1.0 Title Page

Clinical Study Protocol M12-895

A Randomized, Phase 2 Study of the Efficacy and Tolerability of Veliparib in Combination with Temozolomide or Veliparib in Combination with Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Subjects with BRCA1 or BRCA2 Mutation and Metastatic Breast Cancer

Incorporating Amendment 1, Administrative Change 1, Amendments 2, Amendment 2.01 for Sweden, Amendment 3 and Amendment 4

AbbVie Investigational Product:	Veliparib (ABT-888)
Date:	07 June 2019
Development Phase:	2
EudraCT:	2011-002913-12
Study Design:	A Randomized Phase 2 Study of the Efficacy and Tolerability of Veliparib in Combination with Temozolomide or Veliparib in Combination with Carboplatin and Paclitaxel versus Placebo plus Carboplatin and Paclitaxel in Subjects with BRCA1 or BRCA2 Mutation and Metastatic Breast Cancer.
Investigators:	Multicenter Trial: Investigator information is on file at AbbVie.
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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

The purpose of this Amendment is to:

- Modify Study Activities schedule (Section 5.3, Efficacy, Pharmacokinetic, Pharmacodynamic, Pharmacogenetic and Safety Assessments/Variables and Table 5).

  Rationale: *Primary analysis of progression-free survival for this study occurred in 2016. One subject remains on study treatment; this subject was randomized to veliparib/placebo plus carboplatin/paclitaxel and has been on study for over 5 years. There are no other subjects currently on study. Because the one subject on study has been tolerating study treatment for over 5 years, the protocol-specified study activities are being modified to a schedule reflecting standard of care safety monitoring and tumor assessments and to remove study activities not pertinent to safety monitoring.*
- Update language on Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting (Section 6.5, Adverse Event Reporting)

  Rationale: *To reflect current procedures.*
- Update AbbVie contacts

  Rationale: *To reflect changes in Sponsor personnel.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M12-895
Name of Study Drug: Veliparib (ABT-888)	**Phase of Development:** Phase 2
Name of Active Ingredient: Not applicable	**Date of Protocol Synopsis:** 07 June 2019
Protocol Title: A Randomized, Phase 2 Study of the Efficacy and Tolerability of Veliparib in Combination with Temozolomide or Veliparib in Combination with Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Subjects with BRCA1 or BRCA2 Mutation and Metastatic Breast Cancer	
Objectives: The primary objective of the study is to assess the progression-free survival (PFS) of oral veliparib in combination with temozolomide (TMZ) or in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with BRCA1 or BRCA2 mutation and locally recurrent or metastatic breast cancer. The secondary objectives of the study are to assess overall survival (OS), clinical benefit rate (CBR), objective response rate (ORR) in those subjects treated with veliparib in combination with TMZ or treated with veliparib plus carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel. Chemotherapy-Induced Peripheral Neuropathy (CIPN) (as assessed by the EORTC QLQ-CIPN20 questionnaire and NCI-CTCAE 4.0 grading for peripheral neuropathy) will be assessed in those subjects treated with veliparib plus carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel. The tertiary objectives are to assess Eastern Cooperative Oncology Group (ECOG) performance status and quality of life (QoL) and to assess exploratory correlative endpoints.	
Investigators: Multicenter	
Study Sites: Approximately 120	
Study Population: Men and women ≥ 18 years of age with locally recurrent breast cancer, not amenable to therapy with curative intent, or metastatic breast cancer and a documented BRCA1 or BRCA2 deleterious germline mutation. If human epidermal growth factor receptor 2 (HER2) positive, the subject must have received and progressed on at least one prior standard HER2-directed therapy or the subject must be ineligible to receive anti-HER2 therapy.	
Number of Subjects to be Enrolled: Approximately 290 (including approximately 4 subjects enrolled under the original protocol)	
Methodology: This is a Phase 2, randomized, partially blinded, multinational, multicenter study to evaluate the efficacy and tolerability of veliparib in combination with TMZ or veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with BRCA1 or BRCA2 deleterious mutation and locally recurrent or metastatic breast cancer who have received no more than two prior lines of deoxyribonucleic acid (DNA) damaging cytotoxic therapy for metastatic disease. Subject randomization will be stratified by estrogen receptor (ER) and/or progesterone receptor (PgR) positive versus ER and PgR negative, prior cytotoxic therapy versus no prior cytotoxic therapy and ECOG 0-1 versus 2. Subjects will be randomized in a 1:1:1 ratio to one of the three treatment arms.	

Methodology (Continued):

For subjects randomized to the veliparib + TMZ treatment arm, study visits will be conducted at Day 1, Day 15, and Day 22 for the first two cycles and then Day 1 of every cycle thereafter. For subjects randomized to the veliparib/placebo + carboplatin + paclitaxel treatment arms, study visits will be conducted at Day 1, Day 3, and Day 17 of Cycle 1 and Day 1 and Day 3 of every cycle thereafter. For subjects on study treatment more than 5 years, Day 1 visit is not required. BRCA mutation status, as defined by the Sponsor core laboratory, will be documented for all patients. For those patients in which a BRCA1 or BRCA2 mutation was defined by an alternative laboratory, the test will be conducted by the Sponsor core laboratory. For patients who provide informed consent, archival tissue and optional paired tissue biopsies (C1D1 and Final Visit) will be obtained for correlative studies.

Subjects will continue dosing until they meet the defined discontinuation criteria. When a subject meets the criteria for study discontinuation, a Final Visit will be conducted. All subjects will have one Follow-up Visit approximately 30 days after the last dose of veliparib + TMZ or veliparib/placebo + carboplatin + paclitaxel.

Survival information (i.e., the date and cause of death, and post treatment information) will be collected at monthly intervals (or as requested by Sponsor to support data analysis), beginning on the date the subject is registered off study and for up to three (3) years until the endpoint of death, until the subject has become lost to follow-up or until study termination by AbbVie. For subjects on study treatment more than 5 years, there will be no post-treatment follow-up.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

Patients must meet the following criteria to be eligible:

1. ≥ 18 years of age.
2. Histologically or cytologically confirmed breast cancer that is either locally recurrent or metastatic. Locally recurrent disease must not be amenable to surgical resection or radiation with curative intent.
3. Must have a documented 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 by a laboratory other than Sponsor core laboratory, subjects may be enrolled but must be re-tested by Sponsor core laboratory for confirmation of BRCA1 or BRCA2 germline mutations.
4. If HER2 positive (HER2 3+ by immunohistochemistry or amplification by fluorescence in situ hybridization [FISH > 2]), subjects must have received and progressed on at least one prior standard HER2-directed therapy or the subject must be ineligible to receive anti-HER2 therapy.

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 C1D1) with at least one lesion outside previously irradiated areas.
6. ECOG Performance status of 0 to 2.
7. Adequate hematologic, renal, and hepatic function as follows:
   - 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); Leukocytes $> 3,000/mm^3$;
   - Renal Function: Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN) range **OR** creatinine clearance ≥ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal;
   - Hepatic Function: Aspartate aminotransferase (AST) and/or alanine transaminase (ALT) $\leq 2.5 \times$ institutional upper limit of normal. For subjects with liver metastases, AST and/or ALT $< 5 \times$ ULN range; bilirubin $\leq 1.5 \times$ the 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.
8. 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 90 days following completion of therapy. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to initiation. To be considered of non-child bearing potential, postmenopausal women must be amenorrheic for at least 12 months or subjects must be surgically sterile.
   - Total abstinence from sexual intercourse (for a minimum of one complete menstrual cycle prior to study drug administration);
   - Vasectomized male subjects or vasectomized partner of female subjects;
   - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream);
   - 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 for the duration of the study and for 90 days following completion of therapy.
9. 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:

Main Exclusion:

Subjects must meet none of the following exclusion criteria to be eligible:

1. Received anticancer agent(s) or an investigational agent within 21 days prior to C1D1 or radiotherapy within 28 days prior to C1D1. Prior treatment with palliative local breast or bone lesion radiation (other than pelvis) can occur, if administered at least 14 days prior to C1D1. 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 are excluded. Anticancer hormonal therapy must be stopped 7 days before starting C1D1. Subjects receiving bisphosphonates or denosumab are eligible.
2. 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 recurrent breast cancer within the past 6 months will also be considered toward the maximum of 2 prior lines of therapy.
    - A regimen will be considered a line of therapy if it includes a cytotoxic agent administered for more than 1 full cycle. Therapy administered for 1 full cycle or less will not be counted towards the number of lines of therapy unless the patient experienced progression of disease while on that therapy.
    - Previous treatments with hormonal therapy (tamoxifen, aromatase inhibitors) and signal transduction agents (e.g., trastuzumab lapatinib, erlotinib, gefitinib, bevacizumab) are allowed and are not counted towards the prior line of therapy.
3. Prior treatment of breast cancer with temozolomide, a platinum agent, or a Poly-(ADP-ribose)-Polymerase (PARP)-inhibitor.
    - Therapy with temozolomide, a platinum agent, or a PARP inhibitor administered for 1 full cycle or less will not be considered as prior therapy unless the patient experienced progression of disease while on that therapy.
4. Prior taxane therapy administered for the treatment of metastatic breast cancer disease with the below exceptions.
    - Prior taxane therapy for metastatic breast cancer is allowed if the patient received ≤ 1 full cycle (i.e., within 4 weeks for subjects receiving weekly paclitaxel or Abraxane; 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 C1D1.
    - Use of taxanes as adjuvant therapy or to treat locally recurrent disease is permitted, if given more than 6 months prior to C1D1.

In all cases, the subject must be an appropriate candidate for paclitaxel therapy as per standard practice and per the investigator's discretion.

5. A history of or evidence of brain metastases or leptomeningeal disease. Subjects with symptoms to suggest central nervous system (CNS) metastases should have a brain MRI within 28 days of enrollment to confirm the absence of CNS metastases. Contrast CT is acceptable for subjects who are unable to undergo a brain MRI.
6. A history of uncontrolled seizure disorder.
7. Pre-existing neuropathy from any cause in excess of Grade 1.

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

Main Exclusion (Continued):

8. Known history of allergic reactions to cremophor-paclitaxel.
9. Clinically significant uncontrolled condition(s).
    - Active infection;
    - Symptomatic congestive heart failure;
    - Unstable angina pectoris or cardiac arrhythmia;
    - Myocardial infarction within last 6 months;
    - Psychiatric illness/social situations that would limit compliance with study requirements; or
    - Any medical condition which in the opinion of the investigator places the subject at an unacceptably high risk for toxicities.
10. 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. 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.
11. Pregnant or breastfeeding.

Investigational Product:	Veliparib (ABT-888)
Dose:	40 mg twice a day (BID) Days 1 through 7 of 28-day cycle (in combination with temozolomide)
Mode of Administration:	Oral
Reference Therapy:	Temozolomide
Dose:	150 mg/m^2 to 200 mg/m^2 once daily (QD) Days 1 through 5 of 28-day cycle (in combination with veliparib)
Mode of Administration:	Oral
Investigational Product:	Veliparib or Placebo
Dose:	80 mg BID or 120 mg BID Days 1 through 7 of 21-day cycle (in combination with carboplatin + paclitaxel)
Mode of Administration:	Oral
Reference Therapy:	Carboplatin
Dose:	AUC 6 Day 3 of 21-day cycle
Mode of Administration:	Intravenously (IV)

Reference Therapy:	Paclitaxel
Dose:	175 mg/m^2 Day 3 of 21-day cycle
Mode of Administration:	Intravenously (IV)

Duration of Treatment: Subjects with controlled disease (complete response [CR], partial response [PR], or stable disease [SD] per RECIST version 1.1 and with tolerable side effects may continue to receive treatment with veliparib + TMZ until reaching a protocol-defined event of disease progression, or experiencing unmanageable toxicity, or reaching a maximum of 24 cycles of veliparib + TMZ. If TMZ has been discontinued, veliparib will also be discontinued. If the subject has not progressed and the investigator feels there is benefit from continued treatment for longer than 24 cycles, a discussion between the investigator and the AbbVie Medical Monitor is required. If both the investigator and the AbbVie Medical Monitor confirm that the subject would benefit from continued treatment, then the subject may continue to receive veliparib + TMZ until the subject has disease progression or experiences a toxicity that requires discontinuation of further treatment. Subjects randomized to veliparib/placebo + carboplatin + paclitaxel with controlled disease and with tolerable side effects may continue to receive treatment until reaching a protocol-defined event of disease progression or experiencing unmanageable toxicity. If both carboplatin and paclitaxel have been discontinued due to toxicity, veliparib will also be discontinued.

Interim Analyses: To ensure subject safety, an IDMC will review unblinded safety data (which will include all subjects enrolled in the study) when approximately 36 subjects enrolled under Amendment 1 have met at least one of the following criteria:

- Received two 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.

In addition, an interim futility analysis will be conducted and reviewed after the Week 27 tumor assessment of the first 30 subjects who have been documented to have deleterious mutations by the Sponsor core laboratory with at least one measurable lesion at baseline and randomized to the veliparib + TMZ treatment group (across both Group 1 and Group 2). If futility is declared at the time of the futility analysis for the veliparib + TMZ treatment arm, any subjects receiving veliparib + TMZ will be allowed the option of either receiving veliparib + carboplatin + paclitaxel or discontinuing therapy and remain on study and continue to follow the scheduled for study visits and procedures.

Criteria for Evaluation:

Efficacy: Progression-free survival (PFS) using modified RECIST version 1.1 assessment at 9-week intervals. In addition to being reviewed by the investigator and/or site staff, radiographic scans will be sent to a central imaging center for review. Events of disease progression will be determined by the central imaging center. Only subjects with deleterious mutations documented by the Sponsor core lab will be used in the primary efficacy analyses of PFS. Post treatment information and survival information will be collected at monthly intervals (or as requested by Sponsor to support data analysis) beginning on the date the subject is registered off study and for up to three (3) years until the endpoint of death, the subject is lost to follow-up or until the study termination by AbbVie.

The Clinical Benefit Rate (CBR) and Objective Response Rate (ORR) using RECIST (version 1.1) will be assessed.

QoL assessment criteria via the EORTC QLQ-C15/BR23 Scale will be collected pre-dose on C1D1, Day 1 of Cycle 2 and every other cycle thereafter beginning with Cycle 4 (C6, C8, etc.), Final Visit, and at the Follow-up Visit. In addition to the EORTC QLQ-C15/BR23 Scale, subjects randomized to the veliparib/placebo + carboplatin + paclitaxel treatment arms will complete the EORTC QLQ-CIPN20 Scale.

Safety: The safety of each treatment group will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, changes in laboratory determinations, and vital sign parameters. Subjects who did not receive study drug (veliparib or placebo) will not be included in the analyses of safety.

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

Efficacy (Primary and Secondary Endpoints): The analysis of the primary and secondary efficacy endpoints will include only the subjects who have been documented to have deleterious mutations by the Sponsor core lab. Sensitivity analyses will be conducted to evaluate the impact of any discrepancies between results from the local laboratory and from the Sponsor core laboratory.

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 a confirmed event of disease progression (as confirmed by the Central Imaging Center), or to the date of death (all causes of mortality) if disease progression is not reached. Events of death will be included for subjects who had not experienced a confirmed event of disease progression provided the death occurred within 9 weeks of the last available disease progression assessment. If the subject does not have a confirmed 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 available disease progression assessment.

Overall Survival: 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.

Clinical Benefit Rate: Clinical benefit rate (CR, PR, SD or Non-CR/Non-PD) at Week 18 will be defined as the progression-free rate at 18 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 central imaging center). All intent to treat (ITT) subjects will be included in the analysis.

Statistical Methods (Continued):

Objective Response Rate: ORR is defined as the proportion of subjects with confirmed complete or partial response per RECIST (version 1.1) as determined by central imaging center. All subjects who have had at least one measurable lesion at baseline will be included in the ORR calculation.

Chemotherapy-Induced Peripheral Neuropathy: CIPN (as assessed by the EORTC QLQ CIPN20 questionnaire and NCI-CTCAE 4.0 grading for peripheral neuropathy).

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
BCNU	Trade name for Carmustine
BID	Twice a Day
BSA	Body Surface Area
BRCA	Breast Cancer Gene
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CFR	Code of Federal Regulations
CIPN	Chemotherapy-Induced Peripheral Neuropathy
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
ESMO	European Society for Medical Oncology
EORTC	European Organization for Research and Treatment of Cancer
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
LD	Longest Diameter
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
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
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
TMZ	Temozolomide
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

2.0 Table of Contents

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3.0 Introduction

3.1 Breast Cancer

Breast cancer 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] Despite recent advances in breast cancer treatment, with very few exceptions, metastatic breast cancer remains incurable, and the aim of treatment is to palliate symptoms and prolong the time to progression. Although the number of agents approved for the treatment of metastatic 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 BRCA2.[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 BRCA1 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. 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] Second-line therapy with the small molecule anti-HER2 agent lapatinib in combination with capecitabine showed an improved progression-free survival compared to capecitabine alone.[14] Despite these important advances, most subjects eventually progress and metastatic breast cancer is still considered incurable.

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.[15] 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%).[16] The data were recently updated to include 25 patients in the expanded cohort, and it was found that the pathological complete response had fallen to 72%.[17] 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 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%).[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.[19] 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.[15] 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 Temozolomide

One of the most studied alkylating agents in combination with PARP inhibition is temozolomide (TMZ). TMZ is a newer-generation DNA-methylating agent that crosses the blood-brain barrier. TMZ is a prodrug of the active alkylating agent 5 (3 methyltrizen-1-yl) imidazole4-carbozimide (MTIC). Adverse events associated with TMZ observed in previously conducted studies in glioblastoma, include myelosuppression with Grade 3 or 4 neutropenia (reported as adverse event or laboratory abnormality) in 8% of subjects and Grade 3 or 4 thrombocytopenia (reported as adverse event or laboratory abnormality) in 14% of subjects. For additional information regarding TMZ, please refer to the Temodar® package insert or the Temodal Summary of Product Characteristics (SmPC).[20,21] While TMZ is thought to have little activity in unselected breast cancer, recent data suggest that the combination of a PARP inhibitor with TMZ may have utility for metastatic breast cancer in patients who are carriers of BRCA1/2 mutation.[22]

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.[23,24] 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.[26] 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.[27] In

particular, tumor cells with BRCA1 or BRCA2 deficiencies are exquisitely sensitive to PARP inhibition, even in the absence of any other insults.[6,28]

PARP-enabled DNA repair may also compensate for the loss of other repair pathways. Higher expression of PARP in cancer cells compared to normal cells has been linked to drug resistance and the overall ability of cancer cells to sustain genotoxic stress.[29-32]

Consistent with the observation that PARP activity may act as a resistance factor in some tumors, PARP inhibitors have been shown in preclinical models to sensitize tumors to ionizing radiation therapy and a variety of DNA-damaging agents, including alkylators, such as TMZ, and cross-linking agents, such as carboplatin.

3.4 Veliparib

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[33]

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.

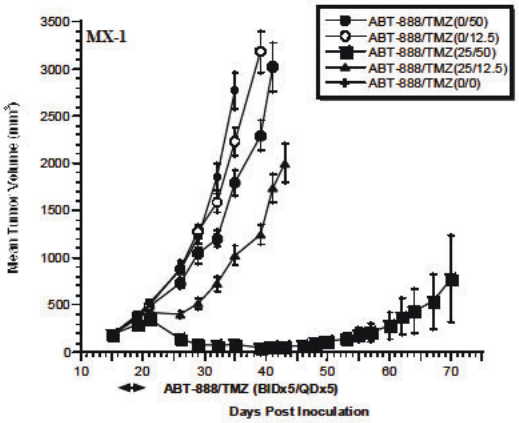
In cellular assays, veliparib increases sensitivity of tumor cells to DNA-damaging agents including TMZ, irinotecan, cyclophosphamide, BCNU, cisplatin, and radiation. In preclinical models one of the most efficacious alkylating agents in combination with PARP inhibition is TMZ. Preclinical studies delivering veliparib by osmotic minipump indicate that maximal efficacy in combination with TMZ is achieved with steady state plasma concentrations of veliparib at 70 ng/mL. No significant increase in body weight loss was observed with these combinations relative to TMZ monotherapy. Human

pharmacokinetics indicate that an oral dose of 40 mg BID, the maximum tolerated dose (MTD) in combination with TMZ, produces an average steady-state AUC_{0-24} of 4.41 µg•hr/mL, exposures greater than those achieved with the preclinical maximally efficacious dose (AUC_{0-24} of 3.0 µg•hr/mL).

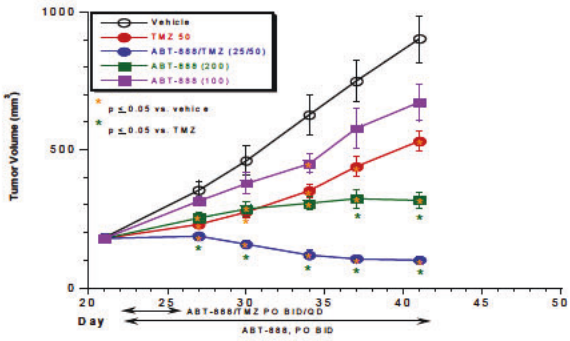
The combination of veliparib + TMZ has demonstrated significant efficacy in a variety of preclinical tumor models, including settings where TMZ alone is ineffective and in both BRCA1- or BRCA2-competent and BRCA1- or BRCA2-mutated backgrounds. In the BRCA-deficient MX-1 breast cancer model, TMZ given alone at the standard dose of 50 mg/kg/day for 5 days exhibits minimal inhibition of tumor growth (35% TGI, Figure 1a) with no evidence of complete pathological tumor regression. In contrast, addition of veliparib at 25 mg/kg/day to the therapy regimen results in profound antitumor activity (97% TGI), including 50% complete tumor regressions. In Capan-1, a human BRCA2-deficient pancreatic cancer cell line (6174delT in Exon 11 resulting in a truncated BRCA2), the combination of veliparib with TMZ resulted in significantly more tumor regressions than either agent alone (Figure 1b).

