This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol and SAP

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Coleman RL, Fleming GF, Brady MF, et al. Integration of veliparib with front-line chemotherapy and maintenance in women with high-grade serous carcinoma of ovarian, fallopian tube, or primary peritoneal origin.

This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

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1.0 Title Page

Clinical Study Protocol M13-694

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

AbbVie Investigational Product: Veliparib (ABT-888)
Date: 18 December 2014
Development Phase: 3
Study Design: This is a Phase 3, placebo-controlled, randomized study of veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in subjects with untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.
EudraCT Number: 2014-005070-11
Investigator: Multicenter Study: Site Investigator information is on file at AbbVie Inc. (AbbVie)
Sponsor: AbbVie Inc. (AbbVie)*
Collaborative Partners: This protocol was designed and developed in collaboration with the Gynecologic Oncology Group Foundation.
GOG Study Number: PROTOCOL GOG-3005
Sponsor/Emergency Contact:

Medical Monitor:

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

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

**Confidential Information**

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.
1.1 Synopsis

AbbVie Inc.  Protocol Number: M13-694

<table>
<thead>
<tr>
<th>Name of Study Drug</th>
<th>Veliparib (ABT-888)</th>
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<tr>
<td>Phase of Development</td>
<td>3</td>
</tr>
<tr>
<td>Name of Active Ingredient</td>
<td>Veliparib</td>
</tr>
<tr>
<td>Date of Protocol Synopsis</td>
<td>18 December 2014</td>
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</table>

Protocol Title: A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Objectives:
The primary objective of the study is to evaluate whether progression-free survival (PFS) is prolonged when veliparib is added to standard platinum-based chemotherapy and then continued as maintenance (Arm 3 versus Arm 1). Progression-free survival as the primary study endpoint will be evaluated in both the whole subject population, as well as a more selective cohort of subjects with BRCA-deficient tumors (gBRCA and/or sBRCA). Secondary objectives include overall survival (OS) (Arm 3 versus Arm 1, and Arm 2 versus Arm 1), safety of all three arms, and disease related symptom (DRS) scores (Arm 3 versus Arm 1 and Arm 2 versus Arm 1) in both the whole population and BRCA-deficient population.

Investigator: Multicenter

Study Sites: Approximately 400 sites

Study Population: Female subjects with previously untreated Stage III or IV high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Number of Subjects to be Enrolled: Approximately 1100

Methodology:
This is a Phase 3, randomized, placebo-controlled, study to evaluate the efficacy and tolerability of veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in the above stated study population. The study will consist of four phases: the Pre-Therapy Phase (Screening), a Combination Therapy Phase, a Maintenance Therapy Phase and a Long-Term Follow-Up Phase.

Pre-therapy (screening) procedures will be performed within 28 days of Cycle 1 Day 1. A computerized tomography (CT) of the abdomen and pelvis (and chest if metastases are present) will be used by Investigators to evaluate disease status per RECIST 1.1. In addition to being reviewed by the Investigator and/or qualified site staff, radiographic scans will be sent to a central imaging center. During the Pre-Therapy Phase, Investigator's will be allowed the choice of either carboplatin AUC 6 in combination with weekly paclitaxel (Q-week) or carboplatin AUC 6 in combination with every 3 weeks paclitaxel (Q3-weeks). Either of these chemotherapy regimens will be administered with either primary or interval cytoreductive surgery. The Investigator's treatment decision will be documented prior to proceeding to randomization.
Methodology (Continued):
Once pre-therapy procedures are complete and eligibility is confirmed, subjects will be randomized 1:1:1 to one of the following three arms. Subjects will be stratified by stage of disease (Stage III versus IV), residual disease and choice of regimen, and region of the world (North America versus Rest of World).
Arm 1: Carboplatin/paclitaxel plus placebo for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;
Arm 2: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;
Arm 3: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by veliparib maintenance therapy for 30 additional 21-day cycles.
During the Combination Therapy Phase, subjects will receive veliparib/placebo orally (PO) twice daily (BID) in combination with intravenous (IV) carboplatin/paclitaxel for six cycles (Cycle 1 through Cycle 6).
Subjects who complete the Combination Therapy Phase and who have not progressed will receive veliparib 400 mg/placebo orally twice daily maintenance therapy for an additional 30 cycles (Cycles 7 – 36) during the Maintenance Therapy Phase.
A Therapy Completion Visit will be performed for all subjects when therapy is discontinued. All subjects will have one Follow-Up Visit approximately 30 days after the Therapy Completion Visit.
Post baseline tumor assessments will be collected every 9 weeks, then at the end of the Combination Phase, then every 12 weeks for 2 years, then every 6 months for up to 3 years then annually (± 7 days) until disease progression per RECIST 1.1.
Post baseline PRO assessments will be collected every other cycle for up to 2 years or until disease progression per RECIST 1.1, whichever is longer. A PRO assessment will also be performed during the Follow-Up Visit.
Post baseline DRS scores will be collected every other cycle for up to 2 years or until disease progression per RECIST 1.1, whichever is later. DRS scores will also be performed during the Follow-Up Visit.
After meeting the protocol criteria for discontinuation, subjects will continue to be followed during the Long-Term Follow-Up Phase for survival, post therapy information and recurrence of disease information.
Survival information and post therapy information will be collected every 3 months until the endpoint of death, the subject is lost to follow-up or until study termination by AbbVie. Additionally, recurrence of disease information will be collected every 6 months for up to 10 years until the endpoint of death, the subject is lost to follow-up or until study termination by AbbVie.
A detailed description of the study visits and procedures are provided in the protocol.

Diagnosis and Main Criteria for Inclusion/Exclusion:
Main Inclusion:
1. Subjects with a histologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, International Federation of Gynecology and Obstetrics (FIGO) Stage III or IV with appropriate tissue available for histologic evaluation.
### Diagnosis and Main Criteria for Inclusion/Exclusion (Continued)

#### Main Inclusion (Continued):

2. Subjects will be required to have high-grade serous adenocarcinoma to be eligible.
3. Subject is willing to undergo testing for gBRCA.
4. Subject must have adequate hematologic, renal, and hepatic function as follows:
   - Hemoglobin $\geq 9.5$ g/dL (5.89 mmol/L);
   - Absolute neutrophil count greater than or equal to $1,500/\mu$L;
   - Platelet count greater than or equal to $100,000/\mu$L;
   - Serum creatinine $\leq 1.0 \times$ ULN range; subjects with a serum creatinine $>1.0 \times$ ULN range must have a creatinine clearance $\geq 60$ mL/min (according to the Cockcroft-Gault equation);
   - Total bilirubin $\leq 1.5 \times$ ULN. Subjects with Gilbert's Syndrome may have a bilirubin $\geq 1.5 \times$ the ULN range if no evidence of biliary obstruction exists;
   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase must be less than or equal to $2.5 \times$ ULN;
   - Albumin $\geq 3.0$ g/dL.
5. Subjects with neuropathy (sensory and motor) less than or equal to Grade 1.
6. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
7. Subject is able to swallow and retain oral medication and does not have uncontrolled emesis.
8. Subjects who undergo primary cytoreductive surgery must be entered between 1 and 12 weeks after surgery. Subjects undergoing interval surgery must have a needle core biopsy confirming the histological diagnosis prior to enrollment.
9. Subjects with measurable disease and non-measurable disease are eligible. Subjects may or may not have cancer-related symptoms.
10. Subject has one of the following available for PD analyses including somatic BRCA testing:
    - Archived diagnostic formalin-fixed paraffin embedded (FFPE) tumor tissue; or tumor tissue biopsy collected prior to Cycle 1 Day 1.

#### Main Exclusion:

1. Subjects with the following histologic cell types are ineligible: endometrioid adenocarcinoma, carcinosarcoma, undifferentiated carcinoma, mixed epithelial adenocarcinoma, adenocarcinoma not otherwise specified, mucinous adenocarcinoma, clear cell adenocarcinoma, low-grade serous adenocarcinoma, or malignant Brenner's tumor.
2. Subjects with synchronous primary endometrial cancer, or a past history of endometrial cancer unless all of the following conditions are met: endometrial cancer stage not greater than IA, no vascular or lymphatic invasion, no poorly differentiated subtypes including serous, clear cell, or other FIGO grade 3 lesions.
3. Subjects with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the last 3 years. Subjects are also excluded if their previous cancer treatment contraindicates this protocol's therapy.
**Diagnosis and Main Criteria for Inclusion/Exclusion (Continued)**

**Main Exclusion (Continued):**

4. Subjects who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded.

5. Subjects who have received prior chemotherapy for any abdominal or pelvic tumor are excluded.

6. Subject has a clinically significant uncontrolled condition(s), including but not limited to:
   - Uncontrolled seizure disorder, or focal or generalized seizure within the last 12 months;
   - Active infection that requires parenteral antibiotics;
   - Known active hepatitis B or hepatitis C with abnormal liver function test or organ dysfunction;
   - Symptomatic congestive heart failure; unstable angina pectoris; serious ventricular cardiac arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or serious cardiac arrhythmia requiring medication (this does not include asymptomatic atrial fibrillation with controlled ventricular rate); or myocardial infarction within the last 6 months;
   - Uncontrolled hypertension (sustained systolic blood pressure > 150 mmHg or diastolic pressure > 100 mmHg despite optimal medical management);
   - Bowel obstruction or gastric outlet obstruction. **Note:** Subjects requiring drainage gastrostomy tube and/or parental hydration and/or nutrition are not eligible;
   - Psychiatric illness/social situations that would limit compliance with study requirements;
   - Any medical condition which in the opinion of the Investigator places the subject at an unacceptably high risk for toxicities.

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

8. Subjects with history or evidence upon physical examination of central nervous system (CNS) disease, including primary brain tumor, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) within 6 months of Cycle 1 Day 1.

9. Subjects under the age of 18.

---

**Investigational Product:** Veliparib (ABT-888) 50 mg or 100 mg

**Doses:**
- Veliparib 150 mg BID with carboplatin/paclitaxel for six 21-day cycles
- Veliparib 400 mg BID maintenance therapy for up to 30 additional 21-day cycles

**Mode of Administration:** Oral

**Reference Therapy:** Placebo (matching 50 mg or 100 mg)

**Doses:**
- Placebo BID with carboplatin/paclitaxel for six 21-day cycles
- Placebo BID maintenance therapy for up to 30 additional 21-day cycles

**Mode of Administration:** Oral
**Duration of Treatment:** Subjects will receive veliparib/placebo PO BID in combination with carboplatin/paclitaxel for six 21-day cycles of therapy. Subjects who have not progressed per RECIST 1.1 will then receive maintenance therapy with veliparib/placebo PO BID for a maximum of an additional thirty 21-day cycles.

**Criteria for Evaluation:**

**Efficacy:**
The primary objective of the study is to evaluate whether PFS is prolonged with the addition of veliparib to carboplatin/paclitaxel and continued as maintenance therapy when compared to chemotherapy alone. This will be evaluated in the whole patient population, as well as a more selective cohort of subjects with \textit{BRCA}-deficient tumors (g\textit{BRCA} and/or s\textit{BRCA}), as dual-primary objectives.

Secondary objectives include analyses of PFS with veliparib in combination with chemotherapy versus chemotherapy alone (no maintenance; Arm 2 versus 1), OS (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), safety of the 3 study arms, and DRS scores (DRS score, Arm 3 versus Arm 1 and Arm 2 versus Arm 1). The secondary objectives will be evaluated in both the whole and \textit{BRCA}-deficient patient populations.

For the primary Patient Reported Outcome (PRO) analysis, the overall mean change from baseline for the DRS scores between the treatment groups will be assessed, using a longitudinal repeated measures model that takes into account the DRS measured at each assessment point up to 2 years or disease progression, whichever is later.

**Pharmacokinetic:**
Sparse pharmacokinetic (PK) samples will be collected for the estimate of population PK parameters of veliparib such as apparent oral clearance (CL/F) and volume of distribution (V/F).

**Pharmacodynamic:**
All subjects must have a pre-therapy tumor biopsy (archived or fresh biopsy) for inclusion in the study. Genetic analysis to determine \textit{BRCA} mutation status will be conducted using tissue and blood specimens to support efficacy endpoints.

Biospecimens will be collected at designated time points throughout the study to conduct research with the intent of identifying biomarkers associated with subject outcome or to better characterize the disease.

**Safety:**
AbbVie will assess adverse events, laboratory data, ECGs and vital signs throughout the study. Adverse events intensity and laboratory evaluation changes will be assessed by utilizing National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.
Statistical Methods:

**Efficacy:**

**Primary Efficacy Endpoint**

The primary efficacy endpoint is progression-free survival (PFS). PFS will be defined as the number of days from the date that the subject was randomized to the date the subject experiences an event of disease progression, according to RECIST criteria version 1.1 (as determined by the Investigator) or to the date of death (all causes of mortality) if disease progression is not reached. All events of disease progression (as determined by the Investigator) will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. However, if a disease progression event occurs after a subject misses two or more consecutive disease progression assessments this subject will be censored at the last disease progression assessment prior to the missing disease progression assessments. All events of death will be included for subjects who had not experienced disease progression provided the death occurred within a time window defined according to the underlying disease assessment interval. If the subject does not have an event of disease progression (as determined by the Investigator) nor has the subject died, the subject's data will be censored at the date of the subject's last disease assessment.

The primary efficacy analyses are defined by comparing PFS in Arm 3 versus Arm 1 in the whole population and the BRCA-deficient population (or only in the whole population based on the pre-specified alpha allocation rule). PFS will be also compared between Arm 2 and Arm 1 as a secondary analysis and between Arm 2 and Arm 3 as an exploratory analysis.

**Secondary Efficacy Endpoints**

**Overall Survival**

Overall survival (OS) 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.

The secondary efficacy analyses for OS are defined by comparing OS in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the whole population and the BRCA-deficient population (or only in the whole population based on the pre-specified alpha allocation rule). OS will be also compared between Arm 2 and Arm 3 as an exploratory analysis.

**Disease Related Symptoms**

The overall mean change from baseline for the DRS scores measured at each assessment point up to 2 years or disease progression will be a secondary endpoint of the study. The overall mean change from baseline for the total DRS scores between the treatment groups will be compared using a longitudinal repeated measures model that takes into account the DRS scores measured at each assessment point up to 2 years. This analysis will include all available data, from baseline out to 2 years or disease progression, whichever is later.
**Statistical Methods (Continued)**

**Efficacy (Continued):**

**Interim Analyses**

For OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the whole population, one efficacy interim will be performed at the time of the corresponding PFS analyses (~Month 36) with a nominal alpha of 0.0001, so that the final OS analyses (~Month 58) have a nominal alpha of 0.0124.

For OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the BRCA-deficient population, two efficacy interims will be performed. The first interim analysis will occur at the time of the corresponding PFS analyses (~Month 36) with a nominal alpha of 0.0001, the second interim analysis will occur at the time of the OS analysis for the whole population (~Month 58) with a nominal alpha of 0.0001, so that the final OS analyses (~Month 77) have a nominal alpha of 0.0124 to have the overall alpha controlled at 0.0125 in the BRCA-deficient population.

**Sample Size Calculation**

The trial will enroll approximately 1100 subjects (with 1:1:1 randomization ratio for Arm 1:Arm 2:Arm 3) in the whole population, including approximately 264 subjects with BRCA-deficient status (assuming 24% of the subjects in the whole population are BRCA deficient) to power the hypotheses specified in the whole and BRCA-deficient populations. Detailed sample size calculation information for each endpoint of the whole and BRCA-deficient populations is provided in Section 8.2.

**Multiplicity Control**

Multiple testing strategies and multiplicity control are detailed in Section 8.1.4.
# 1.2 List of Abbreviations and Definition of Terms

## Abbreviations

<table>
<thead>
<tr>
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<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>absolute neutrophil count</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>ATEMS</td>
<td>AbbVie Temperature Excursion Management System</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the plasma concentration-time curve</td>
</tr>
<tr>
<td>BCS</td>
<td>Biopharmaceutics Classification System</td>
</tr>
<tr>
<td>BID</td>
<td>twice daily</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>breast cancer genes 1 and 2</td>
</tr>
<tr>
<td>BRCA-deficient</td>
<td>clinically significant germline or somatic mutation in BRCA1 or BRCA2</td>
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<tr>
<td>C1D1</td>
<td>Cycle 1 Day 1</td>
</tr>
<tr>
<td>C3D1</td>
<td>Cycle 3 Day 1</td>
</tr>
<tr>
<td>C5D1</td>
<td>Cycle 5 Day 1</td>
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<tr>
<td>CL/F</td>
<td>oral clearance</td>
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<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximum observed plasma concentration</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CTEP</td>
<td>Cancer Therapy Evaluation Program</td>
</tr>
<tr>
<td>CVA</td>
<td>cerebrovascular accident</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>DLT</td>
<td>dose-limiting toxicity</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRS</td>
<td>disease-related symptoms</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>EuroQOL five dimensions, five levels</td>
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<td>ESMO</td>
<td>European Society for Medical Oncology</td>
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<td>FACT</td>
<td>Functional Assessment of Cancer Therapy</td>
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Veliparib (ABT-888)
M13-694 Protocol
EudraCT 2014-005070-11

FDA  US Food and Drug Administration
FFPE  formalin-fixed paraffin embedded
FIGO  International Federation of Gynecology and Obstetrics
gBRCA  clinically significant germline BRCA1 or BRCA2 mutation
G-CSF  granulocyte colony-stimulating factor
GM-CSF  granulocyte macrophage colony-stimulating factor
GCP  Good Clinical Practice
GFR  glomerular filtration rate
GOG  Gynecologic Oncology Group Foundation
GPRD  Global Pharmaceutical Research & Development
HDPE  high-density polyethylene
HR  hazard ratio
ICH  International Conference on Harmonization
IDMC  Independent Data Monitoring Committee
IEC  Independent Ethics Committee
IMP  Investigational Medicinal Product
INR  international normalized ratio
IP  intraperitoneal
IRB  Institutional Review Board
IRT  Interactive Response Technology
ITT  intent-to-treat
IUD  intra-uterine device
IV  intravenous or intravenously
MedDRA  Medical Dictionary for Regulatory Activities
MRI  magnetic resonance imaging
MTD  maximum tolerated dose
NCCN  National Comprehensive Cancer Network
NFOSI-18  NCCN FACT Ovarian Symptom Index-18
NSCLC  non-small cell lung cancer
OS  Overall Survival
PARP  poly-(ADP-ribose)-polymerase
PARPi  PARP inhibitor
PFS  progression-free survival
PO  by mouth
<table>
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<th>Definition</th>
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<tr>
<td>POR</td>
<td>Proof of Receipt</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>PRO</td>
<td>patient-reported outcome</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>partial thromboplastin time</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria In Solid Tumors</td>
</tr>
<tr>
<td>sBRCA</td>
<td>clinically significant somatic BRCA1 or BRCA2 mutation</td>
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<tr>
<td>SGOT</td>
<td>serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TCGA</td>
<td>The Cancer Genome Atlas</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>time to maximum observed plasma concentration</td>
</tr>
<tr>
<td>TTFST</td>
<td>time to the first subsequent therapy</td>
</tr>
<tr>
<td>TTSST</td>
<td>time to the second subsequent therapy</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analog scale</td>
</tr>
<tr>
<td>V/F</td>
<td>volume of distribution</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
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3.0 Introduction

This Phase 3 study is designed to test whether the integration of concurrent and continuation maintenance veliparib (ABT-888), a poly-(ADP-ribose)-polymerase (PARP) inhibitor, with carboplatin/paclitaxel chemotherapy for high grade serous epithelial, ovarian, fallopian tube, or primary peritoneal cancer will improve clinical outcomes.

In this context, it is important to recognize that the potential mechanisms of PARP inhibition differ when directly integrated with platinum-based chemotherapy (enhanced cytotoxicity or therapeutic synergy) compared to use as a single agent after completion of chemotherapy (synthetic lethality in tumors with defective homologous deoxyribonucleic acid [DNA] repair). This Phase 3 study incorporates both of these approaches in the experimental arms.

