilizing RECIST (version 1.1). Assessments will be performed at Screening, at 9-week intervals (from C1D-2) thereafter, and at each blinded and unblinded study treatment Final Visit, if not performed within the last 4 weeks (a 2-week window for obtaining the final visit scan is acceptable for maintaining at least a 6-week interval between scans as per local guidance and regulations).

Overall Survival (OS): will be evaluated according to survival information and post treatment information (including therapy, dates of therapy and response) collected at two month intervals beginning on the date the subject is registered off study and until the endpoint of death, the subject is lost to follow-up or until the study termination by AbbVie.

Criteria for Evaluation (Continued):

PFS2: will be evaluated according to survival information and post treatment information (includes dates of therapy and response per RECIST 1.1) collected at two month intervals.

Statistical Methods: Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05 when rounded.

Sample Size Determination:

Assuming the true hazard ratio for PFS in favor of the veliparib + C/P group is 0.69, a total of 344 PFS events will be needed for the study to have 90% power at 2-sided α level of 0.05 to detect a statistically significant treatment effect for the veliparib + C/P group using the log-rank test for progression free survival. A total of approximately 500 subjects will be enrolled into the study.

Efficacy (Primary and Secondary Endpoints):

The analysis of the primary endpoint and secondary endpoints will include only the subjects who have been documented to have suspected deleterious or deleterious mutations by the Sponsor core lab. The primary and secondary analyses will be based upon the investigator's assessment of response and disease progression per RECIST 1.1. Sensitivity analyses of PFS, ORR, CBR, and duration of overall response based on radiological and clinical assessment by the Central Imaging Center will be conducted.

Progression-Free Survival (PFS): will be defined as the number of days from the date the subject is randomized to the date the subject experiences disease progression, or to the date of death (all causes of mortality) if disease progression is not reached.

Clinical Benefit Rate (CBR): will be defined as the progression-free rate at 24 weeks from the Kaplan-Meier curve for time to progression (defined as from the date of randomization to the date of disease progression).

Overall Survival (OS): Time to death for a given subject will be defined as the number of days from the day the subject is randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurs while the subject is still taking study drug, or after the subject discontinues study drug. If a subject has not died, then the data will be censored at the date when the subject is last known to be alive.

Objective Response Rate (ORR): (CR and PR) will be defined as the proportion of subjects with a complete or partial objective response based on RECIST (version 1.1). All subjects who have had at least one measurable lesion at baseline will be included in the ORR calculation.

PFS2: will be defined as the number of days from the day the subject is randomized to the date that the subject has disease progression or death of any cause on the subsequent therapy, whichever occurs first.

Duration of Overall Response (DOR): will be defined as the number of days from the day the criteria are met for CR or PR (whichever is recorded first) to the date that PD is objectively documented. If a subject is still responding then the subject's data will be censored at date of the last available disease progression assessment. For subjects who never experienced CR or PR, the subject's data will not be included in DOR analysis.

Safety: Safety will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters. Subjects who are randomized but do not receive study drug (veliparib or placebo) will not be included in the analyses of safety. Safety analysis results will be presented by treatment group.

Has been changed to read:

AbbVie	**Protocol Number:** M12-914
Name of Study Drug: Veliparib (ABT-888)	**Phase of Development:** Phase 3
Name of Active Ingredient: Not applicable	**Date of Protocol Synopsis:** 23 July 2020
Protocol Title: A Phase 3 Randomized Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2-Negative Metastatic or Locally Advanced Unresectable *BRCA*-Associated Breast Cancer	
Objectives: The primary endpoint is to assess the progression-free survival (PFS) of veliparib in combination with carboplatin (C) and paclitaxel (P) compared to placebo with C/P in subjects with a *BRCA1* and/or *BRCA2* Mutation and HER2-Negative Metastatic or Locally Advanced Unresectable Breast Cancer. The secondary objectives of the study are to assess overall survival (OS), clinical benefit rate (CBR), objective response rate (ORR), and PFS2 in subjects treated with veliparib in combination with C/P versus subjects treated with placebo with C/P. The tertiary objectives are to assess duration of overall response (DOR), change in ECOG performance status, and change in Quality of Life (QoL).	
Study Sites: Multicenter; Approximately 200	
Study Population: Men and women ≥ 18 years of age with HER2-negative metastatic or locally advanced unresectable breast cancer and clinically significant (suspected deleterious or deleterious) *BRCA1* and/or *BRCA2* germline mutation. Patients with bone-only disease and/or hormone receptor positive (ER and/or PR) disease should be deemed appropriate candidates for combination chemotherapy.	
Number of Subjects to be Enrolled: Approximately 500	
Methodology: This is a Phase 3, randomized, double-blinded study to evaluate the efficacy and tolerability of veliparib in combination with C/P compared to placebo plus C/P in subjects with *BRCA1* or *BRCA2* germline mutation and with HER2-negative metastatic or locally advanced unresectable breast cancer who have received no more than 2 prior lines of cytotoxic therapy for metastatic disease. Veliparib/placebo will be dosed in combination with carboplatin AUC 6 with weekly paclitaxel (80 mg/m^2), on a 21-day cycle. Subject randomization will be in a 2:1 ratio to veliparib/C/P or placebo/C/P and stratified by estrogen receptor (ER) and/or progesterone receptor (PgR) positive versus ER/PgR negative, prior platinum therapy (yes versus no), and CNS metastases (yes versus no). Subjects with *BRCA1/BRCA2* mutation per local lab testing and who meet the remaining eligibility criteria may be randomized. Patients who meet NCCN guidelines for *BRCA1/BRCA2* testing are eligible for testing during the screening period. *BRCA* mutation status will be documented for all subjects by the central laboratory (Myriad). Subjects who discontinue carboplatin and paclitaxel and who have not progressed will continue veliparib/placebo as a single agent at the recommended Phase 2 single agent dose. Subjects will continue dosing until they meet the defined treatment discontinuation criteria. Subjects who discontinue carboplatin, paclitaxel, and veliparib/placebo for reasons other than progression should remain on study. At the time PD is documented according to RECIST 1.1, subjects randomized to placebo may be eligible to crossover to unblinded veliparib monotherapy.	

Methodology (Continued):

Tumor assessments (CT scan or MRI of the full chest, abdomen, pelvis and brain MRI or contrast CT) were performed at screening and then every 9 weeks from C1D-2 until tumor progression to determine the extent of tumor burden per RECIST 1.1. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks from last scan until tumor progression. At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control but must not exceed 24 weeks. Post-baseline brain MRI or contrast CT is only required in subjects with CNS lesions at baseline; in all other subjects, CNS imaging will be obtained as clinically indicated based upon symptoms indicative of CNS disease. Refer to Section 5.3.1.1 and Appendix C, Appendix D, and Appendix E for additional tumor assessment schedule details, including details for subjects on open-label crossover veliparib.

In addition to being reviewed by the investigator and/or site staff, radiographic scans will be sent to a central imaging center for review. Subjects who discontinue study treatment prior to disease progression should remain on study and continue to undergo a modified schedule of assessments until disease progression per RECIST 1.1. For these subjects who meet study treatment discontinuation criteria and who have not progressed (such as subjects who initiate another anti-cancer therapy), tumor assessment data per RECIST 1.1 will continue to be collected to document tumor status and the date of progression. Post treatment information (including dates and response to subsequent therapies) and survival information will be collected every two months beginning on the date the subject has discontinued study therapy until the endpoint of death, the subject is lost to follow-up or until the study termination by AbbVie.

QoL assessment via the EORTC QLQ-C30/BR23 and EQ-5D-5L questionnaires will be collected on C1D-2 pre-dose, Day 1 of Cycle 2 and every other cycle thereafter beginning with Cycle 4 (C6, C8, etc.), Final Visit, and 30-Day Follow-Up Visit. Subjects who crossover to the unblinded veliparib monotherapy arm will continue to have QoL assessments performed as per this schedule (Day 1 of the first and second cycle of unblinded monotherapy and every other cycle thereafter beginning with Cycle 4 until 2nd disease progression or until they meet the defined study treatment discontinuation criteria and at the Final Visit and 30-Day Follow-Up Visit). Pain assessment via the BPI-SF will be collected at every cycle.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Men and women ≥ 18 years of age.
2. Histologically or cytologically confirmed breast cancer that is either locally advanced or metastatic.
   - Locally advanced breast cancer must not be primarily amenable to surgical resection or radiation with curative intent.
   - Patients with bone-only disease and/or hormone receptor positive disease should be deemed by the investigator as appropriate candidates for combination chemotherapy.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

3. Suspected deleterious or deleterious *BRCA1* and/or *BRCA2* germline mutation.
   The investigator should ensure that the testing is consistent with local guidelines, and clinical practice, and that the test uses either 1) direct DNA sequencing/multiplex ligation-dependent probe amplification (MLPA) or 2) a well-characterized methodology previously validated by sequencing, such as that used to assess founder mutations. If testing has been performed prior to Study M12-914, subjects may be enrolled but must be re-tested by the Sponsor core laboratory for documentation of *BRCA1* or *BRCA2* germline mutations.
   Subjects with *BRCA* variants of uncertain significance or polymorphisms in *BRCA1* or *BRCA2* will not be eligible for the study.
4. Breast cancer must be HER2-negative, defined as IHC 0 – 1+ OR HER2-neu negative according to ASCO-CAP guideline recommendations.
5. Measurable or non-measurable (but radiologically evaluable) disease per RECIST version 1.1 on computed tomography (CT) scan (within 28 days of randomization) with at least one lesion outside previously irradiated areas.
6. ECOG Performance status of 0 to 2.
7. Subject is able to swallow and retain oral medication and does not have uncontrolled emesis.
8. Adequate hematologic, renal, and hepatic function as follows (within 28 days of randomization):
   - Bone Marrow: Absolute neutrophil count (ANC) $\geq 1500/mm^3$ ($1.5 \times 10^9/L$); Platelets $\geq 100{,}000/mm^3$ ($100 \times 10^9/L$); Hemoglobin ≥ 9.5 g/dL (5.89 mmol/L);
   - Renal Function: Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN) range OR creatinine clearance ≥ 50 mL/min/1.73 m^2 (according to local assessment method) for subjects with creatinine levels above institutional normal;
   - Hepatic Function: Aspartate aminotransferase (AST) $\leq 2.5 \times$ upper limit of normal; alanine transaminase (ALT) $\leq 2.5 \times$ upper limit of normal; bilirubin $\leq 1.5 \times$ the ULN range. For subjects with liver metastases, AST $< 5 \times$ ULN range; ALT $< 5 \times$ ULN range. Subjects with Gilbert's Syndrome may have a bilirubin $\geq 1.5 \times$ the ULN range if no evidence of biliary obstruction exists;
   - Activated Partial Thromboplastin Time (APTT) must be $\leq 1.5 \times$ the ULN range and international normalized ratio (INR) < 1.5. Subjects on anticoagulant therapy will have an appropriate APTT and INR as determined by the investigator.
9. Women of childbearing potential and men must agree to use adequate contraception (one of the following listed below) prior to study entry, for the duration of study participation, and for 6 months following completion of therapy. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to randomization. To be considered of non-childbearing potential, postmenopausal women must be amenorrheic for at least 12 months or subjects must be surgically sterile.
   - Total abstinence from sexual intercourse (abstinence is only acceptable as a contraceptive method if it is established as the subject's preferred and usual lifestyle);
   - Vasectomized male subjects or vasectomized partner of female subjects;

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or cream); or
- Intra-Uterine Device (IUD).
- Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms and refrain from sperm donation for the duration of the study and for 6 months following completion of therapy.

10. Capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to initiation of any screening or study-specific procedures.

Main Exclusion:

Subjects who meet any of the following exclusion criteria are not eligible:

1. Received anticancer agent(s) or an investigational agent within 21 days prior to C1D-2 or radiotherapy within 28 days prior to C1D-2.
   - Prior treatment with palliative local breast or bone lesion radiation (other than pelvis) can occur, if administered at least 14 days prior to C1D-2.
   - Anticancer hormonal therapy must be stopped 7 days before starting C1D-2.
   - Anti-cancer therapy should not be initiated by the site during the screening period, as a 21-day interval would be needed from the last dose and would lead to additional delays in therapy and potential exclusion of the subject.
2. Received more than 2 prior lines of cytotoxic chemotherapy (e.g., gemcitabine, doxorubicin, capecitabine) for metastatic disease.*
   - Regimens received in the adjuvant/neoadjuvant setting or for locally advanced breast cancer within the past 6 months will also be considered toward the maximum of 2 prior lines of therapy. Adjuvant/neoadjuvant chemotherapy for one cancer event will count as one prior line of therapy, if received within the past 6 months.
   - Previous treatments with hormonal therapy (tamoxifen, aromatase inhibitors) and signal transduction agents (e.g., erlotinib, gefitinib, everolimus, bevacizumab) are allowed and are not counted towards the prior line of therapy.
3. Progressed or recurred within 12 months of completing platinum therapy or received > 1 prior line of platinum therapy for breast cancer in any setting (adjuvant, neoadjuvant or metastatic).
4. Subjects experiencing a significant adverse effect or toxicity (Grade 3 or Grade 4) causally attributed to previous anticancer treatment that has not recovered to at least Grade 2.
5. Prior therapy with PARP inhibitors.*
6. Prior taxane therapy administered for the treatment of metastatic breast cancer with the below exceptions.*
   - Prior taxane therapy for metastatic breast cancer is allowed if the patient received ≤ 1 full cycle (i.e., therapy discontinued within 4 weeks for subjects receiving weekly paclitaxel or Abraxane; therapy discontinued within 3 weeks for subjects receiving paclitaxel or docetaxel every 3 weeks) in the absence of progression or if taxane therapy for metastatic disease was > 12 months prior to C1D-2.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

- Use of taxanes as adjuvant therapy or to treat locally advanced disease is permitted, if given more than 6 months prior to C1D-2.

7. Subjects with active brain metastases or leptomeningeal disease.
   - Subjects should have a brain MRI within 28 days of randomization to confirm the absence of CNS metastases. Contrast CT is acceptable for subjects who are unable to undergo a brain MRI.
   - Subjects with known brain metastases must have clinically controlled neurologic symptoms and have received previous adequate treatment, defined as surgical excision and/or radiation therapy with stable neurologic function and no evidence of Central Nervous System (CNS) disease progression as determined by comparing a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan performed during screening to a prior scan performed at least 4 weeks earlier and provided that the subject is asymptomatic, has no evidence of cavitation or hemorrhage, and does not require corticosteroids (must have discontinued steroids for management of neurological symptoms at least 3 months prior to study drug administration).
8. A history of uncontrolled seizure disorder; including focal or generalized seizure within the past year.
9. Pre-existing neuropathy in excess of Grade 1 (except focal neuropathy such as brachial plexopathy or carpal tunnel syndrome).
10. Major surgery within 3 weeks of randomization.
11. Known history of allergic reaction to cremophor-paclitaxel, carboplatin, Azo-Colourant Tartrazine (also known as FD&C Yellow 5 or E102), Azo-Colourant Orange Yellow-S (also known as FD&C Yellow 6 or E110) or known contraindications to any study supplied drug.
12. Clinically significant uncontrolled condition(s):
    - Active infection;
    - Symptomatic congestive heart failure;
    - Unstable angina pectoris or cardiac arrhythmia;
    - Myocardial infarction within last 6 months;
    - Known active hepatitis B or hepatitis C with abnormal liver function tests or organ dysfunction;
    - Uncontrolled hypertension (sustained systolic blood pressure > 150 mmHg or diastolic pressure > 100 mmHg despite optimal medical management);
    - Psychiatric illness/social situations that would limit compliance with study requirements; or
    - Any medical condition that, in the opinion of the investigator, places the subject at an unacceptably high risk for toxicities.
13. A previous or concurrent cancer that is distinct in primary site or histology from breast cancer, except cervical carcinoma in situ, non-melanoma carcinoma of the skin, or in situ carcinoma of the bladder or another in situ cancer that is considered cured by the Investigator. Any cancer curatively treated greater than 3 years prior to entry is permitted. For these subjects, metastases must be histologically or cytologically confirmed to be breast cancer.
14. Pregnant or breastfeeding.

*Note: For prior chemotherapy, treatment for 1 full cycle or less will not be considered as prior therapy unless the patient experienced progression of disease while on that therapy.

Investigational Product:	Veliparib or Placebo
Dose:	120 mg BID Days –2 through 5 of 21-day cycle in combination with carboplatin and paclitaxel
Mode of Administration:	Oral
Reference Therapy:	Carboplatin
Dose:	AUC 6 Day 1 of 21-day cycle
Mode of Administration:	Intravenously (IV)
Reference Therapy:	Paclitaxel
Dose:	80 mg/m^2 on Days 1, 8, 15 of 21-day cycle
Mode of Administration:	Intravenously (IV)
Investigational Product:	Veliparib or Placebo
Dose:	Starting dose of 300 mg BID Days 1 through 21 of 21-day cycle as single agent therapy, if tolerated, escalation to 400 mg BID will be allowed
Mode of Administration:	Oral
Interim Analyses:	To ensure subject safety, an IDMC reviewed unblinded safety data (which included all subjects enrolled in the study) when approximately 60 subjects met at least one of the following criteria: • Received 6 cycles of treatment • Reached an event of disease progression • Discontinued the study due to toxicity/adverse events Subsequent IDMC reviews of unblinded safety data prior to the primary analysis were carried out based on IDMC recommendations. No additional reviews by the IDMC will occur since the Sponsor management team was unblinded after completing the primary analysis.

Criteria for Evaluation:

Progression-free Survival (PFS): will be evaluated according to progression per RECIST (version 1.1) and survival information (death). Radiologic tumor response and disease progression will be assessed by CT scan utilizing RECIST (version 1.1). Assessments were be performed at Screening, at 9-week intervals (from C1D-2) thereafter until disease progression. Following the primary analysis and implementation of Protocol Amendment 4 the tumor assessment interval may be increased to every 12 weeks from last scan until tumor progression; at investigator discretion, the interval between scans may be longer than 12 weeks but must not exceed 24 weeks.

Clinical benefit rate (CBR), Objective Response Rate (ORR) and Duration of Overall Response (DOR): will be evaluated according to progression per RECIST (version 1.1). Radiologic tumor response and disease progression will be assessed by CT scan utilizing RECIST (version 1.1). Assessments were be performed at Screening, at 9-week intervals (from C1D-2) thereafter. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks from last scan until tumor progression; at investigator discretion, the interval between scans may be longer than 12 weeks but must not exceed 24 weeks.

Criteria for Evaluation (Continued):

Overall Survival (OS): will be evaluated according to survival information and post treatment information (including therapy, dates of therapy and response) collected at two month intervals beginning on the date the subject is registered off study and until the endpoint of death, the subject is lost to follow-up or until the study termination by AbbVie.

PFS2: will be evaluated according to survival information and post treatment information (includes dates of therapy and response per RECIST 1.1) collected at two-month intervals.

Statistical Methods: Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05 when rounded.

Sample Size Determination:

Assuming the true hazard ratio for PFS in favor of the veliparib + C/P group is 0.69, a total of 344 PFS events will be needed for the study to have 90% power at 2-sided α level of 0.05 to detect a statistically significant treatment effect for the veliparib + C/P group using the log-rank test for progression free survival. A total of approximately 500 subjects will be enrolled into the study.

Efficacy (Primary and Secondary Endpoints):

The analysis of the primary endpoint and secondary endpoints will include only the subjects who have been documented to have suspected deleterious or deleterious mutations by the Sponsor core lab. The primary and secondary analyses will be based upon the investigator's assessment of response and disease progression per RECIST 1.1. Sensitivity analyses of PFS, ORR, and CBR based on radiological and clinical assessment by the Central Imaging Center will be conducted.

Progression-Free Survival (PFS): will be defined as the number of days from the date the subject is randomized to the date the subject experiences disease progression, or to the date of death (all causes of mortality) if disease progression is not reached.

Clinical Benefit Rate (CBR): will be defined as the progression-free rate at 24 weeks from the Kaplan-Meier curve for time to progression (defined as from the date of randomization to the date of disease progression).

Overall Survival (OS): Time to death for a given subject will be defined as the number of days from the day the subject is randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurs while the subject is still taking study drug, or after the subject discontinues study drug. If a subject has not died, then the data will be censored at the date when the subject is last known to be alive.

Objective Response Rate (ORR): (CR and PR) will be defined as the proportion of subjects with a complete or partial objective response based on RECIST (version 1.1). All subjects who have had at least one measurable lesion at baseline will be included in the ORR calculation.

PFS2: will be defined as the number of days from the day the subject is randomized to the date that the subject has disease progression or death of any cause on the subsequent therapy, whichever occurs first.