Figure 1. Combination Therapy of Veliparib + TMZ

a.



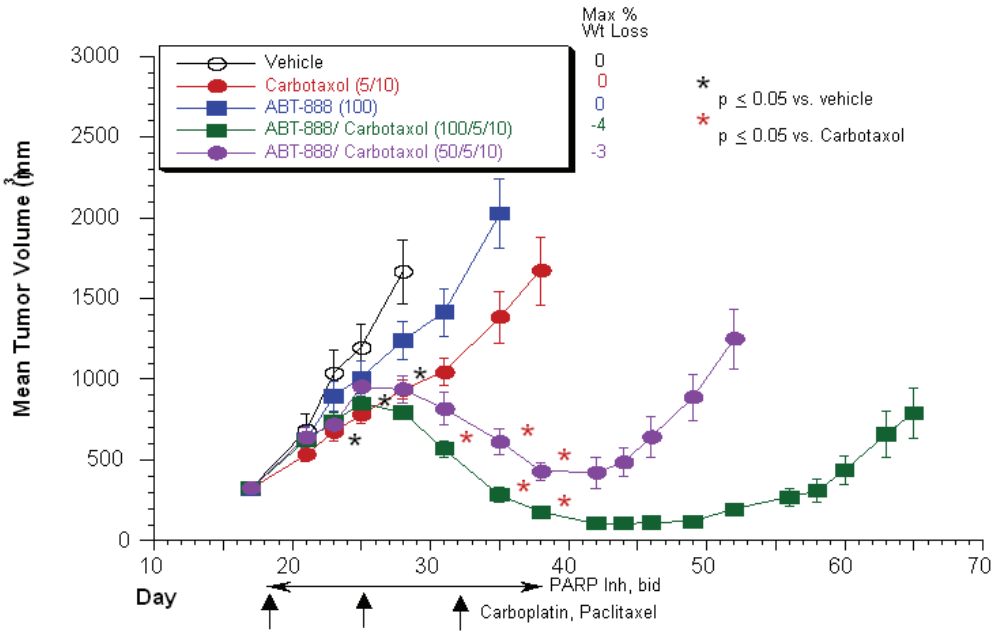
b.



Combination therapy of veliparib + TMZ in BRCA-deficient preclinical models. a) Veliparib was administered at 25 mg/kg/day, BID, orally (PO) for 5 days in combination with TMZ at 50 mg/kg/day, QD, PO for 5 days in the BRCA-mutated MX-1 breast cancer model. b) In the Capan-1 model (BRCA2-deficient pancreatic cancer cell line) TMZ 50 mg/kg/day, QD, PO for 5 days and veliparib 25 mg/kg/day, BID, PO for 5 days in combination were administered on Days 22 to 26. Veliparib as a single agent (100 or 200 mg/kg/day, BID) was administered on Days 22 to 42. Data are mean ± standard error of the mean (N = 10 per treatment group).

Veliparib has also 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 2).

Figure 2. **Veliparib in Combination with Carboplatin in the MX-1 Breast Carcinoma Xenograft Model in SCID Mice**



Veliparib and Neuropathy

Analogues of veliparib attenuated development of mechanical allodynia in vincristine, cisplatin and oxaliplatin preclinical models of chemotherapy-induced pain. Neuropathy was induced in rats by the administration of vincristine. To investigate the ability of PARP inhibitors to attenuate vincristine-induced pain, rats were administered a PARP inhibitor, A-861696 or A-902274, at doses of 25 mg/kg/day or 50 mg/kg/day (IP), for 2 days prior to the initiation of vincristine administration. After 2 days of pre-dosing with the PARP inhibitor, two minipumps were implanted in rats for vincristine and compound administration. Vincristine was administered via a subcutaneous mini-osmotic pump that delivered 30 µg/kg/day (IV) for 12 days. PARP inhibitor, A-861696 or A-902274, or vehicle was administered via a subcutaneous mini osmotic pump that delivered 25 mg/kg/day, 50 mg/kg/day, or vehicle (IP) for 12 days. A positive control group of rats receiving vincristine were dosed acutely with morphine (6 mg/kg, IP) on testing days.

Another control group of rats received saline IV instead of vincristine. Mechanical threshold was determined using von Frey monofilaments. Mechanical allodynia was observed in rats treated with vincristine compared to the saline group. In vincristine treated rats, morphine fully reversed mechanical allodynia on all testing days. PARP inhibitors had no effect in naive rats. The PARP inhibitors, A-861696 and A-902274, attenuated development of mechanical allodynia in the vincristine model of chemotherapy-induced pain (Figure 3).

In mice, neuropathy was induced by administration of cisplatin or oxaliplatin. Mice were administered a PARP Inhibitor, A-861696, at doses of 25 mg/kg/day or 50 mg/kg/day (IP) for 2 days prior to the initiation of cisplatin. The 50 mg/kg dose of A-861696 was administered (IP) for 2 days prior to oxaliplatin administration. After 2 days of pre-dosing with the PARP Inhibitor, mice were co-administered A-861696 with cisplatin or oxaliplatin for 5 days (daily injections, IP), followed by 5 days off, and then followed by 5 daily injections (IP). Cumulative dose of cisplatin was 23 mg/kg. Cumulative dose of oxaliplatin was 30 mg/kg. Behavioral assays were performed on all groups of mice using von Frey monofilaments before dosing, and then at Weeks 3, 6, and 8. Behavioral assays included determining mechanical threshold with von Frey monofilaments, latency to paw withdrawal from a radiant heat source, and number of paw lifts from a cold plate. A-861696 attenuated development of mechanical allodynia in the cisplatin model at Weeks 3, 6, and 8, and in the oxaliplatin model at Week 3 and Week 6 (Figure 4). In addition, A-861696 attenuated development of heat hyperalgesia in the cisplatin model at Week 3 and Week 6. A-861696 attenuated development of cold hyperalgesia in the oxaliplatin model at Week 6. Together, these data establish PARP as a novel mechanism of painful neuropathy. Furthermore, these data suggest therapeutic potential of PARP inhibitors for the prevention of chemotherapy-induced peripheral neuropathy (CIPN).

Figure 3. **Analogues of Veliparib Attenuated Allodynia (Vincristine Model of Chemotherapy-Induced Pain)**

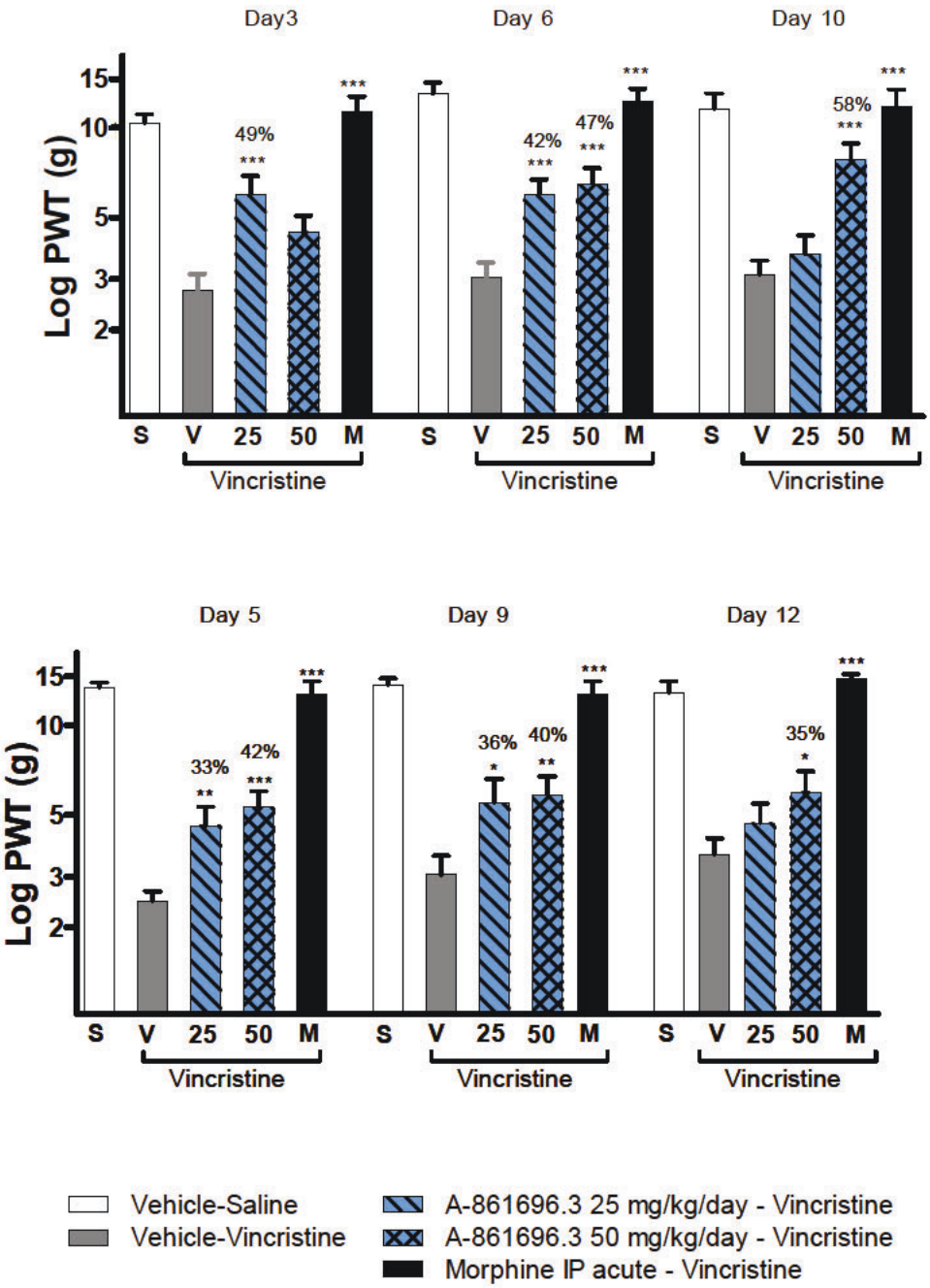
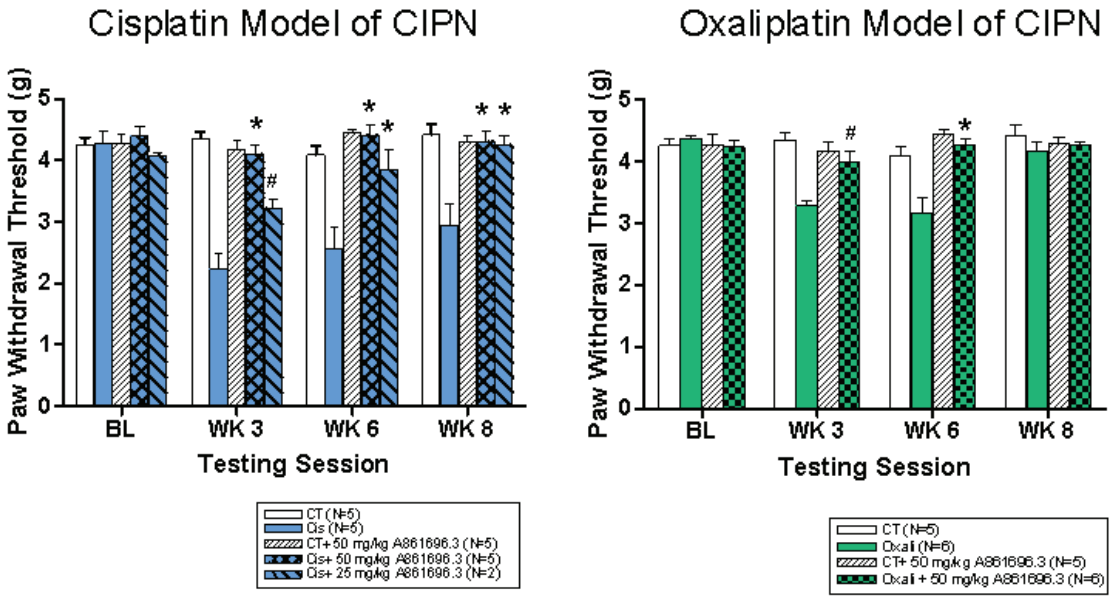


Figure 4. Analogues of Veliparib Attenuated Allodynia (Cisplatin and Oxaliplatin Model of Chemotherapy-Induced Pain)



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 150 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. Preliminary results indicate the absence of a DDI between veliparib and TMZ.

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). Veliparib also

absorbs ultraviolet light and is distributed to both the skin and the eyes following systemic exposure, which poses a potential phototoxicity risk.

3.4.2 Clinical Experience

A Phase 0 dose-ranging pharmacokinetic and pharmacodynamic study has been completed (NCI IND). Thirteen subjects with various types of advanced cancer received a single dose of single-agent veliparib (10 mg, n = 3; 25 mg, n = 3; 50 mg, n = 7). The pharmacokinetic results from this study demonstrated that veliparib is orally bioavailable and primarily cleared through renal excretion, with a half-life of 4 to 5 hours. Additionally, this study provided proof of mechanism, as tumor PARP inhibition (> 90%) was demonstrated in 5 out of 6 human tumor biopsies that were obtained 3 to 6 hours after dosing with either 25 mg or 50 mg veliparib. No serious adverse events, dose-limiting toxicities (DLTs), or deaths were reported for this study.[34]

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 or temozolomide. By a similar mechanism, PARP inhibitors may potentiate the toxicities of the 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.

Study M06-862 is a dose-escalating Phase 1 study of veliparib BID on Days 1 through 7 in combination with TMZ QD on Days 1 through 5 (28-day cycle) in subjects with nonhematologic malignancies. No DLTs were reported for the first 3 dose cohorts (veliparib 10, 20, and 40 mg BID). In cohorts receiving 60 mg and 80 mg, events of Grade 4 thrombocytopenia and neutropenia were reported. The MTD combination dose was defined as veliparib 40 mg BID and TMZ 200 mg/m^2 QD. Although no DLTs were reported in subjects in the 40 mg veliparib BID/200 mg/m^2 TMZ QD dose-escalation cohort, 8 of all 12 subjects receiving 40 mg veliparib BID/200 mg/m^2 in an expanded

safety cohort experienced Grade 3 or 4 neutropenia and/or thrombocytopenia. In general, subjects with these events recovered after dose reduction and remained on study. In order to minimize these hematologic toxicities, the protocol was modified to treat new subjects with 40 mg veliparib BID in combination with 150 mg/m^2 TMZ QD in the first cycle. If a subject did not experience Grade 3 or 4 hematologic toxicities or other clinically significant NCI Common Terminology Criteria for Adverse Events (CTCAE) toxicities greater than Grade 3, the TMZ dose was escalated to 200 mg/m^2 QD. The study also included 20 mg and 30 mg BID expanded safety cohorts who were dosed following the amended protocol. Overall, as the dosage of veliparib increased from 20 to 40 mg BID, there appeared to be a trend of increase in frequency of Grade 3 and 4 hematological toxicities.

Study M10-440 is a Phase 2 randomized, double-blind, placebo-controlled study of veliparib (20 or 40 mg BID) in combination with TMZ (150 mg/m^2/day with possible escalation to 200 mg/m^2). This study is fully enrolled and ongoing (n = 346). The most common adverse events (reported in ≥ 30% of subjects receiving veliparib + TMZ) were nausea, fatigue, constipation, thrombocytopenia, and vomiting.

In a Phase 2, investigator-initiated study,[22] to date, 41 subjects with metastatic breast cancer have received veliparib 40 mg BID Days 1 through 7 plus TMZ 150 to 200 mg/m^2 Days 1 through 5 of a 28-day cycle. In the subjects without known deleterious BRCA1 or BRCA2 mutation, there were no responses. In contrast, the 8 subjects with a known deleterious BRCA1/2 mutation, to date, have demonstrated 1 confirmed CR, 4 PR (3 confirmed), and 3 subjects with progressive disease (ORR) = 50% and CBR = 62.5%). Of the subjects with deleterious mutations of BRCA1/2, there were 3 BRCA1 carriers (1 PR, 2 PD) and 5 BRCA2 carriers (1 CR, 3 PR, and 1 PD). Progression has occurred as the best response in 34 of the 41 subjects, many within 1 to 2 cycles. Adverse events in this study include Grade 3/4 toxicities of thrombocytopenia and neutropenia. There have been no bleeding complications or febrile neutropenia. Hypophosphatemia occurred twice in the same patient and was reported as not related to study drug and was pre-existing. Due to the number of subjects with hematological toxicities, the protocol

was amended in December 2009 to change the dose of veliparib from 40 mg BID to 30 mg BID (in combination with 200 mg/m^2 of TMZ). All of the subjects who responded to veliparib with TMZ received 40 mg BID veliparib initially, then 30 mg BID following the dose-reduction amendment.

This study was amended to include an expanded cohort of 20 BRCA1/2 mutation carriers with metastatic breast cancer to further evaluate safety, tolerability, and efficacy of the veliparib plus TMZ combination in this specific population. Subjects in this cohort have received veliparib 30 mg BID with TMZ 150 to 200 mg/m^2 Days 1 through 5. To date, hematological toxicities have been similar to those observed in the initial cohort; however, the response rate has diminished. In addition to the reduced dose of veliparib, the expansion cohort differed from the initial subjects in that approximately half of the patients had received prior platinum therapy. This is notable, as previous studies suggest that similar mechanisms of resistance can lead to decreased activity of both platinums and PARP inhibitors, such as reversion of BRCA1/2 mutation to a wild-type phenotype.[35,36] Based upon the experience to date across the veliparib program in which hematological toxicities have been manageable with veliparib 40 mg BID and the potential decrease in efficacy at the 30 mg dose, veliparib will be used at 40 mg BID in combination with TMZ (150 to 200 mg/m^2) in this 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 study is a Phase 1 dose escalation study evaluating the addition of veliparib to carboplatin + paclitaxel in subjects with advanced or metastatic solid tumors. 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. At this dose, two out of six subjects developed protocol defined dose limiting toxicities (DLTs). 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 febrile grade 3

neutropenia in a subject who previously received multiple cycles of dacarbazine (an alkylating agent which may cause cumulative bone marrow damage). The event of febrile neutropenia resolved after G-CSF therapy and anti-bacterial therapy, and the subject continued veliparib + carboplatin + paclitaxel therapy. 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 patients with metastatic breast cancer had confirmed responses (3 CR, 5 PR).[37] In a subsequent analysis of preliminary data in refractory triple negative breast cancer receiving veliparib in combination with carboplatin and paclitaxel on either a q 3 week regimen (CTEP 7967) or a weekly regimen (carboplatin AUC 2, paclitaxel 80 mg/m^2; 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 3 week regimen (2 CR, 4 PR).[38]

GOG 9923 is an ongoing Phase 1 dose escalation study that is also evaluating veliparib in combination with carboplatin, paclitaxel, and bevacizumab (initiated in cycle 2) in subjects with advanced or metastatic ovarian cancer (chemotherapy-naïve). The intermittent regimen with veliparib in combination with q-3 weekly carboplatin and paclitaxel has escalated to dose greater than 200 mg BID, further supporting the use of veliparib 120 mg BID in combination with carboplatin and paclitaxel.

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 TMZ resulted in responses in patients with deleterious germline mutations in BRCA1/2, with a 50% ORR. 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.[39] A similar trial in BRCA1/2 mutation

carriers with metastatic ovarian cancer showed a response rate of 33%.[40] Notably, both single-agent studies demonstrated increased response rates with higher doses of PARP inhibitor (olaparib 100 mg BID and 400 mg BID), where both doses are considered biologically active. Together, these results validate the proof of concept that PARP inhibition is an attractive therapeutic target in breast and other cancers.

A therapeutic potential for veliparib has also been suggested in BRCA1/2-mutated breast cancer, and specifically for the utility of the veliparib + TMZ combination. The combination of veliparib and TMZ resulted in dramatic tumor growth delay or regression in many preclinical models, including BRCA-deficient tumor models, where TMZ by itself is not efficacious (Section 3.4.1). Preclinical studies indicate that veliparib may have activity in tumor types in which TMZ is typically *not* thought to have activity (Section 3.4.1), with possible mechanisms including synergism between DNA-damaging agents and inhibitors of DNA repair[41] and prevention of resistance to TMZ, which is thought to be responsible for the low efficacy of TMZ in many tumor types.[42,43] In the ongoing Phase 2 trial in metastatic breast cancer, a 50% CBR (14/28; 1 CR, 6 PR, 7 SD) has occurred to date in patients with deleterious BRCA mutations (including both the original and the expansion cohort). This is in contrast to historical clinical data that suggest that TMZ monotherapy has low activity in breast cancer. Most notably, two Phase 2 studies with a dose-dense TMZ regimen demonstrated no responses (0/18) in patients with metastatic breast cancer and 2 responses (2/51) in patients with brain metastases from histologically confirmed breast cancer.[43,44] While the Phase 2a study indicates that veliparib in combination with TMZ is an active regimen, this study was initially designed as a single-arm study in an unselected patient population; thus, further evaluation is needed to determine the activity of this regimen relative to efficacious regimens in metastatic breast cancer.