While significant strides have been made to tailor the primary treatment of ovarian cancer to improve efficacy and tolerability, the mortality of advanced-stage ovarian cancer has not changed, and additional improvements are needed. The discovery and development of new molecular targeted agents may lead to more effective combination regimens and improved outcomes for patients. Currently, the standard of care for the primary treatment of ovarian, fallopian tube, or primary peritoneal cancer is a combination of platinum and taxane chemotherapy.\textsuperscript{1,2} For patients with early-stage disease, as well as advanced suboptimal Stage III and Stage IV disease, intravenous (IV) carboplatin and paclitaxel is given on an every-3-week (Q3-weeks) cycle for 6 cycles. Weekly administration of paclitaxel has shown a survival benefit compared to every-3-weeks paclitaxel administration for patients with Stage II – IV disease.\textsuperscript{3} For Stage II/III patients with small-volume (optimal) residual disease after primary cytoreductive surgery, a regimen combining intraperitoneal (IP) cisplatin and paclitaxel with IV paclitaxel is often used.\textsuperscript{2} Despite the majority of patients entering a clinical complete remission following initial cytoreductive surgery and chemotherapy, most recur and eventually develop treatment resistant disease.
The clinical development of PARP inhibitors offers promising activity in both breast cancer genes 1 and 2 (BRCA1/2) mutation carriers and sporadic ovarian cancer patients. The Cancer Genome Atlas (TCGA) project has identified that approximately 50% high grade serous ovarian cancers exhibit defects in homologous recombination and DNA repair pathways and many of these defects could be susceptible to targeting with PARP inhibition. In addition, groups have looked at ways to identify homologous recombination-repair-deficient tumors using primary cultures from ascites or genomic profiles of loss of heterozygosity to identify subgroups of ovarian cancer patients who may be more responsive to chemotherapy and PARP inhibitors. This Phase 3 study incorporates this new knowledge regarding the biological subtypes of ovarian, fallopian tube, and primary peritoneal cancer and concepts of synthetic lethality and therapeutic synergy to improve the outcomes for women with high-grade serous ovarian cancer.

PARP Inhibitors

PARP-1 and PARP-2 are nuclear enzymes that recognize DNA damage and facilitate DNA repair. Activation of PARP-1 and PARP-2 enzymes is an essential step in the recognition of DNA damage that results in the poly(ADP-ribosyl)ation of many nuclear target proteins, including those that facilitate DNA repair. Preclinical and clinical data indicate that PARP inhibitors enhance and prolong the effects of DNA-damaging therapies such as carboplatin (enhanced cytotoxicity or therapeutic synergy) and that tumors with DNA-repair deficiencies are particularly sensitive to PARP inhibition, even in the absence of any other DNA-damaging insults (synthetic lethality).

Therapeutic Synergy: Combination with Cytotoxic Chemotherapy

In a variety of preclinical tumor models, including melanoma, prostate, colon, glioma, and BRCA-mutated breast and pancreatic carcinoma, veliparib significantly enhanced the antitumor activity when dosed on a schedule that overlapped the administration of a DNA-damaging agent. Significant inhibition of tumor PAR levels at doses similar to those with antitumor effect was observed, which is consistent with veliparib potentiation of DNA-damaging agents being mediated through mechanistic inhibition of PARP.
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. 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. In particular, tumor cells with \( BRCA1 \) or \( BRCA2 \) deficiencies are exquisitely sensitive to PARP inhibition, even in the absence of any other insults. Deficiencies in homologous recombination, caused by low expression of \( BRCA1 \) have also been observed in tumors not associated with germline \( BRCA \) deficiency (e.g., ovarian cancer, non-small cell lung cancer [NSCLC], and gastric cancer). These tumors would be expected to be sensitive to PARP inhibition.

Platinum agents such as carboplatin and cisplatin cause DNA damage through the formation of interstrand crosslinks. These crosslinks initially cause single-strand DNA breaks that lead to the recruitment and activation of PARP1 and PARP2 to facilitate DNA repair. Thus, PARP inhibitors can augment the DNA damage caused by carboplatin leading to greater tumor cell death, in both \( BRCA \)-proficient and \( BRCA \)-deficient tumors. This is further supported by the Phase 2 study in women with platinum sensitive recurrent serous ovarian cancer receiving either olaparib (200 mg BID) in combination with carboplatin (area under the plasma concentration-time curve [AUC] 4) and paclitaxel followed by olaparib monotherapy maintenance (400 mg BID) versus carboplatin (AUC 6) and paclitaxel with no further therapy in which the olaparib arm showed an improvement in PFS (HR = 0.51, 95% CI 0.34 – 0.77; \( P = 0.0012 \); median PFS 12.2 versus 9.6 months).

Comparative data from a placebo-controlled, randomized, double-blind Phase 2 study in subjects with advanced NSCLC (Study M10-898) further support the concept of therapeutic synergy in a DNA-repair proficient population. In this study, veliparib
120 mg BID on Days 1 to 7 added to standard therapy (carboplatin AUC 6 and paclitaxel 200 mg/m$^2$ on Day 3 on 21-day cycles) improved the median PFS by approximately 1.6 months (HR 0.737; $P = 0.14$) and improved median OS by approximately 2 months (HR 0.769; $P = 0.229$). Comparative safety data demonstrated a modest increase in neutropenia and leukopenia in the veliparib arm without other remarkable differences in treatment toxicity. Leukopenia (all grades) was increased in frequency by < 15% for veliparib- versus placebo-treated subjects, and neutropenia (all grades) was increased in frequency by < 10% for veliparib- versus placebo-treated subjects. No other adverse event was increased by > 5%. Adverse events led to reduction or discontinuation of backbone therapies at similar rates (± 3%) with or without veliparib. These data support the tolerability of the combination and are consistent with a toxicity profile similar in nature to that anticipated for the backbone regimen, with some increase in hematological toxicities and hematological toxicities being the most commonly observed dose limiting toxicity.

Approximately 375 subjects with advanced cancer have been treated with veliparib in combination with carboplatin and paclitaxel in Phase 1 and Phase 2 studies to date. The most commonly observed toxicities in these studies (> 30% of subjects) have included anemia (49.2%), nausea (42.9%), fatigue (40.9%), decreased neutrophil count/neutropenia (40.9% and 20.1%, respectively), decreased white blood cell count (35.8%), alopecia (32.7%), and decreased platelet count (30.3%). Less frequent, but potentially serious events included fever (6.3%), embolism (4.3%), allergic reaction (drug hypersensitivity 3.5%; hypersensitivity 3.1%), and febrile neutropenia (2.8%).

To best elucidate the dose in the intended Phase 3 study population, the GOG has conducted an ongoing Phase 1 dose-escalation study to evaluate the safety and maximum tolerated dose (MTD) of the combination of carboplatin (AUC 6, Q3-weeks), paclitaxel (175 mg/m$^2$ Q3-weeks or 80 mg/m$^2$ weekly [Q-week]), and bevacizumab (15 mg/kg, Q3 weeks; initiated in Cycle 2 followed by bevacizumab maintenance) with escalating doses of either intermittent or continuous veliparib (Study GOG 9923; N = 300). The most common toxicities in all subjects to date (veliparib 30 – 400 mg BID) have been
those commonly observed with the backbone therapy and include myelosuppression (anemia, decreased white blood cell count, neutrophil count, and platelet count (96.3% each); fatigue (81.5%); alopecia (77.8%); nausea (59.3%); constipation and diarrhea (55.6% each); peripheral sensory neuropathy (51.9%); hypertension (40.7%); headache (37.0%), and dyspnea and epistaxis (33.3% each). As expected for carboplatin and paclitaxel, myelosuppression has also been the most commonly observed Grade 3 and 4 toxicities.

With consideration that subjects in the Phase 3 Study M13-694 will have untreated disease, Study GOG 9923 includes a stringent tolerability assessment in the expansion cohorts, with feasibility determined based upon DLTs through 4 cycles in a minimum of 17 subjects at the recommended dose that confirms the ability to deliver multiple cycles of chemotherapy per standard of care. Veliparib 150 mg BID continuous is the recommended dose in combination with both the Q3-weeks paclitaxel and carboplatin and the Q-week paclitaxel and carboplatin regimens. Seventeen evaluable subjects were treated at this dose level in combination with Q3-weeks paclitaxel and carboplatin with 2 DLTs (Grade 3 febrile neutropenia and Grade 3 hyponatremia). One DLT (Grade 3 headache) was observed in the 17 evaluable subjects treated with Q-week paclitaxel and carboplatin at this dose level. The dose for this Phase 3 study is veliparib 150 mg BID administered continuously on Days 1 to 21 of a 21 day cycle for both regimens.

**Synthetic Lethality: Single-Agent Therapy**

The TCGA project has identified that at least 50% of high-grade serous ovarian tumors exhibit defects in homologous recombination pathways that may result in increased sensitivity to PARP inhibitors.\(^23\) This includes approximately 15% to 20% of high-grade serous epithelial ovarian cancers with \(gBRCA\) and an estimated additional 7% with \(sBRCA\). Defects in homologous repair secondary to mutations in the \(BRCA\) genes result in DNA repair via more error prone mechanisms. The combination of defective homologous recombination due to mutations in \(BRCAl/2\) and suppressed base excision repair due to PARP inhibition results in targeted cell death in the tumor cells,\(^23\) and has been called "synthetic lethality."\(^{24,25}\) Durable responses have been observed with
veliparib monotherapy in both \textit{gBRCA} advanced breast cancer\textsuperscript{36} and \textit{gBRCA} recurrent ovarian cancer\textsuperscript{37} supporting the mechanism of synthetic lethality in \textit{BRCA1}/\textit{BRCA2}-mutated tumors.

\textbf{Monotherapy Studies}

Studies showing responses to monotherapy with PARP inhibitors in ovarian cancer have been presented and/or published with veliparib, olaparib, niraparib, and BMN673. In the initial Phase 1 study of olaparib, a cohort of \textit{BRCA} mutation carriers and patients with a strong family history had a favorable response rate of 28\%\textsuperscript{4}. Olaparib was studied further in the \textit{BRCA} population in a Phase 2 dose-finding proof-of-concept study of 100 mg twice daily (BID) and 400 mg BID\textsuperscript{5}. Again, a 33\% response rate was seen at the 400 mg BID dose, but only one third of that was seen at the 100 mg BID dose. This is interesting in light of the pharmacodynamic data from the Phase 1 study that showed that 90\% inhibition of the PARP enzyme was reached at 100 mg BID. Inhibition did not seem to increase further with higher doses when studying peripheral blood mononuclear cells as a surrogate tissue.

Olaparib has also been studied as monotherapy in a group of recurrent high-grade serous ovarian cancer patients or triple-negative breast cancer patients, stratified by whether they had a \textit{BRCA1} or \textit{BRCA2} mutation or not. Of the subjects with ovarian cancer, an objective response rate of 41\% (7/17; 95\% confidence interval [CI] 22 – 64\%) was observed in those with a \textit{BRCA1}/\textit{BRCA2} mutation and of 24\% (11/46; 95\% CI 14 – 38\%) in those without, supporting that underlying defects in DNA damage repair occur in ovarian tumors in the absence of \textit{BRCA1}/\textit{BRCA2} mutations and that these lead to sensitivity to PARP inhibitor single-agent therapy. Similarly, in a randomized, placebo controlled Phase 2 study evaluating olaparib maintenance monotherapy after carboplatin and paclitaxel treatment for platinum-sensitive recurrent serous ovarian cancer, PFS was significantly longer in the olaparib-treated group compared to placebo (hazard ratio [HR] = 0.35; 95\% CI 0.25 – 0.49; \(P < 0.00001\); median 8.4 versus 4.8 months) with clinical benefit observed in \textit{BRCA}-deficient patients (HR = 0.18, \(P < 0.00001\)) and in patients without a \textit{BRCA} mutation (\textit{BRCA} wild type) (HR = 0.53, \(P = 0.007\))\textsuperscript{28}. 

\textsuperscript{28}
In Cancer Therapy Evaluation Program (CTEP) Study 8282, a Phase 1 study in subjects with \textit{gBRCA}-mutated cancer (clinically significant germline \textit{BRCA1} or \textit{BRCA2} mutation), platinum refractory ovarian, fallopian tube, primary peritoneal cancer, or basal-like cancer, the recommended Phase 2 dose was 400 mg BID, with 500 mg BID declared intolerable due to nausea and fatigue. Dose limiting toxicities included Grade 3 nausea and vomiting (400 mg BID) and Grade 2 seizures (400 mg BID and 500 mg BID). Most common all-grade toxicities included fatigue, nausea, and lymphopenia. Durable responses have been observed in the highest dose levels (300 to 500 mg BID) and enrollment in the expansion cohort is ongoing.

Initial results of GOG 280, a Phase 2 study evaluating veliparib 400 mg BID in \textit{gBRCA} subjects with recurrent high-grade serous ovarian cancer and a maximum of 3 prior therapies, demonstrated one confirmed complete response, 12 confirmed partial responses, and 23 subjects with stable disease (\(n = 50\)). The most notable toxicities have been gastrointestinal, with 18 subjects experiencing Grade 1 nausea, 20 subjects experiencing Grade 2 nausea, and 2 subjects experiencing Grade 3 nausea (49 subjects evaluable for toxicity). These toxicities, although not severe, were a common reason for dose delay and dose reduction. Grade 3 and 4 treatment-emergent adverse events that occurred in more than 2 or more subjects (\(\geq 3\%\)) included nausea (3.9\%), small intestinal obstruction (7.8\%), fatigue (5.9\%), decreased lymphocyte count (3.9\%), and hyponatremia (3.9\%).

In total, approximately 400 subjects have been treated with veliparib monotherapy to date, either as single-agent therapy or as maintenance therapy, and the most common toxicities across these studies included nausea, fatigue, anemia, vomiting, decreased white blood cell count, and lymphocyte count. In subjects receiving veliparib for greater than 6 months, no increase in toxicity is observed over time. The safety and efficacy of monotherapy with veliparib from these studies support the further evaluation of maintenance therapy (400 mg BID continuous) in subjects with previously untreated high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.
3.1 Differences Statement

This is the first randomized, Phase 3 study evaluating the addition of veliparib to standard therapy in subjects with previously untreated high-grade serous epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer.

Other Phase 3 veliparib studies include:

- Study M12-914: A Phase 3 Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel with or without the PARP Inhibitor Veliparib (ABT-888) in HER2-Negative Metastatic or Locally Advanced Unresectable BRCA-Associated Breast Cancer.

3.2 Benefits and Risks

Preclinical data demonstrated two areas that warrant caution in the design and execution of human clinical trials: 1) as monotherapy, veliparib induced seizures in beagle dogs at exposures approximately 4-fold above anticipated efficacious clinical exposures at the MTD for veliparib in combination with platinum/paclitaxel (150 mg BID); and 2) in rats, veliparib administration resulted in a reversible and non-lethal exacerbation of temozolomide hematologic toxicity at doses that, in previous studies, resulted in exposures that were similar to or greater than the maximally efficacious exposure (AUC) in the melanoma murine model. In addition to these two risk areas, a trend towards QTc prolongation was observed in anesthetized dogs, albeit at concentrations > 10-fold the
anticipated human efficacious maximum observed plasma concentration ($C_{\text{max}}$). As anticipated, hematological toxicity has been the dose-limiting toxicity for veliparib in combination with cytotoxic chemotherapy in the clinic, occurring at doses and exposures well below those at which seizures have been observed.

Multiple clinical studies are currently evaluating veliparib in combination with cytotoxic chemotherapy in subjects with various solid tumors. The main toxicities observed in these studies are consistent with those known for each background therapy, with myelosuppression being the most common dose-limiting toxicities. Subjects who participate in Study M13-694 will be monitored for hematologic toxicities as well as for potentiation of any toxicity in combination therapy.

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

To date, over 3,000 subjects have been treated with veliparib and uncommon events of seizure have been observed. The majority of cases have occurred with various confounding factors, primarily associated with underlying malignancy. In this study, subjects with an uncontrolled seizure disorder or brain metastases will be excluded.

Best supportive care and treatment will be given as appropriate to each subject. Specifically, biologic response modifiers for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) and colony-stimulating factors (e.g., neulasta, G-CSF, GM CSF, etc.) may be administered according to institutional or clinical practice guidelines (e.g., American Society of Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO]). Prophylactic antiemetics may also be given per National Comprehensive Cancer Network (NCCN), ESMO, or institutional practice guidelines.
The lack of significant interaction with major cytochrome P450 (CYP) enzymes (either inhibition or induction), suggests that potential pharmacokinetic drug interactions with veliparib are unlikely. For this reason, the Phase 3 study does not limit use of other medications on the basis of their CYP interactions. As a Biopharmaceutics Classification System (BCS) Class 1 compound, veliparib exhibits rapid absorption and high solubility. In addition, food does not have a significant effect on veliparib bioavailability. The administration of a high-fat meal had no significant effect on AUC and only caused a slight decrease in veliparib C\text{max} (17%) and a delay of approximately 1 hour in time to C\text{max} (peak time, T\text{max}). For these reasons, veliparib may be administered with or without food. As veliparib is predicted to be predominately excreted in urine, the Phase 3 study will be limited to subjects with adequate renal function (e.g., creatinine clearance ≥ 50 mL/min).

In summary, veliparib is an orally available PARP inhibitor that has been shown to significantly potentiate the effects of platinum/paclitaxel in multiple preclinical models of tumor progression. Potential risks, as identified above, will be minimized by careful patient selection and monitoring to mitigate potential risks to subjects with previously untreated ovarian cancer. The above scientific rationale supports the initiation of the proposed Phase 3 study of veliparib in combination with standard therapy.

4.0 Study Objective

The primary objective of the study is to evaluate whether PFS is prolonged with the addition of veliparib to standard platinum-based chemotherapy (carboplatin/paclitaxel) and then continued as maintenance therapy when compared to chemotherapy alone. This will be evaluated in the whole patient population, as well as a more selective cohort of subjects with BRCA-deficient tumors. The BRCA-deficient population will be defined as subjects with either a germ-line (gBRCA) and/or somatic (sBRCA) deleterious or suspected deleterious mutation in BRCA1 or BRCA2 as determined using centralized testing.
Secondary objectives include evaluations of OS (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), safety of the 3 study arms, and Disease Related Symptom (DRS) scores (Arm 3 versus Arm 1 and Arm 2 versus Arm 1) in both the whole population and *BRCA*-deficient population.

The tertiary objectives include PFS to the second objective radiographic progression (PFS2), time to first subsequent therapy (TTFST), time to second subsequent therapy (TTSST), and other PRO endpoints (which will be specified in a separate analysis plan).

### 5.0 Investigational Plan

This protocol was designed in collaboration between AbbVie and the Gynecologic Oncology Group Foundation.

#### 5.1 Overall Study Design and Plan: Description

This is a randomized, placebo-controlled, double-blind, stratified, multicenter, multi-country Phase 3 study designed to evaluate if PFS is prolonged when veliparib is added to carboplatin/paclitaxel and continued as maintenance therapy in subjects with previously untreated high-grade serous ovarian epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Approximately 1100 subjects at approximately 400 sites will be randomized to receive oral veliparib 150 mg/placebo BID in combination with standard first-line chemotherapy (paclitaxel and carboplatin) followed by oral veliparib 400 mg/placebo BID maintenance therapy (Figure 1). The study was designed to enroll to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.
Figure 1. Study Design

High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
- FIGO Stage III or IV
- No prior systemic therapy
- ECOG 0 to 2
- No CNS metastases

Randomization (1:1:1) 1100 subjects

Combination Therapy
- Cycles 1 to 6 (21-day cycles)
  - Arm 1: Placebo (PO BID) with carboplatin/paclitaxel
  - Arm 2: Veliparib (PO BID) with carboplatin/paclitaxel
  - Arm 3: Veliparib (PO BID) with carboplatin/paclitaxel

Maintenance Therapy
- Cycles 7-36 (21-day cycles)
  - Placebo, PO BID
  - Placebo, PO BID
  - Veliparib, PO BID

Endpoints: Endpoints will be evaluated both in the whole subject population and in subjects with BRCA-deficient tumors as follows:
- Primary Objective: PFS (Arm 3 versus Arm 1)
- Secondary Objectives:
  - PFS (Arm 2 versus Arm 1)
  - OS (Arm 3 versus Arm 1)
  - OS (Arm 2 versus Arm 1)
  - DRS Scores (All Arms)

Choice of Therapy: All subjects will receive:
- Carboplatin AUC 6 Q3-weeks plus
- Paclitaxel Q-week (80 mg/m²), OR Paclitaxel Q3-weeks (175 mg/m²)
- Surgery
  - Primary cytoreductive, OR
  - Interval cytoreductive

BID = twice daily; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; OS = overall survival; PFS = progression-free survival; PO = oral; PRO = patient-reported outcomes; Q-week = weekly; Q3-weeks = every 3 weeks
The study will consist of four phases: a Pre-Therapy Phase (Screening), a Combination Therapy Phase, a Maintenance Therapy Phase, and a Long-Term Follow-Up Phase. An overview of the study design is shown in Figure 2 followed by a description of each phase.
Figure 2. Overall Study Design

**Pre-therapy Phase (Screening)**
- Primary cytoreductive surgery with Carboplatin and Q3-week paclitaxel OR Carboplatin and Q3-weeks paclitaxel
- Interval cytoreductive surgery with Carboplatin and Q3-weeks paclitaxel OR Carboplatin and Q3-weeks paclitaxel
- Physician’s choice
- Stratification factors for randomization:
  - Stage of disease (Stage I, II vs. Stage III, IV)
  - Residual disease & choice of regimen
  - Region of the world (North America vs. Rest of World)

**Combination Phase**
- Arm 1: Placebo with carboplatin/paclitaxel (Cycle 1-6)
- Arm 2: Veliparib with carboplatin/paclitaxel (Cycle 1-6)
- Arm 3: Veliparib with carboplatin/paclitaxel (Cycle 1-6)

**Maintenance Phase**
- Placebo (Cycle 7-36)
- Placebo (Cycle 7-36)
- Veliparib (Cycle 7-36)

**Long-term Follow-up/Study Endpoints**
- Primary: Progression Free Survival (PFS)
- Secondary: Overall Survival & Disease Related Symptom Scores
- Tertiary: FF31 and Time to 1st subsequent therapy
- Tertiary: Time to 2nd subsequent therapy

**Legend:**
- Q3-week schedule = carboplatin AUC 6 + paclitaxel 80 mg/m² weekly; Q3-week schedule = carboplatin AUC 6 + paclitaxel 80 mg/m² every 3 weeks
- Veliparib 150 mg/PO BID, Cycle 1-6 (21 out of 21 days)
- Veliparib 400 mg/PO BID, Cycle 7-36 (21 out of 21 days)
- FF31 will be evaluated in the whole patient population (unselective) and the selective patient population (BRCA deficient).
- Beginning on date of progression, collect more frequently to support endpoint

**Legend (continued):**
- Residual disease and choice of regimen:
  - Q3-week carboplatin/paclitaxel, no residual disease
  - Q3-week carboplatin/paclitaxel, any residual disease
  - Q3-week carboplatin/paclitaxel, no residual disease
  - Q3-week carboplatin/paclitaxel, any residual disease
  - Interval cytoreductive surgery, Q3-weeks carboplatin/paclitaxel
  - Interval cytoreductive surgery, Q3-week carboplatin/paclitaxel

**Client survival and post-therapy information every 6 months**
- Collect recurrence of disease information every 6 months for up to 10 years
Pre-Therapy Phase

During the Pre-Therapy Phase, Investigators will be allowed the choice of either carboplatin AUC 6 in combination with weekly paclitaxel (Q-week) or carboplatin AUC 6 in combination with paclitaxel every 3 weeks (Q3-weeks). Either of these chemotherapy regimens will be administered with primary or interval cytoreductive surgery such that there are the following treatment choices prior to randomization:

1. Primary cytoreductive surgery with carboplatin AUC 6 and weekly paclitaxel;
2. Carboplatin AUC 6 and weekly paclitaxel with interval cytoreductive surgery between Cycle 3 and Cycle 4;
3. Primary cytoreductive surgery with carboplatin AUC 6 and every 3 weeks paclitaxel;
4. Carboplatin AUC 6 and every 3 weeks paclitaxel with interval cytoreductive surgery between Cycle 3 and Cycle 4.