Safety: Safety will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters. Subjects who are randomized but do not receive study drug (veliparib or placebo) will not be included in the analyses of safety. Safety analysis results will be presented by treatment group.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add:

TA MD	Therapeutic Area Medical Director

Section 3.5 Benefits and Risks
Add: new last paragraph

The benefits and risks of study participation have been evaluated in the context of the ongoing COVID-19 pandemic. No data are available to characterize the risk of participation in this trial specific to COVID-19. COVID-19-related risks are not expected to differ substantially between trial participants and the broader population of individuals receiving treatment for advanced breast cancer. In consideration of the life-threatening nature of the disease under study, the benefit/risk balance for participation in this trial is not changed.

Section 4.0 Study Objectives
Second and third paragraph previously read:

The secondary objectives of the study are to assess overall survival (OS), clinical benefit rate (CBR) through the end of Week 24, duration of overall response, objective response rate (ORR) and PFS2 in subjects treated with veliparib in combination with carboplatin and paclitaxel versus placebo in combination with carboplatin and paclitaxel.

The tertiary objectives are to assess ECOG performance status, QoL, and exploratory correlative endpoints.

Has been changed to read:

The secondary objectives of the study are to assess overall survival (OS), clinical benefit rate (CBR) through the end of Week 24, objective response rate (ORR) and PFS2 in subjects treated with veliparib in combination with carboplatin and paclitaxel versus placebo in combination with carboplatin and paclitaxel.

The tertiary objectives are to assess ECOG performance status, QoL, duration of overall response, and exploratory correlative endpoints.

Section 5.1 Overall Study Design and Plan: Description
Subsection Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel)
Third paragraph, last sentence previously read:

Subjects will continue to follow the schedule of assessments as outlined in Appendix C.

Has been changed to read:

For subjects who have been receiving single-agent veliparib/placebo at a stable dose without adjustment for multiple cycles and who have no ongoing study drug related uncontrolled AEs (Adverse Events), it is possible to alternate on-site visits and phone visits every other cycle. At a minimum, these subjects should have an on-site visit every other cycle. If an on-site visit is not possible for 2 consecutive cycles, or if the subject is not on a stable dose or has ongoing study drug-related uncontrolled AEs but wishes to alternate on-site and phone visits every other cycle, the plan for the subject's visits should be discussed with the AbbVie TA MD (see Section 7.0 for contact information). Subjects will continue to follow the schedule of assessments as outlined in Appendix C and Appendix F.

Section 5.1 Overall Study Design and Plan: Description
Subsection Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel)
Fourth paragraph previously read:

Subjects who have discontinued blinded study treatment due to unmanageable toxicity or for reasons other than progression will remain on study and follow a reduced schedule of study assessments (tumor assessment per RECIST 1.1, Performance Status, QLQ C30, BR23, EQ 5D 5L and BPI-SF Questionnaires) and standard of care assessments (physical exam and vital signs) until disease progression as outlined in Appendix E.

Has been changed to read:

Subjects who have discontinued blinded study treatment due to unmanageable toxicity or for reasons other than progression will remain on study, off drug and follow a reduced schedule of study assessments which will include tumor assessments per RECIST 1.1 and survival status assessments, until disease progression as outlined in Appendix E.

Section 5.1 Overall Study Design and Plan: Description
Subsection Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel)
Last paragraph, first sentence previously read:

Once a subject discontinues the blinded portion of the study, a Final Visit will be conducted.

Has been changed to read:

Once a subject discontinues blinded study treatment (including subjects that discontinued treatment due to unmanageable toxicity or for reasons other than progression), a Final Visit will be conducted.

Section 5.1 Overall Study Design and Plan: Description
Subsection Optional Unblinded Veliparib Monotherapy Treatment (Crossover)
First paragraph, first bullet, last paragraph previously read:

Note: Discussion with the Unblinded AbbVie TA MD (see Section 7.0 for contact information) may be needed prior to unblinding and crossover to verify that criteria for unequivocal PD are met.

Has been changed to read:

Note: Discussion with the AbbVie TA MD (see Section 7.0 for contact information) may be needed prior to unblinding and crossover to verify that criteria for unequivocal PD are met.

Section 5.1 Overall Study Design and Plan: Description
Subsection Optional Unblinded Veliparib Monotherapy Treatment (Crossover)
Second paragraph, last sentence previously read:

Transitions that occur after 60 days should be discussed with the Unblinded AbbVie TA MD.

Has been changed to read:

Transitions that occur after 60 days should be discussed with the AbbVie TA MD.

Section 5.1 Overall Study Design and Plan: Description
Subsection Optional Unblinded Veliparib Monotherapy Treatment (Crossover)
Third paragraph, third sentence previously read:

Subjects will follow the schedule of assessments as outlined in Appendix D.

Has been changed to read:

For subjects who have been receiving veliparib monotherapy at a stable dose without adjustment for multiple cycles and who have no ongoing study drug related uncontrolled AEs, it is possible to alternate on-site visits and phone visits every other cycle. At a minimum, subjects should have an on-site visit every other cycle. If an on-site visit is not possible for 2 consecutive cycles, or if the subject is not on a stable dose or has ongoing study drug-related uncontrolled AEs but wishes to alternate on-site and phone visits every other cycle, the plan for the subject's visits should be discussed with the AbbVie TA MD (see Section 7.0 for contact information). Subjects will follow the schedule of assessments as outlined in Appendix D and Appendix F.

Section 5.1 Overall Study Design and Plan: Description
Subsection Optional Unblinded Veliparib Monotherapy Treatment (Crossover)
Fourth paragraph previously read:

Subjects who have discontinued unblinded study treatment due to unmanageable toxicity or for reasons other than progression will remain on study and follow a reduced schedule of study assessments (tumor assessment per RECIST 1.1, Performance Status, QLQ C30,

BR23, EQ 5D 5L and BPI-SF Questionnaires) and standard of care assessments (physical exam and vital signs) until disease progression as outlined in Appendix E.

Has been changed to read:

Subjects who have discontinued unblinded study treatment due to unmanageable toxicity or for reasons other than progression will remain on study, off drug and follow a reduced schedule of study assessments, which will include tumor assessments per RECIST 1.1 and survival status until disease progression as outlined in Appendix E.

Section 5.1 Overall Study Design and Plan: Description
Subsection Optional Unblinded Veliparib Monotherapy Treatment (Crossover)
Last paragraph, first sentence previously read:

Once a subject discontinues the unblinded portion of the study, a Final Visit will be conducted.

Has been changed to read:

Once a subject discontinues the unblinded study treatment (including subjects that discontinued treatment due to unmanageable toxicity or for reasons other than progression), a Final Visit will be conducted.

Section 5.1 Overall Study Design and Plan: Description
Subsection Survival and Post Blinded and Unblinded Study Treatment Information
First sentence previously read:

Once a subject meets study discontinuation criteria, subjects will be followed for survival and post study treatment information as outlined in Section 5.3.1.1 will be collected every two months (unless requested by sponsor more frequently to support data analysis) beginning on the date the subject is registered off study.

Has been changed to read:

Once a subject meets study treatment discontinuation criteria, subjects will be followed for survival and post study treatment information as outlined in Section 5.3.1.1 will be

collected every two months (unless requested by sponsor more frequently to support data analysis) beginning on the date the subject is discontinued from therapy.

Section 5.2.3 Prior and Concomitant Therapy
Last paragraph previously read:

The Blinded AbbVie TA MD identified in Section 6.1.6 should be contacted if there are any questions regarding prior or concomitant therapy.

Has been changed to read:

The AbbVie TA MD identified in Section 6.1.6 should be contacted if there are any questions regarding prior or concomitant therapy(ies).

Section 5.2.3.2 Concomitant Therapy
"Anticancer Agents:"
First paragraph, last sentence previously read:

This should be discussed with the Blinded AbbVie TA MD.

Has been changed to read:

This should be discussed with the AbbVie TA MD.

Section 5.2.3.2 Concomitant Therapy
"Radiation:"
Last paragraph, last sentence previously read:

If a subject becomes a candidate for local treatment with radiation therapy, this should be discussed with the appropriate Blinded or Unblinded AbbVie TA MD and should be consistent with standard or institutional guidelines (a subject with multiple metastases is unlikely to benefit from local therapy).

Has been changed to read:

If a subject becomes a candidate for local treatment with radiation therapy, this should be discussed with the AbbVie TA MD and should be consistent with standard or institutional guidelines (a subject with multiple metastases is unlikely to benefit from local therapy).

Section 5.2.3.2 Concomitant Therapy
"Surgery:"
First paragraph, first sentence previously read:

If the subject requires surgery during the study, timing of the procedure, study drug interruption, and resuming the study drug needs to be discussed with the appropriate Blinded or Unblinded AbbVie TA MD.

Has been changed to read:

If the subject requires surgery during the study, timing of the procedure, study drug interruption, and resuming the study drug needs to be discussed with AbbVie TA MD.

Section 5.2.3.2 Concomitant Therapy
"Surgery:"
Second paragraph previously read:

As a precautionary measure, it is recommended, but not strictly required, that if patients require placement of a central venous access device (CVAD), that procedure should be done 7 days prior to first study treatment start.

Has been changed to read:

As a precautionary measure, it is recommended, but not strictly required, that if subjects require placement of a central venous access device (CVAD), that procedure should be done 7 days prior to first study treatment start.

Section 5.2.3.2 Concomitant Therapy
"Surgery:"
Last paragraph, lasts sentence previously read:

If a subject becomes a candidate for surgical resection, this should be discussed with the appropriate Blinded or Unblinded AbbVie TA MD and should be consistent with standard or institutional guidelines (a subject with multiple metastases is unlikely to benefit from local therapy).

Has been changed to read:

If a subject becomes a candidate for surgical resection, this should be discussed with the AbbVie TA MD and should be consistent with standard or institutional guidelines (a subject with multiple metastases is unlikely to benefit from local therapy).

Section 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart
First sentence previously read:

A schedule of study activities is presented in Appendix C, Appendix D, and Appendix E.

Has been changed to read:

A schedule of study activities is presented in Appendix C, Appendix D, Appendix E, and Appendix F.

Table 2. Schedule Biomarker and Exploratory Research Assessments (Blinded Study Treatment)
Procedure "PD Blood Sampling^{+} Plasma Markers^{a,b}" previously read:

PD Blood Sampling^{+} Plasma Markers^{a,b}

Has been changed to read:

PD Blood Sampling Plasma Markers^{a,b}

Section 5.3.1.1 Study Procedures
First paragraph, first sentence previously read:

The study procedures outlined in Appendix C, Appendix D, and Appendix E are discussed in detail in this section, with the exception of the monitoring of treatment compliance (Section 5.5.6) and the collection of concomitant medication (Section 5.2.3) and adverse event information (Section 6.1).