Therapeutic potential in breast cancer has also been observed with veliparib in combination with carboplatin + paclitaxel. AbbVie is conducting a Phase 1, dose-escalation trial of veliparib with carboplatin + paclitaxel (CTEP 7967) in collaboration with Cancer Therapy Evaluation Program (CTEP). In this study, 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.[45] In the preliminary efficacy analysis, 1 out of 4 chemotherapy-naïve metastatic NSCLC patients had a confirmed response to veliparib with carboplatin + paclitaxel chemotherapy (22% ORR in ECOG trial), and 4 out of 11 patients with metastatic breast cancer had confirmed responses (2 CR, 2 PR), with an additional 2 patients with unconfirmed responses (1 PR, 1 CR). In the CTEP 7967 study, the maximum tolerated dose for veliparib was 120 mg BID with 2 out of 6 patients experiencing DLTs (febrile neutropenia, vomiting). The study also includes a separate, ongoing, dose escalation in patients with BRCA-mutated tumors with veliparib in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2).

In addition to CTEP 7967, veliparib in combination with carboplatin and paclitaxel has been evaluated in GOG 9923. As of 15 Dec 2011, three patients have been treated with veliparib 150 mg BID on Days 1 to 21 with carboplatin AUC 6 and paclitaxel 175 mg/m^2 on Day 1 of a 21-day cycle. No grade 3/4 toxicity or DLTs occurred at the 150 mg BID dose level during DLT evaluation period; thus, in the GOG 9923 study, the veliparib 200 mg BID dose level is currently being evaluated.

Given that the patient population in GOG 9923 is the most similar to Study M12-895 (ovarian cancer patients, many of whom will have BRCA1/2 mutation or have tumors with a BRCAness phenotype) and the similarity in paclitaxel dosing between the two studies, in addition to the data indicating increased response rates with higher doses of the PARP inhibitor, the veliparib 120 mg BID dose was selected for use in combination with carboplatin and paclitaxel in this study. In patients with metastatic breast cancer, previous studies have indicated that a longer duration of first-line chemotherapy is associated with potential benefit in PFS and OS; thus, therapy in this study will be continued until PD or toxicity results in treatment discontinuation.[46]

3.5 Benefits and Risks

This study proposes to establish improved clinical outcomes for patients with metastatic or locally recurrent breast cancer with a deleterious germline mutation of BRCA1 or BRCA2 through the addition of veliparib to therapy with carboplatin and paclitaxel or to temozolomide. Preclinical data demonstrate that veliparib potentiates the anti-tumor activity of platinums and temozolomide, 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 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.

Veliparib in combination with TMZ has been evaluated in 7 AbbVie-sponsored clinical studies in subjects with various solid tumors. Based on preliminary data from the seven studies with veliparib and temozolomide (N = 527), the most common serious adverse event was thrombocytopenia (17 subjects, 3.2%). The most common treatment-emergent adverse events, reported in > 30% of all subjects, were nausea (384 subjects, 72.9%), fatigue (348 subjects, 66.0%), constipation (248 subjects, 47.1%), thrombocytopenia (233 subjects, 44.2%), and vomiting (201 subjects, 38.1%). The preliminary safety results from a randomized Phase 2 placebo-controlled study comparing temozolomide plus veliparib (20 or 40 mg twice daily on Days 1 – 7) every 4 weeks versus temozolomide plus placebo in patients with advanced melanoma indicate that the

toxicity profile of veliparib with temozolomide is similar to that of temozolomide alone, with some increase in the frequency of hematological toxicities (Grade 3 or 4 thrombocytopenia 23.8% versus 15.0%, respectively, and neutropenia 16.0% versus 5.3%). These toxicities are commonly associated with cancer therapy, and standard clinical practices to manage these toxicities are well-established.

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 and temozolomide 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 further evaluation of veliparib in combination with carboplatin and paclitaxel or with temozolomide in the Phase 2 study.

3.6 Differences Statement

This is the first randomized, Phase 2 study of veliparib in locally recurrent or metastatic breast cancer in patients with deleterious germline mutation of BRCA1 or BRCA2.

4.0 Study Objectives

The primary objective of the study is to assess the PFS of oral veliparib in combination with TMZ or in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with BRCA1 or BRCA2 mutation and locally recurrent or metastatic breast cancer.

The secondary objectives of the study are to assess OS, CBR through the end of Week 18, and ORR, in those subjects treated with veliparib in combination with TMZ or treated with veliparib in combination with carboplatin and paclitaxel versus placebo in combination with carboplatin and paclitaxel. In addition, CIPN (as assessed by the EORTC QLQ CIPN20 questionnaire and NCI-CTCAE 4.0 grading for peripheral neuropathy) will be assessed in those 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.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 2 randomized, partially blinded, multinational, multicenter study to evaluate the efficacy and tolerability of veliparib in combination with TMZ or veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in approximately 290 subjects with BRCA1 or BRCA2 mutation as documented by the Sponsor core laboratory and locally recurrent breast cancer (not amenable to therapy with curative intent) or metastatic breast cancer who have received no more than two prior lines of cytotoxic therapy for metastatic disease. Approximately 120 research sites will participate.

Subjects will be randomized in a 1:1:1 ratio to one of the three treatment arms described below. Subject randomization will be stratified by ER-positive and/or PgR-positive versus ER-negative and PgR-negative status, prior cytotoxic therapy versus no prior cytotoxic therapy, and ECOG 0-1 versus 2.

Under the original protocol, approximately 4 subjects were randomized in a 1:1:1 ratio (Group 1) to one of the three treatment arms (1 subject in veliparib 40 mg BID + TMZ arm and a total of 3 subjects in either the veliparib 80 mg BID + carboplatin + paclitaxel or the placebo BID + carboplatin + paclitaxel arms) at approximately 3 research sites.

Subjects randomized under the original protocol will be considered Group 1 and will not be considered towards the primary efficacy analyses.

Following approval of Amendment 1, the veliparib dose in combination with carboplatin and paclitaxel was increased to 120 mg BID. Approximately 290 subjects will be randomized in a 1:1:1 ratio (Group 2) to one of the three treatment arms (veliparib 40 mg BID + TMZ, veliparib 120 mg BID + carboplatin + paclitaxel, placebo BID + carboplatin + paclitaxel) at approximately 120 research sites. Subjects randomized following approval of Amendment 1 will be considered Group 2 and will be considered towards the primary efficacy analyses.

Veliparib + Temozolomide Dosing Arm

Subjects randomized to receive veliparib 40 mg BID + TMZ will self-administer the morning dose of veliparib and TMZ at the same time and the evening dose of veliparib approximately 12 hours after the morning dose in the same calendar day on Days 1 to 7 of each 28-day cycle as per Table 1.

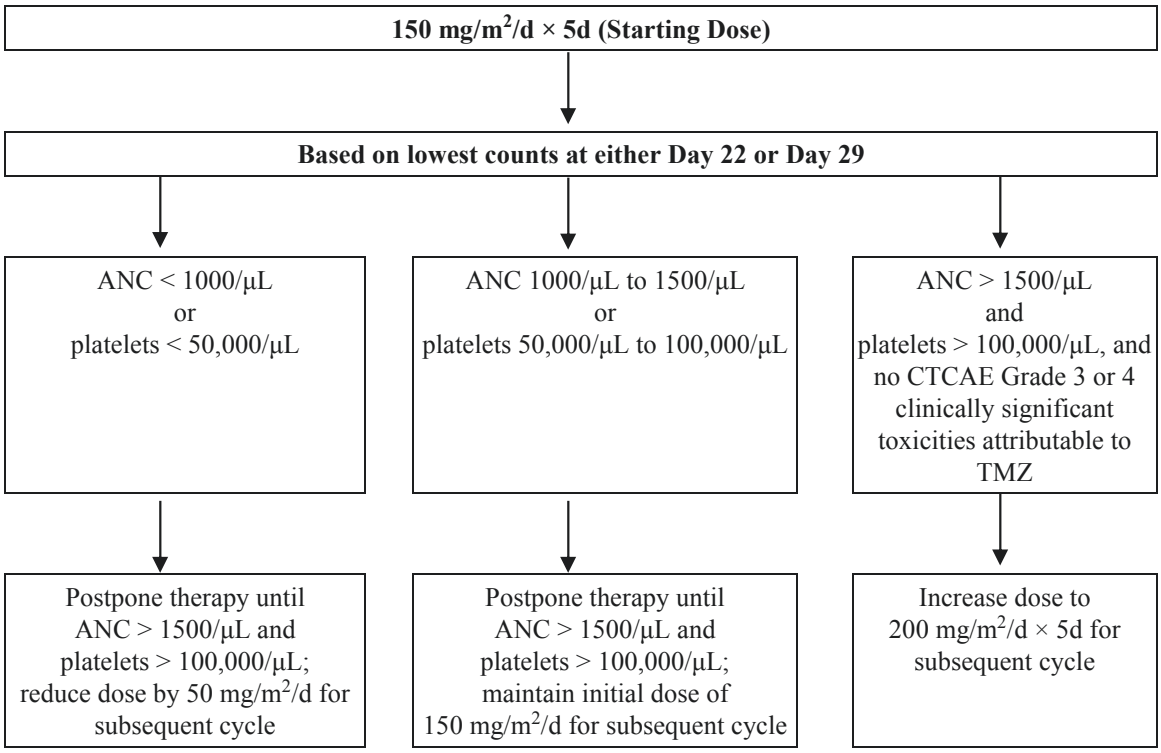
For Cycle 1, the TMZ dose will start at 150 mg/m^2 QD on Days 1 to 5 of each 28-day cycle as per Table 1. The TMZ dose will be determined by body surface area (BSA) calculated from the height obtained at the baseline evaluation and the weight obtained prior to each cycle. The daily dose will be rounded to the nearest 5 mg. However, for subject convenience, the dose may be rounded down to 5% from calculated dose in order to minimize the number of capsules per dose. The exact dose administered will be recorded in the electronic case report form (eCRF).

If during the first cycle, platelets (nadir) are > 100,000/µL and the ANC (nadir) is > 1,500/µL and no Grade 3 or 4 CTCAE nonhematologic toxicities attributable to TMZ are observed, then the TMZ dose will be escalated to 200 mg/m^2 QD (per BSA) for Cycle 2 (Table 2). If the dose was not escalated at Cycle 2, then the dose should not be escalated in future cycles. For all cycles, dose delays and reductions will be managed according to Section 5.7.

Table 1. Treatment Schema for Subjects Randomized to Veliparib + TMZ Treatment Arm

Days	1	2	3	4	5	6	7	8-28
Veliparib	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	No drug dosing
TMZ	Once a day with a m. Veliparib	Once a day with a.m. Veliparib	Once a day with a.m. Veliparib	Once a day with a.m. Veliparib	Once a day with a.m. Veliparib			No drug dosing

Table 2. TMZ Dosing Modification Following Cycle 1



Veliparib or Placebo + Carboplatin and Paclitaxel Dosing Arms

Upon approval of protocol Amendment 1 and the availability of the 40 mg clinical supplies to support a dose of 120 mg BID of veliparib, all subjects randomized to the

veliparib/placebo + carboplatin + paclitaxel treatment arms will receive 120 mg BID of veliparib/placebo. Subjects randomized to the 80 mg BID veliparib/placebo starting dose will continue to receive veliparib/placebo as specified per the original protocol for the duration of their study treatment.

Subjects randomized to receive veliparib/placebo + carboplatin + paclitaxel will self-administer veliparib or placebo on Days 1 to 7 of each 21-day cycle as per Table 3. The evening dose of veliparib/placebo should be administered approximately 12 hours after the morning dose. Carboplatin and paclitaxel will be administered on Day 3 of each 21-day cycle. Paclitaxel will be infused before carboplatin. The dose of carboplatin and paclitaxel will be based upon the baseline weight (C1D1) for all cycles; however, the dose should be recalculated on the basis of new weight, if there is a weight change of > 10% from baseline; adjustments for weight change < 10% are allowed per institutional guidelines. The morning dosing of veliparib/placebo on Day 3 of every cycle should be taken before the carboplatin + paclitaxel infusion per Table 3 below.

Paclitaxel

Subjects should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists according to local institutional standard guidelines, the locally approved product label, local practice, or the applicable summary of product characteristics (SmPC).[47] The medications used for the pretreatment of paclitaxel will be recorded in the eCRF.

Paclitaxel will be administered intravenously over approximately 3 hours at a dose of 175 mg/m^2.

Carboplatin

Carboplatin[48] will be administered intravenously over approximately 15 to 30 minutes at AUC 6, immediately following paclitaxel infusion. The duration of carboplatin infusion may be lengthened according to institutional guidelines. When glomerular filtration rate (GFR) is estimated by serum creatinine using the Isotope Dilution Mass Spectroscopy (IDMS) method, the maximum dose of carboplatin should be limited to 900 mg.

Similarly, when the GFR is estimated using Isotopic/edetic acid (EDTA) clearance, maximum carboplatin dosing should be based upon standard guidelines and institutional practices.

Table 3. Treatment Schema for Subjects Randomized to Veliparib + Carboplatin + Paclitaxel or Placebo + Carboplatin + Paclitaxel Treatment Arms

Days	1	2	3	4	5	6	7	8 – 21
Veliparib or Placebo	Twice a day	Twice a day	Twice a day*	Twice a day	Twice a day	Twice a day	Twice a day	No drug dosing
Carboplatin			IV					No drug dosing
Paclitaxel			IV					No drug dosing

* Veliparib or placebo morning dose should be administered orally in the clinic prior to paclitaxel/carboplatin infusion.

If the Screening Visit is performed more than 7 days prior to Study Day 1, the physical exam must be repeated on C1D1. For Screening labs performed greater than 7 days prior to C1D1, hematology/chemistry should be split at C1D1 and local labs reviewed prior to dosing. Vital signs, laboratory tests, and performance status assessment will be performed on C1D1 for all subjects prior to dosing.

Study procedures will be performed as outlined in Section 5.3.1.1. Subjects will continue dosing until they meet the defined discontinuation criteria discussed in Section 5.4.1. When an investigator has determined that a subject should discontinue the study, a Final Visit will be conducted.

All subjects will have one Follow-up Visit approximately 30 days after the last dose of veliparib + TMZ or veliparib/placebo + carboplatin + paclitaxel. This Follow-up Visit does not need to be conducted if the Final Visit is ≥ 30 days after the last dose of veliparib + TMZ or veliparib + carboplatin + paclitaxel or placebo + carboplatin + paclitaxel.

Post treatment and survival information (i.e., the date and cause of death) will be collected via Interactive Voice or Web Response System (IVRS/IWRS) at monthly intervals (or as requested by Sponsor to support data analysis) beginning on the date the subject is registered off study and continuing for a minimum of three (3) years for all subjects until the endpoint of death, the subject has become lost-to follow-up, or AbbVie terminates the study.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

Subjects will be adult men and women with metastatic breast cancer and a documented 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 recurrent or metastatic. Locally recurrent disease must not be amenable to surgical resection or radiation with curative intent.
3. Must have a documented 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/MLPA or 2) a well-characterized methodology previously validated by sequencing, such as that used to assess founder mutations. If testing has been performed by a laboratory other than the Sponsor core laboratory, subjects may be enrolled but must be re-tested by Sponsor core laboratory for confirmation of BRCA1 or BRCA2 germline mutations.
4. If HER2-positive (HER2 3+ by immunohistochemistry or amplification by FISH > 2), subjects must have received and progressed on at least one prior standard HER2-directed therapy or be ineligible to receive anti-HER2 therapy.

5. Measurable or non-measurable (but radiologically evaluable) disease per RECIST version 1.1 on CT scan (within 28 days of C1D1) with at least one lesion outside previously irradiated areas.

6. ECOG performance status of 0 to 2.

7. Adequate hematologic, renal, and hepatic function as follows (within 28 days of C1D1):

   - 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); Leukocytes $> 3{,}000/mm^3$;
   - Renal Function: Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN) range **OR** creatinine clearance ≥ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal;
   - Hepatic Function: AST and/or ALT $\leq 2.5 \times$ institutional upper limit of normal. For subjects with liver metastases, AST and/or ALT $< 5 \times$ ULN range; bilirubin $\leq 1.5 \times$ the 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.

8. 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 90 days following completion of therapy. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to initiation of treatment. To be considered of non-child bearing potential, postmenopausal women must be amenorrheic for at least 12 months or subjects must be surgically sterile.

   - Total abstinence from sexual intercourse (for minimum of one complete menstrual cycle prior to study drug administration);
   - 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 for the duration of the study and for 90 days following completion of therapy.

9. 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 – 6) To select the appropriate subject population with sufficient disease severity for evaluation.

(7) For the safety of the subjects.

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

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

5.2.2 Exclusion Criteria

Subjects must meet none of the following exclusion criteria to be eligible.

1. Received anticancer agent(s) or an investigational agent within 21 days prior to C1D1 or radiotherapy within 28 days prior to C1D1. Prior treatment with palliative local breast or bone lesion radiation (other than pelvis) can occur, if administered at least 14 days prior to C1D1. Subjects experiencing a significant adverse effect or toxicity (Grade 3 or 4), causally attributed to previous anticancer treatment that has not recovered to at least Grade 2 are excluded. Anticancer hormonal therapy must be stopped 7 days before starting C1D1. Subjects receiving bisphosphonates or denosumab are eligible.
2. 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 recurrent breast cancer within the past 6 months will also be considered towards the maximum of 2 prior lines of therapy.
    - A regimen will be considered a line of therapy if it includes a cytotoxic agent administered for the treatment of breast cancer more than 1 full cycle. Therapy administered for 1 full cycle or less will not be counted towards the number of lines of therapy unless the patient experienced progression of disease while on that therapy.
    - Previous treatments with hormonal therapy (tamoxifen, aromatase inhibitors) and signal transduction agents, (e.g., trastuzumab, lapatinib, erlotinib, gefitinib, bevacizumab) are allowed and are not counted toward the prior line of therapy.
3. Prior treatment of breast cancer with temozolomide, a platinum agent, or a PARP inhibitor.
    - Therapy with temozolomide, a platinum agent, or a PARP inhibitor administered for 1 full cycle or less will not be considered as prior therapy unless the patient experienced progression of disease while on that therapy.
4. 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., within 4 weeks for subjects receiving weekly paclitaxel or Abraxane; 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 C1D1.
- Use of taxanes as adjuvant therapy or to treat locally recurrent disease is permitted, if given more than 6 months prior to C1D1.

In all cases, the subject must be an appropriate candidate for paclitaxel therapy as per standard practice and per the investigator's discretion.

5. A history of or evidence of brain metastases or leptomeningeal disease. Subjects with symptoms suggestive of CNS metastases should have a brain MRI within 28 days of enrollment to confirm the absence of CNS metastases. Contrast CT is acceptable for subjects who are unable to undergo a brain MRI.
6. A history of uncontrolled seizure disorder.
7. Pre-existing neuropathy from any cause in excess of Grade 1.
8. Known history of allergic reaction to cremophor/paclitaxel.
9. 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;
   - 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.

10. 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. 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.
11. Pregnant or breastfeeding.

Rationale for Exclusion Criteria

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

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

(11) The impact of veliparib + TMZ 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 drug 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.

The AbbVie Medical Monitor identified in Section 6.5 should be contacted if there are any questions regarding prior or concomitant therapy.

5.2.3.1 Prior Therapy

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.

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 recurrent disease within the past 6 months will also be considered towards the maximum of two prior lines 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., trastuzumab, lapatinib, erlotinib, gefitinib, bevacizumab), are allowed and will not count toward prior lines of therapy. Anticancer hormonal therapy is not permitted within 7 days prior to C1D1.
Radiation:	Prior treatment with radiation is allowed as long as the last treatment was at least 28 days prior to C1D1. Prior treatment with palliative local breast or bone lesion radiation (other than pelvis) is allowed if last treatment was at least 14 days prior to C1D1.

5.2.3.2 Concomitant Therapy

The locally approved product label, institutional guidelines, local practice, or applicable SmPC for TMZ, carboplatin, and paclitaxel should be referenced for any concomitant therapy guidelines.

Premedication:	The prophylactic use of a 5-HT3-antagonist is strongly recommended before TMZ administration. Additional National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), or institution standard of care/approved prophylactic antiemetics may be given, as appropriate. 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 are not permitted during the treatment portion of the study. All subjects will receive carboplatin + paclitaxel with veliparib/placebo or temozolomide with veliparib during the treatment portion of the study. The locally approved carboplatin, paclitaxel, and temozolomide 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.).

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, bisphosphonates or denosumab) according to institutional guidelines or American Society of Clinical Oncology (ASCO) guidelines. ASCO guidelines recommend a two drug combination of palonosetron and dexamethasone for moderately emetic therapies, such as carboplatin. If palonosetron is not available, any of the first generation 5 HT3 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.[49] Prophylactic antimicrobials should be considered in subjects receiving concurrent immunosuppressive (i.e., corticosteroids) therapy and those with lymphopenia (absolute lymphocyte count < 800) and continued until lymphopenia resolves.
Growth Factors:	Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) and colony-stimulating factors (e.g., neulasta, G-CSF, GM CSF, etc.) may be administered to maintain dose intensity or to avoid dose delays according to standard institutional practice or clinical practice guidelines (e.g., ASCO, ESMO).
Radiation:	Radiation therapy is not allowed during the study. If radiation therapy is needed to treat the symptoms due to underlying breast cancer, the subject will be discontinued from the study (as defined in Section 5.3.4.1).
Surgery:	If the subject requires surgery during the study, then this needs to be discussed with the AbbVie Medical Monitor.

Alternate Therapy	No anticancer Chinese medicine/herbal remedies may be taken concurrently with veliparib (a 14-day washout period must be documented).

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

A schedule of study activities is presented in Table 4 and Table 5. Pharmacodynamic (PD) and pharmacogenetic (PG) assessments will be performed as summarized in Table 6. Pharmacokinetic (PK) assessment will be performed as summarized in Table 7 and Table 8.