The Investigator's treatment decision will be documented prior to proceeding to randomization.

Pre-therapy (screening) procedures will be performed within 28 days of Cycle 1 Day 1 except where noted in Table 1 and Section 5.3.1.1.

Subjects must be willing (and consent) to undergo BRCA1/BRCA2 testing in order to participate on the study. BRCA mutation status will be documented for all subjects by the central laboratory (Myriad).

Once pre-therapy procedures are complete and eligibility is confirmed, subjects will be randomized 1:1:1:1 to one of the following three arms. Subjects will be stratified by stage of disease (Stage III versus Stage IV), residual disease and choice of regimen, and region of the world (North America versus Rest of World). Subject randomization is detailed in Section 8.4.
Arm 1: Carboplatin/paclitaxel plus placebo for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;  
Arm 2: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;  
Arm 3: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by veliparib BID maintenance therapy for 30 additional 21-day cycles.

**Combination Therapy and Maintenance Phases**

During the Combination Therapy Phase, subjects will receive veliparib/placebo by mouth (PO) in combination with intravenous (IV) carboplatin and paclitaxel (Q-week or Q3-weeks) for 6 cycles during the Combination Therapy Phase. Subjects will self-administer veliparib 150 mg/placebo PO BID (approximately 12 hours apart; with or without food) continuously (Days 1 – 21) within each cycle of Cycles 1 – 6.

**Q-Week Paclitaxel Dosing Schedule:**

- Paclitaxel 80 mg/m² IV over approximately 1-hour on Days 1, 8, and 15 prior to carboplatin;
- Carboplatin AUC 6 IV over approximately 30 minutes on Day 1;
- Veliparib 150 mg/Placebo PO BID, continuously on Days 1 – 21.

**Q3-Weeks Paclitaxel Dosing Schedule:**

- Paclitaxel 175 mg/m² IV over approximately 3 hours on Day 1 prior to Carboplatin;
- Carboplatin AUC 6 IV over approximately 30 minutes on Day 1;
- Veliparib 150 mg/Placebo PO BID, continuously on Days 1 – 21.

Subjects who complete the Combination Therapy Phase and who have not progressed per RECIST 1.1 will continue treatment with continuous veliparib 400 mg/placebo PO twice daily on Days 1 – 21 (in all arms) for an additional 30 cycles (Cycles 7 – 36) during the Maintenance Phase.
A Therapy Completion Visit will be conducted when the Investigator determines a subject should discontinue study treatment. All subjects will have one Follow-Up Visit approximately 30 days after the Therapy Completion Visit.

Additional details regarding dosing with veliparib/placebo, carboplatin, and paclitaxel are provided in Section 5.5.1, Appendix D and Appendix E. Guidelines for dose reductions or delays and toxicity management are provided in Section 5.7.

Subjects Undergoing Interval Cytoreductive Surgery

After core needle biopsy to establish diagnosis, subjects will receive 3 cycles of therapy with interval cytoreductive surgery between Cycle 3 and Cycle 4, followed by 3 additional cycles of therapy. Surgery must be performed after the third course of therapy, as soon as nadir counts permit, but within 6 weeks after the completion of the third cycle. The fourth cycle of therapy should be administered as soon as possible, but no more than 6 weeks after surgery.

Cytoreductive surgery should be performed in accordance with the surgical procedures outlined in Appendix C.

**Long-Term Follow-Up Phase**

Subjects who experience an event of disease progression per RECIST 1.1, or meet the criteria for discontinuation in Section 5.4, will continue to be followed for survival, post therapy information, and information on disease recurrence. Survival information and post therapy information will be collected at 3-month intervals until the endpoint of death, the subject is lost to follow-up or until the study termination by AbbVie, whichever occurs first. Information on the recurrence of disease will be collected at 6 month intervals for up to 10 years or until the endpoint of death, the subject is lost to follow-up or until the study termination by AbbVie, whichever occurs first.

Study visits and procedures are detailed in Table 1 and Section 5.3.1.1.
An Independent Data Monitoring Committee (IDMC) will meet to review safety data in an un-blinded fashion per Section 5.5.5.2.

5.2 Selection of Study Population

Women 18 years of age and older with previously untreated (no prior systemic therapy), International Federation of Gynecology and Obstetrics (FIGO) Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Subjects with a histologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, FIGO Stage III or IV with appropriate tissue available for histologic evaluation. FIGO staging is outlined in Appendix F.

2. Subjects will be required to have high-grade serous adenocarcinoma to be eligible. Guidance for identifying high grade serous carcinoma is provided in Appendix G.

3. Subject is willing to undergo testing for \textit{gBRCA}.

4. Subjects must have adequate hematologic, renal, and hepatic function as follows:
   - Hemoglobin $\geq 9.5$ g/dL (5.89 mmol/L);
   - Absolute neutrophil count (ANC) greater than or equal to 1500/µL;
   - Platelet count greater than or equal to 100,000/µL;
   - Serum creatinine $\leq 1.0 \times$ ULN range; subjects with a serum creatinine $>1.0 \times$ ULN range must have a creatinine clearance $\geq 60$ mL/min (according to the Cockcroft-Gault equation);
   - Total bilirubin $\leq 1.5 \times$ ULN. Subjects with Gilbert's Syndrome may have a bilirubin $\geq 1.5 \times$ the ULN range if no evidence of biliary obstruction exists;
   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase must be less than or equal to 2.5 $\times$ ULN;
   - Albumin $\geq 3.0$ g/dL.
5. Subjects with neuropathy (sensory and motor) less than or equal to Grade 1.

6. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

7. Subject is able to swallow and retain oral medication and does not have uncontrolled emesis.

8. Subjects who undergo primary cytoreductive surgery must be entered between 1 and 12 weeks after surgery. Subjects undergoing interval cytoreductive surgery must have a needle core biopsy confirming the histological diagnosis prior to enrollment.

9. Subjects with measurable disease and non-measurable disease are eligible. Subjects may or may not have cancer-related symptoms.

10. Subject has one of the following available for PD analyses including somatic BRCA testing:
    - Archived diagnostic formalin-fixed paraffin embedded (FFPE) tumor tissue; or
    - Tumor tissue biopsy collected prior to Cycle 1 Day 1.

11. Subjects who are not surgically sterilized must agree to use adequate contraception (one of the following listed below) prior to study entry, and until surgery is performed. Subjects who are not surgically sterilized must have a negative serum pregnancy test within 7 days prior to initiation of study drug/placebo. The following measures need to be followed if not surgically sterile:
    - Total abstinence from sexual intercourse as the preferred lifestyle of the subject;
    - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream);
    - Intra-uterine device (IUD).

12. Subject is 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.

**Rationale for Inclusion Criteria**

1 – 2, 5, 8 – 10 To select the subject population with appropriate disease severity for the evaluation  
3 – 4, 6 – 7 For the safety of the subjects  
11 The impact of veliparib and carboplatin or paclitaxel on pregnancies or breastfeeding is unknown  
12 In accordance with harmonized Good Clinical Practice (GCP)

**5.2.2 Exclusion Criteria**

1. Subjects with the following histologic cell types are ineligible: endometrioid adenocarcinoma, carcinosarcoma, undifferentiated carcinoma, mixed epithelial adenocarcinoma, adenocarcinoma not otherwise specified, mucinous adenocarcinoma, clear cell adenocarcinoma, low-grade serous adenocarcinoma, transitional cell carcinoma, or malignant Brenner's tumor.

2. Subjects with synchronous primary endometrial cancer, or a past history of endometrial cancer unless all of the following conditions are met: endometrial cancer stage not greater than IA, no vascular or lymphatic invasion, no poorly differentiated subtypes including serous, clear cell, or other FIGO grade 3 lesions.

3. Subjects with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the last 3 years. Subjects are also excluded if their previous cancer treatment contraindicates this protocol's therapy.

4. Subjects who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded.
5. Subjects who have received prior chemotherapy for any abdominal or pelvic tumor are excluded.

6. Subject has a clinically significant uncontrolled condition(s), including but not limited to:
   - Uncontrolled seizure disorder, or focal or generalized seizure within the last 12 months;
   - Active infection that requires parenteral antibiotics;
   - Known active hepatitis B or hepatitis C with abnormal liver function test or organ dysfunction;
   - Symptomatic congestive heart failure; unstable angina pectoris; serious ventricular cardiac arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or serious cardiac arrhythmia requiring medication (this does not include asymptomatic atrial fibrillation with controlled ventricular rate); or myocardial infarction within the last 6 months;
   - Uncontrolled hypertension (sustained systolic blood pressure > 150 mmHg or diastolic pressure > 100 mmHg despite optimal medical management);
   - Bowel obstruction or gastric outlet obstruction. **Note:** Subjects requiring drainage gastrostomy tube and/or parental hydration and/or nutrition are not eligible;
   - Psychiatric illness/social situations that would limit compliance with study requirements;
   - Any medical condition which in the opinion of the Investigator places the subject at an unacceptably high risk for toxicities.

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

8. Subjects with history or evidence upon physical examination of central nervous system (CNS) disease, including primary brain tumor, any brain metastases, or
history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) within 6 months of Cycle 1 Day 1.

9. Subjects who are pregnant or nursing.

10. Subjects under the age of 18.

11. In the opinion of the Investigator, the subject is an unsuitable candidate to receive veliparib or combination therapy.

**Rationale for Exclusion Criteria**

1 – 5, 10 To select the subject population with appropriate severity for the evaluation

6 – 9, 11 For the safety of the subjects

**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 the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapies.

**5.2.3.1 Prior Therapy**

For the purposes of this protocol, prior 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 prior chemotherapy for any abdominal or pelvic tumor.

Radiation: Subject must have received no prior radiotherapy to any portion of the abdominal cavity or pelvis.

5.2.3.2 Concomitant Therapy

Premedication: Refer to Section 5.5.1.2.

Anticancer Agents: Any anti-cancer therapy including chemotherapy or biological therapy (maintenance therapy) will not be allowed until an event of disease progression per RECIST 1.1 has occurred, with the exception of docetaxel as noted in Section 5.7.1.2.

Supportive Care: Best supportive care and treatment will be given as appropriate to each subject (antibiotics, transfusions, nutritional support, non-radiation palliative treatment for pain) according to institutional guidelines or ASCO or NCCN guidelines. Antiemetic treatment for chemotherapy induced nausea and vomiting and veliparib/placebo monotherapy is outlined in Section 5.7.1.1 and Section 5.7.2.

Growth Factors: Guidelines for the use of hematopoietic cytokines are outlined in Section 5.7.1.1.

Radiation: Concomitant radiation therapy will not be allowed.

Surgery: If the subject requires surgery during the study other than that specified by protocol, then this needs to be discussed with the medical monitor.

Secondary Surgery: The performance of non-emergent abdominal surgery, other than that specified by protocol (such as interval or secondary cytoreductive surgery or second look surgery), prior to documentation of disease progression is not permitted. Non-emergent surgery for other indications, such as ostomy reversal, should be discussed with the medical monitor.

Alternative Therapy: No anti-cancer 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 Pharmacokinetic, Pharmacodynamic Pharmacogenetic and Safety Measurements Assessed and Flow Chart

The study visit and procedure schedule is outlined in Table 1. The schedule for pharmacogenetic and pharmacodynamic sampling (translational research) and pharmacokinetic sampling is presented in Table 2 and Table 3 respectively.
### Table 1. Study Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pre-Therapy Phase (Screening)</th>
<th>Combination and Maintenance Therapy Phases</th>
<th>Long-Term Follow-Up Phase</th>
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<td>Weekly b</td>
<td>Prior to Each Cycle: Comb. Phase Visits</td>
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### Table 1. Study Procedures (Continued)

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<th>Prior to Every Other Cycle:</th>
<th>Prior to Every Other Cycle: Both Phases</th>
<th>Every 9 Wks., End of the Combination Phase, then Every 12 Wks. for 2 Years, Every 6 Months for 3 Years then Annually</th>
<th>Therapy Completion Visit</th>
<th>Follow-Up Visit</th>
<th>Long-Term Follow-Up Phase</th>
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Table 1. Study Procedures (Continued)

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<th>Every 9 Wks., End of the Combination Phase, then Every 12 Wks. for 2 Years, Every 6 Months for 3 Years then Annuallyd</th>
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PS = Performance Status; Comb = Combination; W = Week; Wks = Weeks; AEs = Adverse Events

a. Perform within 28 days prior to Cycle 1 Day 1.
b. Procedures in this column are only required for subjects being treated with weekly paclitaxel (Cycles 1 – 6 only). If dose modification results in discontinuation of the Day 15 paclitaxel infusion, the Day 15 visit may be omitted.
c. Both questionnaires will be collected for 2 years or until disease progression, whichever is later.
d. Can be performed ± 7 days of the scheduled visit.
e. Perform within 30 days of the Therapy Completion Visit.
f. All exams should including weight. Height is obtained at the Pre-Therapy Visit only.
g. If the physical examination is performed within 7 days of Cycle 1 Day 1, it is not required to repeat the exam on Cycle 1 Day 1 unless clinically indicated.
h. Perform at the Therapy Completion Visit only if not performed within the last 4 weeks.
Table 1.  Study Procedures (Continued)

i. Subjects of childbearing potential: a serum pregnancy test will be performed within 7 days of Cycle 1 Day 1. A serum or urine pregnancy test should also be performed prior to dosing on Cycle 1 Day 1 if > 7 days since obtaining screening serum test results. Subjects of childbearing potential who have prolonged interruption of therapy (> 3 months), a pregnancy test (urine or serum) must be performed and confirmed to be negative prior to resuming therapy.

j. Must be obtained within 4 days of re-starting therapy. Any subject whose therapy is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met.

k. For subjects on prophylactic or therapeutic anticoagulation with warfarin, PT/INR should be monitored at screening and before each cycle of therapy. Therapy should be held for PT/INR of > 1.5 × ULN on prophylactic warfarin or > therapeutic range if on full dose warfarin.

l. A baseline (prior to initiating therapy) value is required.

m. CA-125 levels should be drawn prior to each cycle during Cycles 1 – 6 only, then with tumor assessments, and then at the Therapy Completion Visit. Additional CA-125 levels drawn over the course the study will be collected on the appropriate eCRF.

n. Randomization should occur as close as possible to Cycle 1 Day 1.

o. 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. Tumor assessments may also be done as clinically indicated at any time based on symptoms or physical signs suggestive of progressive disease. All scan dates should be calculated from Cycle 1 Day 1. In addition to be reviewed by the Investigator, imaging scans be sent within 5 business days of imaging acquisition to the central imaging vendor.

p. Primary surgery subjects: The post-operative (baseline) scan is required within 4 weeks of starting therapy on Cycle 1 Day 1.

q. Interval surgery subjects: A baseline scan (prior to initiating therapy) is required within 28 days prior to Cycle 1 Day 1.

r. Interval surgery subjects: Pre-operative scan data will be collected after the completion of Cycle 3 on the appropriate eCRF to evaluate disease per RECIST 1.1. A scan of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease prior to re-starting therapy on C4D1. The post-operative scan should be performed immediately following recovery from surgery or within 6 weeks of surgery.

s. Not required if CT of chest already performed at screening.

t. Complete the NFOSI-18 first followed by the EQ-5D-5L. Both questionnaires should be administered before discussing imaging scan results or disease status changes with the subject.

u. Survival information and post-therapy information will be collected every 3 months (i.e., 3, 6, 9, 12 etc.) or as requested by the Sponsor to support data analysis, beginning on the date of disease progression per RECIST 1.1 until the endpoint of death, or until the subject becomes lost to follow-up, or until study termination by AbbVie.

v. Section 5.3.1.2 outlines the data being collected for survival and post-therapy information.

w. Review each subject's calendar and document compliance with veliparib/placebo prior to the start of each cycle.
Table 1. Study Procedures (Continued)

x. Perform weekly for subjects receiving weekly paclitaxel. Weekly AE assessments can be performed by the PI or delegated to qualified medical staff (e.g., a nurse, sub-investigator).

Note: For procedures performed during the Pre-Therapy Phase (screening) and repeated, the later procedure performed prior to dosing will serve as a baseline for clinical assessment. Subsequent study procedures (excluding labs and tumor assessments) should be performed ± 4 days surrounding the scheduled study visit.
Table 2. Schedule of Pharmacogenetic and Pharmacodynamic Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Visit Schedule</th>
<th>Before Drug Administration</th>
<th>Sampling Plan</th>
<th>Specimen Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PG Blood Sampling (Optional)</strong></td>
<td>C1D1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pre-therapy</td>
<td>Blood</td>
<td>Frozen °20°C or colder</td>
</tr>
<tr>
<td>Genetic (DNA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA Sequencing: Bridging Sample</td>
<td>C1D1</td>
<td>Pre-therapy</td>
<td>Blood</td>
<td>Frozen °20°C or colder</td>
</tr>
<tr>
<td>Germline BRCA Sample</td>
<td>C1D1</td>
<td>Pre-therapy</td>
<td>Blood</td>
<td>Frozen °20°C or colder</td>
</tr>
<tr>
<td>Plasma Markers&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C1D1, C3D1, C5D1</td>
<td>Pre-therapy</td>
<td>Blood</td>
<td>Frozen °70°C or colder</td>
</tr>
<tr>
<td>Therapy Completion Visit</td>
<td>At the time of clinic visit</td>
<td></td>
<td>Blood → Plasma</td>
<td>Frozen °70°C or colder</td>
</tr>
<tr>
<td>Serum Markers</td>
<td>C1D1, C3D1, C5D1</td>
<td>Pre-therapy</td>
<td>Blood</td>
<td>Frozen °70°C or colder</td>
</tr>
<tr>
<td>Therapy Completion Visit</td>
<td>At the time of the clinic visit</td>
<td></td>
<td>Blood → Serum</td>
<td>Frozen °70°C or colder</td>
</tr>
<tr>
<td>Pre-therapy tumor biopsy sample (Required):</td>
<td>Pre-therapy Phase&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>Pre-Study Treatment FFPE tissue blocks</td>
<td>(Room Temperature or Refrigerated-FFPE)</td>
</tr>
<tr>
<td>Archival Tissue or Newly Collected Biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On Study tissue sample collection (Optional)</td>
<td>Therapy Completion Visit&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>Archived FFPE tissue blocks</td>
<td>(Room Temperature or Refrigerated-FFPE)</td>
</tr>
</tbody>
</table>

a. Blood samples must be drawn prior to dosing on Day 1 of the applicable cycle.
b. If the sample is not collected on Day 1, it may be collected at any time during the study.
c. An additional sample may be collected at the time of discontinuation due to an adverse event.
d. All subjects must have a pre-therapy tumor biopsy for inclusion on the study.
e. Post-therapy biopsy can be taken from any consenting subjects at the Therapy Completion Visit or any time after enrolling onto the study.