Has been changed to read:

The study procedures outlined in Appendix C, Appendix D, Appendix E, and Appendix F are discussed in detail in this section, with the exception of the monitoring of treatment compliance (Section 5.5.6) and the collection of concomitant medication (Section 5.2.3) and adverse event information (Section 6.1).

Section 5.3.1.1 Study Procedures
Add: new last paragraph

Study visits may be impacted by changes in local regulations due to the COVID-19 pandemic. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted as outlined per the protocol due to travel restrictions or other pandemic-related reasons, the site should contact the Sponsor for further guidance.

Section 5.3.1.1 Study Procedures
Subsection <u>Pregnancy Test (In Women of Childbearing Potential)</u>
First paragraph, first sentence previously read:

For female subjects of childbearing potential, a serum pregnancy test will be done at screening and a negative urine pregnancy test will be done prior to randomization (within 24 hours).

Has been changed to read:

For female subjects of childbearing potential, a serum pregnancy test will be done at screening and a urine pregnancy test will be done prior to randomization (within 24 hours).

Section 5.3.1.1 Study Procedures
Subsection Pregnancy Test (In Women of Childbearing Potential)
Second paragraph previously read:

If pregnancy results are equivocal (e.g., false positive due to B-hCG being a tumor marker) in subjects with evidence to support lack of pregnancy (e.g., surgically sterile), the results should be discussed with the Blinded AbbVie TA MD and the investigator's interpretation along with supporting information documented in the source documents.

Has been changed to read:

If pregnancy results are equivocal (e.g., false positive due to B-hCG being a tumor marker) in subjects with evidence to support lack of pregnancy (e.g., surgically sterile), the results should be discussed with the AbbVie TA MD and the investigator's interpretation along with supporting information documented in the source documents.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Third paragraph, second sentence previously read:

When necessary, local labs can be split and used determine subject eligibility upon discussion with the Blinded AbbVie TA MD.

Has been changed to read:

When necessary, local labs can be split and used to determine subject eligibility upon discussion with the AbbVie TA MD.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Add: new fourth, fifth, and sixth paragraph

Due to travel restrictions and other changes in local regulations in cases of state of emergency or pandemic or other special situations that prevent the site from collecting a Central Laboratory sample, if possible, sites should arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained per the protocol, the site should discuss with the AbbVie TA MD prior to continuing dosing.

AbbVie may discontinue the requirement for concurrent samples to be sent to the central laboratory, and require instead local laboratory results only at protocol-specified timepoints, at any time during the course of the study.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Fourth paragraph
Add: new fourth sentence

For visits conducted by phone as outlined in Appendix F, lab tests do not need to be performed and are to be collected at a minimum at the on-site visits (every other cycle).

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessments (Radiologic)
Second paragraph previously read:

Axial plane CT scans of the full chest, abdomen, pelvis (or MRI), and brain MRI or contrast CT to determine the extent of tumor burden will be performed for all tumor assessments at Screening (within 28 days of randomization), every 9 weeks from C1D-2 (tumor assessments may be conducted 5 days prior or 5 days following the scheduled assessment) until progression, and at each blinded and unblinded study treatment Final

Visit (if not performed within the last 4 weeks) with a 2-week window to allow for local regulatory requirements. Subjects who have discontinued study treatment due to unmanageable toxicity or reasons other than progression will continue to complete tumor assessments every 9 weeks until unequivocal progression per RECIST 1.1 is documented. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study, unless evidence of tumor metastasis warrants otherwise.

Has been changed to read:

Axial plane CT scans of the full chest, abdomen, pelvis (or MRI), and brain MRI or contrast CT to determine the extent of tumor burden were performed for all tumor assessments at Screening (within 28 days of randomization), and every 9 weeks from C1D-2 (tumor assessments could be conducted 5 days prior or 5 days following the scheduled assessment) until progression. For subjects in the blinded treatment period, following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks from last scan (tumor assessments may be conducted 10 business days prior or 10 business days following the scheduled assessment). At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control but must not exceed 24 weeks.

For subjects on open-label crossover veliparib, tumor assessments will be conducted every 9 weeks (± 5 business days) from C1D1. Following the primary analysis and implementation of Protocol Amendment 4, if a crossover subject has disease control after 6 scans while following the 9 week scan interval schedule, the tumor assessment frequency can be increased to every 12 weeks (± 10 business days) from the last scan. At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control, but must not exceed 24 weeks.

Subjects who have discontinued study treatment due to unmanageable toxicity or reasons other than progression will remain on study but off drug and continue to complete

scheduled tumor assessments until unequivocal progression per RECIST 1.1 is documented as per Appendix E.

Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study, unless evidence of tumor metastasis warrants otherwise.

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessments (Radiologic)
Last paragraph
Add: new last sentence

AbbVie may discontinue the requirement for radiology scans to be sent to the central imaging center or the requirement for completing central reviews at any time during the course of the study.

Section 5.3.1.1 Study Procedures
Subsection ECOG Performance Status
First paragraph previously read:

ECOG performance status will be assessed as outlined in Appendix C, Appendix D, and Appendix E.

Has been changed to read:

ECOG performance status will be assessed as outlined in Appendix C, Appendix D, Appendix E, and Appendix F.

Section 5.3.1.1 Study Procedures
Subsection Patient Reported Outcomes (PRO) Questionnaires
First paragraph, sixth and seventh sentence previously read:

Subjects who have discontinued study treatment prior to disease progression will continue to complete the PRO questionnaires as outlined in the schedule of assessments in Appendix E. These subjects may complete the questionnaires by telephone or during their scheduled clinic visit.

Has been changed to read:

For subjects who are eligible to alternate on-site visits and phone visits, the PRO questionnaires should still be completed at the phone visits. PRO questionnaires to be completed for the cycle during which the phone visit occurs should be provided to the subject by the investigator or designee during the preceding on-site visit, so these can be completed at home as outlined in the schedule of assessments in Appendix F.

Section 5.3.1.1 Study Procedures
Subsection Patient Reported Outcomes (PRO) Questionnaires
Second paragraph, third sentence previously read:

It comprises 23 items divided in four functioning scales (body image, sexual functioning, sexual satisfaction, and future perspective) and four symptom scales (side effects of systemic therapy, breast symptoms, arm symptoms, and upset by hair loss).

Has been changed to read:

It comprises of 23 items divided in four functioning scales (body image, sexual functioning, sexual satisfaction, and future perspective) and four symptom scales (side effects of systemic therapy, breast symptoms, arm symptoms, and upset by hair loss).

Section 5.3.1.1 Study Procedures
Subsection Patient Reported Outcomes (PRO) Questionnaires
Add: new last paragraph

Due to the COVID-19 pandemic and any local restrictions, sites may administer PRO questionnaires over the phone as needed. Sites may read the PRO questions and response options to the subject and record the subject's responses. Sites may send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with who collected the information.

Section 5.3.1.1 Study Procedures
Subsection <u>Dispensing Study Drug</u>
Add: new third and fourth paragraph

Depending on local regulations due to the COVID-19 pandemic, provision of study drug for direct-to-patient (DTP) and direct-from patient (DFP) transfer will be available upon request. AbbVie has contracted with third party vendors for sites to ship study drug DTP and DFP. Sites will be able to use the third party vendor and/or another local courier for drug shipment, as needed. If necessary, notify AbbVie if DTP and/or DFP shipping will be used.

Sites will be responsible to:

- Meet IRB/IEC reporting requirements and submit the booking form (which will be provided to site by the courier) to the local IRB/IEC, as applicable.
- Submit the booking form at least 72 business hours before the drug needs to be picked up, or as per the requirements of the courier.
- Discuss the DTP and DFP process with the subject including:
  - Obtain consent to provide delivery information to the courier and document this in the source.
  - Obtain results of required safety procedures before registering subject dispensation of study drug in IRT.
  - Confirm the subject will be available to accept delivery.
  - Confirm the subject will maintain the drug containers, as well as any unused drug for return to site.
- Follow up with the subject after shipment is received.
- Retain documentation of the shipment for IP accountability and monitoring.

Section 5.3.1.1 Study Procedures
Subsection Dispensing Study Drug
Heading "Blinded Study Treatment"
Add: new fourth and fifth paragraph

On Day 1, subjects on blinded single-agent veliparib/placebo will be given study drug for dosing through Day 21.

For subjects who are eligible to alternate on-site visits and phone visits every other cycle, during the on-site visits, the investigator or designee should dispense blinded study drug via IRT and subject dosing cards for 2 consecutive cycles, as outlined in the schedule of assessments in Appendix F.

Section 5.3.1.1 Study Procedures
Subsection Dispensing Study Drug
Heading "Unblinded Study Treatment"
Add: new last paragraph

For subjects who are eligible to alternate on-site visits and phone visits every other cycle, during the on-site visits, the investigator or designee should dispense unblinded study drug via IRT and subject dosing cards for 2 consecutive cycles, as outlined in the schedule of assessments in Appendix F.

Section 5.3.1.1 Study Procedures
Subsection Post-Progression/Survival Follow-Up Information
First paragraph previously read:

Once a subject meets study discontinuation criteria, subjects will continue to be followed during the Post Treatment Follow-Up Phase for survival (i.e., the date and cause of death) and post-therapy information, including date of progression to the first post-study therapy. These data will be collected on the appropriate eCRF at 2 month intervals (or as requested by Sponsor to support data analysis), beginning on the date the subject is registered off study until the endpoint of death, the subject has become lost-to follow-up, or AbbVie terminates the study.

Has been changed to read:

Once a subject meets study treatment discontinuation criteria, subjects will continue to be followed during the Post Treatment Follow-Up Phase for survival (i.e., the date and cause of death) and post-therapy information, including date of progression to the first post-study therapy. These data will be collected on the appropriate eCRF at 2 month intervals (or as requested by Sponsor to support data analysis), beginning on the date the subject discontinued from study therapy until the endpoint of death, the subject has become lost-to follow-up, or AbbVie terminates the study.

Section 5.3.1.1 Study Procedures
Subsection Post-Progression/Survival Follow-Up Information
Add: new fourth paragraph

Subjects who have discontinued study treatment due to unmanageable toxicity or reasons other than progression will remain on study, off drug and continue to be followed for survival and post-treatment therapy information at 2 months intervals (or as requested by Sponsor to support data analysis) as outlined in the schedule of assessments in Appendix E.