Table 4. Study Activities (Subjects Randomized to Veliparib + TMZ Treatment Arm)

Activity	Screening	Cycle 1 (Day)			Cycle 2 (Day)			Day 1 of Each Cycle (Starting with C3)	Day 1 of Every Other Cycle (Starting with C4	Every 9 Weeks from C1D1[j]	Final Visit[m]	30-Day Follow-up Visit[o]	Post Treatment Follow-up[p]
		1	15	22	1	15	22						
Informed Consent[a]	X												
Medical and Cancer History	X												
Physical Exam (including weight)	X[b]	X[c]	X	X	X	X	X	X			X	X	
12-lead ECG	X	X[d]									X[k]		
Vital Signs	X	X	X	X	X	X	X	X			X	X	
Pregnancy Test (women of childbearing potential)	X	X											
Hematology[e]	X	X[f]	X	X	X	X	X	X[g]			X	X	
Chemistry[e]	X	X[f]	X		X	X		X[g]			X	X	
Urinalysis[e]	X	X[f]			X			X[g]			X		
APTT/PT/INR	X												
BRCA1/2 germline mutation testing[h]	X												

Table 4. Study Activities (Subjects Randomized to Veliparib + TMZ Treatment Arm) (Continued)

Activity	Screening	Cycle 1 (Day)			Cycle 2 (Day)			Day 1 of Each Cycle (Starting with C3)	Day 1 of Every Other Cycle (Starting with C4)	Every 9 Weeks from C1D1[j]	Final Visit[n]	30-Day Follow-up Visit[o]	Post Treatment Follow-up[p]
		1	15	22	1	15	22						
Tumor Assessment	X[i]									X[j]	X[k]		
Full Body Bone Scan	X[l]												
Performance Status (ECOG)	X	X	X	X	X	X	X	X			X	X	
EORTC QLQ-C15/BR23		X[m]			X				X		X	X	
AE Assessment		X	X	X	X	X	X	X			X	X	
Randomization		X											
Dispense veliparib, TMZ		X			X			X					
Survival													X

Note: Study procedures (excluding labs) may be performed within four (4) days surrounding the scheduled study visit date.

Table 4. Study Activities (Subjects Randomized to Veliparib + Temozolomide Treatment Arm) (Continued)

a. Must be performed prior to the initiation of any screening or study-specific procedures.
b. Height will be recorded at Screening Visit only.
c. Physical exam not required, if performed within 7 days prior to C1D1, unless clinically indicated.
d. An ECG will be completed on C1D1 (at approximately 2 hours after the first dose of veliparib + TMZ).
e. Refer to Table 9 for detailed list of tests to be performed and frequency.
f. For Screening labs performed greater than 7 days prior to C1D1, hematology/chemistry should be split at C1D1 and local labs reviewed prior to dosing.
g. For Day 1 of each cycle after Cycle 2, clinical laboratory test may be collected within 48 hours of dosing veliparib/TMZ. A certified local laboratory may be used 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.
h. If BRCA germline mutation status is known from Sponsor core laboratory, the subject will not be retested.
i. The baseline tumor assessment, including diagnostic CT scans of the chest, abdomen, and pelvis, will be obtained no more than 28-days prior to C1D1.
j. Tumor assessments will be conducted every 9 weeks (tumor assessments may be conducted 8 days prior or 2 days following the scheduled assessment from C1D1).
k. To be performed at the Final Visit, only if not performed within the last 4 weeks.
l. Full body bone scan will be obtained no more than 28-days prior to C1D1.
m. Should be completed on C1D1 prior to dosing.
n. When an investigator has determined that a subject should discontinue the study, a Final Visit will be conducted.
o. All subjects will have one Follow-up Visit approximately 30 days after the last dose of study drug unless the subject had a Final Visit conducted ≥ 30 days after the last dose of study drug.
p. Information pertaining to survival and post treatment therapy will be collected monthly (unless requested by Sponsor more frequently to support data analysis) beginning on the date the subject is registered off study for a minimum of three (3) years until the endpoint of death, until the subject has become lost to follow-up, or until study termination by AbbVie.

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms)

Activity	Screening	C1D1	C1D3	C1D17	Day 1 of Each Cycle (Starting with Cycle 2)[r]	Day 3 of Each Cycle[r]	Day 1 of Every Other Cycle (Starting with C4)	Every 9 Weeks from C1D1[j]	Final Visit[n]	30-Day Follow-up Visit[o]	Post Treatment Follow-up[p]
Informed Consent[a]	X										
Medical and Cancer History	X										
Physical Exam (including weight)	X[b]	X[c]		X	X				X	X	
12-lead ECG	X		X[d]						X[k]		
Vital Signs	X	X	X	X	X	X			X	X	
Pregnancy Test (women of childbearing potential)	X	X									
Hematology[e]	X	X[f]		X	X[g]				X	X	
Chemistry[e]	X	X[f]		X	X[g]				X	X	
Urinalysis[e]	X	X[f]			X[g]				X		
APTT/PT/INR	X										
BRCA1 and 2 germline mutation testing[h]	X										

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms) (Continued)

Activity	Screening	C1D1	C1D3	C1D17	Day 1 of Each Cycle (Starting with Cycle 2)[r]	Day 3 of Each Cycle[r]	Day 1 of Every Other Cycle (Starting with C4)	Every 9 Weeks from C1D1[j]	Final Visit[n]	30-Day Follow-up Visit[o]	Post Treatment Follow-up[p]
Tumor Assessment	X[i]							X	X[k]		
Full Body Bone Scan	X[l]										
Performance Status (ECOG)	X	X		X	X				X	X	
CIPN Assessment (QLQ-CIPN20)		X[m]			X		X		X	X	
EORTC QLQ-C15/BR23		X[m]			X		X		X	X	
AE Assessment		X		X	X				X	X	
Randomization		X									
Dispense veliparib or placebo		X			X						
Administer paclitaxel premedication[q]			X			X					
Administer carboplatin + paclitaxel			X			X					
Survival											X

Note: Study procedures (excluding labs) may be performed within four (4) days surrounding the scheduled study visit date.

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms) (Continued)

a. Must be performed prior to the initiation of any screening or study-specific procedures.
b. Height will be recorded at Screening Visit only.
c. Physical exam not required, if performed within 7 days prior to C1D1, unless clinically indicated.
d. An ECG will be completed on C1D3 (at approximately 2 hours after the morning dose of veliparib/placebo).
e. Refer to Table 9 for detailed list of tests to be performed and frequency.
f. For Screening labs performed greater than 7 days prior to C1D1, hematology/chemistry should be split at C1D1 and local labs reviewed prior to dosing.
g. For Day 1 of each cycle after Cycle 1, clinical laboratory test may be collected up to 48 hours prior to dosing veliparib/placebo. A certified local laboratory may be used 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. If, based on these results, the subject is not anticipated to be able to receive carboplatin + paclitaxel on Day 3 of the cycle, then veliparib/placebo on Day 1 should be held until dosing of the entire regimen can resume. For subjects on study treatment for more than 5 years, central laboratory testing is no longer required.
h. If BRCA germline mutation status is known from Sponsor core laboratory, the subject will not be retested.
i. The baseline tumor assessment, including diagnostic CT scans of the chest, abdomen, and pelvis, will be obtained no more than 28 days prior to C1D1.
j. Tumor assessments will be conducted every 9 weeks (tumor assessments may be conducted 8 days prior or 2 days following the scheduled assessment from C1D1). For subjects on study treatment more than 5 years, tumor assessments will be conducted every 6 months.
k. To be performed at the Final Visit, only if not performed within the last 4 weeks.
l. Full body bone scan will be obtained no more than 28 days prior to C1D1.
m. Should be completed on C1D1 prior to dosing.
n. When an investigator has determined that a subject should discontinue the study, a Final Visit will be conducted. For subjects on study treatment more than 5 years, 12-lead ECG, urinalysis, CIPN Assessment (QLQ-CIPN20), EORTC QLQ-C15/BR23, and tumor assessments do not need to be performed at Final Visit.
o. All subjects will have one Follow-up Visit approximately 30 days after the last dose of study drug unless the subject had a Final Visit conducted ≥ 30 days after the last dose of study drug. For subjects on study treatment more than 5 years, CIPN Assessment (QLQ-CIPN20) and EORTC QLQ-C15/BR23 do not need to be performed at the Follow-up Visit.
p. Information pertaining to survival and post treatment therapy will be collected monthly (unless requested by Sponsor more frequently to support data analysis) beginning on the date the subject is registered off study for a minimum of three (3) years until the endpoint of death, until the subject has become lost to follow-up, or until study termination by AbbVie. For subjects on study treatment more than 5 years, there will be no post-treatment follow-up.

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms) (Continued)

q. 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.

r. For subjects remaining on study for more than 1 year, select Day 1 procedures can be performed on Day 3 after discussion with the AbbVie Medical Monitor. For subjects on study treatment more than 5 years, Day 1 visit is not required. Physical Exam, Hematology, Chemistry, Performance Status (ECOG), AE assessment, and Dispense Veliparib/Placebo can be performed on Day 3 instead. Urinalysis, CIPN Assessment (QLQ-CIPN20), and EORTC QLQ-C15/BR23 no longer need to be performed on either Day 1 or Day 3 for these subjects.

Table 6. Schedule Pharmacodynamic and Pharmacogenetic Assessments

Procedure	Visit Schedule[f]	Before Drug Administration	Sampling Plan Specimen Matrix
PD Blood Sampling[+] Plasma Markers[a,b]	C1D1, C2D1, and Day 1 of every 10th cycle (C10, C20, etc.)	Pre-dose	Blood → Plasma Frozen –70°C or colder
	Final Visit	At the time of the clinic visit	
Serum Markers	C1D1, C2D1, and Day 1 of every 10th cycle (C10, C20, etc.)	Pre-dose	Blood → Serum Frozen –70°C or colder
	Final Visit	At the time of the clinic visit	
BRCA Sequencing: Bridging Sample	C1D1		Blood Frozen –20°C or colder
Circulating tumor cells (CTC)[c] **US Sites Only**	C1D1 and C2D1	Pre-dose	Blood Shipped Fresh on the day of collection (must be kept ambient until shipped)
	C1D15[d]/C1D17[e] and Final Visit	At the time of the clinic visit	
Optional with Consent **Serial Biopsies***	C1D1	Pre-dose	Flash Frozen –70°C and FFPE 4°C
	Final Visit	At the time of clinic visit	
Optional with Consent **Tissue Sample Collection*** IHC/FISH	FFPE tissue blocks		Diagnostic, formalin fixed, paraffin embedded (FFPE) tissue blocks 4°C
Optional with Consent **PG Blood Sampling*** Genetic (DNA)	C1D1		Blood Frozen –20°C or colder

a. An additional sample may be collected at the time of discontinuation due to an adverse event.

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

c. CTC/DNA repair collection should not be the first tube drawn. For US sites only.

d. For subjects randomized to the veliparib + TMZ treatment arm.

e. For subjects randomized to the veliparib/placebo + carboplatin + paclitaxel treatment arms.

f. For subjects on study treatment more than 5 years, any sampling scheduled for Day 1 of every 10th cycle or Final Visit will no longer be required.

* Optional with consent.

\+ If a drug interruption is needed, the subject will continue to have study visits as planned; however, PD samples will not be drawn during this period.

Table 7. Schedule of Pharmacokinetic Assessment (Subjects Randomized to Veliparib + TMZ Treatment Arm)

Procedure	Visit Schedule	Before Drug Administration	After Veliparib AM Dose	Sampling Plan
				Specimen Matrix
Veliparib PK Sampling[a]	C1D1	--	0.5, 1, 2, 3 h	Blood → Plasma Frozen –20°C or colder

a. All samples should be drawn in conjunction with clinical lab blood draws.

Note: The date and time of sample collection and the date and time of the morning dose of veliparib will be captured on the eCRF.

Table 8. Schedule of Pharmacokinetic Assessments (Subjects Randomized to Veliparib or Placebo + Carboplatin + Paclitaxel Treatment Arms)

Procedure	Visit Schedule	Before Drug Administration	After Veliparib AM Dose	Sampling Plan
				Specimen Matrix
Veliparib PK Sampling[a,]	C1D3	0 h[a]	0.5, 1, 2, 3 h	Blood → Plasma Frozen –20°C or colder
Veliparib PK Sampling[a,]	C2D3	0 h[a]	-	Blood → Plasma Frozen –20°C or colder
Paclitaxel PK Sampling[+]	C1D3	--	2 h 55 min after start of Paclitaxel infusion[b]	Blood → Plasma Frozen –20°C or colder
Free Platinum (for Carboplatin)*[+] Pharmacokinetic Sampling	C1D3	--	25 min after start of the carboplatin infusion[c]	Blood → Plasma Frozen –80°C or colder

a. Before the administration of the morning dose of veliparib. The morning dose of veliparib/placebo should be dosed in the clinic prior to carboplatin + paclitaxel on C1D3 and C2D3.

b. Approximately 3 hours after the morning veliparib dose.

c. Approximately 3.5 hours after the morning veliparib dose.

* Sites without an -80 freezer, must ship samples the same day.

\+ If a drug interruption is needed, the subject will continue to have study visits as planned; however, PK samples will not be drawn during this period.

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

5.3.1.1 Study Procedures

The study procedures outlined in Table 4 and Table 5 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 6.0). All study data will be recorded within the EDC system.

Screening procedures will occur within 28 days prior to C1D1 (excluding BRCA testing which may occur greater than 28 days prior to C1D1). 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. For Day 1 of each cycle after Cycle 2, lab samples may be collected up to 48 hours prior to dosing veliparib/TMZ. For Day 1 of each cycle after Cycle 1, lab samples may be collected up to 48 hours prior to dosing veliparib/placebo. For subjects on study treatment more than 5 years, laboratory samples may be collected up to 4 days prior to dosing carboplatin/paclitaxel on Day 3.

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. A separate informed consent will be required for the optional pharmacogenetic testing, needle/excisional/punch biopsy, and archival tissue collection. 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:
  - 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 C1D1 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 C1D1, PE is not required on C1D1, unless clinically indicated. Clinically

significant changes from baseline will be documented in the source documentation and eCRF as adverse events.

12-lead Electrocardiogram (ECG)

For subjects randomized to the veliparib + TMZ treatment arm, a resting 12-lead ECG will be performed at the Screening Visit within 28 days of C1D1 (prior to the first dose of veliparib/TMZ to document the baseline status of the subject). C1D1 (at approximately 2 hours after the morning dose of study drug), and Final Visit (if not performed within the last 4 weeks). For subjects randomized to the veliparib/placebo + carboplatin + paclitaxel treatment arms, a resting 12-lead ECG will be performed at the Screening Visit within 28 days of C1D1 (prior to the first dose of veliparib/placebo to document the baseline status of the subject), C1D3 (at approximately 2 hours after the morning dose of veliparib/placebo), and at the Final Visit (if not performed within the last 4 weeks). 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. Final Visit ECG will not be required for subjects on study treatment more than 5 years.

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

For female subjects of childbearing potential, a serum pregnancy test will be performed within 7 days of C1D1 and a urine pregnancy test will be done at the C1D1 visit prior to the first dose of study drug. A serum pregnancy test can be performed at C1D1 and analyzed locally prior to randomization. If a serum pregnancy test is performed on C1D1,

a urine pregnancy test does not need to be completed. Subjects considered not of childbearing potential must be documented as being surgically sterile or postmenopausal (for at least 1 year).

The C1D1 urine pregnancy test results must be reviewed and determined to be negative prior to dosing. If the urine pregnancy test is positive at C1D1, it should be confirmed by a serum pregnancy test and dosing should be delayed. The test may be repeated at the discretion of the investigator at any time during the study.

Clinical Laboratory Tests

All subjects will undergo the laboratory assessments outlined in Table 9.

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. The appropriate certifications will be collected from both the central and local laboratories, as needed.

For subjects remaining on study treatment for more than 5 years, use of the certified central laboratory will be discontinued. A certified local reference laboratory will perform CBC and chemistry test prior to dosing carboplatin/paclitaxel. Local laboratory results should be documented in the source and the electronic data capture (EDC) system as appropriate. Samples will no longer be sent to the central laboratory for analysis.

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 C1D1, hematology/chemistry should be split at C1D1 and local labs reviewed

prior to dosing. For subjects randomized to veliparib + TMZ, for Day 1 of each cycle after Cycle 2, lab samples may be collected up to 48 hours prior to dosing veliparib/TMZ. For subjects randomized to veliparib/placebo + carboplatin + paclitaxel, for Day 1 of each cycle after Cycle 1, lab samples may be collected up to 48 hours prior to dosing veliparib/placebo. For subjects on study treatment more than 5 years, lab samples may be collected up to 4 days prior to dosing carboplatin/paclitaxel.

- Urinalysis samples will be collected at Screening and on Day 1 of each subsequent cycle. Urinalysis will no longer be required for subjects on study treatment more than 5 years.
- APTT/INR will be collected at Screening.
- BRCA1 and BRCA2 germline mutation will be collected at Screening (unless BRCA germline mutation status is known per previous Sponsor core laboratory testing).
- For subjects randomized to the veliparib + TMZ treatment arm, chemistry samples will not be collected on C1D22 and C2D22.

In addition:

- For subjects randomized to the veliparib + TMZ treatment arm, only hematology samples will be collected Day 22 of Cycle 1 and Cycle 2.

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 9. 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) Estimated glomerular filtration rate (eGFR) 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.

** Collected prior to C1D1 (unless BRCA germline mutation status is known per previous Sponsor core laboratory testing).

*** For subjects on study treatment for more than 5 years, hematology and chemistry laboratory tests should be per local standard of care/institutional guidelines, and should include neutrophils, platelets, SGOT/AST, SGPT/ALT, total bilirubin, and alkaline phosphatase.

BRCA1/BRCA2 Testing

BRCA1 and BRCA2 Germline Mutation Testing

The diagnosis of a 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 unknown significance 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 BRCA1 or BRCA2 mutation.

  If the diagnostic testing for BRCA1/BRCA2 was not conducted by the Sponsor core laboratory, the investigator should ensure that the testing 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 C1D1.

  Note: These subjects may be eligible for randomization prior to receiving results from the Sponsor core laboratory.

- Subjects who are considered high risk for carrying a BRCA1/BRCA2 mutation are eligible for Sponsor core BRCA testing if they meet one of the following criteria (per the most current NCCN guidelines):[50]
  - Breast cancer diagnosed at age ≤ 45 years;
  - Breast cancer diagnosed at age ≤ 50 years with ≥ 1 first-, second-, or third-degree blood relative with breast cancer diagnosis ≤ 50 years and/or ≥ 1 first-, second-, or third-degree blood relative with epithelial ovarian/fallopian peritoneal cancer at any age;

- Diagnosed at age ≤ 60 years with a triple negative breast cancer;
- Diagnosed at age ≤ 50 years with a limited family history;
- Two breast primaries (i.e., bilateral disease or two or more clearly separate ipsilateral primary tumors) when first breast cancer diagnosis occurred ≤ age 50 years;
- Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer;
- Diagnosed at any age, with ≥ 2 first-, second-, or third-degree relatives with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age;
- Breast cancer diagnosed at any age with ≥ 2 first-, second-, or third-degree relatives with pancreatic cancer at any age;
- Individual from a family with a known deleterious BRCA1/BRCA2 mutation;
- Ashkenazi Jewish descent;
- Personal history of male breast cancer; or
- First-, second-, or third-degree male relative with breast cancer.

Note: Patients who pre-qualify with one or more of these criteria will be eligible to screen for BRCA1/BRCA2 mutation by the Sponsor core laboratory. These subjects may be eligible for randomization upon receipt of documentation of a deleterious germline BRCA1/BRCA2 mutation by the Sponsor core laboratory. Germline mutation testing obtained greater than 28 days prior to Cycle 1 Day 1 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 to be tested at a future date.

Tumor Assessments (Radiologic)

Appropriate diagnostic CT assessments using modified RECIST version 1.1[51] 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, and pelvis (or MRI) to determine the extent of tumor burden will be performed for all tumor assessments at Screening (within 28 days of C1D1), every 9 weeks from C1D1 (tumor assessments may be conducted 8 days prior or 2 days following the scheduled assessment), and at the Final Visit (if not performed within the last 4 weeks). For subjects on study treatment more than 5 years, tumor assessments will be conducted every 6 months (± 6 weeks) from C1D1 instead of every 9 weeks from C1D1, and will not be required at Final Visit. 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.

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. Subjects

who discontinue treatment for reasons other than radiographic disease progression will continue to be followed every 9 weeks from C1D1 to determine the extent of tumor burden, until disease progression occurs. For subjects on study treatment more than 5 years, tumor assessments will be discontinued if subject discontinues treatment for any reason.

In addition to being reviewed by the investigator and/or site staff, radiology scans will be sent to a central imaging center (Perceptive) within 2 days of collection for review. Subject treatment management will be based on review by the local investigator and/or site staff. The central imaging center will provide instructions regarding the preparation and shipment of the images. Radiology scans will be assessed by the central imaging center according to RECIST (version 1.1) as outlined in Section 5.3.4. Interpretations from the central imaging center will not be sent to the site. For subjects on study treatment more than 5 years, radiology scans will not be sent to the central imaging vendor.

All events of disease progression must be confirmed by the central imaging center (except for subjects on study treatment more than 5 years). The investigator should treat according to clinical judgment. However, it is recommended that the subjects interrupt dosing, but remain on study, until the investigator and/or site staff receives notification from AbbVie or the central imaging vendor that the subject's event of disease progression was confirmed. If progression is not confirmed, the subject should remain on study and continue to undergo the scheduled assessment until objective evidence of progression is obtained.

ECOG Performance Status

ECOG performance status will be assessed at all visits, unless indicated otherwise.

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.

Interim Futility Analysis: Procedures if Futility Is Declared

An interim futility analysis will be conducted after the Week 27 tumor assessment of the first 30 subjects randomized to the veliparib + TMZ treatment arm. If futility is declared at the time of the futility analysis for the veliparib + TMZ treatment arm, any subjects receiving veliparib + TMZ will be allowed the option of either 1) receiving 120 mg BID veliparib + carboplatin + paclitaxel or 2) discontinuing therapy.