Note: If a drug interruption is needed, the subject will continue to have study visits as planned; however, the above samples will not be drawn during the time of study drug interruption.
### Table 3. Schedule of Pharmacokinetic Sampling

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Visit Schedule</th>
<th>Before Drug Administration</th>
<th>After Veliparib AM Dose</th>
<th>Specimen Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib PK Sampling</td>
<td>C1D1</td>
<td>1, 2, 3 hours</td>
<td></td>
<td>Blood → Plasma Frozen –20°C or colder</td>
</tr>
<tr>
<td>Veliparib PK Sampling</td>
<td>C2D1, C3D1, C4D1</td>
<td>0-hour^a</td>
<td></td>
<td>Blood → Plasma Frozen –20°C or colder</td>
</tr>
</tbody>
</table>

^a Before the administration of the morning dose of veliparib/placebo. The morning dose of veliparib/placebo should be dosed in clinic prior to carboplatin and paclitaxel on C1D1, C2D1, C3D1 and C4D1.

**Notes:**
- If a drug interruption is needed, the subject will continue to have study visits as planned; however PK samples will not be drawn during the time of study drug interruption.
- The date and time of sample collection and the date and time of the last two doses of veliparib/placebo will be captured on the eCRF.
5.3.1.1 Study Procedures

5.3.1.1.1 Pre-Therapy, Combination, and Maintenance Phases

The study procedures outlined in Table 1 are discussed in further detail in this section, with the exception of tumor assessment criteria (RECIST 1.1 is discussed in Section 5.3.3.1), the monitoring of treatment compliance (discussed in Section 5.5.6) and adverse event information (discussed in Section 6.1.1). All study data will be recorded on electronic case report forms (eCRFs) with supporting source documentation.

Study Visits

For procedures performed during the Pre-Therapy Phase (screening) and repeated, the later procedure performed prior to dosing on Cycle 1 Day 1 will serve as a baseline for clinical assessment. Subsequent study procedures (excluding labs and tumor assessments) should be performed 4 days prior to the scheduled study visit date.

During the Combination Phase (Cycles 1 – 6), the frequency of study visits will vary depending on the dosing schedule chosen for paclitaxel. Subjects receiving weekly paclitaxel will have weekly study visits. Subjects receiving Q3-weeks paclitaxel will have study visits on Day 1 of every cycle. General chemotherapy guidelines are provided in Appendix D.

During the Maintenance Therapy Phase, all subjects will have study visits on Day 1 of every other cycle.

Baseline scans for primary and interval cytoreductive surgery are discussed in this section under the Tumor Assessment subheading. All post-baseline tumor assessments can be performed ± 7 days of the scheduled visit.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study procedures are undertaken or before any
prohibited medications are withheld from the subject in order to participate in this study. Informed consent will be required for the optional research tests. 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 a study-specific procedure has been performed (e.g., local laboratories drawn), but subject does not randomize into the study. The reason for screen failure will be documented in the source documents and will be captured in the eCRF.

**Medical History**

The medical history includes complete medical history, including documentation of any clinically significant medical condition(s); history of tobacco and alcohol use; presence and severity of any symptoms/conditions associated with ovarian cancer and detailed ovarian oncology history (histology, tumor staging, residual disease at the completion of surgery [if applicable], date of diagnosis, tumor burden, metastatic sites, and results of tumor molecular analysis/profiling, if available).

On Cycle 1 Day 1 any changes observed from the pre-therapy procedures (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**

Physical examinations, including body weight, will be performed per Table 1. If the pre-therapy physical examination is performed within 7 days of Cycle 1 Day 1, it is not required to repeat the exam on Cycle 1 Day 1 unless clinically indicated. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events.

Height will be measured at the Pre-Therapy Visit only. For height and weight, subject should not wear shoes.
Vital Signs

Vital signs will be performed per Table 1. Vital sign determinations include sitting blood pressure, heart rate and body temperature. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

Weekly Paclitaxel Dosing Schedule: During weekly study visits, vital signs can be performed by PI or delegated to qualified medical staff (e.g., a nurse, sub-investigator, etc.).

Adverse Event Assessment

AE assessments will be performed per Table 1.

Weekly Paclitaxel Dosing Schedule: During weekly study visits, AE assessments can be performed by the PI or delegated to qualified medical staff (e.g., a nurse, sub-investigator, etc.).

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed per Table 1. 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.

ECOG Performance Status

The ECOG performance status will be assessed per Table 1 as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully Active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>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.</td>
</tr>
</tbody>
</table>
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.

**Pregnancy Test (In Women of Childbearing Potential)**

For female subjects of childbearing potential, a serum pregnancy test will be performed within 7 days of Cycle 1 Day 1. A serum or urine pregnancy test should also be performed prior to dosing on Cycle 1 Day 1 if > 7 days since obtaining screening serum test results. If a serum pregnancy test is performed on Cycle 1 Day 1, a urine pregnancy test does not need to be completed. Pregnancy tests may also be repeated during the study according country requirements. Subjects considered not of childbearing potential must be documented as being surgically sterile or postmenopausal (amenorrheic for at least 12 months).

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

The Cycle 1 Day 1 urine pregnancy test results must be reviewed and determined to be negative prior to dosing. If the urine pregnancy test is positive at Cycle 1 Day 1, it should be confirmed by a serum pregnancy test and dosing should be delayed.

For female subjects of childbearing potential, who have prolonged interruption of therapy (> 3 months), a pregnancy test (urine or serum) must be performed and confirmed to be negative prior resuming therapy. In situations of suspected pregnancy, pregnancy testing will be performed as soon as possible. In addition, pregnancy testing may be repeated at the discretion of the investigator at any time during the study.
Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately (Section 6.8).

**Clinical Laboratory Tests**

Samples for chemistry, hematology, and urinalysis will be collected per Table 1 using a certified local laboratory. Specific laboratory tests are outlined in Table 4.

All laboratory samples will be assessed using a certified local reference laboratory and these data will be used for all data analysis. The appropriate certifications will be collected from the local laboratories, as needed.

Qualified medical staff at the site will review, initial and date all local laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.1.1.
### Table 4. Clinical Laboratory Tests

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Clinical Chemistry</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Blood urea nitrogen (BUN)</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Serum creatinine**</td>
<td>Ketones</td>
</tr>
<tr>
<td>Red blood cell (RBC) count</td>
<td>Total bilirubin</td>
<td>pH</td>
</tr>
<tr>
<td>White blood cell (WBC) count</td>
<td>Serum glutamic-pyruvic transaminase (SGPT/ALT)</td>
<td>Protein</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Serum glutamic-oxaloacetic transaminase (SGOT/AST)</td>
<td>Blood</td>
</tr>
<tr>
<td>Bands (if indicated)</td>
<td>Alkaline phosphatase</td>
<td>Glucose</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Sodium</td>
<td>Urobilinogen</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Potassium</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Basophils (if indicated)</td>
<td>Chloride</td>
<td>Serum Pregnancy Tests</td>
</tr>
<tr>
<td>Eosinophils (if indicated)</td>
<td>Calcium</td>
<td>* Human Chorionic Gonadotropin (hCG)**</td>
</tr>
<tr>
<td>Platelet count (estimate not acceptable)</td>
<td>Inorganic phosphorus</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Uric acid</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration</td>
<td>Total protein</td>
<td></td>
</tr>
<tr>
<td>RBC distribution width</td>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Platelet count (estimate not acceptable)</td>
<td>Albumin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coagulation</th>
<th>Special Chemistry</th>
<th>Tumor Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Partial Thromboplastin Time (aPTT)*</td>
<td><em>BRCA1 and BRCA2 germline mutation</em>*</td>
<td>CA-125</td>
</tr>
<tr>
<td>International Normalized Ratio (INR)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Collected per Table 1.
** Collected prior to C1D1.

### Tumor Assessments

Tumor assessments will be performed per Table 1. A CT scan of the abdomen and pelvis (and chest, if metastases are present) using RECIST 1.1 will be used in the evaluation of tumor responses, as appropriate. Subjects will continue to be monitored by the same diagnostic method as outlined in Section 5.3.3.1 (Methods for Evaluation of Disease).

**Primary surgical subjects:** The post-operative (baseline) scan must be performed within 4 weeks of starting therapy on Cycle 1 Day 1.
**Interval surgery subjects:** A pre-therapy (screening) baseline scan is required to be performed on interval surgery subjects within 28 days prior to Cycle 1 Day 1. Pre-operative scan data will be collected after the completion of Cycle 3 on the appropriate eCRF to evaluate disease per RECIST 1.1. A scan of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease prior to re-starting therapy on Cycle 4 Day 1. The post-operative scan should be performed immediately following recovery from surgery or within 6 weeks of surgery.

Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects who discontinue therapy for reasons other than disease progression will continue to be followed as per the scheduled tumor assessments to determine the extent of tumor burden, until disease progression occurs.

In addition to being reviewed by the Investigator and/or qualified medical site staff, imaging scans should be sent within 5 business days of imaging acquisition to an independent central imaging vendor. AbbVie may discontinue this requirement at any time during the course of the study. The central imaging vendor will provide instructions regarding the preparation and shipment of the images. Imaging scans will be assessed independently by the central imaging vendor. Interpretations from the central imaging vendor will not be sent to the study site.

**Randomization and Subject Number Assignment**

Interactive Response Technology (IRT) will be utilized to register (screen and randomize) subjects on study. The site will contact the IRT to obtain a screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., labs are 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 meet the eligibility criteria and complete all pre-therapy (screening) procedures will proceed to randomization. The site will need to also access the IRT
system and a unique randomization number will be provided. During the randomization process, subjects will be randomized in a 1:1:1 ratio to one of 3 treatment arms:

Arm 1: Carboplatin/paclitaxel plus placebo for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles.

Arm 2: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles.

Arm 3: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by veliparib maintenance therapy for 30 additional 21-day cycles.

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 IRT vendor.

**Dispensing Study Drug**

Randomized subjects will receive sufficient quantities of veliparib/placebo for 21 days in each 21-day cycle during the Combination Phase and the Maintenance Phase. The IRT will assign every bottle of veliparib/placebo to be dispensed to a subject. Prior to each cycle (per Table 1), site personnel must contact IRT for the next bottle number assignment. Veliparib/Placebo cannot be dispensed without contacting the IRT. AbbVie or designee will provide specific instructions on the use of IRT.

Trained site personnel will administer IV carboplatin and paclitaxel. Subjects will be supervised at the time of the infusion.

Subjects will be provided with veliparib/placebo self-administration instructions and subject dosing cards. Subjects will be instructed to store veliparib/placebo according to specific directions included in Section 5.5.2.3. Subjects should return bottles of veliparib or placebo (empty, partially filled, or full) to the study site prior to each cycle and at the Therapy Completion Visit.
**Disease Related Symptom Scores**

Two PRO questionnaires will be administered (per Table 1): the NCCN Functional Assessment of Cancer Therapy (FACT) Ovarian Symptom Index-18 (NFOSI-18) questionnaire, and the EQ-5D-5L/VAS.\(^{30,31}\)

The NFOSI-18 consists of 18 items and separates disease related symptoms from treatment related side effects. Four subscale scores will be constructed: a 9-item based disease related symptoms (DRS) score, a 1-item based disease related emotional well-being (DRS-E) score, a 5-item based treatment side effect (TSE) subscale, and a 3-item based functional well-being (FWB) subscale score.\(^{32}\) The DRS score will be used as a secondary endpoint of the study.

The EuroQol 5 Dimensions (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations. The EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health.

**Order of Administration**

Subjects will be asked to complete the NFOSI-18 first, followed by the EQ-5D-5L. To minimize response bias, the questionnaires should be administered before discussing imaging scan results or disease related clinical changes with the subject. Subjects should be encouraged to respond to all of the questions. Clarification can be given regarding the intention of each question even when the question(s) do not seem relevant to their situation. While the subject is still at the site, the Investigator or a designee will need to check the forms returned by the subject for completeness. If a subject is unable to complete a form(s) for any reason, it should be documented in the source.
Subjects Who Cannot Come to the Site

In the event a subject is unable to come to the site (e.g., physical condition is a barrier), the questionnaires may be sent (e.g., mail, courier, email, electronically, etc.) with a request to complete them and return to the site as instructed by site staff.

5.3.1.2 Long-Term Follow-Up Phase

Survival Information and Post-Therapy Information

During the Long-Term Follow-Up, subjects will be followed for survival, post-therapy information, and disease recurrence.

Survival (i.e., the date and cause of death) and post-therapy information will be collected on the appropriate eCRF at 3-month intervals (*or as requested by sponsor to support data analysis*) beginning on the date of disease progression and continuing either until the endpoint of death, until the subject is lost to follow-up, or until the study termination by AbbVie. The following will be collected for post-therapy information:

- Name(s) of post-therapy regimens;
- Post-therapy dates of initiation and completion;
- Response to subsequent therapies and reason for discontinuation.

Subject must request to be withdrawn specifically from survival follow-up; this request must be documented in the subject's medical record and signed by the investigator. If the subject withdraws from survival follow-up, the site staff may use a public information source (such as county records) to obtain information about survival status only, as appropriate per local regulations.

Assessment for Recurrence

All subjects will be followed for the recurrence of disease. Data will be collected in on the appropriate eCRF at 6-month intervals (*or as requested by sponsor to support data analysis*) beginning on the date of disease progression and continuing either until the
endpoint of death, until the subject is lost to follow-up, or until the study termination by AbbVie.

5.3.1.3 Blood Samples for Pharmacogenetic Analysis (Optional)

Collection and Shipment of Pharmacogenetic Samples

One 4 mL whole blood sample for DNA isolation will be collected on Cycle 1 Day 1 from each subject who consents to provide a sample for PG analysis. If the sample is not collected on Cycle 1 Day 1, it may be collected at any time throughout the study.

The sample collection tubes will minimally be labeled with "PG-DNA," protocol number and subject number. Samples will be shipped frozen to AbbVie or a designated laboratory for DNA extraction and long-term storage. Instructions for the preparation and shipment of PG samples will be provided in the study-specific laboratory manual.

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 analysis. 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 destroyed by AbbVie when this research is completed. These samples will not be stored longer than 20 years or per country requirement.

5.3.1.4 Collection and Handling of Pharmacodynamic Samples

Blood and tumor tissue will be used to determine germline and somatic BRCA mutation status respectively. Other exploratory pharmacodynamic correlative studies will be performed. Serum, plasma and tissue specimens may be utilized to evaluate known and novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status. PD variables will be further discussed in Section 5.3.7.
Germline *BRCA* Sample (*gBRCA*)

Each subject will have blood collected as described in Table 2 for *gBRCA* testing. The *gBRCA* status of each patient will be determined using the sponsor core laboratory. Genetic risk assessment and counseling should proceed per NCCN guidelines or the standard policy of the institution.

*BRCA* Sequencing Bridging Sample

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

Blood Collection for Plasma Markers

Approximately 12 mL (C1D1 and Therapy Completion Visit) or 6 mL (all other time points) of blood will be collected pre-dose by venipuncture at time points outlined in conjunction with PK samples, if possible. The collection, processing and storage should be performed as described in the study-specific laboratory manual. The complete process of centrifugation, transfer to cryovial and freezing should be accomplished in less than 1 hour from the time of blood draw.

Blood Collection for Serum Markers

Approximately 5 mL of blood will be collected pre-dose by venipuncture as outlined in Table 2. The collection should be performed as described in the study-specific laboratory manual. 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.

Tumor Biopsy Tissue Collection

Pre-Therapy Tumor Biopsy Sample (Archived or Newly Collected Biopsy) (**Required**)  

Subjects must consent to provide available archival tissue. A portion of this biopsy will be used to assess *BRCA* status therefore all subjects must have a pre-therapy biopsy for
inclusion on the study. Only one of the following forms of pre-therapy tumor tissue (archived tissue or newly collected biopsy) is required:

- **Archived biopsy:** The most recent archived biopsy is preferred and should be obtained during Screening, if possible. If no archived material is available, a fresh biopsy should be collected from subjects according to institutional procedures for subjects willing to participate on study.

- **Newly Collected biopsy:** Sample should be collected during Screening period, and fixed in formalin and embedded in paraffin according to institutional procedures. Tumor samples should be stored according to Institutional procedures until shipment to AbbVie or an AbbVie-designated contract research organization (CRO). AbbVie or a designated CRO will prepare the samples for analysis.

While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study-specific laboratory manual.

**On Study Tumor Biopsy (Optional)**

An optional post-therapy tumor tissue biopsy should be collected at the time point outlined in Table 2 from subjects who are willing to consent. Institutional procedures should be followed to fix and embed the collected biopsy in paraffin. While tissue blocks are preferred, slides prepared by the local pathology laboratory are acceptable, and should be prepared as described in the study-specific laboratory manual.

**Shipment of Pharmacodynamic Samples**

All pharmacodynamics samples should be labeled and shipped as outlined in the study specific laboratory manual. Also, pathology reports showing histologic confirmation of ovarian, fallopian tube or primary peritoneal cancer should be labeled and shipped as outlined in the study-specific laboratory manual. An inventory of the samples being shipped will accompany the package.
5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Veliparib Pharmacokinetic Specimen Collection

Approximately 3 mL of blood will be collected by venipuncture for veliparib concentrations at 0 hours (just before morning dose of veliparib) and other time points as specified per Table 3. The date/time of collection of each blood sample and the last two doses of veliparib/placebo taken prior to the blood sample collection will be recorded. Refer to the study-specific laboratory manual for detailed instructions on sample collection, processing and shipment.

5.3.2.2 Measurement Methods

Plasma concentrations of veliparib will be determined using validated method under the supervision of the Drug Analysis Department at AbbVie. Plasma concentrations of veliparib metabolite(s) may be determined using validated or non-validated methods.

5.3.3 Efficacy Variables

The primary efficacy endpoint is PFS. The secondary efficacy endpoints are OS and DRS. The tertiary efficacy endpoints are PFS2, time from randomization to first subsequent therapy or death (TTFST), and time from randomization to second subsequent therapy or death (TTSST), and additional PRO endpoints.

5.3.3.1 RECIST 1.1 for Disease Status (PFS)

Radiographic response criteria will be assessed using RECIST 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 disease at baseline are eligible. Subjects with measurable disease can have objective tumor response evaluated by RECIST 1.1. Measurable disease is defined by the presence of at least one measurable lesion.

**Measurability**

<table>
<thead>
<tr>
<th>Measurable Lesions</th>
<th>Lesions accurately measured in at least one dimension with a minimum size of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Longest diameter $\geq 10$ mm (CT scan slice thickness no greater than 5 mm)</td>
</tr>
<tr>
<td></td>
<td>- 10 mm caliper measurement by clinical exam</td>
</tr>
</tbody>
</table>

| 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, lymphangitic involvement of skin or lung and also 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 $\geq 15$ 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 $\geq 10$ to $< 15$ mm short axis. |
**Special Considerations Regarding Lesion Measurability**

<table>
<thead>
<tr>
<th>Bone lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as MRI/CT can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cystic lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesions with prior local treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.</td>
</tr>
</tbody>
</table>

**Methods for Evaluation of Disease**

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed.

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 \( \geq 10 \) mm diameter as assessed using calipers.
(e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Conventional CT should be performed with cuts of 5 mm or less in slice thickness contiguously. This applies to tumors of the chest and abdomen. A scale should be incorporated into all radiographic measurements. MRI can be performed if required by local law, but should have sponsor approval.

If prior to enrollment, it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI should be used to evaluate the subject at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be made based upon discussion with the medical monitor.

For accurate objective response evaluation, ultrasound (US) 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 partial response (PR) and complete response (CR) in rare cases.

**Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

**CA-125 levels:** CA-125 alone cannot be used to assess response. If CA-125 is initially above the upper normal limit, it must normalize for a subject to be considered in complete clinical response.
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. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

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 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 if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (SOD) for all target lesions will be calculated and reported as the baseline sum SOD. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline SOD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) including pathological lymph nodes 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 SOD of target lesions, taking as reference the baseline SOD.

**Progressive Disease (PD):** At least a 20% increase in the SOD 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 lesion is believed to be 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.