Section 5.3.3 Efficacy Variables
Second and third sentence previously read:

The secondary efficacy endpoints will be OS, CBR, ORR, PFS2 and DOR. The tertiary endpoints will include change in ECOG performance status, change in QoL indices.

Has been changed to read:

The secondary efficacy endpoints will be OS, CBR, ORR, and PFS2. The tertiary endpoints will include DOR, change in ECOG performance status, and change in QoL indices.

Section 5.3.5 Safety Variables
Third paragraph previously read:

During the conduct of the study, an IDMC will review unblinded safety data.

Has been changed to read:

An IDMC reviewed unblinded safety data intermittently prior to the primary analysis. No additional reviews by the IDMC will occur since the Sponsor management team was unblinded after completing the primary analysis.

Section 5.4.1 Discontinuation of Individual Subjects
First paragraph, first sentence previously read:

Subjects will receive therapy until disease progression according to Section 5.3.4, RECIST 1.1, unmanageable toxicity (per discussion with appropriate Blinded or Unblinded AbbVie TA MD), or they meet the study treatment discontinuation criteria as outlined below.

Has been changed to read:

Subjects will receive therapy until disease progression according to Section 5.3.4, RECIST 1.1, unmanageable toxicity (per discussion with the AbbVie TA MD), or they meet the study treatment discontinuation criteria as outlined below.

Section 5.4.1 Discontinuation of Individual Subjects
Add: new fourth paragraph

In cases of state of emergency or pandemic situations, if subjects withdraw consent from study treatment, they should be considered as on study, off drug and follow the schedule of assessments per Appendix E, if the subject consents to continued follow up.

Section 5.4.1 Discontinuation of Individual Subjects
Fourth paragraph, first and second sentence previously read:

When a subject discontinues either the blinded or unblinded portion of the study, a Final Visit will be conducted. During a Final Visit, the reasons for the discontinuation from the study treatment will be recorded and a physical examination, vital signs measurement, laboratory analyses, performance status, ECG (if not performed within the last 4 weeks),

QoL assessment, tumor assessment (if not performed within the last 4 weeks), collection of unused study drug, and an assessment of adverse events will be performed.

Has been changed to read:

When a subject discontinues either the blinded or unblinded study treatment, a Final Visit will be conducted. During a Final Visit, the reasons for the discontinuation from the study treatment will be recorded and a physical examination, vital signs measurement, laboratory analyses, performance status, ECG (if not performed within the last 4 weeks), QoL assessment, collection of unused study drug, and an assessment of adverse events will be performed.

Section 5.4.1 Discontinuation of Individual Subjects
Sixth paragraph previously read:

When a subject discontinuation is planned without the subject reaching a protocol-defined endpoint, the investigator will notify the appropriate Blinded or Unblinded AbbVie TA MD or the clinical team representative (Section 6.1.6) via telephone, as soon as possible (provided, in each case, subject care and safety are not compromised). If not notified prior to discontinuation, the Blinded or Unblinded AbbVie TA MD may contact the site to discuss the reason for withdrawal from the study.

Has been changed to read:

When a subject discontinuation is planned without the subject reaching a protocol-defined endpoint, the investigator will notify the AbbVie TA MD or the clinical team representative (Section 6.1.6) via telephone, as soon as possible (provided, in each case, subject care and safety are not compromised). If not notified prior to discontinuation, the AbbVie TA MD may contact the site to discuss the reason for withdrawal from the study.

Section 5.4.1.1 Discontinuation of Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel)
First paragraph, fourth sentence previously read:

Discontinuation of carboplatin and paclitaxel in the absence of toxicity requiring dose modification should be discussed with the Blinded AbbVie TA MD.

Has been changed to read:

Discontinuation of carboplatin and paclitaxel in the absence of toxicity requiring dose modification should be discussed with the AbbVie TA MD.

Section 5.4.2 Discontinuation of Entire Study
First paragraph
Add: new last sentence

If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

Section 5.5.1 Treatments Administered
Subsection <u>Paclitaxel</u>
Add: new last paragraph

If needed per dose modifications guidelines, it is recommended that growth factors (i.e., filgrastim, peg-filgrastim) dosed according to institutional standard will be administered daily subcutaneously starting 24 – 72 hours after the last dose of carboplatin/paclitaxel or after last dose of weekly paclitaxel. Pegfilgrastim should not be used for subjects receiving Day 15 paclitaxel as they do not have a 2-week chemotherapy-free interval.

Section 5.5.1 Treatments Administered
Subsection <u>Carboplatin</u>
Add: new last paragraph

If needed per dose modifications guidelines, it is recommended that growth factors (i.e., filgrastim, peg-filgrastim) dosed according to institutional standard will be administered

daily subcutaneously starting 24 – 72 hours after the last dose of carboplatin/paclitaxel or after last dose of weekly paclitaxel.

Section 5.5.5 Blinding
Last sentence previously read:

Following progression of disease, a separate unblinded study team will be responsible for study conduct and data monitoring for subjects who crossover to veliparib monotherapy.

Has been changed to read:

Following progression of disease, a separate unblinded study team was responsible for study conduct and data monitoring for subjects who crossed over to veliparib monotherapy.

After completion of the primary analysis the sponsor was unblinded to treatment assignment. A separate unblinded study team is no longer responsible for study conduct and data monitoring for subjects who crossover to veliparib monotherapy. Primary site monitors, investigators and subjects continue to be blinded to treatment assignment until disease progression, after which unblinding to determine eligibility for crossover can be requested.

Section 5.5.5.1 Blinding of Investigational Product
Second sentence previously read:

The Blinded AbbVie TA MD (listed in Section 6.1.6) must be notified before the blind is broken unless identification of the study drug is required for medical emergency, i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject's conditions (e.g., antidote is available).

Has been changed to read:

The AbbVie TA MD (listed in Section 6.1.6) must be notified before the blind is broken unless identification of the study drug is required for medical emergency, i.e., situation in

which the knowledge of the specific blinded treatment will affect the immediate management of the subject's conditions (e.g., antidote is available).

Section 5.5.6 Treatment Compliance
Fifth paragraph, first sentence previously read:

The study coordinator will document compliance on the appropriate eCRF.

Has been changed to read:

The study coordinator will document subject study drug administration details on the appropriate eCRF.

Section 5.7 Dose Reductions or Delays
Third paragraph previously read:

The Blinded AbbVie TA MD is to be contacted for subjects who require cycle delays of > 28 days due to toxicity.

Has been changed to read:

The AbbVie TA MD is to be contacted for subjects who require cycle delays of > 28 days due to toxicity.

Section 5.7 Dose Reductions or Delays
Last paragraph previously read:

In the case of delays, interruptions or study treatment discontinuation, tumor assessments should continue at intervals of 9 weeks from C1D-2.

Has been changed to read:

In the case of delays, interruptions or study treatment discontinuation, tumor assessments should have continued at intervals of 9 weeks from C1D-2. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks (or not to exceed 24 weeks for subjects with durable disease control, at investigator discretion) from last scan.

Due to the COVID-19 pandemic, temporary study drug interruption may occur. The AbbVie TA MD is to be contacted for subjects who require cycle interruptions of > 28 days.

Section 5.7.1.1 Carboplatin + Paclitaxel Dose Reduction and Delays
Second paragraph previously read:

On Day 1 of each cycle, ANC must be ≥ 1,500/mm^3 and platelet count must be ≥ 100,000/mm^3. If the counts are lower than the limit, treatment should be delayed until recovery to the required ANC and platelet count.

Has been changed to read:

It is recommended that treatment on Day 1 of each cycle proceeds only if ANC is ≥ 1500 cells/mm^3 and the platelet count is ≥ 100,000/mm^3. Recommended dose modifications/delays based on hematologic toxicities on Day 1 are outlined in Table 8. For subjects with an ANC of 1000 – 1499/mm^3 or platelet count 75,000 – 99,999/mm^3 on Day 1, dosing may continue without modification or delay until recovery, at investigator discretion, if drug-related toxicity has been ruled out. If ANC is below 1000/mm^3 or the platelet count is below 75,000/mm^3, treatment should be delayed until recovery.

Table 9. Blinded Study Treatment (Veliparib/Placebo + Carboplatin + Paclitaxel) Dose Reduction and Delays for Hematologic Toxicities on Day 8 or 15
Table note "Note:," last sentence previously read:

Pegfilgrastim should not be used for patients receiving Day 15 paclitaxel as they do not have a 2-week chemotherapy-free interval.

Has been changed to read:

Pegfilgrastim should not be used for subjects receiving Day 15 paclitaxel as they do not have a 2-week chemotherapy-free interval.

Section 5.7.1.2 Veliparib or Placebo Dose Reductions and Delays in Combination with Carboplatin + Paclitaxel
Item 3, last sentence previously read:

The treatment plan for subjects who experience a robust and durable response (such as a confirmed CR following 10 or more cycles of therapy) and for whom the investigator considers the potential risks of continued cytotoxic chemotherapy outweigh the benefits should be discussed with the Blinded AbbVie TA MD prior to initiating single-agent blinded veliparib/placebo.

Has been changed to read:

The treatment plan for subjects who experience a robust and durable response (such as a confirmed CR following 10 or more cycles of therapy) and for whom the investigator considers the potential risks of continued cytotoxic chemotherapy outweigh the benefits should be discussed with the AbbVie TA MD prior to initiating single-agent blinded veliparib/placebo.

Section 5.7.1.2 Veliparib or Placebo Dose Reductions and Delays in Combination with Carboplatin + Paclitaxel
Item 5 previously read:

For any ≥ Grade 2 event of seizure attributed to veliparib/placebo, veliparib/placebo is to be interrupted, brain CT or MRI obtained, and the event should be discussed with the Blinded AbbVie TA MD.

Has been changed to read:

For any ≥ Grade 2 event of seizure attributed to veliparib/placebo, veliparib/placebo is to be interrupted, brain CT or MRI obtained, and the event should be discussed with the AbbVie TA MD.

Section 5.7.1.3 Blinded Veliparib/Placebo and Unblinded Veliparib Monotherapy Dose Reductions and Delays
Frist paragraph, last sentence previously read:

If veliparib/placebo monotherapy is initiated, the starting dose should be 300 mg for 2 weeks followed by an increase to 400 mg, if well tolerated.

Has been changed to read:

If veliparib/placebo monotherapy is initiated, the starting dose should be 300 mg BID for 2 weeks followed by an increase to 400 mg BID, if well tolerated.