Subjects who choose to receive treatment with veliparib + carboplatin + paclitaxel must be allowed at least 28 days to washout from veliparib + TMZ and will be allowed up to 60 days between the last treatment with veliparib + TMZ and the initial dose of veliparib + carboplatin + paclitaxel. The investigator will contact the AbbVie Medical Monitor for direction regarding subjects who require a treatment gap of more than 60 days.

For subjects who choose to receive veliparib + carboplatin + paclitaxel, the investigator must attest that the subjects continue to meet eligibility criteria and have adequate hematologic, renal, and hepatic function as follows:

- Bone Marrow: ANC ≥ 1500/mm^3 (1.5 × 10^9/L); Platelets ≥ 100,000/mm^3 (100 × 10^9/L); Hemoglobin ≥ 9.5 g/dL (5.89 mmol/L); Leukocytes > 3,000/mm^3;
- Renal Function: Serum creatinine ≤ 1.5 × ULN range **OR** creatinine clearance ≥ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal;
- Hepatic Function: AST and/or ALT ≤ 2.5 × institutional upper limit of normal. For subjects with liver metastases, AST and/or ALT < 5 × ULN range; bilirubin ≤ 1.5 × the ULN range. Subjects with Gilbert's syndrome may have a bilirubin ≥ 1.5 × the ULN range, if no evidence of biliary obstruction exists;
- APTT must be ≤ 1.5 × the ULN range and INR < 1.5. Subjects on anticoagulant therapy will have an appropriate PTT and INR, as determined by the investigator.

The investigator must also attest that the subject does not have any clinically significant uncontrolled conditions including, but not limited to:

- Active infection;
- Symptomatic congestive heart failure;
- Unstable angina pectoris or cardiac arrhythmia;
- Myocardial infarction within last 6 months;
- Psychiatric illness/social situations that would limit compliance with study requirements; or
- Any medical condition which in the opinion of the investigator places the subject at an unacceptably high risk for toxicities.

CIPN Assessment

CIPN (as assessed by the EORTC QLQ CIPN20 questionnaire and NCI-CTCAE 4.0 grading for peripheral neuropathy) will be assessed on C1D1, C2D1 and every other cycle thereafter beginning with Cycle 4 (C6, C8, etc.) Final Visit, and at the Follow-up Visit in subjects randomized to the veliparib/placebo + carboplatin + paclitaxel treatment arms.

CIPN assessment will no longer be required at any visit for subjects on study treatment for more than 5 years.

Quality of Life

To assess the subject's QoL, the EORTC QLQ-C15/BR23 (including questions on cognition) questionnaires (Appendix C and Appendix D), respectively) will be administered at C1D1 pre-dose, C2D1, and every other cycle thereafter beginning with Cycle 4 (C6, C8, etc.), Final Visit, and at the Follow-up Visit. The subject will complete quality of life questionnaire worksheets. Site personnel will check the worksheets returned by the subject for completeness before the subject leaves the clinic. If the subject is unable to complete the form, qualified site personnel may administer the questionnaires via interview and complete the worksheets for the subject. EORTC QLQ-C15/BR23 questionnaires will no longer be administered at any visit for subjects on study treatment for more than 5 years.

The EORTC QLQ-C15/BR23 is a 38-item questionnaire that was developed to assess health-related quality of life among subjects with breast cancer. Scores can be calculated from the EORTC QLQ-C15/BR23, including physical and emotional well-being, and breast symptom-specific questions.[52] *Note: The QlQ-BR23 is a module of the QLQ-C30. The QLQ-C30 (30-item questionnaire) is not being used for this study; therefore, the QLQ-BR23 questionnaire administered to the study subjects will begin with question number 31.*

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 5.2.1 and none of the exclusion criteria in Section 5.2.2 will proceed to randomization. The site will access the system on or prior to the subject's C1D1 visit and a unique randomization number will be provided.

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.

Dispensation of Study Drug

Subjects randomized to the veliparib + TMZ treatment arm will receive sufficient quantities of veliparib for 7 days of administration in each 28-day cycle and sufficient quantities of TMZ for 5 days of administration in each 28-day cycle. Veliparib + TMZ will be dispensed prior to dosing at each cycle (Day 1 of each cycle).

For subjects randomized to the veliparib/placebo + carboplatin + paclitaxel treatment arms, subjects will receive sufficient quantities of veliparib or placebo for 7 days of administration in each 21-day cycle and sufficient quantities of carboplatin at a dose of AUC 6 and paclitaxel at a dose of 175 mg/m^2. Trained site personnel will administer the carboplatin + paclitaxel intravenously on Day 3 of each 21-day cycle. Subjects will be supervised at the time of the infusion. For subjects on study treatment more than 5 years, veliparib/placebo may be dispensed at the Day 3 visit instead of the Day 1 visit. Sufficient medication will be dispensed to cover an entire cycle. The site is advised to contact the subject on the morning of Day 1 to reiterate the dosing instructions of veliparib/placebo. It is recommended the site contact the subject on Day 7 to instruct about ceasing dosing.

The IVRS/IWRS will assign bottles of veliparib or placebo and bottles/cartons of TMZ 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. Site personnel must contact

the IVRS/IWRS for the bottle number assignments no more than 5 days before Day 1 of each cycle (or Day 3 for subjects on study treatment more than 5 years who are having veliparib/placebo dispensed at Day 3). 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.

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).

Subjects will be provided with self-administration instructions and subject dosing cards. Subjects will be instructed to store veliparib or placebo and TMZ according to specific directions included in Section 5.5.2.2. Subjects should return bottles of veliparib or placebo and TMZ (empty, partially filled, or full) to the study site prior to each cycle and at the Final Visit.

Post treatment Information

Post treatment information will be collected via IVRS/IWRS at monthly intervals (or as requested by Sponsor to support data analysis) beginning on the date the subject is registered off study and for up to three (3) years until the endpoint of death, the subject has become lost-to follow-up, or AbbVie terminates the study.

All subjects will be followed for survival information (i.e., the date and cause of death) unless the subject requests to be withdrawn specifically from study survival follow-up; this request must be documented in the subject's medical record and signed by the investigator.

If the subject withdraws from the study 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.

No post-treatment information will be collected for subjects on study treatment for over 5 years.

If known, post treatment anticancer therapies, dates of initiation, and end dates will be reported.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis

If PG testing is performed, results from individual subjects will be kept coded and confidential and will not be given to anyone not directly involved with this research study. AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. Samples will be coded so that subject identities will not be available to the scientists conducting the genotyping analyses. Individual subject results will not be provided to the investigator, so that neither the subject nor the investigator will have knowledge of specific subject genotypes. AbbVie will keep the DNA samples until they are destroyed by AbbVie when this research is completed. These samples will not be stored longer than 20 years.

Collection of Pharmacogenetic Sample (Optional)

One 4-mL whole blood sample for DNA isolation will be collected at C1D1 from each subject who consents to provide samples for PG analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Whole blood will be collected by standard phlebotomy techniques, as described below:

- Collect approximately 4 mL of blood into an appropriately labeled EDTA tube.
- Immediately invert the collection tube 8 to 10 times to reduce the likelihood of clot formation.
- The sample collection tubes will be labeled as "PG Sample," with the protocol number, subject number, and study day and/or collection date.
- Store samples at –20°C or colder within 30 minutes of the blood draw until shipped/transported.

Shipment of Pharmacogenetic Samples

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

5.3.1.3 Blood Samples for Pharmacodynamic Analysis

PD correlative studies are exploratory in nature. Serum and plasma specimens may be utilized to evaluate known and novel markers (nucleic acids, peptides/proteins, and metabolites) of disease status. Additional studies may include assessment of methylation and mutational status of circulating DNA for biomarkers that correspond with patient response to treatment. Tissue biopsies and/or circulating tumor cells may be examined for the tumor-specific alterations of cellular proteins/peptides and/or nucleic acids. Furthermore, tumor tissues may be examined for resistance factors, including, but not limited to acquiring secondary mutations known to restore BRCA function. AbbVie may examine the underlying causes of these alterations through determination of the amplification/mutation or methylation status of various genes, for example genes involved in DNA repair and tumor suppression. PD variables will be further discussed in Section 5.3.8.

Blood Collection for Plasma Markers

Whole blood samples (approximately 12 mL at C1D1 and 6 mL at all other time points) will be collected by any standard phlebotomy technique from a peripheral venous access point to obtain plasma sample aliquots at the following time points: pre-dose on C1D1, C2D1, Day 1 of every 10th cycle (C10, C20, etc.) and the time of the clinic visit for the Final Visit. For subjects on study treatment more than 5 years, sampling scheduled for Day 1 of every 10th cycle or Final Visit will no longer be required.

Handling and Processing of Plasma Markers

The complete process of centrifugation, transfer to cryovial, and freezing should be accomplished in less than 1 hour from blood draw. Samples should be processed as follows:

1. Collect the blood sample into appropriately labeled 6-mL EDTA (purple top) tubes (use 2 tubes for C1D1).
2. Immediately invert the tubes 8 to 10 times to reduce the likelihood of clot formation.
3. Centrifuge the blood samples at 1100 to 1300 × g for 15 minutes using a refrigerated centrifuge at 2°C to 8°C.
4. Within 15 minutes, transfer the plasma sample into labeled 2-mL cryovials (divide the plasma between a total of four 2-mL cryovials for C1D1 and between a total of two 2-mL cryovials for all subsequent samples). The cryovials should be labeled with the study drug number, sample matrix (plasma), protocol number, subject number, time point, and date.
5. Store the samples immobile and upright at –70°C or colder until shipped frozen to designated laboratory. For sites that do not have access to a –70°C freezer, more frequent shipments (e.g., monthly versus quarterly) to the central laboratory may be required.

Blood Collection for Serum Markers

Approximately 5 mL of blood will be collected by venipuncture into a 5-mL SST (gold top) tube at the following time points: pre-dose on C1D1, C2D1, Day 1 of every 10th cycle (C10, C20, etc.) and at the time of clinic visit for the Final Visit. For subjects on study treatment more than 5 years, any sampling scheduled for Day 1 of every 10th cycle or Final Visit will no longer be required. The collection should be performed as described below. The complete process of clot formation, centrifugation, transfer to

cryovials, and freezing should be accomplished in less than 90 minutes from the time of blood draw.

- Collect the blood sample into a 5-mL SST (gold top) tube.
- Immediately invert the collection tube 5 times.
- Allow blood to clot for a minimum of 30 minutes in a vertical position, until a dense clot is observed.
- Centrifuge sample at 1100 to 1300 × g for 15 minutes at room temperature to ensure adequate separation of the serum.
- Within 15 minutes, transfer the serum into two separate 2-mL labeled cryovials and freeze at –70°C or colder.
- Store samples at –70°C or colder until they are shipped to the central laboratory on dry ice sufficient for 3 days.

Shipment of Plasma and Serum Marker Samples

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

Blood Collection for BRCA Bridging Sample

Two 4-mL whole blood samples for DNA isolation will be collected at C1D1 from each subject for BRCA testing at the Sponsor core laboratory and at an FDA-approved study laboratory.

Whole blood will be collected by standard phlebotomy techniques, as described below:

- Collect approximately 4 mL of blood into 2 appropriately labeled EDTA tubes.
- Immediately invert the collection tube 8 to 10 times to reduce the likelihood of clot formation.
- Store samples at –20°C or colder within 30 minutes of the blood draw, until shipped/transported on dry ice sufficient to last during shipment/transport to a

designated lab. Samples should not be allowed to thaw prior to arrival at the designated laboratory.

Shipment of Plasma BRCA Bridging Samples

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

Blood Collection and Shipment for Circulating Tumor Cells (CTC) (US Sites Only)

Approximately 10 mL of blood will be collected by any standard phlebotomy technique from a peripheral venous access point into appropriately labeled 10-mL Cellsave tube at the following time points C1D1 and C1D15 for subjects randomized to the veliparib + TMZ treatment arm, C1D1 and C1D17 for subjects randomized to the veliparib/placebo + carboplatin + paclitaxel treatment arms, C2D1 and Final Visit (for subjects in all treatment arms in the US only).

- Remove the tube from the adapter and gently invert it 8 times to mix and prevent clotting (inadequate or delayed mixing may result in inaccurate test results).
- The sample requires shipment to AbbVie on the day of collection and, therefore, if sample is collected on Friday, it should be shipped for Monday delivery.
- The specimen will be labeled with the study drug number, sample matrix (blood), assay type (CTC), protocol number, subject number, and collection date.
- The specimen will be packed and shipped in a styrofoam container overnight to AbbVie.
- Notify AbbVie of shipment via e-mail to [redacted] and/or [redacted] and fax the completed form to +1[redacted]

Shipping address:

[redacted]
AbbVie
[redacted]
1150 S. Northpoint Blvd.
Waukegan, IL 60085
Phone: [redacted]

Tissue Collection for IHC and FISH DNA Mutational/Methylation Analysis

Archived Tissue Samples

If available, fixed samples from most recent pathological analysis will be collected from subjects (with consent).

Immunohistochemistry (IHC), tumor DNA methylation and mutational analysis, FISH, and/or quantitative polymerase chain reaction (qPCR) may be performed on tissue slides from archived, diagnostic, formalin-fixed, paraffin-embedded (FFPE) tissue blocks from all subjects who consent in the study.

The site may either submit an archived tissue block or cut tissue section on slides. From each representative FFPE tumor tissue, the local pathology laboratory should apply 10 slices of tissue with a thickness of approximately 4 to 6 microns and 5 slices of tissue with a thickness of approximately 10 microns to positively charged slides to be used for IHC, mutational, and FISH analysis. Therefore, a minimum of 15 slices of tissue sections should be collected from each subject block. In cases where there is not enough appropriate tissue available to provide these sections, the investigator will communicate with the pathology laboratory to determine the maximum number of slides that can be provided and relay that information to AbbVie prior to slide preparation.

To ensure optimal sampling, two quality control slides must also be prepared by the pathology laboratory and included in the shipment of slides to the designated lab. These

quality control slides will be representative of the beginning and of the end of the tissue section. These slides are to be stained using hematoxylin and eosin (H&E) and reviewed by the local pathologist to ensure the diagnostic quality of viable tumor and normal cells (i.e., large regions of necrosis or areas composed primarily of fibrous connective tissue or adipose tissue are not the predominant feature). The remaining tissue prepared for the unstained slides will be procured from the sections closest to the section that is of adequate diagnostic quality.

Included with each shipment should be a copy of the pathology report with all specific subject identification information removed or blacked out and a completed shipment inventory form. The FFPE tissue block or slide boxes should be labeled with study drug number, sample matrix (tissue), protocol number, subject number, and collection date. Slide boxes should be packaged using suitable shipping materials and sent to the designated lab at ambient temperature. If the blocks are to be returned, please provide clear instructions and the return address.

Serial Biopsies When Deemed Feasible by the Investigator

Biopsies (needle, punch, or excisional) will be obtained at the C1D1 visit prior to therapy and at the Final Visit, when feasible, for all subjects who consent and who have readily accessible tumor tissue. Because of the concern regarding increased risk associated with lung, mediastinal lymph nodes, and liver biopsies, no lung, liver, or mediastinal lymph node biopsies will be performed as part of this study.

It is preferred that at least 2 core biopsies be obtained. These biopsies should be at least 18 gauge in diameter and at least 1 cm in length. Alternatively, biopsies for superficial lesions (cutaneous and subcutaneous), may be obtained via punch or excisional biopsy. For excisional and punch biopsies, a single specimen is adequate provided it can be bisected into 2 adequate samples. It is estimated that there will be between 2 to 5 million cells from each biopsy. All biopsies should be labeled with study drug number, sample matrix (tissue biopsy), protocol number, subject number, and collection date.

One core or one portion of the punch or excisional biopsy should be fixed in formalin for between 8 to 24 hours, then embedded in paraffin. These samples will be stored at 4°C to maintain the sample integrity until shipment to the designated laboratory. These samples will be shipped at ambient temperature. Upon notification from AbbVie, the samples will be shipped to the designated laboratory. These samples can be batched and shipped either monthly or quarterly depending on the number of samples.

The second core or second portion of the punch or excisional biopsy specimen should be placed into a properly labeled cryovial. The label on the cryovial should be wrapped with scotch tape so that the ends of the tape overlap and the label is completely covered. This tumor sample, whether obtained via needle, excisional, or punch biopsy will be flash-frozen in liquid nitrogen immediately after collection (alternatively, a dry ice bath with ethanol or methanol may be used). This specimen will be stored frozen at –70°C.

5.3.1.4 Collection and Handling of Pharmacodynamic Samples

The blood and tissue samples for PG and PD analyses will be shipped from the study site to a designated laboratory according to instructions in the laboratory manual from AbbVie. Samples will be labeled with the drug number name, type of sample (e.g., blood), assay type (e.g., DNA), the protocol number, the subject number, and the study day and/or collection date. An inventory of the samples included must accompany the package.

5.3.2 Drug Concentration Measurements

Pharmacokinetic variables are discussed in Section 5.3.6.

5.3.2.1 Collection of Samples for Analysis

Plasma Samples for Subjects Randomized to Veliparib + TMZ Arm

Blood samples for determination of plasma concentration of veliparib will be collected only from those subjects randomized to receive veliparib + TMZ on C1D1. The date and time of sample collection and the date and time of the morning dose of veliparib will be

captured on the eCRF. Approximately 4 mL of blood will be collected by venipuncture into one 4-mL potassium EDTA (purple cap) tube in conjunction with clinical lab blood draws (if possible) per Table 7. 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.

Sufficient blood will be collected to produce approximately 1.5 mL of plasma for each sample. The date and time of collection for each sample will be recorded.

Plasma Samples for Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Arms

Blood samples for determination of plasma concentration of veliparib, paclitaxel, and free platinum (for carboplatin) will be collected from subjects randomized to receive veliparib/placebo + carboplatin + paclitaxel on C1D3 and determination of plasma concentration of veliparib on C2D3. 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 4 mL of blood will be collected by venipuncture into one 4-mL potassium EDTA (purple cap) tube in conjunction with clinical lab blood draws (if possible) per Table 8. 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.

Sufficient blood will be collected to produce approximately 1.5 mL of plasma for each sample. The date and time of collection for each sample will be recorded.

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

5.3.2.2 Handling/Processing of Samples

Blood Samples for Veliparib and Paclitaxel Pharmacokinetic Analysis

The complete process of centrifugation, transfer to polypropylene tubes, and freezing should be accomplished within 60 minutes from blood draw. The processing of pharmacokinetic samples should be performed, as described below:

- Collect the blood sample in a 4-mL EDTA (purple top) tube.
- Immediately invert the collection tubes 8 to 10 times.
- Centrifuge sample at 1100 to 1300 × g for 10 minutes at 2° to 8°C. If a refrigerated centrifuge is not available, the samples must be thoroughly chilled in an ice water bath prior to centrifugation and then must be removed from the centrifuge as soon as the rotor comes to a complete stop and either placed back in the ice water bath or immediately processed and frozen.
- 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.

Blood Samples for Free Platinum Pharmacokinetic Analysis

The complete process of centrifugation, transfer to polypropylene tubes and freezing should be accomplished within 60 minutes from blood draw. The processing of PK samples should be performed, as described below:

- Collect the blood sample in a 4-mL EDTA (purple top) tube.
- Immediately invert the collection tubes 8 to 10 times.
- Centrifuge sample at 1100 to 1300 × g for 10 minutes at 2° to 8°C. If a refrigerated centrifuge is not available, the samples must be thoroughly chilled in an ice water bath prior to centrifugation and then must be removed from the centrifuge as soon as the rotor comes to a complete stop and either placed back in the ice water bath or immediately processed and frozen.
- Transfer plasma into an appropriately labeled (drug name, type of sample, protocol number, subject number, treatment cycle and day, the planned time of sample collection relative to dosing and the sample collection date) screw-capped polypropylene tube and pack on dry ice for shipping.

- Samples for free platinum analysis should be shipped on dry ice to the central lab on the same day of draw. Note: Samples will freeze when placed upright in the dry ice.
- If plasma samples cannot be shipped same day of draw, then samples must be frozen upright at –80°C or colder within 1 hour after collection and must be shipped frozen to the central laboratory within 5 days. 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, paclitaxel, and free platinum (plasma ultrafiltrate) will be determined under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

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 C1D1) thereafter, and at the Final Visit, if not performed within the last 4 weeks. Assessments will be modified for subjects on study treatment more than 5 years as indicated in Section 5.3.1.1.

The primary efficacy endpoint will be PFS. The secondary endpoints will be OS, CBR, and ORR in those subjects treated with veliparib plus TMZ or treated with veliparib plus carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel and to assess CIPN (as assessed by the EORTC QLQ-CIPN20 questionnaire and NCI-CTCAE 4.0 grading for peripheral neuropathy) in those subjects treated with veliparib plus carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel. The tertiary endpoints will include ECOG performance status, QoL, and exploratory correlative studies.

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 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 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 measurements should be taken using calipers and recorded in metric notation, if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days prior to the beginning of treatment.

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 axial contiguous 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 assessments of response (CR or PR) must be confirmed by scans not less than 4 weeks apart.

All other lesions (or sites of disease), including pathological lymph nodes 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 timepoints 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 and normalization of tumor marker level. 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) and/or maintenance of tumor marker level above the normal limits.

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. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain, which reveals metastases. The subject's brain metastases are considered evidence of progressive disease even if he or she did not have brain imaging at baseline.

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.

5.3.4.1 Definition of Disease Progression

Disease progression will be defined as progression of disease by RECIST version 1.1. Clinical data that support progression will be collected and submitted for central review (i.e., report of skin lesions measurements, cytology, bone scan).