**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).

*Note:* If CA-125 is initially above the upper normal limit, it must normalize for a subject to be considered in complete clinical response.

**Non-CR/Non-PD:** Persistence of one or more non-target lesion(s).

**Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

In this setting, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare. In the absence of radiographic or clinical evidence of progressive disease, a rise in CA-125 alone is not sufficient to declare progression.

**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
finding thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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

**Overall Response:**

The overall assessment of the tumor burden will include assessment of target (for subjects with measurable disease) and non-target lesion as follows:

**Calculating Final Response:**

<table>
<thead>
<tr>
<th>Target Lesion</th>
<th>Non-Target Lesion</th>
<th>Unequivocal New Lesion*</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD or not evaluated</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD or not evaluated</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>Non-PD</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

* Equivocal new lesions will not allow for CR but will otherwise not impact the overall response.
Calculating Final Response for Non-Measurable Disease:

<table>
<thead>
<tr>
<th>Overall Response for Subjects with Non-Measurable Disease at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Target Lesion</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
</tr>
<tr>
<td>Not all evaluated</td>
</tr>
<tr>
<td>Unequivocal PD</td>
</tr>
<tr>
<td>Any</td>
</tr>
</tbody>
</table>

5.3.4 Safety Variables

AbbVie will assess adverse events, laboratory data, ECGs and vital signs throughout the study. Adverse events intensity and laboratory evaluation changes will be assessed by utilizing National Cancer Institute (NCI) CTCAE Version 4.0.

During the conduct of the study, the AbbVie medical and safety team will be monitoring blinded, subject laboratory results and serious adverse event data as they are reported.

5.3.5 Pharmacokinetic Variables

A nonlinear mixed effect modeling analysis will be conducted to estimate the population pharmacokinetic parameters of veliparib such as apparent oral clearance (CL/F) and volume of distribution (V/F).

AbbVie or a designated laboratory will store the pharmacokinetic 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 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.

5.3.6 Pharmacogenetic Variables

DNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to veliparib (or other study treatment) in terms of PK,
efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, genes believed to be related to the disease or 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 multi-study assessment of genetic factors involved in the response to veliparib, drugs of this class, or the disease state. The samples may also be used for the development of diagnostic tests related to veliparib, drugs of this class, or the disease state. The results of PG analyses may not be reported with the study summary.

5.3.7 Pharmacodynamic Variables

Biomarker samples will be used to determine germline and somatic BRCA status. In addition, exploratory biomarker analysis may be evaluated in this protocol with the goal of exploring the relationship between tumor response and/or disease status.

Biomarker samples (blood, plasma, serum, and tissue) collected may be evaluated for genetic lesions whether they occur by amplification, chromosomal loss and/or mutational/methylation with the intent of identifying potential associations with subject outcome or to better characterize the disease. These characterizations may be included, but are not limited, characterization of gene methylation/mutational status or copy number changes of genes, particularly those involved in DNA repair pathways. Additional analysis aimed at identifying underlying defects in the homologous recombination pathway, regardless of etiology, may be performed and associated with response.

Biomarker samples may additionally be evaluated for levels of biomarkers including nucleic acids, proteins/peptides and metabolites. For example protein analysis of relevant proteins, including but not limited to, DNA repair proteins, such as PARP-1 and ERCC1, may be performed on tumor tissue obtained from each consented subject.

Samples collected during the course of this study may be used to investigate new scientific questions related to this study as they arise. 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.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will receive therapy until disease progression according to RECIST 1.1. Subjects who discontinue therapy for reasons other than disease progression will continue to be followed as per the scheduled tumor assessments to determine the extent of tumor burden, until disease progression occurs.

Each subject also has the right to withdraw from therapy at any time. Additionally, the Investigator may discontinue a subject from therapy at any time for any reason if he/she considers it necessary, including the occurrence of noncompliance with the protocol.

Each subject will discontinue therapy (as applicable) if any of the following occur:

- The subject experiences an unmanageable toxicity or requires an alternate anticancer agent(s) that is not specified in the protocol.
- Subject requires cancer-directed radiotherapy or surgery related to clinical disease progression.
- Subject is suspected to be pregnant; pregnancy is confirmed or begins breastfeeding during the combination and maintenance therapy phases of the study.
- The subject or subject's legally acceptable representative decides to withdraw consent for any reason.
- Any other medical reason that AbbVie or the study Investigator deems appropriate.

Discontinued subjects will not be replaced.
A Therapy Completion Visit will be conducted for all subjects when therapy is discontinued. All subjects will have one Follow-Up Visit approximately 30 days after the Therapy Completion Visit. Subjects starting any new cancer therapy within the 30 days after the last dose of study drug must complete the 30-day follow-up assessments in advance of starting any anti-cancer therapy. This Follow-Up Visit does not need to be performed for subjects who have had a Therapy Completion Visit conducted ≥ 30 days after the last dose of study drug.

Once an event of progression occurs, subjects will be registered off study and continue to be followed during the Long-Term Follow-Up Phase (per Table 1 and Section 5.3.1.2).

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.

In the event a subject withdraws from the study, pharmacodynamic samples stored for long term biomarker research will also be destroyed upon written request (samples will not be stored for more than 20 years). In the event that destruction is not possible, they will no longer be linked to the subject. If the subject changes his/her consent, and the samples have already been tested, those results will still remain part of the overall research data.

In the event that a subject becomes pregnant during the study, the administration of study drug to that subject must be discontinued immediately. The site must report the pregnancy by telephone within 24 hours to one of the AbbVie representatives listed in Section 7.0.

5.4.2 Discontinuation of Carboplatin/Paclitaxel and Veliparib/Placebo

Carboplatin, paclitaxel, and veliparib/placebo, dose reductions or delays and discontinuation will occur as outlined in Section 5.7.
5.4.3 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/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 due to safety concerns.

The following procedures for study discontinuation will be followed:

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

5.5 Treatments

5.5.1 Treatments Administered

Subjects will receive the following:

- Carboplatin/Paclitaxel plus placebo PO BID for six 21-day cycles, followed by maintenance therapy with placebo PO BID for up to an additional thirty 21-day cycles;
- Carboplatin/Paclitaxel plus veliparib 150 mg PO BID for six 21-day cycles, followed by maintenance therapy with placebo PO BID for up to an additional thirty 21-day cycles; or
● Carboplatin/Paclitaxel plus veliparib 150 mg PO BID for six 21-day cycles, followed by maintenance therapy with veliparib 400 mg PO BID for up to an additional thirty 21-day cycles.

General chemotherapy guidelines are found in Appendix D.

5.5.1.1 Administration of Veliparib/Placebo

Subjects will self-administer the morning dose of veliparib/placebo and the evening doses of veliparib/placebo approximately 12 hours after the morning dose with or without food in the same calendar day, starting on Day 1 of each cycle. Veliparib/Placebo will be taken 1 hour prior to paclitaxel.

During the maintenance phase (Cycles 7 – 36) standard antiemetic therapy may be administered as appropriate, including a combination of standard antiemetics (i.e., 5-HT3 receptor antagonists, steroids, and prochlorperazine, and/or promethazine).

It is recommended that if a subject misses a scheduled dose of veliparib/placebo and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. 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 veliparib/placebo, another dose will be administered. The dose may only be repeated once. If more than 15 minutes has passed from the time of oral dosing then no additional doses will be taken.

5.5.1.2 Administration of Carboplatin/Paclitaxel

Investigators should evaluate subjects for carboplatin and paclitaxel treatment per the locally approved product label, local practice, or applicable SmPC. Due to the risk of immediate hypersensitivity reaction, paclitaxel should always be administered before carboplatin.
Best supportive care and treatment for nausea and vomiting can be provided according to institutional guidelines or American Society of Clinical Oncology (ASCO) or NCCN guidelines.

For example, 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-HT$_3$ receptor antagonists may be used, preferably ondansetron or granisetron. ASCO dosing guidelines are as follows:

- Palonosetron 0.25 mg IV OR 0.50 mg oral, Day 1 only
- Dexamethasone 8 mg (IV or oral), Days 1 to 3

NK1 antagonist 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 or Fosaprepitant 150 mg IV Day 1
- 5-HT$_3$ receptor antagonist dosing

Dexamethasone: 12 mg (IV or oral) on Day 1 and 8 mg (IV or oral) Days 2 and 3 or Days 2 – 4 (with aprepitant) or Dexamethasone: 12 mg (IV or oral) on Day 1 and 8 mg (IV or oral) on Day 2 and 8 mg (IV or oral) twice per day on Days 3 and 4 (with fosaprepitant).33

5.5.1.2.1 Paclitaxel

Pre-Medication for Paclitaxel

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 Summary of Product Characteristics (SmPC, i.e., premedication with corticosteroids, diphenhydramine, and H2 antagonists).
**Weekly Paclitaxel**

For subjects receiving paclitaxel 80 mg/m$^2$, paclitaxel will be administered over approximately 1-hour as an IV infusion on Days 1, 8, and 15 of each 21-day cycle × 6 cycles.

**Every 3-Weeks Paclitaxel**

For subjects receiving paclitaxel 175 mg/m$^2$, paclitaxel will be administered as an IV infusion over approximately 3 hours on Day 1 of each 21-day cycle × 6 cycles.

### 5.5.1.2.2 Carboplatin

Carboplatin AUC 6 will be administered as a 30-minute IV infusion, following paclitaxel administration on Day 1 of each 21-day cycle × 6 cycles. Carboplatin dose calculation instructions can be found in Appendix E.

### 5.5.2 Identity of Investigational Products

Information regarding the veliparib formulation to be used in this study is presented in Table 5.

#### Table 5. Identity of Investigational Product

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Dosage Form</th>
<th>Strength</th>
<th>Route of Administration</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib (ABT-888)</td>
<td>Capsule</td>
<td>50 mg or 100 mg</td>
<td>Oral</td>
<td>AbbVie</td>
</tr>
<tr>
<td>Placebo</td>
<td>Capsule</td>
<td>Placebo to match 50 mg and 100 mg</td>
<td>Oral</td>
<td>AbbVie</td>
</tr>
</tbody>
</table>

### 5.5.2.1 Standard of Care Medicinal Products

Information regarding carboplatin and paclitaxel to be used in this study is presented in Table 6.
Table 6. **Standard of Care Medicinal Products**

<table>
<thead>
<tr>
<th>Standard of Care Products</th>
<th>Dosage Form</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin (commercially available)*</td>
<td>Solution in a vial</td>
<td>Intravenously</td>
</tr>
<tr>
<td>Paclitaxel (commercially available)*</td>
<td>Solution in a vial</td>
<td>Intravenously</td>
</tr>
</tbody>
</table>

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

Note: AbbVie will not be providing either carboplatin or paclitaxel during the study.

### 5.5.2.2 Packaging and Labeling

Veliparib (ABT-888) will be packaged in high-density polyethylene (HDPE) bottles containing either 50 mg, 100 mg, or matching placebo capsules. Bottles of 50 mg and matching placebo will contain 44 capsules (this includes 2 additional capsules in each bottle dispensed per cycle to cover loss, spillage or replacement due to vomiting within 15 minutes). Bottles of 100 mg and matching placebo will contain 44 capsules (this includes 2 additional capsules in each bottle dispensed per cycle to cover loss, spillage or replacement due to vomiting within 15 minutes). Each bottle label will include all information as required by local regulations and must remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

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

### 5.5.2.3 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 7, until they are dispensed for subject use or are returned to AbbVie.
Table 7. Study Drug Storage Conditions

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Country</th>
<th>Storage Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib (ABT-888) or placebo</td>
<td>All countries, except</td>
<td>Store at 15° to 25°C (59° to 77°F)</td>
</tr>
<tr>
<td></td>
<td>Australia/New Zealand</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Australia/New Zealand</td>
<td>Store below 25°C</td>
</tr>
</tbody>
</table>

Investigational products are for investigational use only, and are to be used only within the context of this study. The clinical supplies for this study must be maintained under adequate security and stored under conditions specified on the label.

The controlled storage area should have a temperature recording device. A storage temperature log is to be maintained to document proper storage conditions. The room temperature storage must be recorded each business day to document proper function.

Malfunctions or temperature excursions outside the specified storage range for veliparib or matching placebo must be reported to the sponsor immediately. Sites should use the AbbVie Temperature Excursion Management System (ATEMS) module via IRT, if available, or fax copies of the temperature log indicating the extent of the excursion (time, duration of the temperature excursion, min/max values and study drug affected) to AbbVie Global Drug Supply Management including the Storage Temperature Excursion Reporting Form.

This information will be used to determine the continued acceptability of the drug.

In case of a temperature excursion, study medication should be quarantined and not dispensed until AbbVie Global Pharmaceutical Research & Development (GPRD) or ATEMS deems the medication as acceptable.

**Storage and Disposition of Carboplatin and Paclitaxel**

**Paclitaxel**

Vials must be stored between 15° to 25°C (59° to 77°F) (or per locally approved label or SmPC) in the provided cartons to protect from light.
Carboplatin

Vials must be stored between 15°C to 25°C (59° to 77°F) (or per locally approved label or SmPC) in the provided cartons to protect from light.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects in the study will be randomized using an IRT. Before the study is initiated, directions for the IRT will be provided to each site. The site will contact the IRT to obtain a Screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., laboratory samples 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. For others, the site will access the system and a unique randomization number will be provided. Note: The Investigator's treatment decision must be documented prior to accessing the IRT for subject randomization.

The IRT will randomize subjects into the 3 treatment arms in a 1:1:1 ratio. Subject randomization will be stratified by stage of disease (III versus IV), residual disease and choice of regimen, and region of the world (North America versus Rest of the World). The stratification factors used for the randomization should be the last values on the date of randomization and should be consistent with those on the eCRF.

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 IRT vendor.

5.5.4 Selection and Timing of Dose for Each Subject

All randomized subjects will receive veliparib 150 mg/placebo PO BID in combination with chemotherapy (carboplatin/paclitaxel) for 6 cycles followed by veliparib 400 mg/placebo PO BID as single-agent therapy for up to thirty additional 21-day cycles. Veliparib/placebo will be dosed starting on Day 1 of each cycle and dosed continuously
(21/21 days). One dose will be taken in the morning and the second dose will be taken in the evening (approximately 12 hours after the morning dose). The morning dose of veliparib/placebo should be dosed in clinic prior to carboplatin and paclitaxel on Day 1 of Cycles 1, 2, 3, and 4 for PK sampling purposes.

All randomized subjects will also receive carboplatin (AUC 6) on Day 1 of each cycle and paclitaxel (80 mg/m$^2$ on Days 1, 8, and 15 of each cycle, or 175 mg/m$^2$ on Day 1 of each cycle) (unless a delay is required per locally approved product labels or SmPCs). The paclitaxel infusion should be given first.

5.5.5 Blinding

AbbVie (with the exception of AbbVie Drug Supply Management), the Investigator, the study site personnel and subject will remain blinded to each subject's therapy with veliparib or placebo throughout the course of the study.

All subjects will be treated with open-label carboplatin and paclitaxel.

The IRT will provide access to blinded subject therapy information during the double blind period.

AbbVie must be notified before the blind is broken unless identification of the investigational product is required for medical emergency, i.e., situation in which the knowledge of the specific blinded therapy will affect the immediate management of the subject's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

5.5.5.1 Blinding of Investigational Product

The IRT will provide access to blinded subject therapy 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 treatment is required, every effort must be made to contact the medical monitor (listed in Section 6.7) prior to contacting the IRT
for 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.

5.5.5.2 Blinding of Data for Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will review safety data for this study in an un-blinded fashion approximately 12 months and 24 months from the date the first subject is randomized. Details of the IDMC review will be outlined in the IDMC Charter. Aggregate clinical safety data will be reviewed on a real-time basis throughout the course of the study.

5.5.6 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

Veliparib/Placebo should be taken as directed by the Investigator. Carboplatin and paclitaxel will be administered intravenously by trained site personnel.

Subjects will be instructed to return all veliparib/placebo bottles (empty, partially filled or full) to the study site personnel prior to each cycle and at the Therapy Completion Visit. The site staff will document the bottles returned and the number of capsules per bottle on the appropriate form.

Upon completion or termination of the study, all original bottles/cartons containing unused veliparib/placebo (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 bottles will be performed at the site.
Unless otherwise directed by the Investigator, a subject will be considered compliant with veliparib/placebo if 80% of the assigned dose is taken during a cycle. Compliance below 80% will require counseling of the subject by study site personnel.

5.5.7 Drug Accountability

The site will record the dose of carboplatin and paclitaxel given to each subject in the source documents and on the eCRF. As the Investigator will obtain both carboplatin and paclitaxel commercially, site inventory and accountability of carboplatin and paclitaxel will not be performed, and drug accountability forms will not be provided.

Upon receipt of a shipment of veliparib/placebo, the representative at each site will 1) open and inspect the shipment; 2) verify that the veliparib/placebo 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; 4) register the shipment as received via the IRT. 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 IRT.

An overall accountability of the study drug will be performed and verified by the site monitor throughout the study and at the study site closeout visit. An accurate running inventory of veliparib/placebo will be maintained utilizing the IRT drug accountability module and, if required, according to your institutional policy and will include the lot number, POR number(s), the bottle/kit numbers, and the date veliparib/placebo was dispensed for each subject.

Upon completion or termination of the study, all original containers containing unused study drug (empty containers will be defaced and discarded on site) will be returned to a destruction facility according to instructions from AbbVie or if prearranged between the sponsor and site, destruction of used and unused veliparib/placebo in bottles will be performed at the site.
The study Investigator or his/her designated representative agrees not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator listed on the FDA 1572 or Investigator Information and Agreement (IIA) form.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The proposed Phase 3 study will evaluate the efficacy and tolerability of veliparib in combination with standard chemotherapy compared to chemotherapy alone in women with previously untreated, Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Treating physicians will be allowed the choice of treating with either paclitaxel on a weekly schedule or every 3 weeks schedule in combination with carboplatin AUC 6 such that there are the following treatment choices prior to randomization:

1. Primary cytoreductive surgery with carboplatin and weekly paclitaxel (21-day cycle)
2. Carboplatin and weekly paclitaxel (21-day cycle) with interval cytoreductive surgery after Cycle 3
3. Primary cytoreductive surgery with carboplatin and Q3-weeks paclitaxel (21-day cycle)
4. Carboplatin and Q3-weeks paclitaxel (21-day cycle) with interval cytoreductive surgery after Cycle 3

Following the Investigator's choice of therapy, subjects will be randomized in a 1:1:1 ratio to one of the following:

- Carboplatin/paclitaxel plus placebo for 6 cycles followed by placebo maintenance therapy for up to an additional 30 cycles (Cycles 7 – 36)
- Carboplatin/paclitaxel plus veliparib for 6 cycles followed by placebo maintenance therapy for up to an additional 30 cycles (Cycles 7 – 36)
• Carboplatin/paclitaxel plus veliparib for 6 cycles followed by veliparib maintenance therapy for up to an additional 30 cycles (Cycles 7 – 36)

These regimens are supported as category 1 level of evidence by NCCN guidelines and consistent with current standard of care. This design will allow the effect of adding veliparib to standard chemotherapy to be assessed separately from the effect of adding veliparib as induction therapy and maintenance therapy. A hierarchical testing sequence will be used to accommodate the 3-arm design and to test the primary and secondary endpoints. A pre-specified alpha allocation rule is used to control the whole population and in the BRCA-deficient population.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be used in this study.

The efficacy measurements in this study are standard and validated. Progression-free survival is a widely accepted endpoint of clinical importance for the evaluation of subjects with previously untreated ovarian cancer. Additionally, RECIST 1.1 is a validated guideline for the measurement of responses in subjects with advanced or metastatic solid tumors.

5.6.3 Suitability of Subject Population

The proposed Phase 3 study will evaluate the efficacy and tolerability of veliparib in combination with standard chemotherapy compared to chemotherapy alone in subjects with previously untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. The study will enroll subjects ≥ 18 years of age with a histologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma FIGO Stage III or IV, with appropriate tissue available for histologic evaluation. The proposed inclusion and exclusion criteria are anticipated to result in a study subject population representative of ovarian cancer patients who are receiving front line systemic therapy with carboplatin and paclitaxel according to current practice guidelines.
5.6.4 Selection of Doses in the Study

The doses of standard chemotherapy (carboplatin and paclitaxel) are identical to those used as standard first-line therapy for the treatment of ovarian cancer and to those used in the GOG 9923 study. The dose of veliparib in combination with carboplatin and paclitaxel is based upon the GOG 9923 study in subjects with newly diagnosed ovarian cancer in which the recommended dose of veliparib in combination with carboplatin and paclitaxel was determined to be 150 mg PO BID, and as verified by assessment of tolerability beyond cycle 1 during the expansion phase. This Phase 3 study will allow subjects to receive veliparib 400 mg PO BID maintenance therapy following the completion of 6 cycles of chemotherapy with veliparib/placebo. This dose has been selected based upon the recommended Phase 2 dose (CTEP 8282) and additional safety and efficacy data in Phase 2 studies in gBRCA breast cancer (CTEP 8264) and ovarian cancer (GOG 280) in which durable responses were observed to single-agent therapy.