Section 5.7.1.3 Blinded Veliparib/Placebo and Unblinded Veliparib Monotherapy Dose Reductions and Delays
Third paragraph previously read:

Subjects should have an Absolute Neutrophil Count (ANC) $\geq 1{,}500/mm^3$ and a platelet count $\geq 100{,}000/mm^3$ prior to initiating the subsequent cycle. For any subject who experiences Grade 3 or 4 toxicity despite optimal supportive care and the toxicity is not attributable to underlying disease, the veliparib/placebo dose will be held until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 is present at the time of study entry.

Has been changed to read:

It is recommended that treatment on Day 1 of each cycle proceeds only if ANC is ≥ 1500 cells/mm^3 and the platelet count is $\geq 100{,}000/mm^3$. Dosing may continue in subjects with ANC and/or platelet counts ranges of ANC of $1000 – 1499/mm^3$ or platelet count $75{,}000 – 99{,}999/mm^3$ without modification at investigator discretion if drug-related toxicity has been ruled out.

For any subject who experiences Grade 3 or 4 toxicity despite optimal supportive care and the toxicity is not attributable to underlying disease, the veliparib/placebo dose will be held until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 is present at the time of study entry.

Section 5.7.1.3 Blinded Veliparib/Placebo and Unblinded Veliparib Monotherapy Dose Reductions and Delays
Sixth paragraph, first bullet, last sub-bullet previously read:

For any > Grade 2 event of seizure attributed to veliparib/placebo, veliparib/placebo is to be interrupted, brain CT or MRI obtained, and the event should be discussed with the appropriate blinded or unblinded AbbVie TA MD.

Has been changed to read:

For any > Grade 2 event of seizure attributed to veliparib/placebo, veliparib/placebo is to be interrupted, brain CT or MRI obtained, and the event should be discussed with the AbbVie TA MD.

Section 5.7.1.3 Blinded Veliparib/Placebo and Unblinded Veliparib Monotherapy Dose Reductions and Delays
Last paragraph, last sentence previously read:

This should be discussed with the appropriate blinded or unblinded AbbVie TA MD.

Has been changed to read:

This should be discussed with the appropriate AbbVie TA MD.

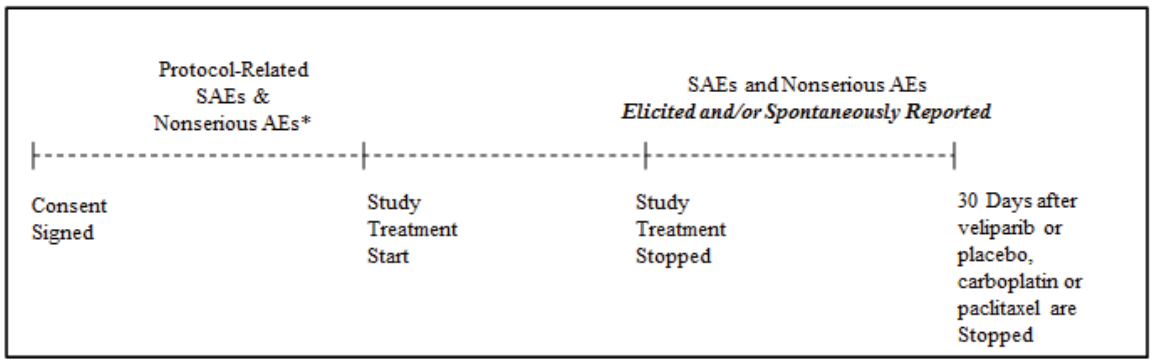
Section 5.7.1.4 Allergic Reaction/Hypersensitivity
Subsection <u>Carboplatin:</u>
Last sentence previously read:

This should be discussed with the Blinded AbbVie TA MD.

Has been changed to read:

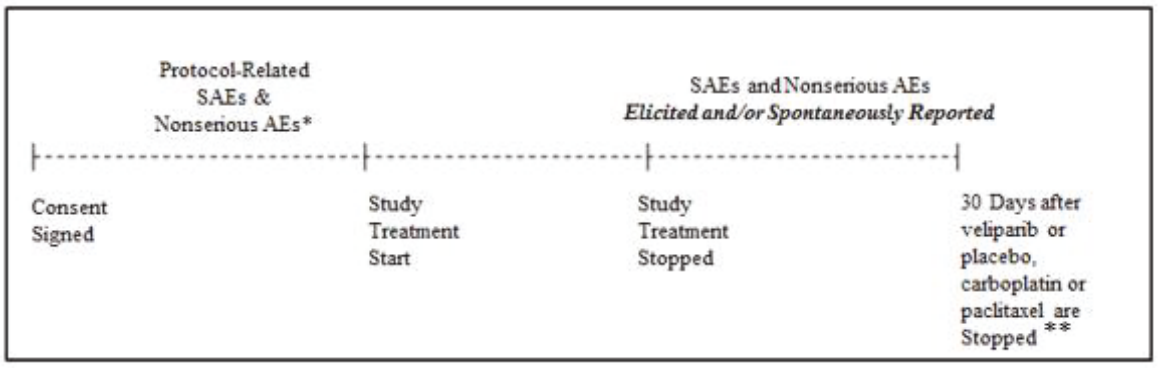
This should be discussed with the AbbVie TA MD.

Figure 2. Adverse Event Collection
Previously read:



* Only if considered by the Investigator to be causally related to study-required procedures.

Has been changed to read:



* Only if considered by the Investigator to be causally related to study-required procedures.

** Adverse events of myelodysplastic syndrome, acute myeloid leukemia or any second primary malignancy should be reported throughout the entire duration of follow-up phase even if the onset is > 30 days following discontinuation of study treatment.

Section 6.1.6 Adverse Event Reporting
First paragraph, last sentence previously read:

Serious adverse events that occur prior to the site having access to the Rave (EDC) system should be faxed to AbbVie Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Has been changed to read:

Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be faxed to AbbVie Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Section 6.1.6 Adverse Event Reporting
Second, third, fourth, and fifth paragraph previously read:

For safety reporting related questions or concerns for the blinded study treatment arm, contact the Oncology Safety Team at:

Oncology Group Safety Desk
AbbVie
Dept. R48S, Bldg. AP30
1 North Waukegan Road
North Chicago, IL 60064

Office: + 1 847 935-2609
Fax: + 1 847 785-8224
Email: SafetyManagement_Oncology@abbvie.com

For safety reporting related questions or concerns for the unblinded veliparib monotherapy (crossover) treatment arm, contact the Oncology Safety Team at:

Email: M12-914_Unblinded_Team@abbvie.com

For any emergent safety concerns for the blinded study treatment arm, please contact the Blinded AbbVie TA MD.

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Mobile:
Fax:
Email: [redacted]

For any emergent safety concerns for the unblinded veliparib monotherapy (crossover) treatment arm, please contact the Unblinded AbbVie TA MD.

[redacted]
AbbVie
Foundation Neuroscience Center
200 Sidney Street
Cambridge, MA 02139

Office:
Mobile:
Email: [redacted]

Has been changed to read:

For safety reporting related questions or concerns, contact the Oncology Safety Team at:

AbbVie Oncology Safety Team
Bldg. AP51
1 North Waukegan Road
North Chicago, IL 60064
Office: + 1 847 935-2609
Email: SafetyManagement_Oncology@abbvie.com

For any emergent safety concerns for the blinded study treatment arm or unblinded veliparib monotherapy (crossover) treatment arm, please contact the AbbVie TA MD.

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Office:
Cell:
Email: [redacted]

Section 6.1.6 Adverse Event Reporting
Last paragraph, first sentence previously read:

In the EU, the Sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

Has been changed to read:

In the EU, AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

Section 6.1.6 Adverse Event Reporting
Add: new eighth and ninth paragraph

Due to the COVID-19 pandemic and evolving local regulations, urgent safety measures may need to be employed in order to protect participating subjects from any immediate hazard. Such events and measures should be reported to the sponsor emergency medical contact listed above immediately.

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. If a subject has a confirmed or suspected COVID-19 infection, the investigator should contact the AbbVie TA MD before reintroducing study drug.

Section 7.0 Protocol Deviations
Contact Information previously read:

Blinded Team
Primary Contact:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Cell:
Email:

Blinded Team
Alternate Contact:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Mobile:
Fax:
Email:

Unblinded Team
Primary Contact:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office [redacted]
Cell:
Email: M12-914_UNBLINDED_TEAM@abbvie.com

Unblinded Team
Alternate Contact:

[redacted]
AbbVie
Foundational Neuroscience Center
200 Sidney Street
Cambridge MA 02139

Office: [redacted]
Cell:
Email: M12-914_UNBLINDED_TEAM@abbvie.com

Has been changed to read:

Primary Contact:

[redacted]
AbbVie
Ing. E. Butty 240 [redacted]
C1001AFB, Buenos Aires, Argentina
Cell:
Email: [redacted]

Alternate Contact:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Office:
Cell:
Email: [redacted]

Alternate Contact:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Phone:
Fax:
Mobile: [redacted]

Section 8.1.2.2 Secondary Efficacy Endpoints
First paragraph previously read:

Secondary efficacy analyses comparing the effects of veliparib 120 mg BID + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel on the following set of endpoints will be performed: overall survival (OS), clinical benefit rate (CBR) through the end of Week 24, objective response rate (ORR), duration of response (DOR), and progression-free survival on subsequent therapy (PFS2).

Has been changed to read:

Secondary efficacy analyses comparing the effects of veliparib 120 mg BID + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel on the following set of endpoints will be performed: overall survival (OS), clinical benefit rate (CBR) through the end of Week 24, objective response rate (ORR) and progression-free survival on subsequent therapy (PFS2).

Section 8.1.2.2 Secondary Efficacy Endpoints
Delete: fifth paragraph

Duration of response will be defined as the number of days from the day that the criteria are met for CR or PR, whichever is recorded first, to the date that progressive disease is documented. If a subject's response is ongoing at the analysis cutoff date then the subjects data will be censored at the date of the last disease progression assessment performed prior to the cutoff. Subjects who never experience a confirmed PR or CR will not be included in the analysis.

Section 8.1.2.3 Tertiary Efficacy Endpoints
First paragraph previously read:

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses will be performed comparing the effects of veliparib 120 mg BID + carboplatin + paclitaxel versus placebo + carboplatin + paclitaxel on duration of overall response, quality of life, and performance status.

Has been changed to read:

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses will be performed comparing the effects of veliparib 120 mg BID + carboplatin + paclitaxel versus placebo + carboplatin + paclitaxel on duration of response (DOR), quality of life, and performance status.