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. Clinical progression may be characterized, but not limited to, an increase of at least 2 points in ECOG performance status attributable to cancer progression, requirement for palliative radiation, chemotherapy, or surgery, or death from disease progression.

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.

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.

During the conduct of the study, an IDMC will review unblinded safety data. Please refer to Section 8.1.9 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 the PK parameters of veliparib, including maximum observed plasma concentration (C_{max}), the time of C_{max} (peak time, T_{max}), and the area under the plasma concentration-time curve (AUC) will be determined using noncompartmental methods, if the data warrant.

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 Pharmacogenetic Variables

DNA samples may be analyzed for genetic factors contributing to the subject's response to veliparib, or other study treatment, in terms of pharmacodynamics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug-metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to veliparib or drugs of this class. The samples may also be used for the development of diagnostic tests related to veliparib (or drugs of this class). The results of pharmacogenetic analyses may not be reported with the study summary.

5.3.8 Pharmacodynamic Variables

Several putative biomarkers of efficacy and response may be evaluated with the goal of defining the relationship between drug concentration, PARP inhibition, and disease status. The biomarker analysis may include the examination of plasma and serum components such as, nucleic acids, proteins/peptides, and metabolites. If warranted, additional studies may include the analysis of the methylation and mutational status of circulating DNA or RNA and quantification and characterization of circulating tumor cells isolated from an individual. Characteristics of tumor tissue and tumor nucleic acids may be explored and examined in archived or fresh tissue biopsies, circulating tumor cells, and cell-free nucleic acids isolated from blood components. These characterizations may be included, but are not limited, quantification of protein, nucleic acid, or metabolites, and characterization of gene methylation/mutational status or post-translational modification of proteins, particularly those involved in DNA repair pathways. 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.

Plasma and Serum Markers

Examination of the plasma and serum components subjects on the veliparib clinical trial may reveal patterns of nucleic acid, protein/peptide, and metabolite concentrations that may be further evaluated in future clinical studies to determine any prognostic value and any correlation with clinical response. Samples may be analyzed for markers (e.g., CA15-3 and HER2/NEU) that could be either prognostic or predictive of drug-response.

Stratification Markers

Genetic amplification, chromosomal loss, and/or mutational status of various genes, including, but not limited to those, in the DNA repair pathway represent genetic lesions potentially associated with subject outcome. Gene and protein expression, FISH, and/or mutational methylation analysis may be conducted on tissue from archived serial biopsy tumor samples, CTC, and/or nucleic acids extracted from plasma from subjects participating in this study to assess modifications, which may prove to be informative. The potential relationship between amplification/loss/mutation of these entities and the clinical outcome in these subjects may be examined as a patient stratification tool.

DNA methylation regulates gene expression (inactivates certain genes) and aberrant methylation of specific genes is associated with cancer development and poor clinical outcome. Tumor-derived DNA may be examined for variable methylation status of genes that are known to have prognostic implications associated with subjects enrolled in this trial. The list of potential genes includes, but is not restricted to: RASSF1A, CDH1, Cyclin D2, and TWIST.

Protein RNA and DNA Analysis on Tissue and Plasma

Tissue slides from diagnostic biopsies, serial biopsies, and CTC may be used to assess molecular characteristics and/or expression of protein, nucleic acids, and metabolites.

Additionally, these samples may be examined for mutations and/or methylation of nucleic acids. Protein analysis of relevant proteins, including but not limited to, DNA repair proteins, such as ERCC1 and XPF, may be performed on sources of tumor tissue obtained from each consented subject when feasible. Mutational analysis of tumor-derived DNA may include, but is not limited to, acquired secondary mutations in the BRCA genes that have been reported to restore the activity of the molecule. These analyses might reveal putative stratification and/or resistance markers for correlation with efficacy.

If warranted, circulating tumor-derived nucleic acids may be extracted from plasma and quantitated and/or assessed for methylation and mutational status of genes relevant to veliparib mechanism of action, including the DNA repair genes. Genes relevant to the mechanism of action of the combination therapy agents TMZ, carboplatin and/or paclitaxel may also be investigated. If tumor tissue, CTCs, and plasma are available from the same patient, the results of studies will be compared to assess correlation of the methodologies.

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.

Circulating Breast Cancer Cells

Cancer cells derived from the primary breast cancer tumor may be found circulating in the blood. These tumor cells can be enriched and enumerated using cell selection and breast cancer cell labeling techniques. The quantification and characterization at the protein and molecular levels (nucleic acids and metabolites) of these tumor cells may contain information correlated with drug-responsiveness, resistance factors, and clinical outcomes.

5.4 Removal of Subjects from Therapy or Assessment

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 be withdrawn from the study, if any of the following occur:

- The subject experiences disease progression as defined by RECIST version 1.1;
- If the subject discontinues for symptomatic deterioration, every effort will be made to document objective progression even after discontinuation of treatment;
- The investigator believes it is in the best interest of the subject;
- Clinically significant deterioration of the subject's medical status, as determined by the investigator;
- The subject requires alternative anticancer agents, or radiation therapy 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.

5.4.1 Discontinuation of Individual Subjects

When a subject discontinuation is planned without the subject reaching a protocol-defined endpoint, the investigator will notify the AbbVie Medical Monitor (Section 6.5) or the clinical team representative (Section 7.0) 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 Medical Monitor may contact the site to discuss the reason for withdrawal from the study.

The investigator must report the withdrawal to the IVRS/IWRS system within 3 days of the subject's discontinuation visit.

When a subject discontinues the study, a Final Visit will be conducted (preferably prior to the initiation of another anticancer therapy). 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. Following discontinuation of the study drug, the subject will be treated in accordance with the investigator's best clinical judgment.

At the Final Visit, the reasons for the discontinuation from the study 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, as soon as possible after discontinuation from the study. For subjects on study treatment more than 5 years, 12-lead ECG, urinalysis, CIPN Assessment (QLQ-CIPN20), and EORTC QLQ-C15/BR23, and tumor assesement do not need to be performed at Final Visit.

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. For subjects on study treatment more than 5 years, CIPN Assessment (QLQ-CIPN20) and EORTC QLQ-C15/BR23 do not need to be performed at the Follow-up Visit.

If a subject is discontinued from the study 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.

Subjects who discontinue treatment with veliparib + TMZ or veliparib/placebo + carboplatin + paclitaxel prior to reaching an event of disease progression should remain on study and continue to follow the schedule for study visits and procedures until disease

progression is experienced, if possible. For subjects on study treatment more than 5 years, the subject will be discontinued from study if discontinuing treatment for any reason.

Overall survival and post treatment information will be collected via IVRS/IWRS at monthly intervals (or as requested by Sponsor to support data analysis) beginning on the date the subject is registered off study and continuing for a minimum of 3 years on all subjects until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study. For subjects on study treatment for more than 5 years, overall survival and post treatment information are not required.

In the event that a positive result is obtained on a pregnancy test for a subject during the study, the administration of study drug to that subject must be discontinued immediately. The site must report the positive pregnancy test result 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 Veliparib and TMZ

Subjects will receive veliparib + TMZ for up to 24 cycles or until reaching a protocol-defined event of disease progression or experiencing unmanageable toxicity. If the subject has not progressed and the investigator feels there is benefit to continue treatment beyond 24 cycles, a discussion between the site and the AbbVie Medical Monitor (Listed in Section 6.5) to discuss continued treatment is required. If both the investigator and the AbbVie Medical Monitor confirm that the subject would benefit to continue treatment, the subject may continue to receive veliparib + TMZ until the subject has disease progression or experiences a toxicity that requires discontinuation of further treatment. If toxicities have resulted in discontinuation of either veliparib or TMZ, both are to be discontinued.

Subjects who discontinue treatment with veliparib + TMZ prior to reaching an event of disease progression should remain on study and continue to follow the schedule for study visits and procedures until disease progression is experienced.

5.4.1.2 Discontinuation of Veliparib or Placebo and 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. If toxicities have resulted in discontinuation of both carboplatin and paclitaxel, veliparib will also be discontinued. At the investigator's discretion, carboplatin and paclitaxel administration may continue after veliparib has been discontinued.

Subjects who discontinue treatment with veliparib/placebo + carboplatin + paclitaxel prior to reaching an event of disease progression should remain on study and continue to follow the schedule for study visits and procedures until disease progression is experienced.

5.4.2 Discontinuation of Entire Study

Survival (i.e., the date and cause of death) and post treatment information including therapies received will be collected via IVRS/IWRS at monthly (or as requested by Sponsor to support data analysis) beginning on the date the subject is registered off study and continuing for a minimum of 3 years on all subjects until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study. For subjects on study treatment for more than 5 years, survival follow-up is not required.

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.

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 1:1:1 ratio to receive one of the following treatments

- Veliparib 40 mg BID Days 1 through 7 + TMZ 150 to 200 mg/m^2 QD Days 1 through 5 in each 28-day cycle;
- Veliparib 80 mg (for subjects randomized under the original protocol) or Veliparib 120 mg (for subjects randomized after approval of protocol Amendment 1) BID Days 1 through 7 + Carboplatin AUC 6 administered on Day 3 and Paclitaxel 175 mg/m^2 administered on Day 3 of each 21-day cycle;
- Placebo BID Days 1 through 7 + Carboplatin AUC 6 administered on Day 3 and Paclitaxel 175 mg/m^2 administered on Day 3 of each 21-day cycle.

5.5.1.1 Veliparib + TMZ Treatment

Subjects will self-administer the morning dose of veliparib and TMZ at the same time under fasting conditions (to reduce the chance of nausea and vomiting per the TMZ label recommendation) and the evening doses of veliparib approximately 12 hours after the

morning dose with or without food in the same calendar day. For Cycle 1, the TMZ dose will start at a dose of 150 mg/m^2 QD per body surface area (BSA) on Days 1 through 5 of each 28-day cycle. If during the first cycle, platelets (nadir) are > 100,000/μL and the ANC (nadir) is >1,500/μL and no Grade 3 or 4 CTCAE nonhematologic toxicities attributable to TMZ are observed, then the TMZ dose will be escalated to 200 mg/m^2 QD for Cycle 2. The TMZ dose will be determined using the BSA calculated from the height obtained at the baseline evaluation and the weight obtained prior to each cycle. The daily dose will be rounded to the nearest 5 mg. However, for subject convenience, the dose may be rounded down to 5% from calculated dose, in order to minimize the number of capsules per dose. The exact dose administered will be recorded in the eCRF.

It is recommended that if a subject misses a scheduled dose of veliparib and/or TMZ 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.

If the subject vomits within 15 minutes of taking the TMZ, another dose should not be administered. If the subject vomits within 15 minutes of taking veliparib, and the veliparib capsules are intact, another full dose should be administered. The dose may only be repeated once. If more than 15 minutes have passed from the time of oral dosing, then no additional doses should be taken.

5.5.1.2 Veliparib + Carboplatin/Paclitaxel and Placebo + Carboplatin + Paclitaxel Treatment

Subjects will self-administer the morning dose of veliparib/placebo and the evening dose of veliparib/placebo approximately 12 hours after the morning dose with or without food in the same calendar day for Days 1 through 7 of the 21-day cycle. If the subject vomits within 15 minutes of taking veliparib and all veliparib capsules remain intact, another full dose should be administered. Carboplatin and paclitaxel will be administered on Day 3 of

every cycle. Paclitaxel will be infused prior to carboplatin. Dosing of veliparib/placebo on Day 3 of every cycle should be done before carboplatin + paclitaxel infusion.

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 3 hours at a dose of 175 mg/m^2.

Carboplatin

Carboplatin will be administered intravenously over approximately 15 to 30 minutes at (AUC 6 mg/mL/min) immediately following paclitaxel infusion.

The 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 results for the calculation of carboplatin dosing is strongly encouraged.

Similarly, when the GFR is estimated using isotopic/EDTA clearance, maximum carboplatin dosing should be based upon standard guidelines and institutional practices.

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.

5.5.2 Identity of Investigational Products

Information about veliparib, placebo, TMZ, carboplatin, and paclitaxel formulations to be used in this study is presented in Table 10.

Table 10. Identity of Investigational Products

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Veliparib (ABT-888)	Capsule	10 mg active 20 mg active 40 mg active 20 mg placebo 40 mg placebo	Oral	AbbVie
Temozolomide (commercially available)	Capsule	5 mg 20 mg 100 mg	Oral	Schering® Corporation a subsidiary of MERCK & CO., INC. or Merck Sharp & Dohme Limited or generic manufacturer
Carboplatin (commercially available)	Solution in a vial	150 mg/15 mL aqueous solution 450 mg/45 mL aqueous solution	Intravenously	Generic manufacturer
Paclitaxel (commercially available)	Solution in a vial	100 mg/16.7 mL non-aqueous solution	Intravenously	Generic manufacturer

AbbVie will supply veliparib capsules, a matching placebo for veliparib, and temozolomide capsules. 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

For the veliparib 40 mg BID + TMZ treatment arm, veliparib will be packaged in bottles containing 16 capsules per bottle (this includes 2 additional capsules in each bottle). For the veliparib/placebo 120 mg + carboplatin and paclitaxel treatment arms, veliparib and placebo will be packaged in bottles containing 64 capsules of 20 mg active or placebo per bottle and/or 48 capsules of 40 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.

TMZ will be packaged in bottles/cartons containing 5 capsules per bottle/cartons and will be supplied by AbbVie. The site staff must complete all blank spaces on the label prior to dispensing drug to the subject. TMZ may be dispensed to subjects in pharmacy bottles according to institutional guidelines.

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 Drugs

All clinical supplies provided by AbbVie must be stored in a secure place at the proper storage conditions as presented in Table 11, 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 11. Study Drug Storage Conditions

Study Drug	Country**	Storage Conditions
Veliparib or placebo	US	Store at 15° to 25°C (59° to 77°F).
	EU	Store at 15° to 25°C (59° to 77°F).
	Australia	Store below 25°C.
Temozolomide	US	Store at 15° to 25°C (59° to 77°F).
	EU	Store at 15° to 30°C (59° to 86°F).
	Australia	Store below 25°C.
Carboplatin	US	Store at 15° to 25°C (59° to 77°F).
	EU	Store at 15° to 25°C (59° to 77°F).
	Australia	Store below 25°C.
Paclitaxel	US	Store at 15° to 25°C (59° to 77°F).
	EU	Store at 15° to 25°C (59° to 77°F).
	Australia	Store below 25°C.

US = United States; EU = European Union

** For countries not listed, 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 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 5.2.1, and none of the exclusion criteria in Section 5.2.2 will proceed to randomization. The site will access the system on or prior to the subject's C1D1 and a unique randomization number will be provided.

For Group 1 of the study, the IVRS/IWRS will randomize subjects in a 1:1:1 ratio, with a third of the subjects being randomized to the veliparib 40 mg BID + TMZ treatment arm, a third to the veliparib 80 mg BID + carboplatin + paclitaxel arm, and a third to the placebo BID + carboplatin + paclitaxel arm. Subject randomization will be stratified by ER and/or PgR positive versus ER and PgR negative, prior cytotoxic therapy versus no prior cytotoxic therapy, and ECOG 0-1 versus 2.

For Group 2 of the study, the IVRS/IWRS will randomize subjects in a 1:1:1 ratio, with a third of the subjects being randomized to the veliparib 40 mg BID + TMZ treatment arm, a third to the veliparib 120 mg BID + carboplatin + paclitaxel arm, and a third to the placebo BID + carboplatin + paclitaxel arm. Subject randomization will be stratified by ER and/or PgR positive versus ER and PgR negative, prior cytotoxic therapy versus no prior cytotoxic therapy, and ECOG 0-1 versus 2.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects will be randomized into 1 of 3 treatment arms.

Subjects randomized to the veliparib + TMZ treatment arm will self-administer the morning dose of veliparib and TMZ at the same time under fasting conditions (to reduce the chance of nausea and vomiting per the TMZ label recommendation) and the evening dose of veliparib approximately 12 hours after the morning dose with or without food in the same calendar day. For Cycle 1, the TMZ dose will start at a dose of 150 mg/m^2/day on Days 1 through 5 of each 28-day cycle. The TMZ dose will be determined using the BSA calculated from the height obtained at the baseline evaluation and the weight obtained prior to each cycle.

Subjects randomized to the veliparib/placebo + carboplatin + paclitaxel or placebo treatment arms will self-administer the morning dose of veliparib/placebo and the evening dose of veliparib approximately 12 hours after the morning dose with or without food in the same calendar day. Subjects randomized to these 2 treatment arms will return to the site on Day 3 of each cycle to have their carboplatin and paclitaxel administered intravenously.

5.5.5 Blinding

This is a partially blinded study. AbbVie, the investigator, the study site personnel, and the subject will remain blinded to each subject's treatment with veliparib or placebo in the carboplatin + paclitaxel arms throughout the course of the study. The IVRS/IWRS will provide access to blinded subject treatment information for subjects randomized to the veliparib/placebo + carboplatin + paclitaxel treatment arms during the study in the case of a medical emergency.

All subjects randomized to the veliparib + TMZ treatment arm will be treated in an open-label fashion.

5.5.5.1 Blinding of Investigational Product

The IVRS/IWRS will provide access to blinded subject treatment information for an individual subject in the case of a medical emergency. In the event of a medical emergency in which the investigator believes that knowledge of study drug treatment is required, every effort must be made to contact the AbbVie Medical Monitor (listed in Section 6.5) prior to contacting the IVRS/IWRS for treatment unblinding (as long as subject safety is not compromised). 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, TMZ, carboplatin, and paclitaxel only to subjects enrolled in the study in accordance with the protocol. Veliparib, placebo, TMZ, carboplatin, and paclitaxel must not be used for reasons other than those described in the protocol.

Veliparib or placebo and TMZ 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 or placebo bottles and TMZ bottles/cartons (empty, partially filled, or full) to the study site personnel prior to each cycle and at the Final Visit. The study site personnel will document the bottles/cartons of veliparib, placebo or TMZ 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, TMZ, carboplatin (when supplied by AbbVie), and paclitaxel (when supplied by AbbVie).

The study coordinator will document compliance 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 or TMZ 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, TMZ, 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, TMZ, 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, TMZ, 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, TMZ, carboplatin, and paclitaxel were dispensed for each subject.

Upon completion or termination of the study, all original bottles/cartons containing unused veliparib, placebo, TMZ, 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, TMZ, 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, TMZ, carboplatin, or paclitaxel to any persons not enrolled in the study or not named as a subinvestigator 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 TMZ or 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 2, randomized, partially blinded study to evaluate the efficacy and tolerability of veliparib in combination with TMZ and in combination with carboplatin +

paclitaxel compared to an active, placebo-controlled arm of carboplatin + paclitaxel. 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. Additionally, the design allows for the comparison of veliparib + TMZ, a regimen for which non-randomized, Phase 2 data indicate activity,[23] to an active comparator regimen, as TMZ alone would not be a viable comparator. 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 design does not allow crossover, as both PFS and OS will be assessed.

The randomization will be 1:1:1 so each arm will contain approximately the same number of subjects. Randomization will be stratified on the basis of ER and/or PgR positive versus ER negative and PgR negative, prior cytotoxic therapy versus no prior cytotoxic therapy, and ECOG 0-1 versus 2.

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 BRCA1 or BRCA2 mutation carriers with histologically (or cytologically) confirmed locally recurrent (not amenable to therapy with curative intent) or metastatic breast cancer will be enrolled into the study. If the subject is HER2 positive, the subject must have received and progressed on at least one prior standard anti-HER2 therapy or the subject must be ineligible to receive anti-HER2 therapy. Subjects must have had no more than two prior 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

Veliparib 40 mg BID + TMZ 200 mg/m^2 QD was defined as MTD combination dose in the Phase 1 study, M06-862. Additionally, the veliparib PK results following the 20 and 40 mg BID doses achieved the exposures (AUC) that were effective in murine efficacy models and PARP inhibition in humans (CTEP Phase 0). In a Phase 2 investigator-initiated study to date, 41 subjects with MBC have received veliparib 40 mg BID Days 1 through 7 plus TMZ 150 to 200 mg/m^2 QD Days 1 through 5 of a 28-day cycle. Because of the number of subjects with hematological toxicities, the protocol was amended in December 2009 to change the dose of veliparib from 40 mg BID to 30 mg BID. All of the subjects who responded to veliparib + TMZ received 40 mg BID veliparib initially, then 30 mg BID following the dose reduction amendment. The study was also amended to include an expansion cohort to further evaluate the safety and tolerability of veliparib 30 mg BID + TMZ. To date, hematological toxicities have been similar to that observed in the initial cohort; however, the response rate has diminished. On the basis of experience to date across the veliparib program (including Phase 2 studies in metastatic melanoma, hormone-refractory prostate cancer, and high grade serous ovarian cancer) in which hematological toxicities have been manageable with veliparib 40 mg BID and the potential decrease in efficacy at the 30 mg dose, veliparib will be used at 40 mg BID in combination with TMZ.

The initial starting dose of 80 mg BID veliparib in this trial was derived from the results obtained in the CTEP 7967 study. Selection of the initial dose for this study is discussed in Section 3.4.2.

The 120 mg BID dose of veliparib was determined to be the recommended phase two dose (RPTD), based on the current data available from the GOG 9923 (Phase 1 dose escalation study in subjects with advanced or metastatic ovarian cancer) study. As of 15 December 2011, three patients have been treated with veliparib 150 mg BID on Days 1 to 21 with carboplatin AUC 6 and paclitaxel 175 mg/m^2 on Day 1 of a 21-day cycle. No grade 3/4 toxicity or DLTs occurred at the 150 mg BID dose level during DLT

evaluation period; thus, in the GOG 9923 study, the veliparib 200 mg BID dose level is currently being evaluated.