The maximum dose of veliparib for any subject in this study is 150 mg BID in combination with carboplatin and paclitaxel for 21 of 21 days per cycle over 6 cycles and 400 mg BID as single-agent therapy for 21 of 21 days per cycle over 30 cycles.

5.7 Dose Reductions or Delays

In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and therapy delays as specified. Any subject whose therapy is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. The therapy schedule will then proceed in the usual sequence.

5.7.1 Dose Reductions or Delays for Carboplatin and Paclitaxel with Placebo/Veliparib (Cycles 1 – 6)

If a subject experiences an adverse event that results in a delay in starting a cycle or requires that therapy to be delayed or interrupted during a cycle, the subject will complete the planned activities per Table 1 and Section 5.3.1.1. For subjects receiving carboplatin...
and paclitaxel with veliparib/placebo (Cycles 1 – 6), re-escalation of the dose following dose reductions is not allowed.

**5.7.1.1 Guidelines for Hematologic Toxicity**

Initial therapy modifications will consist of cycle delay and/or dose reduction as directed. Treatment decisions will be based on the ANC rather than the total white cell count.

Cycles 1 – 6 will not begin until the ANC is ≥ 1000 cells/mm$^3$ and the platelet count is ≥ 75,000/mm$^3$. While subjects with an ANC 1000 – 1499/mm$^3$ or platelet count 75,000 – 99,000/mm$^3$ will be able to proceed with therapy; dose modifications will be required as indicated in Table 8 and Table 9. Therapy will be delayed for a maximum of three weeks until these values are achieved. The medical monitor should be notified for subjects who fail to recover counts within 3 weeks as indicated in Table 8 and Table 9.

For the weekly regimen, the Day 8 and 15 weekly paclitaxel dose will not be given unless the ANC ≥ 500 cells/mm$^3$ and the platelet count ≥ 50,000 cells/mm$^3$. For subjects with an ANC < 500 cells/mm$^3$ or platelets < 50,000 cells/mm$^3$, the dose will be omitted and dose reductions as outlined in Table 10 will be used for the following cycle. Within a given cycle, if the Day 8 dose is held and the counts recover by Day 15, the Day 15 dose may be given.

**Guidelines for the Use of Hematopoietic Cytokines**

The use of hematopoietic cytokines is restricted as noted:

In general, subjects will NOT receive prophylactic filgrastim (G-CSF), PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless they experience therapy delays, dose omissions, or recurrent neutropenic complications as specified. In particular, hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, subjects may also receive growth factors for the management of neutropenic complications in accordance with institutional treatment guidelines.
If needed per dose modifications guidelines, it is recommended that filgrastim (dosed according to institutional standard) will be administered daily subcutaneously starting 24 – 72 hours after the last dose of chemotherapy. Pegfilgrastim should not be used for subjects receiving Day 15 paclitaxel as they do not have a 2-week chemotherapy-free interval. For subjects receiving Day 15 paclitaxel who require the addition of filgrastim per dose modification guidelines, doses should be given daily on Days 16 – 18 of the cycle.

Subjects will NOT receive prophylactic thrombopoietic agents.

Subjects may receive erythropoietin, iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in subjects with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.

Subjects may NOT receive amifostine or other protective reagents.

**Modifications for Hematologic Toxicity:**

For dose-limiting hematological toxicity or for ANC < 1000 cells/mm$^3$ and/or platelets < 75,000/mm$^3$ on Day 1, the cycle should be delayed until the ANC recovers to ≥ 1,000 cells/mm$^3$ and the platelet count recovers to ≥ 75,000/mm$^3$ (Grade 1).

Dose-limiting toxicities will be defined as below and will be handled according to Table 8 (Q3-weeks) and Table 9 (Q-week). Veliparib/Placebo is continued despite chemotherapy delays in the absence of a dose-limiting toxicity.
For dose-limiting neutropenia, veliparib/placebo is held until the ANC recovers to \( \geq 1,000 \text{ cells/mm}^3 \). For dose-limiting thrombocytopenia, veliparib/placebo should be held until the platelet count recovers to \( \geq 75,000/\text{mm}^3 \). Once veliparib/placebo is reinstituted, the dose will remain the same.

Dose-limiting hematological toxicities will include the following:

- Febrile neutropenia
- Prolonged Grade 4 neutropenia persisting for greater than 7 days
- Grade 4 thrombocytopenia \(< 25,000/\text{mm}^3 \)
- Bleeding associated with Grade 3 thrombocytopenia \((25,000 \text{ to } < 50,000/\text{mm}^3)\)

There will be no modifications for uncomplicated Grade 4 neutropenia lasting \( \leq 7 \) days or for uncomplicated Grade 3 thrombocytopenia.

No dose modifications will be made for anemia. Subjects may receive red blood cell transfusions and/or erythropoiesis stimulating agents using standard supportive care guidelines.

Table 8. Q3-Week Schedule Dose Modifications for Dose Limiting Hematologic Toxicity or Reduced ANC \((1000 – 1499/\text{mm}^3)\) or Reduced Platelets \((75,000 – 99,000/\text{mm}^3)\) on Day 1

<table>
<thead>
<tr>
<th>ANC</th>
<th>PLT</th>
<th>First Occurrence</th>
<th>Second Occurrence</th>
<th>Third Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF</td>
<td>Reduce carboplatin one AUC unit (AUC 4)</td>
<td>Discontinue veliparib/placebo and notify medical monitor</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF</td>
<td>Reduce carboplatin one AUC unit (AUC 4)</td>
<td>Discontinue veliparib/placebo and notify medical monitor</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5)</td>
<td>Reduce carboplatin one AUC unit (AUC 4)</td>
<td>Discontinue veliparib/placebo and notify medical monitor</td>
</tr>
</tbody>
</table>
Table 9. Q-Week Schedule Dose Modifications for Dose-Limiting Hematologic Toxicity or Reduced ANC (1000 – 1499/mm³) or Reduced Platelets (75,000 – 99,000/mm³) on Day 1

<table>
<thead>
<tr>
<th>ANC</th>
<th>PLT</th>
<th>First Occurrence</th>
<th>Second Occurrence</th>
<th>Third Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF</td>
<td>Discontinue Day 15 paclitaxel dose</td>
<td>Discontinue veliparib/placebo and notify medical monitor</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF</td>
<td>Reduce carboplatin one AUC unit (AUC 4) and discontinue Day 15 paclitaxel dose</td>
<td>Discontinue veliparib/placebo and notify medical monitor</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5)</td>
<td>Reduce carboplatin one AUC unit (AUC 4)</td>
<td>Discontinue veliparib/placebo and notify medical monitor</td>
</tr>
</tbody>
</table>

Note: For subjects who have had 2 dose reductions for ANC only and then develop thrombocytopenia only, an additional dose modification is allowed but should be discussed with the medical monitor.

Table 10. Q-Week Dosing Schedule Modifications for Hematologic Toxicity on Day 8 or 15

<table>
<thead>
<tr>
<th>ANC &lt; 500</th>
<th>PLT &lt; 50</th>
<th>First Occurrence</th>
<th>Second Occurrence</th>
<th>Third Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes No</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF with the next cycle</td>
<td>Discontinue Day 15 paclitaxel dose with the next cycle</td>
<td>Discontinue veliparib/placebo and notify medical monitor</td>
<td></td>
</tr>
<tr>
<td>Yes Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF with the next cycle</td>
<td>Reduce carboplatin one AUC unit (AUC 4) and discontinue Day 15 paclitaxel dose with the next cycle</td>
<td>Discontinue veliparib/placebo and notify medical monitor</td>
<td></td>
</tr>
<tr>
<td>No Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5) with the next cycle</td>
<td>Reduce carboplatin one AUC unit (AUC 4) with the next cycle</td>
<td>Discontinue veliparib/placebo and notify medical monitor</td>
<td></td>
</tr>
</tbody>
</table>

Note: For subjects who have had 2 dose reductions for ANC only and then develop thrombocytopenia only, an additional dose modification is allowed but should be discussed with the medical monitor.

Modifications for Delayed Hematologic Recovery:

Delay on the basis of neutropenia (Delay-ANC) is defined if the ANC is < 1000 cells/mm³ within 24 hours prior to Day 1 of each cycle of scheduled therapy.
Delay on the basis of thrombocytopenia is defined if the platelet count is < 75,000/mm$^3$ within 24 hours prior to Day 1 of each cycle of scheduled therapy.

Modifications noted below in Table 11 (Q3-weeks) and Table 12 (Q-week) are only required for management of delays in the absence of dose reductions stipulated by nadir DLT-ANC and/or DLT-PLT (as noted above in Table 8 and Table 9) and for subjects being treated per the Q-week schedule in the absence of dose reductions stipulated by hematologic toxicity on Days 8 or 15 (as noted above in Table 10). In other words, if the subject experiences DLT-ANC and Delay-ANC, make the modifications as indicated for the nadir counts without additional modifications based on delayed recovery. Veliparib/Placebo is continued despite chemotherapy delays in the absence of a DLT.

**Table 11. Q3-Week Dosing Schedule Modifications for Delayed Hematologic Recovery**

<table>
<thead>
<tr>
<th>Category</th>
<th>Delay (days)</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay-ANC</td>
<td>1 – 7</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td>8 – 21</td>
<td>Follow Table 8 for dose modifications with next cycle</td>
</tr>
<tr>
<td></td>
<td>&gt; 21</td>
<td>Follow Table 8 for dose modifications with next cycle and notify medical monitor</td>
</tr>
<tr>
<td>Delay-PLT</td>
<td>1 – 7</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td>8 – 21</td>
<td>Follow Table 8 for dose modifications with next cycle</td>
</tr>
<tr>
<td></td>
<td>&gt; 21</td>
<td>Follow Table 8 for dose modifications with next cycle and notify medical monitor</td>
</tr>
</tbody>
</table>
Table 12. Q-Week Dosing Schedule Modifications for Delayed Hematologic Recovery

<table>
<thead>
<tr>
<th>Category</th>
<th>Delay (days)</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay-ANC</td>
<td>1 – 7</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td>8 – 21</td>
<td>Follow Table 9 for dose modifications with next cycle</td>
</tr>
<tr>
<td></td>
<td>&gt; 21</td>
<td>Follow Table 9 for dose modifications with next cycle and notify medical monitor</td>
</tr>
<tr>
<td>Delay-PLT</td>
<td>1 – 7</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td>8 – 21</td>
<td>Follow Table 9 for dose modifications with next cycle</td>
</tr>
<tr>
<td></td>
<td>&gt; 21</td>
<td>Follow Table 9 for dose modifications with next cycle and notify medical monitor</td>
</tr>
</tbody>
</table>

5.7.1.2 Guidelines for Non-Hematologic Toxicity

Management of therapy related Grade 3 or Grade 4 non-hematological toxicity (excluding alopecia, fatigue, hypersensitivity reaction, nausea, vomiting, constipation, diarrhea, hypokalemia, hypomagnesemia, hypocalcemia, hyponatremia, and hypophosphatemia) should follow the dose level modifications as indicated specifically in this section. The table below should be used for dose level modifications related to non-hematologic toxicity.

Table 13. Modifications for Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen –2 Level</th>
<th>Regimen –1 Level</th>
<th>Regimen Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (Q3-week)</td>
<td>110 mg/m² Day 1</td>
<td>135 mg/m² Day 1</td>
<td>175 mg/m² Day 1</td>
</tr>
<tr>
<td>Paclitaxel (Q-week)</td>
<td>60 mg/m² Days 1, 8</td>
<td>80 mg/m² Days 1, 8</td>
<td>80 mg/m² Days 1, 8, 15</td>
</tr>
<tr>
<td>Carboplatin (Q-week and Q3-week)</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Veliparib/Placebo</td>
<td>50 mg BID</td>
<td>100 mg BID</td>
<td>150 mg BID</td>
</tr>
</tbody>
</table>

Peripheral Neuropathy

Peripheral neuropathy Grade 2 (or greater) requires reduction of one dose level in paclitaxel (both dosing schedules) and delay in all subsequent therapy for a maximum of three weeks until recovered to Grade 1. If peripheral neuropathy fails to recover to
Grade 1 by a maximum delay of three weeks from time therapy is due, the medical monitor should be contacted. If Grade 2 (or greater) neuropathy recurs after 2 dose reductions of paclitaxel, the medical monitor should be contacted. Docetaxel may be substituted if neuropathy results in discontinuation of paclitaxel. A washout of 7 days from veliparib/placebo is required before starting docetaxel. Veliparib/Placebo is not permitted in combination with docetaxel. Subjects requiring a switch to docetaxel during Cycles 1 – 6 will be allowed to proceed with veliparib/placebo monotherapy beginning in Cycle 7.

Seizures

Any event of seizure, regardless of grade or attribution requires discontinuation of veliparib/placebo and discussion with the medical monitor regarding the decision to resume treatment.

Renal Toxicity

Renal toxicity (associated with reduction in glomerular filtration rate [GFR]) is not expected from carboplatin as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule of the regimen. As such, there are no specific dose modifications for renal toxicity. However, the target AUC dose of carboplatin must be recalculated each cycle in any subject who develops renal insufficiency, defined by serum creatinine > 1.5 × ULN, Grade ≥ 2.

Hepatic Toxicity

Hepatic toxicity is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel and delay in subsequent therapy for a maximum of three weeks until recovered to ≤ Grade 1. If Grade 3 (or greater) elevations do not recover within three weeks or recur despite dose modification, the medical monitor should be contacted.
**Hypersensitivity Reaction**

In general, the occurrence of a hypersensitivity reaction to carboplatin or paclitaxel is not considered a dose-limiting toxicity. Subjects may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made. However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the subject will discontinue this agent. Severe hypersensitivity reactions to paclitaxel do not have to proceed with a rechallenge. Docetaxel may be substituted for paclitaxel. **A washout of 7 days from veliparib/placebo is required before starting docetaxel.**

**Veliparib/Placebo is not permitted in combination with docetaxel.** Subjects requiring a switch to docetaxel during Cycles 1 – 6 will be allowed to proceed with veliparib/placebo monotherapy beginning in Cycle 7.

**Other Toxicity**

There will be no dose modifications for alopecia, nausea, constipation, diarrhea, hypokalemia, hypocalcemia, hypomagnesemia, hyponatremia, hyponatremia, or hypophosphatemia. It is recommended that routine medical measures be employed to manage nausea, constipation, diarrhea, and electrolyte abnormalities.

**Nausea, Vomiting, or Fatigue**

Nausea, vomiting, or fatigue ≥ Grade 3 which persists despite supportive medications with symptoms thought to be secondary to veliparib/placebo and not related to carboplatin, paclitaxel, or disease progression, veliparib/placebo will be held until symptoms resolve to ≤ Grade 1. These cases should all be discussed with the medical monitor, as it is unlikely for veliparib to be the predominant cause of nausea, vomiting, or fatigue. Veliparib will then be restarted at the next lower dose level. No more than 2 dose reductions are allowed prior to discontinuation of veliparib.
If veliparib/placebo is discontinued during Cycles 1 – 6, the subject will resume veliparib/placebo dosing with Cycle 7 (the maintenance phase) if therapy toxicity resolves to ≤ Grade 1.

Dose modifications for other non-hematologic toxicities will occur as follows:

- For any Grade 3 non-hematologic adverse event (except controllable nausea/vomiting, constipation, diarrhea, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, or hyponatremia) considered to be related to study treatment, therapy should be held until symptoms resolve to ≤ Grade 1 or to baseline and reduce the dose of the drug(s) most likely to have caused the toxicity by one dose level. If a Grade 3 adverse event persists for > three weeks or recurs after resumption of therapy, the subject may be taken off therapy after discussing with the medical monitor.

- Any Grade 4 non-hematologic adverse event (except controllable nausea/vomiting, constipation, diarrhea, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, or hyponatremia) considered to be related to therapy should be discussed with the medical monitor and the subject may either be taken off therapy or dose reductions implemented.

5.7.2 **Veliparib/Placebo Monotherapy Dose Reductions and Delays (Cycles 7 – 36)**

Subjects who complete six cycles of carboplatin and paclitaxel and who have not progressed will receive single-agent, blinded veliparib/placebo starting at 400 mg. If subjects have discontinued veliparib/placebo during the chemotherapy phase, veliparib/placebo may be reinitiated during the maintenance phase once therapy related toxicity resolve to ≤ Grade 1 or baseline.

The following are guidelines for dose reductions, delays and discontinuation of veliparib/placebo monotherapy. Subjects will follow the schedule of procedures outlined in Table 1.
Subjects should have an ANC ≥ 1,000/mm$^3$ and a platelet count ≥ 75,000/mm$^3$ prior to initiating Cycle 7.

Subjects should have an ANC ≥ 1,500/mm$^3$ and a platelet count ≥ 100,000/mm$^3$ prior to initiating subsequent cycles (Cycle 8 and beyond).

For any subject who experiences Grade 3 or 4 toxicity despite optimal supportive care (with the exception of anemia, alopecia, and non-treatment related clinically insignificant laboratory abnormalities), and the toxicity is not attributable to underlying disease, the veliparib/placebo dose will be held until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 is present at the time of study entry.

Study drug interruptions for events that are clearly not related to therapy (e.g., underlying cancer, planned surgical procedures, or acute viral illnesses, do not necessitate a dose reduction.

The timing of the dose resumption should be at the Investigator's discretion. In the cases of delays, tumor assessments should continue per Table 1.

The dose of veliparib will be reduced by one dose level (per Table 14) for subjects experiencing the following toxicities if attributed to veliparib/placebo:

**Hematological Toxicities**

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

**Non-Hematological Toxicities**

- Any CTCAE ≥ Grade 3 toxicity that represents at least 2 grade increase from baseline with the following clarifications:
○ Excludes nausea, vomiting, diarrhea, and tumor pain that have not received optimal treatment with antiemetics, antidiarrheals, or analgesics.

○ A rise in creatinine to Grade 3, only if not corrected to Grade 1 or baseline within 24 hours with IV fluids.

○ Metabolic toxicities, only if unable to be corrected to Grade 2 or less within 24 hours (such as glucose changes, hypokalemia, hypomagnesemia, hyperuricemia, hypophosphatemia, and hyponatremia). Grade 4 metabolic toxicities that are symptomatic will result in dose reduction regardless of duration or ability to correct.

○ For any > Grade 2 event of seizure attributed to veliparib/placebo, veliparib/placebo is to be interrupted, brain CT or MRI obtained, and the event should be discussed with the medical monitor.

Re-escalation may be permitted on the veliparib monotherapy arm only if toxicity resolved to Grade 1 or lower and can be maintained with optimal supportive care. In addition, temporary dose reductions or interruptions for Grade 1 or Grade 2 nausea or vomiting are considered intolerable despite optimal treatment will be allowed. This should be discussed with the medical monitor.

Table 14. Veliparib/Placebo Monotherapy Dose Levels

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Veliparib/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose Level</td>
<td>400 mg BID</td>
</tr>
<tr>
<td>Dose Level –1</td>
<td>300 mg BID</td>
</tr>
<tr>
<td>Dose Level –2</td>
<td>250 mg BID*</td>
</tr>
</tbody>
</table>

* If veliparib 250 mg/placebo BID is not tolerable, veliparib/placebo will be discontinued. There will be no dose reductions below the 250 mg BID dose.

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 considered as having "no reasonable possibility" of being associated with 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. Worsening in severity of a reported adverse event should be reported as a new 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 6.8 regarding toxicity management]) and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a 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. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed
earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

All protocol-related nonserious AEs must be collected from the signing of the study specific informed consent until therapy administration. In addition, adverse events with onset or worsening reported by a subject from the time that the first dose of study drug (veliparib or placebo) is administered until 30 days have elapsed following discontinuation of study drug administration will be considered as treatment-emergent adverse events.

6.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie 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). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. 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.

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 Events Expected Due to Ovarian, Fallopian Tube, or Primary Peritoneal Cancer or Progression of Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Events that are clearly consistent with ovarian cancer or the expected progression of ovarian cancer, including but not limited to abdominal pain, abdominal distension, ascites, intestinal obstruction, colonic obstruction, small intestinal obstruction, pleural effusion, and constipation should be considered as expected. A list of expected adverse events is presented in Appendix H of the protocol. These adverse events may occur alone or in various combinations and are considered expected adverse events in ovarian subjects.

6.3 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. 32
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.

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 eCRFs also need to be updated and need to include the new AE serial number.

### 6.4 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug (for the purpose of this section, therapy is considered veliparib/placebo plus carboplatin/paclitaxel):

- **Reasonable Possibility**
  - An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.