Duration of response will be defined as the number of days from the day that the criteria are met for CR or PR, whichever is recorded first, to the date that progressive disease is

documented. If a subject's response is ongoing at the analysis cutoff date then the subjects data will be censored at the date of the last disease progression assessment performed prior to the cutoff. Subjects who never experience a confirmed PR or CR will not be included in the analysis.

Section 8.1.3 Timing of Efficacy Analyses and Safety Evaluations
Third paragraph
Add: new fourth and fifth sentence

Additional OS analyses may be performed before the 'Final OS analysis,' if requested by regulatory agencies or otherwise warranted. For each additional interim analysis of OS, a small amount of alpha (0.00001) will be spent.

Section 8.1.5 Secondary Analyses of Efficacy
Last sentence previously read:

P values for secondary efficacy analyses will be subject to multiple comparison adjustments using the fixed sequence testing method, with analyses performed in the following order: OS, CBR, ORR, PFS2 and DOR.

Has been changed to read:

P values for secondary efficacy analyses will be subject to multiple comparison adjustments using the fixed sequence testing method, with analyses performed in the following order: OS, CBR, ORR, and PFS2.

Section 8.1.5.4 PFS2
Previously read:

The distribution of PFS2 will be estimated for each treatment group using Kaplan-Meier methodology and compared between veliparib 120 mg BD + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel treatment groups using the log-rank test, stratified by ER and/or PgR positive versus ER/PgR negative and prior platinum therapy (yes versus no).

Has been changed to read:

The distribution of PFS2 will be estimated for each treatment group using Kaplan-Meier methodology and compared between veliparib 120 mg BID + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel treatment groups using the log-rank test, stratified by ER and/or PgR positive versus ER/PgR negative and prior platinum therapy (yes versus no).

Section 8.1.6 Tertiary Analyses of Efficacy
Add: new section title

8.1.6 Tertiary Analyses of Efficacy

Section 8.1.6 Tertiary Analyses of Efficacy
Delete: section title

8.1.6 Tertiary Analyses of Efficacy

Section 8.1.8 Interim Analysis
First and second paragraph previously read:

An independent data monitoring committee (IDMC) will review the unblinded safety data for this veliparib Phase 3 study (which will include all subjects enrolled in the study) when approximately 60 subjects have met at least one of the following criteria:

- Received 6 cycles of treatment
- Reached an event of disease progression
- Discontinued the study due to toxicity/adverse events

BRCA status discordances between Sponsor core laboratory and local labs will also be assessed internally at the time of the interim analysis. Subsequent reviews will be based on recommendations from the IDMC.

Has been changed to read:

An independent data monitoring committee (IDMC) reviewed the unblinded safety data for this veliparib Phase 3 study (including all subjects enrolled in the study) when approximately 60 subjects met at least one of the following criteria:

- Received 6 cycles of treatment
- Reached an event of disease progression
- Discontinued the study due to toxicity/adverse events

BRCA status discordances between Sponsor core laboratory and local labs were assessed internally at the time of the interim analysis. Subsequent IDMC reviews of unblinded safety data prior to the primary analysis were carried out based on IDMC recommendations. No additional reviews by the IDMC will occur since the Sponsor management team was unblinded after completing the primary analysis.

Section 8.1.10.8 Multiplicity Adjustments
First paragraph previously read:

If the veliparib treatment group demonstrates statistically significantly better PFS than the placebo group, then the secondary endpoints will be tested using the fixed sequence testing procedure with the following testing order: OS, CBR, ORR, DOR, and PFS2.

Has been changed to read:

If the veliparib treatment group demonstrates statistically significantly better PFS than the placebo group, then the secondary endpoints will be tested using the fixed sequence testing procedure with the following testing order: OS, CBR, ORR, and PFS2.

Section 9.2 Ethical Conduct of the Study
Add: new last paragraph

In the event that the COVID-19 pandemic leads to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of

the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

Section 9.3 Subject Information and Consent
Add: new last paragraph

Due to the COVID-19 pandemic, modifications to the protocol may be necessary. Subjects should be informed of the changes to the conduct of the study relevant to their participation (e.g., cancellation of visits, change in laboratory testing site, drug delivery method, etc.). Documentation of this notification and verbal consent should be maintained at the site. A signed and dated informed consent form should be obtained from the subject afterwards as soon as possible, if required by local regulations.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Global Drug Supply
		Statistics
		Clinical
		Clinical
		Bioanalysis
		Statistics
		Pharmacokinetics

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical
		Clinical
		Clinical
		Pharmacokinetics

Appendix C. Study Activities for Blinded Study Treatment (Veliparib/Placebo + Paclitaxel + Carboplatin)
Header row, column "Day 1 of Subsequent Cycles" previously read:

Day 1 of Subsequent Cycles

Has been changed to read:

Day 1 of Subsequent Cycles[t]

Appendix C. Study Activities for Blinded Study Treatment (Veliparib/Placebo + Paclitaxel + Carboplatin)
Header row, column "Every 9 Weeks from C1D 2" previously read:

Every 9 Weeks from C1D 2

Has been changed to read:

Every 12 Weeks[l]

Appendix C. Study Activities for Blinded Study Treatment (Veliparib/Placebo + Paclitaxel + Carboplatin)
Activity "AE Assessment" previously read:

Activity	Screening	C1D-2	C1D1	C1D8[a]	C1D15[a]	Day 1 of Subsequent Cycles	Days 8 and 15 of Subsequent Cycles[a]	Every 9 Weeks from C1D 2
AE Assessment		X	X	X	X	X	X	X

Has been changed to read:

Activity	Screening	C1D-2	C1D1	C1D8[a]	C1D15[a]	Day 1 of Subsequent Cycles[t]	Days 8 and 15 of Subsequent Cycles[a]	Every 12 Weeks
AE Assessment		X	X	X	X	X	X	

Appendix C. Study Activities for Blinded Study Treatment (Veliparib/Placebo + Paclitaxel + Carboplatin)
Delete: Activity "Survival"

Activity	Screening	C1D-2	C1D1	C1D8[a]	C1D15[a]	Day 1 of Subsequent Cycles	Days 8 and 15 of Subsequent Cycles[a]	Every 9 Weeks from C1D 2
Survival								

Appendix C. Study Activities for Blinded Study Treatment (Veliparib/Placebo + Paclitaxel + Carboplatin)
Table note "h.," "j.," "l.," and "Note:" previously read:

h. For Day 1 visits, study samples for central laboratory analysis may be performed within 72 hours prior to dosing. For Day 8 and Day 15 visits, study samples for central laboratory analysis may be performed within 24 hours of the scheduled day. There is no visit window for C1D-2 as any sample prior to randomization is still considered to be screening. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions but this cannot replace the central laboratory analysis on a protocol defined visit.

j. For patients on prophylactic or therapeutic anticoagulation with warfarin, INR should be monitored before each treatment. Treatment should be held for INR of > 1.5 × ULN on prophylactic warfarin or > therapeutic range if on full dose warfarin.

l. Tumor assessments to support evidence of PD for PFS and/or PFS2 endpoints will be conducted every 9 weeks until PD, death or withdrawal of consent for follow-up until PD. (tumor assessments may be conducted 5 days prior or 5 days following the scheduled assessment from C1D-2).

Note: Study procedures (excluding labs and tumor assessments) may be performed four (4) days prior to the scheduled study visit date. C1D1 procedures may be performed within 24 hours surrounding the scheduled study visit.

Has been changed to read:

h. For Day 1 visits, study samples for central laboratory analysis may be performed within 72 hours prior to dosing. For Day 8 and Day 15 visits, study samples for central laboratory analysis may be performed within 24 hours of the scheduled day. There is no visit window for C1D-2 as any sample prior to randomization is still considered to be screening. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions but this cannot replace the central laboratory analysis on a protocol defined visit, unless AbbVie removes the requirements for sites to send clinical laboratory samples to the central laboratory or under special situations (i.e., pandemic) that are approved by the Sponsor and allowed as per local regulation.

j. For subjects on prophylactic or therapeutic anticoagulation with warfarin, INR should be monitored before each treatment. Treatment should be held for INR of > 1.5 × ULN on prophylactic warfarin or > therapeutic range if on full dose warfarin.

l. Tumor assessments to support evidence of PD for PFS endpoint were conducted every 9 weeks until PD, death or withdrawal of consent for follow-up until PD. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks (tumor assessments may be conducted ± 10 business days following the scheduled assessment from last scan). At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control but must not exceed 24 weeks.

Note: Study procedures (excluding labs and tumor assessments) may be performed four (4) business days prior to the scheduled study visit date. C1D1 procedures may be performed within 24 hours surrounding the scheduled study visit.

Appendix C. Study Activities for Blinded Study Treatment (Veliparib/Placebo + Paclitaxel + Carboplatin)
Add: new table note "t."

For subjects who have been receiving single-agent veliparib/placebo at a stable dose without adjustments for multiple cycles and who have no ongoing study drug related uncontrolled AEs, it is possible to alternate on-site visits and phone visits every other cycle. Study procedures for phone visits are detailed in the Appendix F.

Appendix D. Study Activities for Unblinded Veliparib Monotherapy (Crossover Treatment)
Previously read:

Activity	C1D1	C1D15[g]	Day 1 of Each Cycle Starting with C2	Every 9 Weeks from C1D1
Physical Exam (including weight)	X	X	X	
12-lead ECG	X[f]			
Vital Signs	X	X	X	
Pregnancy Test (women of childbearing potential)[h]				
Hematology/Chemistry[a,b]	X	X	X	
Urinalysis	X			
Tumor Assessment[c]	X[d]			X
Performance Status (ECOG)	X		X	
QLQ C30, BR23, EQ 5D 5L Questionnaires	X		X[e]	
BPI-SF Questionnaire	X		X	
AE Assessment	X	X	X	X
Dispense veliparib	X		X	

a. Refer to Table 4 for detailed list of tests to be performed and frequency.

b. Study samples for central laboratory analysis may be performed within 72 hours of the scheduled day. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions but this cannot replace the central laboratory analysis on a protocol defined visit.

c. Tumor assessments will be conducted every 9 weeks (tumor assessments may be conducted 5 days prior or 5 days following the scheduled assessment from C1D1).

d. To be performed if a tumor assessment has not been performed within 4 weeks.

e. QLQ C30, BR23, EQ 5D 5L questionnaires will be administered every other cycle prior to dosing beginning with Cycle 2 (C2, C4, C6 etc.).

f. ECG must be obtained 1 hour after dosing with veliparib.

g. If the subject tolerates 300 mg BID for 2 weeks veliparib may be increased to 400 mg BID at the investigator's discretion.

h. Pregnancy tests may be repeated during the study according country requirements.