The maximum dose of veliparib for any subject under this protocol is 120 mg BID.

5.7 Dose Reductions or Delays

If a subject experiences an adverse event that results in a delay in starting a cycle or requires that study regimen is delayed or interrupted during a cycle, the subject will complete the planned activities per Section 5.3.1 until resuming treatment. The intention is for veliparib to be administered concurrently with TMZ or 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, neuropathy, 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 chemotherapy.

If chemotherapy must be withheld because of hematological toxicity, CBC and platelet counts should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

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. In the case of delays, CT scans should continue to be assessed at intervals of 9 weeks from C1D1.

Since fatigue can be a symptom of cancer progression, dose reduction for fatigue will only be done if the fatigue is deemed to be drug-related in the investigator's opinion.

Investigators should evaluate subjects for carboplatin and paclitaxel or temozolomide treatment per the locally approved product label, local practice, or applicable SmPC.

5.7.1 Veliparib + TMZ Dose Reduction and Delays

The following are guidelines for dose reduction, delay, and discontinuation of veliparib (and TMZ for subjects randomized to the veliparib + TMZ treatment arm of the study (Table 12).

5.7.1.1 Veliparib Dose Reduction and Delays

- Veliparib should be discontinued at the same time as discontinuation of TMZ.
- For any subject who experiences Grade 3 or 4 toxicity that is not attributable to TMZ or the underlying disease, the veliparib 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. Two dose reductions are allowed. The dose of veliparib will be reduced to 30 mg BID (dose level –1) and may be reduced again to 20 mg BID (dose level –2) for reasons of toxicity. Any dose reduction beyond 20 mg BID will result in veliparib discontinuation and removal of the subject from protocol-directed therapy. When veliparib is discontinued, TMZ must also be discontinued.
- Any ≥ Grade 2 event of seizure attributed to veliparib requires interruption of veliparib and discussion with the AbbVie Medical Monitor regarding the decision to resume treatment.

The AbbVie Medical Monitor should be contacted (see Section 6.5) for subjects who require more than a 2-week delay in the re-initiation of the next cycle.

5.7.1.2 TMZ Dose Reduction and Delays

Clinically significant hematological toxicities should result in TMZ dose reduction or delay. During treatment, CBCs should be monitored and the next cycle of therapy should not be started until the ANC is > 1,500/μL and platelet count is > 100,000/μL. For any Grade 3 or 4 toxicities attributable to TMZ, dose reduction and/or delay guidelines should be followed per Table 12. Dose reductions in the next cycle should be based on lowest blood counts and worst nonhematologic toxicity observed in the previous cycle. The 75 mg/m^2/day is the lowest dose of TMZ allowed in this study. Subjects must stop TMZ

and veliparib if they are at the 75 mg/m^2/day dose level of TMZ and require an additional dose reduction (Table 12) because of toxicities. Subjects will be removed from protocol-directed therapy if this occurs. When TMZ is discontinued, veliparib must also be discontinued.

Table 12. Veliparib and TMZ Dose Reduction or Delay Starting in Cycle 2 and All Subsequent Cycles

	Adverse Event	Dose Reduction
Hematologic Toxicity Attributable to TMZ	ANC < 1000/µL* and/or Platelets < 50,000/µL*	1. Hold TMZ and veliparib. Check CBC weekly until recovery to: ANC > 1500/µL **and** platelets > 100,000/µL **and** 2. Reduce TMZ dose by one dose level at the next cycle**
	ANC 1000/µL* to 1500/µL* Platelets 50,000/µL* to 100,000/µL*	1. Hold TMZ and veliparib. Check CBC weekly until recovery to ANC > 1500 µL **and** platelets > 100,000/µL **and** 2. Maintain Current TMZ Dose at the next cycle
	Adverse Event	**Dose Reduction**
Nonhematologic Toxicity Attributable to TMZ	Nausea/Vomiting CTC ≥ Grade 3 despite optimal antiemetic therapy	1. Hold TMZ + veliparib. Delay cycle until Grade 1 (or Grade 2 if present at baseline) **and** 2. Reduce TMZ dose by one dose level for the next cycle**
	Fatigue, constipation, anorexia and headaches CTC ≥ Grade 3	
	Any other CTC ≥ Grade 3 deemed to be clinically significant by PI	
	Adverse Event	**Dose Reduction**
Attributable to Veliparib	Any Grade 3 or 4 toxicity which is not attributable to TMZ or underlying disease	1. Hold TMZ + veliparib. Delay cycle until Grade 1 (or Grade 2 if present at baseline) **and** 2. Reduce veliparib dose by one dose level for the next cycle***

* Regardless of attribution.

** TMZ dose cannot be reduced below 75 mg/m^2/day. TMZ will be discontinued, if further dose reduction is required below the 75 mg/m^2/day. The subject will be removed from protocol directed therapy if this occurs. If TMZ is discontinued, veliparib must also be discontinued.

*** Two dose reductions of veliparib will be allowed. Subjects must discontinue veliparib, if they require an additional dose reduction because of toxicities. The subject will be removed from protocol-directed therapy if this occurs. If veliparib is discontinued, TMZ must also be discontinued.

TMZ Dose Level Definition Summary

Dose Level	Temozolomide Dose
1	200 mg/m^2/day
2	150 mg/m^2/day
3	100 mg/m^2/day
4	75 mg/m^2/day

Note: Refer to Table 2 for TMZ Dosing Modifications following Cycle 1.

Veliparib Dose Level Definition Summary

Dose Level	Veliparib Dose BID	Strength	Capsules per Dosing
Starting Dose Level	40 mg	40 mg	1 BID
Dose Level –1	30 mg	20 mg 10 mg	1 BID 1 BID
Dose Level –2	20 mg	20 mg	1 BID

5.7.2 Veliparib + Carboplatin + Paclitaxel and Placebo + Carboplatin + Paclitaxel Dose Reduction and Delays

The following are guidelines for dose reduction, delay, and discontinuation of veliparib/placebo + carboplatin + paclitaxel (Table 13) for subjects randomized to these treatment arms.

5.7.2.1 Veliparib or Placebo Dose Reductions and Delays

The following are guidelines for dose reduction, delay, and discontinuation of veliparib.

For any subject who experiences Grade 3 or 4 toxicity, which is attributable to veliparib or placebo but not carboplatin, paclitaxel, or the underlying disease, veliparib or placebo will be stopped until the toxicity resolves to ≤ Grade 1 or to baseline if Grade 2 is present at the time of study entry. After recovery to ≤ Grade 1 toxicity, the subject is allowed to resume veliparib or placebo dosing at 1 dose level lower than the current level. If a dose reduction of veliparib or placebo is needed, the dose will be decreased by one dose level for each dose reduction. Any dose reduction beyond dose level –2 will result in veliparib

discontinuation. At the investigator's discretion, carboplatin and paclitaxel administration may continue after veliparib has been discontinued.

Veliparib or Placebo Dose Level Definition Summary

Dose Level	Veliparib or Placebo (subjects with starting dose 80 mg BID)	Strength	Capsules per Dosing
Starting Dose Level	80 mg	20 mg	4 BID
Dose Level –1	60 mg	20 mg	3 BID
Dose Level –2	40 mg	20 mg	2 BID

Dose Level	Veliparib or Placebo (subjects with starting dose 120 mg BID)	Strength	Capsules per Dosing
Starting Dose Level	120 mg	40 mg	3 BID
Dose Level –1	80 mg	40 mg	2 BID
Dose Level –2	40 mg	40 mg	1 BID

5.7.2.2 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. If the investigator considers an event attributable to carboplatin and/or paclitaxel and not veliparib/placebo, the investigator may consider reducing carboplatin and/or paclitaxel, but not veliparib or placebo. Guidelines for dose reduction, delay, and discontinuation are included in Table 13.

Treatment should be delayed until the toxicity resolves to ≤ Grade 1 or to baseline if Grade 2 toxicity is present at the time of study entry. 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. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and nonhematologic parameters have been met. Treatment could be postponed for up to 28 days because of toxicity, and longer toxicity-related delay will

lead to paclitaxel or carboplatin discontinuation. No dose escalation is planned for this study.

If a dose reduction of paclitaxel is needed, the dose will be decreased to 135 mg/m^2 for the first dose reduction and to 110 mg/m^2 for the second. If a dose reduction of carboplatin is required, the dose reduction will be decreased by 1 AUC for each reduction, with a minimum AUC of 4. Subjects may have 2 dose reductions of each agent and then that agent will be discontinued. If the subject remains on chemotherapy (carboplatin and/or paclitaxel) following dose modifications, veliparib or placebo may be continued. However, if both carboplatin and paclitaxel have been discontinued, then veliparib or placebo must also be discontinued.

For any Grade 3 or 4 toxicities not mentioned in the table, 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 per the guidelines at the beginning of Section 5.7.

Table 13. Veliparib/Placebo + Carboplatin + Paclitaxel Dose Reduction and Delays

	Adverse Event	Dose Reduction/Delay		
		Paclitaxel	Carboplatin	Veliparib or Placebo
Hematological toxicity attributable to any or all treatment	ANC 1000 – 1499/mm^3 or Platelets 75000 – 99999/mm^3 within 24 hours prior to scheduled therapy	Hold until recovery to ANC ≥ 1500/mm^3 and Platelets ≥ 100,000/mm^3. Resume at the same level after recovery.	Hold until recovery to ANC ≥ 1500/mm^3 and Platelets ≥100,000/mm^3. Resume at the same level after recovery.	No change in dose. Delay so dosing corresponds to carboplatin + paclitaxel administration.
	ANC < 1000/mm^3 or Platelets 25000 – 74999/ mm^3 within 24 hours prior to scheduled therapy[a]	Hold until recovery to ANC ≥ 1500/mm^3 and Platelets ≥ 100,000/mm^3. Resume at the same level after recovery.	Hold until recovery to ANC ≥ 1500/mm^3 and Platelets ≥ 100,000/mm^3. Reduce by 1 dose level.	No change in dose. Delay so dosing corresponds to carboplatin + paclitaxel administration.
	Platelets < 25000/ mm^3 within 24 hours prior to scheduled therapy or Platelets 25000-50000/mm^3 complicated by bleeding, easy bruising, petechiae, or requiring platelet transfusion	Hold until recovery to Platelets ≥ 100,000/mm^3. Resume at one dose level below current dose level.	Hold until recovery to Platelets ≥ 100,000/mm^3. Resume at one dose level below current dose level.	No change in dose. Delay so dosing corresponds to carboplatin + paclitaxel administration.
	Prolonged neutropenia (ANC < 500/mm^3 for ≥ 7 days)	Hold until recovery to ANC ≥ 1500/mm^3. Resume at one dose level below current dose level.	Hold until recovery to ANC ≥ 1500/mm^3. Resume at one dose level below current dose level.	No change in dose. Delay so dosing corresponds to carboplatin + paclitaxel administration.
	Febrile neutropenia (ANC ≤ 1000/mm^3 with temperature of > 38.5°C[a])	Hold until recovery to ANC ≥ 1500/mm^3. Resume at one dose level below current dose level.	Hold until recovery to ANC ≥ 1500/mm^3. Resume at the same level after recovery.	No change in dose. Delay so dosing corresponds to carboplatin + paclitaxel administration.
	Anemia[b]	No reduction or delay.	No reduction or delay.	No reduction or delay.

Table 13. Veliparib/Placebo + Carboplatin + Paclitaxel Dose Reduction and Delays (Continued)

	Adverse Event	Dose Reduction/Delay		
		Paclitaxel	Carboplatin	Veliparib or Placebo
Hepatic Toxicity[c]	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.
Nonhematologic Grade 3 or 4 toxicity attributable to any or all treatment	Grade 3 or 4 nausea/vomiting despite optimal antiemetic treatment[d]	Hold until nausea/vomiting have resolved to ≤ Grade1. Resume at one dose level below current dose level.	Hold until nausea/vomiting have resolved to ≤ Grade 1. Resume at one 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. Resume at one dose level below current dose level.	Hold until stomatitis has resolved to ≤ Grade 1. Resume at one dose level below current dose level.	Hold until stomatitis has resolved to ≤ Grade 1. Resume at previous dose.
	≥ Grade 2 neuropathy[e]	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.	Hold until recovery to Grade 1 or less. Resume at the same level after recovery.	Hold until recovery to Grade 1 or less. Resume at the same level after recovery.

Table 13. Veliparib/Placebo + Carboplatin + Paclitaxel Dose Reduction and Delays (Continued)

		Dose Reduction/Delay		
	Adverse Event	**Paclitaxel**	**Carboplatin**	**Veliparib or Placebo**
Toxicity attributable to veliparib and not carboplatin or paclitaxel, nor underlying disease	Any Grade 3 or 4 toxicity	Hold until recovery to ≤ Grade 1 or to baseline. Resume at the same level after recovery.	Hold until recovery to ≤ Grade 1 or to baseline. Resume at the same level after recovery.	Hold until recovery to ≤ Grade 1 or to baseline. After recovery, resume at one dose level below the current dose level.

a. Consider granulocyte colony-stimulating factor according to the locally approved product label, institutional guidelines, local practice, or applicable SmPC.

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

c. 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 patient's study treatment will be discontinued.

d. 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.

e. 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.

6.0 Adverse Events

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 drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, 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 Definitions

6.1.1 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 6.7) regarding toxicity management)] and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during the study 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 condition. 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 performed will be considered an adverse event.

6.1.2 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.
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.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

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

6.2 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).[53]

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.

6.3 Relationship to Study Drug

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

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the study drug and an Other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

For causality assessments, events meeting the categories of probably or possibly related will be considered "associated." Events that are probably not or not related will be considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of possibly, probably not, or not related to study drug is given, an Other cause of event must be provided by the Investigator for the serious adverse event.

6.4 Adverse Event Collection Period

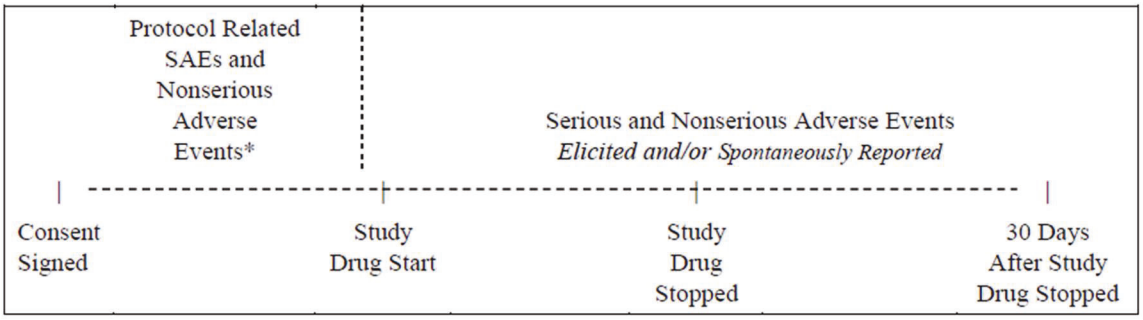
All protocol related serious adverse events and nonserious adverse events must be collected from the signing of the study-specific informed consent until study drug administration.

In addition, all adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug 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, TMZ, 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 5.

Figure 5. Adverse Event Collection



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

6.5 Adverse Event Reporting

In the event of a serious adverse event, whether related to AbbVie study medication or not, the Investigator will notify 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® (EDC) system or if Rave is not operable should be sent to 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 related concerns, contact the Oncology Safety Management Team at:

Oncology Group Safety Management
AbbVie
Dept. R478S, 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 any emergent safety concerns, please contact the physician listed below:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Mobile:
Fax:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: +1 (973) 784-6402

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines. Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI) for veliparib and Summary of Product Characteristics (SmPC) will be the RSI for carbloplatin, paclitaxel, and temozolomide. The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

6.6 Pregnancy

In the event of a positive pregnancy test, subjects must immediately discontinue study drug and must be discontinued from the study (Section 5.4). The investigator must report the positive pregnancy test to the appropriate contact listed in protocol Section 6.5 within 1 working day of the site becoming aware of the pregnancy.

All subjects should be informed that contraceptive measures should be taken throughout the study and for 90 days after discontinuing study drug. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. The investigator must follow the pregnancy to completion and provide an update to AbbVie after delivery.

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.

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.

6.7 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 (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 to be either possibly related or probably related to the study drug (Section 6.1.1).

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

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.

7.0 Protocol Deviations

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB, and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact his or her assigned clinical monitor or the following AbbVie representatives:

Clinical Team Lead:

[redacted]

AbbVie Corporation
8401 Trans-Canada Highway
Saint-Laurent, Québec
H4S 1Z1
Canada

Office:
Fax:
Email: [redacted]

Scientific Director:

[redacted]

AbbVie
[redacted]

North Chicago, IL 60064

Office:
Fax:
Email: [redacted]

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. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

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 in Group 2 of the study and who have been documented to have 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 drug (veliparib or placebo) will be included in the safety analysis.

Comparisons will be performed between veliparib 40 mg BID + TMZ and placebo BID + carboplatin + paclitaxel as well as between veliparib 120 mg BID + carboplatin + paclitaxel and 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 drug (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 drug.

Baseline characteristic data will be summarized with all randomized subjects for Group 1 (veliparib 40 mg BID + TMZ, veliparib 80 mg BID + carboplatin + paclitaxel, placebo BID + carboplatin + paclitaxel) and Group 2 (veliparib 40 mg BID + TMZ, veliparib 120 mg BID + carboplatin + paclitaxel, placebo BID + carboplatin + paclitaxel) of the study separately.

8.1.1.1 Demographics

Continuous demographic data (e.g., age, height, and weight) will be summarized with means, standard deviation, minimum, maximum, and range. Frequencies and percentages will be computed for the following parameters: gender, race, BRCA1, BRCA2, ER/PgR

status, HER2 status, triple negative breast cancer, number and sites of metastases, prior cytotoxic therapy use, and 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 + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel among subjects who have been documented to have deleterious mutations by the Sponsor core lab. Comparisons between treatment groups will be performed using a Hochberg testing procedure for multiplicity adjustment (see Section 8.1.10.8 for details).

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 a confirmed event of disease progression (as determined by the central imaging center), or to the date of death (all causes of mortality), if disease progression is not reached. All confirmed events of disease progression will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. Events of death will be included for subjects who had not experienced a confirmed event of disease progression, provided the death occurred within 9 weeks of the last available disease progression assessment (by central imaging center). If the subject does not have a confirmed 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 available disease progression assessment (by central imaging center).

8.1.2.2 Secondary Efficacy Endpoints

Secondary efficacy analyses comparing the effects of veliparib + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + 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 18, objective response rate (ORR), and CIPN. Only subjects with deleterious mutations documented by the Sponsor core lab will be included in the analyses of the secondary efficacy analyses.

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

Clinical benefit rate (CR, PR, SD or Non-CR/Non-PD) at Week 18 will be defined as the progression-free rate at 18 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 central imaging center). Time to progression will be defined as the number of days from the date the subject was randomized to the date the subject experiences a confirmed event of disease progression (as determined by the central imaging center). If a subject does not have a confirmed event of disease progression, the subject's data will be censored at the date of the subject's last available disease progression assessment (by central imaging center). All ITT subjects who had deleterious mutations documented by the Sponsor core lab will be included in the analysis.

Objective response rate is calculated as the proportion of subjects who have confirmed PR or CR based on assessment by the central imaging center. All ITT subjects who have at least one measurable lesion at baseline and had deleterious mutations documented by the Sponsor core lab will be included in the analysis.

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 + TMZ and placebo + carboplatin + paclitaxel as well as veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel on quality of life and performance status. All ITT subjects will be included in the analysis.

8.1.3 Timing of Efficacy Analyses and Safety Evaluations

Timing of efficacy analyses and safety evaluations will be based on data from Group 2 of the study only.

When both the 159th PFS event across all three treatment arms (if the veliparib + TMZ treatment arm is not terminated due to futility) and the 112th PFS event in the double-blind portion of the study occur, 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. For all efficacy analyses, the data cutoff date will be the date of the159th PFS event across all three treatment arms (if the veliparib + TMZ treatment arm is not terminated due to futility) or the 112th PFS event in the double-blind portion of the study, whichever is later. The exact data cutoff date will be specified in the SAP.

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

Overall survival will be collected on all subjects for a minimum of 3 years after they discontinue from the study. After a total of 194 death events across all three treatment arms (if the veliparib + TMZ treatment arm is not terminated due to futility) or a total of 136 death events for the double-blind portion of the study, whichever is later. The clinical database data will be extracted once again for documentation and a "Final OS Analysis" will be performed on this dataset. The exact data cutoff date will be specified in the SAP.

8.1.4 Primary Analysis of Efficacy

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

8.1.5 Secondary Analyses of Efficacy

If only one veliparib treatment group is statistically significantly better than the placebo group for the primary endpoint of PFS, then 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, ORR, CBR through the end of Week 18, and CIPN. For each secondary endpoint, Hochberg testing procedure will be used to preserve the family-wise error rate for multiple comparisons.

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 + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel using the log-rank test, stratified by ER/PgR (ER and/or PgR positive versus ER and PgR negative) and prior cytotoxic therapy use (yes versus no).

8.1.5.2 Clinical Benefit Rate

Clinical benefit rate (CR, PR, SD or Non-CR/Non-PD) at Week 18 will be defined as the progression-free rate at 18 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 central imaging center). A test statistic based on Kaplan-Meier estimates of the progression-free probability at 18 weeks (Rx Day 126) and the estimated variance will be constructed to test the null hypothesis that the clinical benefit rate at Week 18 for the two treatment groups (between veliparib + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel) are the same. Clinical benefit rate (CR, PR, SD, or Non-CR/Non-PD) will be computed for all ITT subjects.