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

The Investigator will assess the relationship of each adverse event to veliparib, to carboplatin, to paclitaxel, and to ovarian cancer. Most events will be reasonably related to one treatment or to ovarian cancer, though some events may be reasonably related to more than one or to none. For causality assessments, events assessed as having a reasonable
possibility of being related to veliparib will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator’s opinion of no reasonable possibility of being related to veliparib, to carboplatin, to paclitaxel, and to ovarian cancer is given, an Other cause of event must be provided by the Investigator for the serious adverse event.

6.5 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 therapy administration.

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

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

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection

<table>
<thead>
<tr>
<th>Protocol-Related SAEs &amp; AEs*</th>
<th>SAEs and Nonserious AEs Elicited and/or Spontaneously Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Signed</td>
<td>Study Drug Start</td>
</tr>
<tr>
<td></td>
<td>Study Drug Stopped</td>
</tr>
<tr>
<td></td>
<td>30 Days After Study Drug Stopped</td>
</tr>
</tbody>
</table>

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

6.6.1 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (Section 6.5) that are more likely related to disease progression will therefore be an expected adverse event and will not be an expedited report.

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

6.6.2 Lack of Efficacy or Worsening of Disease

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

6.6.3 Reporting Serious Adverse Events

In the event of a serious adverse event, whether associated with therapy 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 EDC system (RAVE®). Serious adverse events that occur prior to the site having access to the
RAVE® system or if RAVE® is not operable should use the SAE Non-CRF paper forms and send them to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Serious adverse events which are considered expected due to the underlying ovarian, fallopian tube, or primary peritoneal cancer as described in Section 6.2 would not be expedited as individual safety case reports to regulatory authorities.

For safety concerns, contact the Oncology Safety Management Team at:

Oncology Safety Management Team
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office: 
Fax: 
Email: 

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

Medical Monitor:
Sponsor/Emergency Contact:

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:

Phone: [redacted]

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 reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure for veliparib or SmPC for carboplatin and paclitaxel.

6.7 Pregnancy

In the event of a positive pregnancy test, subjects must immediately discontinue therapy and must be discontinued from the study. The Investigator must report the positive pregnancy test to the appropriate contact listed in protocol Section 6.6 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 therapy. 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.

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.

6.8 Toxicity Management

Management of toxicity should be performed by Investigators according to standard medical practice and according to local label for toxicity due to carboplatin or paclitaxel. Guidelines for carboplatin, paclitaxel, and veliparib/placebo dose reductions and delays are provided in Section 5.7.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and the following AbbVie Clinical Monitors:
Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a one-sided $P$ value $\leq 0.025$. 
The date of randomization (enrollment) is defined as the date that the Interactive Response Technology (IRT) issues a randomization number.

The primary, secondary, and exploratory efficacy analyses will be performed on the intent-to-treat (ITT) population.

All subjects who receive at least one dose of the study drug will be included in the safety analysis.

8.1 Statistical and Analytical Plans

8.1.1 Baseline Characteristics

All baseline summary statistics and analyses will be based on characteristics obtained prior to randomization. Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to randomization.

Baseline characteristic data will be summarized with all randomized subjects for Arms 1, 2, and 3 of the study separately.

8.1.1.1 Demographics

Continuous demographic variables such as age, height, weight and gender will be summarized with means, standard deviation and range. Frequencies and percentages will be computed for the categorical parameters such as race, gender, BRCA-deficiency status, stage of the disease, residual disease, choice of regimen, and region.

8.1.1.2 Medical History

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 endpoint is progression-free survival (PFS). PFS will be defined as the number of days from the date that the subject was randomized to the date the subject experiences an event of disease progression, according to RECIST criteria version 1.1 (as determined by the investigator) or to the date of death (all causes of mortality) if disease progression is not reached. All events of disease progression (as determined by the investigator) will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. However, if a disease progression event occurs after a subject misses two or more consecutive disease progression assessments this subject will be censored at the last disease progression assessment prior to the missing disease progression assessments. All events of death will be included for subjects who had not experienced disease progression provided the death occurred within the expected time windows defined according to the underlying disease assessment interval (every 9 weeks, then at the end of the Combination Phase, then every 12 weeks for 2 years, then every 6 months for 3 years, and then annually). If the subject does not have an event of disease progression (as determined by the investigator) nor has the subject died, the subject's data will be censored at the date of the subject's last disease assessment.

The primary efficacy analyses are defined by comparing PFS in Arm 3 versus Arm 1 in the whole population and the BRCA-deficient population (or only in the whole population based on the pre-specified alpha allocation rule). PFS will be also compared between Arm 2 and Arm 1 as a secondary analysis and between Arm 2 and Arm 3 as an exploratory analysis.

The distribution of PFS will be estimated for each treatment arm using Kaplan-Meier methodology. For the whole population, PFS will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen, and BRCA-deficient status. For the BRCA-deficient population,
PFS will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen as applicable.

Median PFS time will be estimated and 95% confidence interval for the estimated median PFS time will be presented for each treatment arm.

### 8.1.2.2 Secondary Efficacy Endpoints

#### 8.1.2.2.1 Overall Survival (OS)

OS 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.

The secondary efficacy analyses for OS are defined by comparing OS in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the whole population and the BRCA-deficient population (or only in the whole population based on the pre-specified alpha allocation rule). OS will be also compared between Arm 2 and Arm 3 as an exploratory analysis.

The distribution of OS will be estimated for each treatment arm using Kaplan-Meier methodology. For the whole population, OS will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen, and BRCA-deficient status. For the BRCA-deficient population, OS will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen as applicable.

Median OS time will be estimated and 95% confidence interval for the estimated median OS time will be presented for each treatment arm.
8.1.2.2 Patient Reported Outcomes

Disease Related Symptoms

The overall mean change from baseline for the DRS scores measured at each assessment point up to 2 years or disease progression will be a secondary endpoint of the study. The overall mean change from baseline for the total DRS scores between the treatment groups will be compared using a longitudinal repeated measures model that takes into account the DRS scores measured at each assessment point up to 2 years or disease progression, whichever is later.

8.1.2.3 Tertiary Efficacy Endpoints

8.1.2.3.1 PFS2, TTFST, and TTSST

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

Time to the first subsequent therapy (TTFST) will be defined as the number of days from the day the subject is randomized to the start of the first subsequent therapy or death of any cause. If the subject does not have an event of TTFST, the subject's data will be censored at the date of the subject's last visit or survival follow-up.

Time to the second subsequent therapy (TTSST) will be defined as the number of days from the day the subject is randomized to the start of the second subsequent therapy or death of any cause. If the subject does not have an event of TTSST, the subject's data will be censored at the date of the subject's last visit or survival follow-up.

PFS2, TTFST, and TTSST will be summarized and analyzed using the same methodologies as PFS.
8.1.2.3.2 Additional PRO Endpoints

Additional analysis based on other PRO endpoints will be specified in a separate PRO analysis plan.

8.1.3 Interim Efficacy Analyses

For OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the whole population, one efficacy interim analysis will be performed at the time of the corresponding PFS analyses (~Month 36) with a nominal alpha of 0.0001, so that the final OS analysis (~Month 58) have a nominal alpha of 0.0124.

For OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the BRCA-deficient population, two efficacy interim analyses will be performed. The first interim analysis will occur at the time of the corresponding PFS analyses (~Month 36) with a nominal alpha of 0.0001, the second interim analysis will occur at the time of the OS analysis for the whole population (~Month 58) with a nominal alpha of 0.0001, so that the final OS analyses (~Month 77) have a nominal alpha of 0.0124 to have the overall alpha controlled at 0.0125 in the BRCA-deficient population.

The nominal alpha of the final OS analyses may be slightly different as the timings of the interims are rough estimates.

8.1.4 Multiplicity Adjustment

This is a three-arm, randomized, placebo-controlled Phase 3 clinical trial. All of the subjects will receive six cycles of carboplatin and paclitaxel. The backbone chemotherapy regimen will not be randomized, but selected by the treating physician and subject prior to randomization. In addition to the chemotherapy, subjects will be randomly allotted to receive either placebo or a veliparib. While 6 cycles of chemotherapy are planned, the randomized treatment (placebo or veliparib) will be continued during a maintenance phase of treatment.
Table 15. Study Treatment Arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: C/P + placebo → placebo</td>
<td>Reference regimen</td>
</tr>
<tr>
<td>Arm 2: C/P + veliparib → placebo</td>
<td>Veliparib administered in the combination therapy phase only</td>
</tr>
<tr>
<td>Arm 3: C/P + veliparib → veliparib</td>
<td>Veliparib administered in both combination therapy and maintenance therapy phases</td>
</tr>
</tbody>
</table>

Note: [+] indicates 'concurrent with;' [→] indicates 'followed by;' [C/P] indicates 'backbone chemotherapy' (i.e., carboplatin/paclitaxel).

There are two populations of interest: whole population and BRCA-deficient population.

For the whole population, the hypotheses of interest are listed below:

Table 16. The Null Hypotheses of Interest in the Whole Population

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (Arm 3 versus Arm 1)</td>
<td>PFS (Arm 2 versus Arm 1)</td>
</tr>
<tr>
<td>OS (Arm 3 versus Arm 1)</td>
<td>OS (Arm 2 versus Arm 1)</td>
</tr>
<tr>
<td>DRS (Arm 3 versus Arm 1)</td>
<td>DRS (Arm 2 versus Arm 1)</td>
</tr>
</tbody>
</table>

PFS = Progression Free Survival; OS = Overall Survival; DRS = Disease Related Symptom

Note: PFS (Arm 3 versus Arm 1) denotes the null hypothesis: Arm 3 (C/P + veliparib → veliparib) does not increase PFS compared to Arm 1 (C/P + placebo → placebo). Other notations in this table are defined similarly.

For the BRCA-deficient population, the hypotheses of interest are the same as for the whole population (Table 17).

Table 17. The Null Hypotheses of Interest in BRCA-Deficient Population

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (Arm 3 versus Arm 1)</td>
<td>PFS (Arm 2 versus Arm 1)</td>
</tr>
<tr>
<td>OS (Arm 3 versus Arm 1)</td>
<td>OS (Arm 2 versus Arm 1)</td>
</tr>
<tr>
<td>DRS (Arm 3 versus Arm 1)</td>
<td>DRS (Arm 2 versus Arm 1)</td>
</tr>
</tbody>
</table>

PFS = Progression Free Survival; OS = Overall Survival; DRS = Disease Related Symptom

The expected proportion of BRCA-deficient subjects is approximately 24% in the whole population. Due to the challenge of obtaining the testing results of BRCA-deficient status
prior to randomization, the test results will be available for all subjects during the trial. A pre-specified alpha allocation rule is defined as below for 2 scenarios, based on the proportion of the subjects with \textit{BRCA}-deficient status obtained prior to the database lock. In Scenario 1 (Figure 4), \textit{BRCA}-deficient subjects account for at least 18\% of the whole population; in Scenario 2, \textit{BRCA}-deficient subjects account for less than 18\% of the population.
Figure 4. Testing Procedures for the Hypotheses in the Whole and BRCA-Deficient Populations

Total type I error = 0.025

Whole population
\((\alpha = 0.0125)\)

- PFS (Arm 3 vs. Arm 1) at \(\alpha\)
  - Hochberg Procedure at \(\alpha\)
    - OS (Arm 3 vs Arm 1) at \(\alpha/2\) or \(\alpha\)
    - PFS (Arm 2 vs Arm 1) at \(\alpha/2\) or \(\alpha\)
    - If both tests are rejected
      - OS (Arm 2 versus Arm 1) at \(\alpha\)
        - Hochberg Procedure at \(\alpha\)
          - DRS (Arm 3 vs Arm 1) at \(\alpha/2\) or \(\alpha\)

BRCA-deficient population
\((\alpha = 0.0125)\)

- PFS (Arm 3 vs. Arm 1) at \(\alpha\)
  - PFS (Arm 2 vs. Arm 1) at \(\alpha\)
  - OS (Arm 3 vs. Arm 1) at \(\alpha\)
  - OS (Arm 2 vs. Arm 1) at \(\alpha\)
  - DRS (Arm 3 vs Arm 1) at \(\alpha\)
  - DRS (Arm 2 vs. Arm 1) at \(\alpha\)
Scenario 1: If the BRCA-deficient subjects consist of at least 18% of the whole population:

- The entire one-sided type I error of 0.025 will be equally allocated to the whole population and the BRCA-deficient population, or 0.0125 for each population,
- The testing procedures of the hypotheses within each population are defined as below and illustrated by the flow chart in Figure 4 as above.
  - For the whole population, assuming \( \alpha \) (0.0125 in this case) is allocated, follow the below steps in order:
    1. Test PFS (Arm 3 versus Arm 1) at level \( \alpha \),
       - If it's rejected, proceed to Step 2,
       - Otherwise stop and accept subsequent hypotheses,
    2. Test PFS (Arm 2 versus Arm 1) and OS (Arm 3 versus Arm 1) using a Hochberg procedure at level \( \alpha \),
       - Test PFS (Arm 2 versus Arm 1) at level \( \alpha/2 \) and let \( P \) be the \( P \) value of the test,
       - If \( P \leq \alpha/2 \), reject PFS (Arm 2 versus Arm 1) and test OS (Arm 3 versus Arm 1) at level \( \alpha \),
       - If \( \alpha/2 < P \leq \alpha \), test OS (Arm 3 versus Arm 1) at level \( \alpha \) (reject PFS [Arm 2 versus Arm 1] if OS [Arm 3 versus Arm 1] is rejected at \( \alpha \), otherwise accept both hypotheses and stop),
       - If \( P > \alpha \), accept PFS (Arm 2 versus Arm 1) and test OS (Arm 3 versus Arm 1) at level \( \alpha/2 \),
       - If both PFS (Arm 2 versus Arm 1) and OS (Arm 3 versus Arm 1) are rejected, proceed to Step 3, otherwise stop and accept subsequent hypotheses,
    3. Test OS (Arm 2 versus Arm 1) at level \( \alpha \),
       - If it's rejected, proceed to Step 4, otherwise stop and accept subsequent hypotheses,
4. Test DRS (Arm 3 versus Arm 1) and DRS (Arm 2 versus Arm 1) using a Hochberg procedure at level $\alpha$,
   ○ For the $BRCA$-deficient population, assuming $\alpha$ (0.0125 in this case) is allocated, hypotheses will be tested by a fixed-sequence procedure in the following testing order:
     1. PFS (Arm 3 versus Arm 1),
     2. PFS (Arm 2 versus Arm 1),
     3. OS (Arm 3 versus Arm 1),
     4. OS (Arm 2 versus Arm 1),
     5. DRS (Arm 3 versus Arm 1),
     6. DRS (Arm 2 versus Arm 1).

Scenario 2: If $BRCA$-deficient subjects account for less than 18% of the whole population:

- The entire one-sided type I error of 0.025 will be allocated to the whole population only and the hypotheses in the $BRCA$-deficient population will not be formally tested, but will be analyzed as exploratory analyses.
- The testing procedures of the hypotheses within the whole population will be the same as those described in Scenario 1, with $\alpha$ being 0.025.

For Scenario 1, between the two populations (whole population and $BRCA$-deficient population), a one-sided $\alpha$ of 0.0125 is allocated to each population based on the Bonferroni adjustment so that the total one-sided $\alpha$ is 0.025; within each population, a gate-keeping procedure is used to control the type I error rate at 0.0125. Therefore, the overall type I error is controlled at one-sided 0.025 level.

For Scenario 2, only the whole population will be formally tested and a gate-keeping procedure is used to test all of the hypotheses within the whole population, so the overall type I error rate is controlled at one-sided 0.025 level.
The final testing procedure will be either Scenario 1 or Scenario 2, depending on the proportion of $BRCA$-deficient subjects in the whole population, which will be based on the $BRCA$-deficient test results obtained prior to the database lock. If the proportion of the $BRCA$-deficient subjects is below the target of 24% under Scenario 1, considerations may be given to increase the sample size in the whole population or follow the subjects for longer duration to ensure sufficient power to test the primary objective in the $BRCA$-deficient population. Details of the potential increase in sample size will be determined prior to completion of enrollment and included in a final statistical analysis plan prior to the data base lock.

The final multiple testing procedure will be based on the pre-specified rules as above, and will be determined in a blinded fashion before the database is locked. It will be also specified in the statistical final analysis plan (SAP) before the database is locked. The algorithm to determine the final testing procedure only utilizes the testing results of the $BRCA$-deficient status of the subjects during the study, and does not utilize any efficacy or safety data, so no bias or inflation of type I error is expected.

8.1.5 Safety

The safety of veliparib containing arms 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 were randomized but did not receive study drug (veliparib or placebo containing regime) will not be included in the analyses of safety.

8.1.5.1 Duration of Study Drug

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

8.1.5.2 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 summarized by preferred terms within a System and Organ Class according to the most current Medical Dictionary for Regulatory Activities (MedDRA) dictionary. In addition, the percentage of subjects experiencing an adverse event at a NCI CTCAE Version 4.0 toxicity grade, and relationship to study drug will be provided. The percentages of subjects experiencing an adverse event will be compared between Arm 2 and 3 versus Arm 1 using Fisher's exact test.

The frequencies and percentages of subjects experiencing a treatment-emergent Grade 3 or Grade 4 peripheral neuropathy will be summarized and compared between the treatment arms using CMH test stratified by the stratification factors.

8.1.5.3 Serious Adverse Events

Serious adverse events will be summarized using the same methods as Adverse Events described above.

8.1.5.4 Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of the last dose of study drug, (2) for deaths occurring more than 30 days of 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.

8.1.5.5 Analyses of Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, then an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline
measurement or do not have any post-baseline measurements will not be included. Comparisons of the differences in mean changes from baseline for Arm 2 and 3 versus Arm 1 will be made using ANOVA with treatment group as the factor for each post-baseline visit.

8.1.5.6 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 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 last post-baseline measurement collected no more than 30 days after the last dose of study drug.

The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post baseline grades of 3 to 4 will be compared between Arm 2 and 3 and Arm 1 using Fisher's exact test.

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.

8.1.6 Pharmacokinetic Analysis

The pharmacokinetic parameters of rate of absorption (Ka), apparent volume of distribution (V/F) and oral clearance (CL/F) for veliparib may be estimated using a nonlinear mixed-effect population modeling approach with NONMEM software and reported in a separate pharmacokinetic report.
8.2 Determination of Sample Size

The study aims to power for the PFS and OS endpoints in both the whole and the BRCA-deficient populations.

8.2.1 Total Sample Size

The trial will enroll approximately 1100 subjects (with 1:1:1 randomization ratio for Arm 1:Arm 2:Arm 3) in the whole population, including approximately 264 subjects with BRCA-deficient status (assuming 24% of the subjects in the whole population are BRCA-deficient) to power the hypotheses specified in the whole and BRCA-deficient populations. Detailed sample size calculation information for each endpoint of the whole and BRCA-deficient populations is provided in Table 18.

8.2.2 For the Hypotheses in the Whole Population

**PFS (Arm 3 Versus Arm 1):**

Testing of PFS (Arm 3 versus Arm 1, as shown in Figure 4 and Table 15) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the whole population. The power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a PFS hazard ratio of 0.7 in Arm 3 versus Arm 1, up to a total of 446 events will be needed for the test to have 94% power to detect a statistically significant treatment effect. Assuming a median PFS of 15.5 months in Arm 1 and an enrollment period of 18 months, and taking into account a dropout rate of 10%, approximately 367 subjects are needed per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) in order to have a matured PFS endpoint at around 36 months.

**PFS (Arm 2 Versus Arm 1):**

Testing of PFS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the PFS event rate relative to reference...
regimen in Arm 1 (C/P + placebo → placebo) in the whole population. This hypothesis will be assessed with the stratified log-rank test at a one sided alpha level of 0.00625 or 0.0125 under the scenario 1, based on the Hochberg procedure specified in Section 8.1.4. The power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.00625. Assuming a PFS hazard ratio of 0.7 in Arm 2 versus Arm 1, up to a total of 446 events will be needed for the test to have 90% power to detect a statistically significant treatment effect based on the alpha level of 0.00625. Assuming median PFS of 15.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10%, approximately 367 subjects are needed per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) to have a mature PFS endpoint at around 36 months. The actual alpha level will be determined by the test result for OS (Arm 3 versus Arm 1) based on the Hochberg testing procedure specified in Section 8.1.4. The alpha level of 0.00625 in this power calculation is based on the conservative scenario that assumes the hypothesis for OS (Arm 3 versus Arm 1) is not rejected.