Notes: The unblinded verliparib monotherapy schedule of assessments should be followed for subjects who were previously randomized to placebo and who discontinue study treatment because of disease progression.

Study procedures (excluding labs and tumor assessments) may be performed four (4) days prior to the scheduled study visit date. C1D1 procedures may be performed within 24 hours surrounding the scheduled study visit.

Has been changed to read:

Note: The following schedule of assessments should be followed for subjects who crossed over (were previously randomized to placebo, discontinued study treatment because of disease progression and received Sponsor approval for crossover treatment).

Activity	C1D1	C1D15[g]	Day 1 of Each Cycle Starting with C2[i]	Every 9 Weeks from C1D1[c]
Physical Exam (including weight)	X	X	X	
12-lead ECG	X[f]			
Vital Signs	X	X	X	
Pregnancy Test (women of childbearing potential)[h]				
Hematology/Chemistry[a,b]	X	X	X	
Urinalysis[a]	X			
Tumor Assessment[c]	X[d]			X
Performance Status (ECOG)	X		X	
QLQ C30, BR23, EQ 5D 5L Questionnaires	X		X[e]	
BPI-SF Questionnaire	X		X	
AE Assessment	X	X	X	
Dispense veliparib	X		X	

a. Refer to Table 4 for detailed list of tests to be performed and frequency.

b. Study samples for central laboratory analysis may be performed within 72 hours of the scheduled day. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions but this cannot replace the central laboratory analysis on a protocol defined visit, unless AbbVie removes the requirements for sites to send clinical laboratory samples to the central laboratory or under special situations (i.e., pandemic) that are approved by the Sponsor and allowed as per local regulation.

c. Tumor assessments will be conducted every 9 weeks (± 5 business days from the scheduled C1D1 assessment. Following the primary analysis and implementation of Protocol Amendment 4, if a crossover subject has disease control after 6 scans while following the 9 week scan interval schedule, the tumor assessment frequency can be changed to every 12 weeks from last scan (± 10 business days). At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control but must not exceed 24 weeks.

d. To be performed if a tumor assessment has not been performed within 4 weeks.

e. QLQ C30, BR23, EQ 5D 5L questionnaires will be administered every other cycle prior to dosing beginning with Cycle 2 (C2, C4, C6 etc.).

f. ECG must be obtained 1 hour after dosing with veliparib.

g. If the subject tolerates 300 mg BID for 2 weeks veliparib may be increased to 400 mg BID at the investigator's discretion.

h. Pregnancy tests may be repeated during the study according country requirements.

i. For subjects who have been receiving veliparib monotherapy at a stable dose without adjustments for multiple cycles and who have no ongoing study drug related uncontrolled AEs, it is possible to alternate on-site visits and phone visits every other cycle. Study procedures for phone visits are detailed in the Appendix F.

Notes: Study procedures (excluding labs and tumor assessments) may be performed four (4) business days prior to the scheduled study visit date. C1D1 procedures may be performed within 24 hours surrounding the scheduled study visit.

Appendix E. Study Procedures for Post Treatment Phase
Appendix title and text previously read:

Appendix E. Study Procedures for Post Treatment Phase

Procedure	Discontinuation of Therapy Without Disease Progression		Discontinuation of Therapy due to Disease Progression		
	3 Weeks Post Study Treatment Discontinuation	Every 9 Weeks from C1D-2 Until Disease Progression	Final Visit[a]	30-Day Follow-Up Visit[b]	Post Treatment Follow-Up
Physical Exam (including weight)	X	X	X	X	
12-lead ECG			X		
Vital Signs	X	X	X	X	
Hematology/Chemistry[d]	X[d]	X[d]	X	X	
Urinalysis[d]			X		
Tumor Assessment[e]		X	X[f]		
Full Body Bone Scan[g]					
Performance Status (ECOG)	X	X	X	X	
QLQ C30, BR23, EQ 5D 5L Questionnaires[h]	X	X	X	X	
BPI-SF Questionnaire[i]	X	X	X	X	
AE Assessment[j]	X	X	X	X	
Survival[c]					X

a. When a subject discontinues the blinded or unblinded portion of the study, a Final Visit will be conducted.

b. All subjects will have one Follow-up Visit approximately 30 days after they have met study discontinuation criteria. This Follow-up Visit does not need to be performed for subjects who have had a Final Visit conducted ≥ 30 days after the last dose of study drug or for subjects who are entering unblinded veliparib monotherapy treatment. Follow-up visits should not precede a Final Visit.

c. If a subject meets criteria for study discontinuation, survival and post treatment therapy will be collected every two months (unless requested by sponsor more frequently to support data analysis) beginning on the date the subject is registered off study. All randomized subjects should be followed for disease progression (PFS) and for the second progression (PFS2), until the endpoint of death (OS), until the subject has become lost to follow-up, or until study termination by AbbVie.

d. Refer to Table 4 for detailed list of tests to be performed and frequency. Laboratory assessments will only be completed for AE follow-up or reported SAEs.

e. Tumor assessments to support evidence of PD for PFS and/or PFS2 endpoints will be conducted every 9 weeks until PD, death or withdrawal of consent for follow-up until PD (tumor assessments may be conducted 5 days prior or 5 days following the scheduled assessment from C1D-2).

f. To be performed at the Final Visit, only if not performed within the last 4 weeks. A 2-week window for obtaining the final visit scan is acceptable for maintaining at least a 6-week interval between scans as per local guidance and regulations.

g. Full body bone scans to be obtained as clinically indicated.

h. QLQ C30, BR23, EQ 5D 5L questionnaires will be administered every 6 weeks in clinic or by telephone.

i. BPI-SF questionnaires will be administered every 3 weeks in clinic or by telephone.

j. AE assessments will be performed until 30 days following study treatment discontinuation and for SAEs per Section 6.1.5.

Note: Study procedures (excluding labs and tumor assessments) may be performed four (4) days prior to the scheduled study visit date.

Has been changed to read:

Appendix E. Study Activities for Post Treatment Phase

Activity	Discontinuation of Therapy Without Disease Progression			Discontinuation of therapy without disease progression (on study, off drug)[a,b,d]
	Final Visit[a]	30-Day Follow-Up Visit[b]	Post Treatment Follow-Up	Every 12 weeks from last scan[e]
Physical Exam (including weight)[d]	X	X		
12-lead ECG	X			
Vital Signs[d]	X	X		
Hematology/Chemistry[d]	X	X		
Urinalysis[d]	X			
Tumor Assessment				X[e]
Performance Status (ECOG)	X	X		
QLQ C30, BR23, EQ 5D 5L Questionnaires	X	X		
AE Assessment[d]	X	X		
Survival[c]			X	X

a. When a subject discontinues the blinded or unblinded study treatment, a Final Visit will be conducted.

b. All subjects will have one Follow-up Visit approximately 30 days after the last dose of study drug. This Follow-up Visit does not need to be performed for subjects who have had a Final Visit conducted ≥ 30 days after the last dose of study drug or for subjects who are entering unblinded veliparib monotherapy treatment. Follow-up visits should not precede a Final Visit.

c. If a subject meets criteria for discontinuation of therapy, survival and post treatment therapy will be collected every two months (unless requested by sponsor more frequently to support data analysis) beginning on the date the subject discontinues therapy. All randomized subjects should be followed for disease progression (PFS) and for the second progression (PFS2), until the endpoint of death (OS), until the subject has become lost to follow-up, or until study termination by AbbVie.

d. Refer to Table 4 for detailed list of tests to be performed and frequency. Laboratory assessments, physical examinations and vital signs will only be completed for AE follow-up or reported SAEs after the 30-day follow-up visit per Section 6.1.5.

e. Tumor assessments to support evidence of PD for PFS endpoint were conducted every 9 weeks until PD, death or withdrawal of consent for follow-up until PD. Following the primary analysis and implementation of Protocol Amendment 4, the tumor assessment interval may be increased to every 12 weeks (tumor assessments may be conducted ± 10 business days following the scheduled assessment from last scan). At the investigator's discretion, the interval between scans may be longer than every 12 weeks for subjects who have durable disease control, but must not exceed 24 weeks.

Note: Study procedures (excluding labs and tumor assessments) may be performed four (4) business days prior to the scheduled study visit date.

Appendix F. Study Activities for Blinded or Unblinded Study Treatment Phone Visit
Add: new appendix title and text

Appendix F. Study Activities for Blinded or Unblinded Study Treatment Phone Visit

Activity	Day 1 Phone Visit[a]
Performance Status (ECOG)	X
QLQ C30, BR23, EQ 5D 5L Questionnaires[b]	X[c]
BPI-SF Questionnaire[b]	X
AE and Concomitant Medication Assessment	X[d]
Treatment Compliance Assessment	X[d]
Disease Progression Assessment	X[d]
Dispense Veliparib or Placebo[e]	X

a. For subjects who have been receiving single-agent veliparib/placebo at a stable dose without adjustments for multiple cycles and who have no ongoing study drug related uncontrolled AEs, it is possible to alternate on-site visits and phone visits by the investigator or designee every other cycle. At a minimum, subjects should have an on-site visit every other cycle. If an on-site visit is not possible for 2 consecutive cycles, or if the subject is not on a stable dose or has ongoing study drug related uncontrolled AEs but wishes to alternate on-site and phone visits, the plan for the subject's visits should be discussed with the AbbVie TA MD (see Section 7.0 for contact information).

b. During the on-site visits the Investigator or designee will provide the PRO Questionnaires (QLQ C30, BR23, EQ 5D 5L and BPI-SF) for the next cycle to the subject, so these can be completed at home.

c. QLQ C30, BR23, EQ 5D 5L questionnaires will be administered every other cycle prior to dosing beginning with Cycle 2 (C2, C4, C6, etc.). If questionnaires were completed during an on-site visit, they may not be required at the subsequent phone visit.

d. In addition to assessing AEs and Concomitant Therapies, the investigator or designee should assess treatment compliance and to the extent possible, assess for any clinical evidence of disease progression. If there are concerns about new or worsening AEs or if there is suspicion of disease progression, an unscheduled on-site visit, local labs, and/or tumor assessment should be scheduled.

e. During the on-site visits, the Investigator or designee will dispense medication for 2 cycles via IRT and the double amount of Dosing Cards, so subjects can complete them for both cycles.

Note: Phone visit may be performed four (4) business days prior or after the scheduled study visit date.

Appendix K. General Chemotherapy Guidelines
Last bullet, last sentence previously read:

Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

Has been changed to read:

Subjects are permitted to have chemotherapy doses recalculated for < 10% weight changes.