8.1.5.3 Objective Response Rate

The objective response rate (CR and PR) will be computed for all ITT subjects with at least one measurable lesion at baseline. The proportion of subjects with a confirmed 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 the treatment groups (veliparib + TMZ and placebo + carboplatin + paclitaxel as well as veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel) using CMH test stratified by ER/PgR (ER and/or PgR positive versus ER and PgR negative) and prior cytotoxic therapy use (yes versus no). In addition, 95% confidence interval will be constructed for ORR.

8.1.5.4 Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Chemotherapy-Induced Peripheral Neuropathy (CIPN) assessed by EORTC QLQ-CIPN20 questionnaire and NCI CTCAE 4.0 grading for peripheral neuropathy will be analyzed appropriately as identified in published literature. All subjects with at least one dose of study drug and with deleterious mutations documented by the Sponsor core lab will be included.

8.1.6 Tertiary Analyses of Efficacy

8.1.6.1 Quality of Life

The quality of life instrument EORTC QLQ-C15/BR23 will be summarized appropriately, as identified in published literature.

8.1.6.2 Performance Status

Analyses of changes from baseline will be performed for each scheduled postbaseline visit and for the Final Visit for ECOG performance status using an analysis of covariance (ANCOVA) model with treatment group as the factor and baseline value as a covariate. Postbaseline measurements more than seven days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any postbaseline 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 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 + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel.

PFS, ORR, CBR, and duration of overall response based on radiological and clinical assessment by Investigator 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 anticancer therapies after discontinuation of the study, the primary efficacy and secondary efficacy endpoints of PFS, and overall survival will be

censored at the date of subject's initiation of other anticancer 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 drug, 2) using a Cox proportional hazard model to explore the effect of baseline factors including (but not limited to) the following: ER/PgR status, BRCA1/2 status, prior cytotoxic therapy use, ECOG performance status, stage of the disease, and others, 3) subgroup analysis by ER/PgR status, BRCA1/2 status, prior cytotoxic therapy use, 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) will review the safety data for this veliparib Phase 2 study after approximately 36 subjects in Group 2 of the study have met at least one of the criteria:

- Received two 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.

In addition, an interim futility analysis will be conducted after the Week 27 tumor assessment of the first 30 subjects who have been documented to have deleterious mutations by the Sponsor core laboratory with at least one measurable lesion at baseline and randomized to the veliparib + TMZ treatment group (across both Group 1 and

Group 2). This interim futility analysis will be reviewed by IDMC. If there are less than 5 responders (CR+PR) in the 30 subjects, then futility will be declared for the veliparib + TMZ treatment group. This futility criterion corresponds to Bayesian posterior probability of at least 90% that the true objective response is ≤ 25%.

If futility is declared at the time of the futility analysis, any remaining subjects on veliparib + TMZ will be given the option either to receive veliparib 120 mg BID + carboplatin + paclitaxel or discontinue therapy.

8.1.9 Safety Assessments

The safety of veliparib + TMZ, veliparib + carboplatin + paclitaxel, and placebo + carboplatin + paclitaxel will be assessed by evaluating study drug 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 drug (veliparib or placebo) will not be included in the analyses of safety.

Safety summaries will be presented by treatment group (veliparib 40 mg BID + TMZ, veliparib BID + carboplatin + paclitaxel or placebo BID + carboplatin + paclitaxel) for Group 1 and Group 2 of the study, separately. In addition, the safety data from the veliparib 40 mg BID + TMZ group in both Group 1 and Group 2 of the study may be combined.

Statistical comparisons will only be made for Group 2 of the study.

8.1.10 Statistical Analyses of Safety

8.1.10.1 Duration of Study Drug

A summary of the number of days and/or cycles subjects were exposed to study drug 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 drug.

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)[54] adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE version 4.0 toxicity grade, and relationship to study drug will be provided. Comparisons of the percentages of subjects experiencing an adverse event between veliparib + TMZ and placebo + carboplatin + paclitaxel as well as 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 drug in this study, 2) for deaths occurring off treatment within 30 days after the last dose of study drug, and 3) for all deaths in this study regardless of the number of days after the last dose of study drug.

8.1.10.5 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled postbaseline 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. Postbaseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any postbaseline measurements will not be included. Comparisons of the differences in mean changes from baseline between veliparib + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel will be made using ANCOVA with treatment group as the factor and baseline as a covariate.

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 drug, and as the grade of the last postbaseline measurement collected no more than 30 days after the last dose of study drug. If multiple values are available for a postbaseline 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 or no grade to maximum postbaseline grades of 3 to 4, and from baseline grades of 0 to 2 or no grade to final postbaseline grades of 3 to 4 between veliparib + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel will be performed using Fisher's exact tests. Additional analyses including all measurements collected, regardless of the number of days after the last dose of study drug, will be performed.

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 drug, 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 drug, will be included in these listings.

8.1.10.8 Multiplicity Adjustments

The Hochberg testing procedure will be used to preserve the family-wise error rate for multiple comparisons. For the primary endpoint PFS, a Hochberg testing procedure will be used where the larger *P* value for the comparisons of veliparib + TMZ and placebo + carboplatin + paclitaxel as well as veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel will be compared to an $\alpha = 0.05$. If statistically significant, ($P \leq 0.05$) then both comparisons will be considered significant. If the larger *P* value is not statistically significant, then the smaller *P* value will be compared to an $\alpha = 0.025$. Nominal *P* values will be reported. Furthermore, if both veliparib treatment groups are statistically better than the placebo group for primary efficacy endpoint PFS, fixed-sequence testing method and Hochberg testing procedure will be used for the secondary endpoints.

An additional 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 deaths 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 183 deaths). Statistical significance for OS will be declared if a significant result is obtained for either analysis, consistent with group-sequential testing methods.

8.1.10.9 Censoring Dates for Subjects that had the Blind Broken

All subjects that had the study blind broken prior to an event of disease progression or prior to the last date of evaluation will be censored on the last date of evaluation or on the day the study blind was broken, whichever was earlier.

8.2 Determination of Sample Size

Assuming the true hazard ratio in favor of the veliparib 40 mg BID + TMZ or veliparib 120 mg BID + carboplatin + paclitaxel treatment group is 0.58 for PFS, a total of 159 PFS events will be needed for the study to have at least 80% power at 2-sided α level of 0.05 to detect a statistically significant treatment effect for the veliparib 40 mg BID + TMZ treatment group or the veliparib 120 mg BID + carboplatin + paclitaxel treatment group using the log-rank test for PFS. If the veliparib 40 mg BID + TMZ treatment group is terminated for reasons of futility, a total of 112 PFS events in the double-blind portion of the study will provide at least 80% power at 2-sided α level of 0.05 (or 74% power at 2-sided α level of 0.025) to detect a statistically significant treatment effect for the veliparib 120 mg BID + carboplatin + paclitaxel treatment group using the log-rank test for PFS.

In addition, assuming the true hazard ratio in favor of the veliparib 40 mg BID + TMZ or veliparib 120 mg BID + carboplatin + paclitaxel treatment group is 0.61 for OS, a total of 194 death events will be needed for the study to have at least 80% power at 2-sided α level of 0.05 to detect a statistically significant treatment effect for the veliparib 40 mg BID + TMZ treatment group or the veliparib 120 mg BID + carboplatin + paclitaxel treatment group using the log-rank test for OS. If the veliparib 40 mg BID + TMZ treatment group is terminated for reasons of futility, a total of 136 death events in the double-blind portion of the study will provide approximately 80% power at 2-sided α level of 0.05 (or 74% power at 2-sided α level of 0.025) to detect a statistically significant treatment effect for the veliparib + carboplatin + paclitaxel treatment group using the log-rank test for OS.

Accounting for the number (4) of subjects enrolled under the original protocol (Group 1 of the study), a total of approximately 290 subjects with BRCA mutation as documented by the Sponsor core laboratory will be enrolled into the entire study.

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 the subject's Study Day 1 and a unique randomization number will be provided. The randomization numbers for Group 1 of the study will assign subjects in 1:1:1 ratio to veliparib 40 mg BID + TMZ, veliparib 80 mg BID + carboplatin paclitaxel, or placebo BID + carboplatin + paclitaxel. The randomization numbers for Group 2 of the study will assign subjects in 1:1:1 ratio to veliparib 40 mg BID + TMZ, veliparib 120 mg BID + carboplatin + paclitaxel, or placebo BID + carboplatin + paclitaxel. The randomization will be stratified by ER/PgR (ER and/or PgR positive versus ER and PgR negative), prior cytotoxic therapy use (yes versus no), and ECOG 0-1 versus 2.

Two sets of subject randomization schedules will be generated by the Clinical Statistics Department at AbbVie prior to the start of the study — one for Group 1 of the study and the other for Group 2 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.

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.

PG analysis, needle/excisional/punch biopsy and archived tissue sample collection will only be performed if the subject has voluntarily consented to participate after the nature of the testing has been explained and the subject has had the opportunity to ask questions. Informed consent for PG sample, needle/excisional/punch biopsy and archived tissue collection must be signed before testing is performed. If the subject does not consent to the PG and/or tissue sample collection it will not impact the subject's participation in the study.

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-C15/BR23 and CIPN20) 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

12.1 Use of Information

Any PG research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision-making or subject management. Hence, neither the Investigator, the subject, nor the subject's physician (if different than the Investigator) will be informed of individual subject PG results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic 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. Aggregate PG information from this study may be used in scientific publications or presented at medical conventions. PG information will be published or presented only in a way that does not identify any individual subject.

12.2 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

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 Agency for the Evaluation of Medicinal Products (EMEA) 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 TMZ, 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 Randomized, Phase 2 Study of the Efficacy and Tolerability of Veliparib in Combination with Temozolomide or Veliparib in Combination with Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Subjects with BRCA1 or BRCA2 Mutation and Metastatic Breast Cancer
Protocol Date:	07 June 2019

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]		Clinical
		Clinical
		Clinical
		Statistics

Appendix C. EORTC QLQ-C15-PAL (Version 1)

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.

Your year of birth (Year):

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

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
2. Do you need to stay in bed or a chair during the day?	1	2	3	4
3. 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
4. Were you short of breath?	1	2	3	4
5. Have you had pain?	1	2	3	4
6. Have you had trouble sleeping?	1	2	3	4
7. Have you felt weak?	1	2	3	4
8. Have you lacked appetite?	1	2	3	4
9. Have you felt nauseated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
10. Have you been constipated?	1	2	3	4
11. Were you tired?	1	2	3	4
12. Did pain interfere with your daily activities?	1	2	3	4
13. Did you feel tense?	1	2	3	4
14. Did you feel depressed?	1	2	3	4

For the following question please circle the number between 1 and 7 that best applies to you.

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix D. 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 E. EORTC QLQ-CIPN20

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. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have tingling fingers or hands?	1	2	3	4
32. Did you have tingling toes or feet?	1	2	3	4
33. Did you have numbness in your fingers or hands?	1	2	3	4
34. Did you have numbness in your toes or feet?	1	2	3	4
35. Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36. Did you have shooting or burning pain in your toes or feet?	1	2	3	4
37. Did you have cramps in your hands?	1	2	3	4
38. Did you have cramps in your feet?	1	2	3	4
39. Did you have problems standing or walking because of difficulty feeling the ground under your feet?	1	2	3	4
40. Did you have difficulty distinguishing between hot and cold water?	1	2	3	4
41. Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
42. Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
43 Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
44. Did you have difficulty walking because your feet dropped downwards?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
45. Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
46. Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
47. Did you have blurred vision?	1	2	3	4
48. Did you have difficulty hearing?	1	2	3	4
Please answer the following question only if you drive a car				
49. Did you have difficulty using the pedals?	1	2	3	4
Please answer the following question only if you are a man				
50. Did you have difficulty getting or maintaining an erection?	1	2	3	4

Appendix F. 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: [redacted] Phone: [redacted]
Fax:
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Has been changed to read:

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

Section 1.2 Synopsis
Subsection Methodology:
Second paragraph
Add: new third sentence

For subjects on study treatment more than 5 years, Day 1 visit is not required.

Section 1.2 Synopsis
Subsection Methodology:
Last paragraph
Add: new last sentence

For subjects on study treatment more than 5 years, there will be no post-treatment follow-up.

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms)
Header row, column "Day 3 of Each Cycle" previously read:

Day 3 of Each Cycle

Has been changed to read:

Day 3 of Each Cycle[r]

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms)
Table note "g."
Add: new last sentence

For subjects on study treatment for more than 5 years, central laboratory testing is no longer required.

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms)
Table note "j."
Add: new last sentence

For subjects on study treatment more than 5 years, tumor assessments will be conducted every 6 months.

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms)
Table note "n."
Add: new last sentence

For subjects on study treatment more than 5 years, 12-lead ECG, urinalysis, CIPN Assessment (QLQ-CIPN20), EORTC QLQ-C15/BR23, and tumor assessments do not need to be performed at Final Visit.

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms)
Table note "o."
Add: new last sentence

For subjects on study treatment more than 5 years, CIPN Assessment (QLQ-CIPN20) and EORTC QLQ-C15/BR23 do not need to be performed at the Follow-up Visit.

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms)
Table note "p."
Add: new last sentence

For subjects on study treatment more than 5 years, there will be no post-treatment follow-up.

Table 5. Study Activities (Subjects Randomized to Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arms)
Table note "r."
Add: new second, third, and fourth sentence

For subjects on study treatment more than 5 years, Day 1 visit is not required. Physical Exam, Hematology, Chemistry, Performance Status (ECOG), AE assessment, and Dispense Veliparib/Placebo can be performed on Day 3 instead. Urinalysis, CIPN Assessment (QLQ-CIPN20), and EORTC QLQ-C15/BR23 no longer need to be performed on either Day 1 or Day 3 for these subjects.

Table 6. Schedule Pharmacodynamic and Pharmacogenetic Assessments
Header row, column "Visit Schedule" previously read:

Visit Schedule

Has been changed to read:

Visit Schedule[f]

Table 6. Schedule Pharmacodynamic and Pharmacogenetic Assessments
Add: new table note "f."

For subjects on study treatment more than 5 years, any sampling scheduled for Day 1 of every 10th cycle or Final Visit will no longer be required.

Section 5.3.1.1 Study Procedures
Last paragraph
Add: new last sentence

For subjects on study treatment more than 5 years, laboratory samples may be collected up to 4 days prior to dosing carboplatin/paclitaxel on Day 3.

Section 5.3.1.1 Study Procedures
Subsection 12-lead Electrocardiogram (ECG)
Add: new last sentence

Final Visit ECG will not be required for subjects on study treatment more than 5 years.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Add: new fourth paragraph

For subjects remaining on study treatment for more than 5 years, use of the certified central laboratory will be discontinued. A certified local reference laboratory will perform CBC and chemistry test prior to dosing carboplatin/paclitaxel. Local laboratory results should be documented in the source and the electronic data capture (EDC) system as appropriate. Samples will no longer be sent to the central laboratory for analysis.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Fourth paragraph
Add: new last sentence

For subjects on study treatment more than 5 years, lab samples may be collected up to 4 days prior to dosing carboplatin/paclitaxel.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Fourth paragraph, first bullet
Add: new last sentence

Urinalysis will no longer be required for subjects on study treatment more than 5 years.

Table 9. Clinical Laboratory Tests
Add: new table note "*"**

For subjects on study treatment for more than 5 years, hematology and chemistry laboratory tests should be per local standard of care/institutional guidelines, and should include neutrophils, platelets, SGOT/AST, SGPT/ALT, total bilirubin, and alkaline phosphatase.

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessments (Radiologic)
Second paragraph
Add: new second sentence

For subjects on study treatment more than 5 years, tumor assessments will be conducted every 6 months (± 6 weeks) from C1D1 instead of every 9 weeks from C1D1, and will not be required at Final Visit.

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessments (Radiologic)
Fourth paragraph
Add: new last sentence

For subjects on study treatment more than 5 years, tumor assessments will be discontinued if subject discontinues treatment for any reason.

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessments (Radiologic)
Fifth paragraph
Add: new last sentnece

For subjects on study treatment more than 5 years, radiology scans will not be sent to the central imaging vendor.

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessments (Radiologic)
Last paragraph first sentence previously read:

All events of disease progression must be confirmed by the central imaging center.

Has been changed to read:

All events of disease progression must be confirmed by the central imaging center (except for subjects on study treatment more than 5 years).

Section 5.3.1.1 Study Procedures
Subsection CIPN Assessment
Add: new last sentence

CIPN assessment will no longer be required at any visit for subjects on study treatment for more than 5 years.

Section 5.3.1.1 Study Procedures
Subsection Quality of Life
First paragraph
Add: new last sentence

EORTC QLQ-C15/BR23 questionnaires will no longer be administered at any visit for subjects on study treatment for more than 5 years.

Section 5.3.1.1 Study Procedures
Subsection Dispensation of Study Drug
Second paragraph
Add: new fourth, fifth, sixth, and seventh sentence

For subjects on study treatment more than 5 years, veliparib/placebo may be dispensed at the Day 3 visit instead of the Day 1 visit. Sufficient medication will be dispensed to cover an entire cycle. The site is advised to contact the subject on the morning of Day 1 to reiterate the dosing instructions of veliparib/placebo. It is recommended the site contact the subject on Day 7 to instruct about ceasing dosing.

Section 5.3.1.1 Study Procedures
Subsection Dispensation of Study Drug
Third paragraph, second sentence previously read:

Site personnel must contact the IVRS/IWRS for the bottle number assignments no more than 5 days before Day 1 of each cycle.

Has been changed to read:

Site personnel must contact the IVRS/IWRS for the bottle number assignments no more than 5 days before Day 1 of each cycle (or Day 3 for subjects on study treatment more than 5 years who are having veliparib/placebo dispensed at Day 3).

Section 5.3.1.1 Study Procedures
Subsection Post treatment Information
Add: new fourth paragraph

No post-treatment information will be collected for subjects on study treatment for over 5 years.

Section 5.3.1.3 Blood Samples for Pharmacodynamic Analysis
Subsection Blood Collection for Plasma Markers
Add: new last sentence

For subjects on study treatment more than 5 years, sampling scheduled for Day 1 of every 10^{th} cycle or Final Visit will no longer be required.

Section 5.3.1.3 Blood Samples for Pharmacodynamic Analysis
Subsection Blood Collection for Serum Markers
Add: new second sentence

For subjects on study treatment more than 5 years, any sampling scheduled for Day 1 of every 10th cycle or Final Visit will no longer be required.

Section 5.3.3 Efficacy Variables
First paragraph
Add: new last sentence

Assessments will be modified for subjects on study treatment more than 5 years as indicated in Section 5.3.1.1.

Section 5.4.1 Discontinuation of Individual Subjects
Fourth paragraph
Add: new last sentence

For subjects on study treatment more than 5 years, 12-lead ECG, urinalysis, CIPN Assessment (QLQ-CIPN20), and EORTC QLQ-C15/BR23, and tumor assesement do not need to be performed at Final Visit.

Section 5.4.1 Discontinuation of Individual Subjects
Fifth paragraph
Add: new last sentence

For subjects on study treatment more than 5 years, CIPN Assessment (QLQ-CIPN20) and EORTC QLQ-C15/BR23 do not need to be performed at the Follow-up Visit.

Section 5.4.1 Discontinuation of Individual Subjects
Seventh paragraph
Add: new last sentence

For subjects on study treatment more than 5 years, the subject will be discontinued from study if discontinuing treatment for any reason.

Section 5.4.1 Discontinuation of Individual Subjects
Eighth paragraph
Add: new last sentence

For subjects on study treatment for more than 5 years, overall survival and post treatment information are not required.

Section 5.4.2 Discontinuation of Entire Study
First paragraph
Add: new last sentence

For subjects on study treatment for more than 5 years, survival follow-up is not required.

Section 5.7 Dose Reductions or Delays
First paragraph, last sentence previously read:

All toxicities, with the exception of anemia, alopecia, neuropathy, 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.

Has been changed to read:

All toxicities, with the exception of anemia, alopecia, neuropathy, 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 chemotherapy.

Section 6.5 Adverse Event Reporting
Third and fourth paragraph previously read:

For any emergent safety concerns, please contact the AbbVie Medical Monitor.

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Mobile:
Fax:
Email: [redacted]

Should in case of subject safety concerns or medical emergencies the Primary Study Designated Physician be unavailable, please call the following central back-up number:

Has been changed to read:

For any emergent safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:
[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Mobile:
Fax:
Email: [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Section 6.5 Adverse Event Reporting
Last paragraph previously read:

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. The safety reference material used for SUSAR reporting will be the most current version of the Investigator's Brochure for veliparib or SmPC for TMZ, carboplatin, and paclitaxel.

Has been changed to read:

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines. Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI) for veliparib and Summary of Product Characteristics (SmPC) will be the RSI for carbloplatin, paclitaxel, and temozolomide. The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

Section 6.6 Pregnancy
First paragraph, first sentence previously read:

In the event of a positive pregnancy test, subjects must immediately discontinue study drug and must be discontinued from the study.

Has been changed to read:

In the event of a positive pregnancy test, subjects must immediately discontinue study drug and must be discontinued from the study (Section 5.4).

Section 7.0 Protocol Deviations
Contact information previously read:

Clinical Team Lead:

[redacted]
Clinical Field Operations, GPRD
Knollstr. 50
67061 Ludwigshafen
Germany

Office:
Mobile:
Fax:
Email: [redacted]

Medical Monitor:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Mobile: [redacted]
Fax:
Email:

Has been changed to read:

Clinical Team Lead:

[redacted]
AbbVie Corporation
8401 Trans-Canada Highway
Saint-Laurent, Québec
H4S 1Z1
Canada

Office:
Fax:
Email: [redacted]

Scientific Director:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Fax:
Email: [redacted]

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Global Drug Supply
		Clinical
		Statistics
		Clinical
		Clinical
		Pharmacokinetics

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Statistics