**OS (Arm 3 Versus Arm 1):**

Testing of OS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the whole population. This hypothesis will be assessed with the stratified log-rank test at a one sided alpha level of 0.00625 or 0.0125 under scenario 1, based on the Hochberg procedure specified in Section 8.1.4. The power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.00625. Assuming an OS hazard ratio of 0.7 in Arm 3 versus Arm 1, up to a total of 350 events will be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming a median OS of 41.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10% and an efficacy interim analysis that occurs at the time of the PFS analysis, approximately 367 subjects are needed per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) to have a mature OS endpoint at around 58 months. The actual alpha level will be determined by the $P$ values for the test result of PFS (Arm 2 versus Arm 1) based on the
Hochberg procedure specified in Section 8.1.4. The alpha level of 0.00625 in this power calculation is based on the conservative scenario that assumes the hypothesis for PFS (Arm 2 versus Arm 1) is not rejected.

**OS (Arm 2 Versus Arm 1):**

Testing of OS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the whole population. The power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.0125. Assuming an OS hazard ratio of 0.7 in Arm 2 versus Arm 1, up to a total of 350 events will be needed for the test to have 86% power to detect a statistically significant treatment effect. Assuming a median OS of 41.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10% and an efficacy interim analysis that occurs at the time of the PFS analysis, approximately 367 subjects are needed per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) to have a mature OS endpoint at around 58 months. OS (Arm 2 versus Arm 1) will be tested only if all of the previous hypotheses are rejected based on the Hochberg procedure specified in Section 8.1.4.

**8.2.3 For the Hypotheses in the BRCA-Deficient Population**

**PFS (Arm 3 Versus Arm 1):**

Testing of PFS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. The power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a hazard ratio for PFS of 0.5 in Arm 3 versus Arm 1, up to a total of 79 events will be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming median PFS of 21 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1
randomization ratio (Arm 3 versus Arm 1) are needed to have a matured PFS endpoint at around 36 months taking into account of a dropout rate of 10%.

**PFS (Arm 2 Versus Arm 1):**

Testing of PFS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. The power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a hazard ratio for PFS of 0.5 in Arm 2 versus Arm 1, up to a total of 79 events will be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming median PFS of 21 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) are needed to have a matured PFS endpoint at around 36 months taking into account of a dropout rate of 10%.

**OS (Arm 3 Versus Arm 1):**

Testing of OS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. The power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a hazard ratio for OS of 0.5 in Arm 3 versus Arm 1, up to a total of 79 events will be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming median OS of 53 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) are needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the PFS analysis and OS analysis for the whole population.
OS (Arm 2 Versus Arm 1):

Testing of OS (Arm 2 versus Arm 1) evaluates whether the veliparib containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. The power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a hazard ratio for OS of 0.5 in Arm 2 versus Arm 1, up to a total of 79 events will be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming median OS of 53 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) are needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the PFS analysis and OS analysis for the whole population.
### Table 18.  Power and Sample Size Calculation

<table>
<thead>
<tr>
<th>Type I Error</th>
<th>Population</th>
<th>No. of Subjects per Arm (N)</th>
<th>Power</th>
<th>Expected Hazard Ratio</th>
<th>No. of Events Needed for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
<th>Power</th>
<th>Expected Hazard Ratio</th>
<th>No. of Events Needed for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha = 0.0125: for PFS (Arm 3 versus Arm 1) in the whole population, and PFS and OS endpoint in the BRCA population</td>
<td>Whole</td>
<td>367</td>
<td>94%</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>86%(^a)</td>
<td>0.7</td>
<td>350</td>
<td>58</td>
</tr>
<tr>
<td>BRCA-deficient</td>
<td>88</td>
<td>80%</td>
<td>0.5</td>
<td>79</td>
<td>36</td>
<td>80%(^b)</td>
<td>0.5</td>
<td>79</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>alpha = 0.00625: for PFS (Arm 2 versus Arm 1) and OS (Arm 3 versus Arm 1) in the whole population</td>
<td>Whole</td>
<td>367</td>
<td>90%</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>80%</td>
<td>0.7</td>
<td>350</td>
<td>58</td>
</tr>
</tbody>
</table>

PFS = progression-free survival; OS = overall survival

a. Assumes an efficacy interim analysis at Month 36 with alpha spending of 0.0001. The nominal alpha for the final analysis is 0.0124.

b. Assumes 2 efficacy interim analyses (at Month 36 and Month 58, respectively) with alpha spending of 0.0001 at each of the 2 interim analyses. The nominal alpha for the final analysis is 0.0124.

Note: All calculations take into account a 10% dropout rate. An enrollment period of 18 months with linear enrollment rate is assumed. The actual endpoint mature time may vary depending on the true enrollment pattern.
8.3 Timing for Analyses and Unblinding of the Study

As shown in Table 18, the estimated PFS endpoint mature time is approximately 36 months for both the whole and the BRCA-deficient population, and the estimated OS endpoint mature time is approximately 58 months for the whole population and 77 months for the BRCA-deficient population. AbbVie will unblind the data to perform the primary analyses when required numbers of PFS endpoints are accrued in both the whole population and BRCA-deficient population. Subsequently all subjects will be followed as planned for survival and investigators and subjects will remain blinded to reduce bias. The subsequent OS analyses will occur when the required numbers of OS endpoints are accrued.

8.4 Randomization Methods

An Interactive Response Technology (IRT) system will be utilized to randomize subjects. Before the study is initiated, directions for the IRT will be provided to each site. The investigational site will contact the IRT on or prior the subject's Cycle 1 Day 1 visit and a unique randomization number will be provided.

Subject randomization will be stratified into 24 groups as defined by combining categories of the three randomization stratification factors listed as below:

1. Stage of the disease:
   - III
   - IV

2. Residual disease and choice of regimen:
   - Q3-weeks carboplatin/paclitaxel, no residual disease
   - Q3-weeks carboplatin/paclitaxel, any residual disease
   - Q-week carboplatin/paclitaxel, no residual disease
   - Q-week carboplatin/paclitaxel, any residual disease
   - Interval cytoreductive surgery, Q3-weeks carboplatin/paclitaxel
   - Interval cytoreductive surgery, Q-weeks carboplatin/paclitaxel
3. Region:
   - North America
   - Rest of the world

Cancer stage at diagnosis and maximal residual disease following cytoreductive surgery are major prognostic factors of survival. Complete (no visible residual disease) and optimal (residual disease < 1 cm) primary surgical cytoreduction is also associated with prolonged survival in advanced epithelial ovarian cancer.\textsuperscript{36,37} To control for these known prognostic factors, randomization will be stratified by (Stage III versus IV) and residual disease (any residual disease versus no visual residual disease) following initial cytoreductive surgery. Residual disease following interval cytoreduction will be captured for subjects receiving treatment with carboplatin and paclitaxel as the data will not be available at randomization but could still influence outcomes/prognosis. Randomization will also be stratified by choice of therapy to minimize the impact of potential heterogeneity between these regimens and for region to account for regional differences in treatment decisions and surgical practices.

During randomization, subjects within each of the 24 stratification groups will be randomized in a 1:1:1 ratio to treatment Arms 1, 2 and 3, respectively.

The stratification factors used for the randomization should be the last values on or prior to the date of randomization and should be consistent with those on the eCRF.

Randomization to Arms 1, 2, and 3 will occur until the required number of subjects is enrolled as defined in Section 8.2.

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 Conference 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, International Conference on Harmonization (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 and 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 main study 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 and post-therapy 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 and 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.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating 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 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 principal 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

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 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 patient management. Hence, neither the Investigator, the subject, nor the subject's physician (if different from 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.
12.1 Publication

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

13.0 Completion of the Study

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

The Investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

The global end-of-study is defined as the date of the last subject's last visit, or the date of the last subject's last follow-up contact, whichever is later. The sponsor may also end the study upon confirmation that the primary endpoint was statistically met.
14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for veliparib and the product labeling for carboplatin and paclitaxel.

2. I have read this protocol and agree that the study is ethical.

3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.

4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Protocol Date: 18 December 2014

__________________________________________________________
Signature of Principal Investigator Date

__________________________________________________________
Name of Principal Investigator (printed or typed)
15.0 Reference List


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

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Functional Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Clinical</td>
</tr>
<tr>
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<td>Pharmacokinetics</td>
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<td>GDSM</td>
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</table>
Appendix C. Ovarian Surgical Procedure

Purpose: Maximum resection of ovarian cancer and to obtain an accurate staging of ovarian cancer to allow selection of optimal postoperative therapy.

Indications: All cases of ovarian cancer, including borderline tumors of the ovary.

Contraindications: Poor surgical risk.

Content of Procedure

1. The abdominal incision must be adequate to explore the entire abdominal cavity and allow safe cytoreductive surgery. A vertical incision is recommended but not required.

2. The volume of any free peritoneal fluid should be estimated. Free peritoneal fluid is to be aspirated for cytology. If no free peritoneal fluid is present, separate peritoneal washings will be obtained from the pelvis, paracolic gutters and infradiaphragmatic area. These may be submitted separately or as a single specimen. Subjects with Stage III or IV disease do not require cytologic assessment.

3. All peritoneal surfaces including the undersurface of both diaphragms and the serosa and mesentery of the entire gastrointestinal tract will be visualized and palpated for evidence of metastatic disease.

4. Careful inspection of the omentum and removal if possible of at least the infracolic omentum will be accomplished. At minimum a biopsy of the omentum must be obtained.

5. If possible an extrafascial total abdominal hysterectomy and bilateral salpingo oophorectomy will be performed. If this is not possible, a biopsy of the ovary and sampling of the endometrium must be performed. The surgery section (§4.1) in selected ovarian cancer protocols may permit a unilateral salpingo oophorectomy.

6. If possible, all remaining gross disease within the abdominal cavity is resected.
7. If there is no evidence of disease beyond the ovary or pelvis, the following must be done.
   a. Peritoneal biopsies from:
      i. Cul-de-sac
      ii. Vesical peritoneum
      iii. Right and left pelvic sidewalls
      iv. Right and left paracolic gutters
   b. Biopsy or scraping of the right diaphragm
   c. Selective bilateral pelvic and periaortic lymph node sampling.

8. Selective pelvic and periaortic lymph node sampling must be done in the following situations:
   a. Subjects with tumor nodules outside the pelvis which are ≤ 2 cm (presumed Stage IIIB) must have bilateral pelvic and periaortic lymph node biopsies
   b. Subjects with Stage IV disease and those with tumor nodules outside the pelvis which are greater than 2 cm do not require pelvic or periaortic lymph node biopsies unless the only nodule greater than 2 cm is a lymph node in which case it must be biopsied.

Histologically confirmed metastatic nodal disease makes further node sampling unnecessary.
Appendix D. General Chemotherapy Guidelines

- A subject will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

- It will be acceptable for individual chemotherapy doses to be delivered within a 24-hour window before and after the protocol-defined date for "Day 1" treatment. If the treatment due date is a Friday, and the subject cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (Day 3 past due).

- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.

- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately ± 5% of the calculated dose).

- Chemotherapy doses are required to be recalculated if the subject has a weight change of greater than or equal to 10%. Subjects are permitted to have chemotherapy doses recalculated for < 10% weight changes.
Appendix E. Carboplatin Dose Calculation Instructions

Dosing of Carboplatin:

1. The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

2. The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 × ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

3. Carboplatin doses are required to be recalculated if the subject has a weight change of greater than or equal to 10%. Subjects are permitted to have chemotherapy doses recalculated for < 10% weight changes.

4. At the time of dose modification, if the subject's age had changed (the subject has had a birthday), the site can use the current age.

5. In subjects with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a minimum value of 0.7 mg/dl. For trials where subjects enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.
CALVERT FORMULA:

Carboplatin dose (mg) = target AUC × (GFR + 25)

**NOTE:** the GFR used in the Calvert formula should not exceed 125 ml/min. **Maximum** carboplatin dose (mg) = target AUC (mg/min) × 150 ml/min. **The maximum allowed doses of carboplatin are:**

- AUC 6 = 900 mg
- AUC 5 = 750 mg
- AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

\[
\text{Creatinine Clearance (mL/min)} = \left[\frac{140 - \text{Age (years)}}{72}\right] \times \text{Weight (kg)} \times 0.85 \times \text{serum creatinine (mg/dl)}
\]

**Notes:**

1. Weight in kilograms (kg)
   a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: [http://www.nhlbisupport.com/bmi/](http://www.nhlbisupport.com/bmi/)
   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25
   c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**
   d. Adjusted weight calculation:
      - Ideal weight (kg) = (((Height (cm)/2.54) – 60) × 2.3) + 45.5
• Adjusted weight (kg) = (Actual weight – Ideal weight) × 0.40) + Ideal weight

2. The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity:

If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

Adverse Effects That May Be Associated with An Uneventful Procedure

<table>
<thead>
<tr>
<th>System</th>
<th>Grade (up to and including)</th>
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<tbody>
<tr>
<td>Hematopoietic</td>
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<tr>
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<td>Gastrointestinal</td>
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<td>Fever</td>
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<tr>
<td>Allergic</td>
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Appendix F. FIGO Stage Grouping for Primary Carcinoma of the Ovary

These categories are based on findings at clinical examination and/or surgical exploration. The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspicious areas outside the pelvis.

<table>
<thead>
<tr>
<th>STAGE I: Tumor confined to ovaries</th>
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<tbody>
<tr>
<td>IA</td>
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<td>IC1</td>
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<td>IC2</td>
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<tr>
<td>IC3</td>
</tr>
</tbody>
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**STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer**

| IIA | Extension and/or implant on uterus and/or fallopian tubes |
| IIB | Extension to other pelvic intraperitoneal tissues |

**STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastases to the retroperitoneal lymph nodes**

<table>
<thead>
<tr>
<th>IIIA (positive retroperitoneal lymph nodes and/or microscopic metastases beyond the pelvis)</th>
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<tbody>
<tr>
<td>IIIA1</td>
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<tr>
<td>IIIA1 (i)</td>
</tr>
<tr>
<td>IIIA1 (ii)</td>
</tr>
<tr>
<td>IIIA2</td>
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<td>IIIB</td>
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</table>
IIIC | Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen

STAGE IV: Distant metastases excluding peritoneal metastases

IVA | Pleural effusion with positive cytology

IVB | Hepatic and/or splenic parenchymal metastases, metastases to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Other major recommendations are as follows:

- Histologic type including grading should be designated at staging
- Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible
  - Tumors that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to Stage II if tumor cells are histologically proven to be present in the adhesions
Appendix G. Guidance for Identifying High Grade Serous Carcinoma

The following should be considered when determining a diagnosis of high grade serous carcinoma:

- Diagnosed as Grade 2 or Grade 3 serous carcinoma using Shimizu-Silverberg grading scheme.
- Wide spectrum of architectural patterns, including solid, glandular, and cribriform patterns, and patterns resembling transitional cell carcinoma. At least focal papillae and micropapillae with gaping and slit-like architectural features are present.
- Histologic variants such as transitional cell carcinoma or serous carcinoma with microcystic features.
- High nuclear grade, with extreme nuclear size variability (> 5×).
- More than 10 mitotic figures per 10 high power fields.
- Typically disseminated at presentation. WT1 expression should be sought for Stage I tumors.
- WT1, p53, and/or p16 overexpression may be sought if the differential diagnosis includes low grade serous carcinoma, endometrioid carcinoma, or clear cell carcinoma.
- Can be distinguished from serous borderline tumor by the presence of high nuclear grade if obvious stromal invasion is not identified after examination of multiple sections.
## Appendix H. Adverse Events Expected Due to Ovarian, Fallopian Tube, or Primary Peritoneal Cancer or Progression of Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

<table>
<thead>
<tr>
<th>Adverse Events Expected Due to Ovarian Cancer or Progression of Ovarian Cancer*</th>
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<tbody>
<tr>
<td>Abdominal pain</td>
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<tr>
<td>Abdominal distension</td>
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<tr>
<td>Ascites</td>
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<tr>
<td>Intestinal obstruction</td>
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<tr>
<td>Colonic obstruction</td>
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<tr>
<td>Small intestinal obstruction</td>
</tr>
<tr>
<td>Pleural effusion</td>
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<td>Constipation</td>
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* Coding Guidelines for MedDRA Term Selection, AbbVie Global Pharmaceutical Research and Development (GPRD), Global Pharmacovigilance and Clinical Project Team, current version on file at AbbVie.
### Document Approval

Study M13694 - A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel with or without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer - 18Dec2014

**Version:** 2.0  **Date:** 22-Dec-2014 02:55:22 PM  **Abbott ID:** 12222014-00F9F680A395D2-00002-en

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Clinical Study Protocol M13-694

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Incorporating Amendment 1

AbbVie Investigational Product: Veliparib (ABT-888)

Date: 26 May 2016

Development Phase: 3

Study Design: This is a Phase 3, placebo-controlled, randomized study of veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in subjects with untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.

EudraCT Number: 2014-005070-11

Investigator: Multicenter Study: Site Investigator information is on file at AbbVie Inc. (AbbVie)

Sponsor: AbbVie Inc. (AbbVie)*

Collaborative Partners: This protocol was designed and developed in collaboration with the Gynecologic Oncology Group (GOG) Foundation. The study is also being conducted in collaboration with the Australia New Zealand Gynecologic Oncology Group (ANZGOG).

GOG Study Number: PROTOCOL GOG-3005
Sponsor/Emergency Contact:

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

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

**Confidential Information**

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1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

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The purpose of this amendment is to modify the starting dose of maintenance therapy and to clarify language as follows:

- Allow subjects to begin the Maintenance Phase with single agent veliparib/placebo at 300 mg BID. Escalation to 400 mg BID is permitted at the Investigator's discretion. A study visit will be required to determine if each subject is able to escalate to 400 mg BID.
  
  **Rationale:** Recent VeliBRCA study data supports the 300 mg BID dose with similar efficacy to the GOG280 study. Early discontinuations have been observed during the transition from 150 mg to 400 mg blinded study drug, after chemotherapy is completed.

- Specify study procedures for subjects who discontinue therapy prior to progression.
  
  **Rationale:** For clarity

- Specify study procedures for subjects who discontinue study therapy due to progression.
  
  **Rationale:** For clarity

- Clarify the collection time frame for scans during the Combination and Maintenance Phases, including post-operative scans for interval surgery subjects.
  
  **Rationale:** For clarity

- Add Japan-specific protocol language requirements.
  
  **Rationale:** To facilitate the inclusion of Japanese sites in the study.

- Clarify that the optional tissue sample collection does not require a separate biopsy procedure and may be collected during routine procedures
  
  **Rationale:** For clarity
● Clarify pregnancy test requirements for women of childbearing potential and women not of childbearing potential.

  **Rationale:** For clarity

● Allow twice daily dosing to occur 8 – 12 hours apart.

  **Rationale:** Pharmacokinetic data demonstrates minimal changes in $C_{\text{max}}$ and $C_{\text{min}}$; therefore, variation in dosing interval will be allowed.

● Remove urobilinogen, bilirubin, uric acid and LDH tests from the list of required chemistries.

  **Rationale:** Lab tests are not performed routinely in this patient population.

● Correct typographical errors and minor language or word revisions as needed throughout the document.

  **Rationale:** For clarity

● Add requirement for site un-blinding requests.

  **Rationale:** Establish a process for unblinding requests from sites.

● Modifications made throughout the dose reductions and delays section of the protocol (Section 5.7, Dose Reductions or Delays)

  **Rationale:** For clarity

● Clarify AE and SAE collection period during the phases of the study.

  **Rationale:** For clarity

An itemized list of all changes made to the protocol under this amendment can be found in Appendix I.
1.0 Title Page

Clinical Study Protocol M13-694

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Incorporating Amendments 1 and 2

AbbVie Investigational Product: Veliparib (ABT-888)
Date: 21 September 2016
Development Phase: 3
Study Design: This is a Phase 3, placebo-controlled, randomized study of veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in subjects with untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.
EudraCT Number: 2014-005070-11
Investigator: Multicenter Study: Site Investigator information is on file at AbbVie Inc. (AbbVie)
Sponsor: AbbVie Inc. (AbbVie)*
Collaborative Partners: This protocol was designed and developed in collaboration with the Gynecologic Oncology Group (GOG) Foundation. The study is also being conducted in collaboration with the Australia New Zealand Gynecologic Oncology Group (ANZGOG).
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Sponsor/Emergency Contact:

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The purpose of this amendment is to modify the starting dose of maintenance therapy and to clarify language as follows:

- Adjust stratification factors to include germline BRCA (gBRCA) mutation status (gBRCA positive versus gBRCA negative or Unknown).

  **Rationale:** During the IDMC review of the study's randomization across the treatment arms, an imbalance of BRCA positive subjects in one or more of the three treatment groups was identified. One of the suggested recommendations was to add germline BRCA (gBRCA) mutation status as a randomization stratification factor. The IDMC recommendation is to ensure that any potential treatment effect will be interpretable across the three treatment groups and will not be confounded by subjects' BRCA tumor mutation status. AbbVie agreed with the proposed IDMC’s recommendation to add gBRCA as a stratification factor, and adjusted the regional stratification factor to prevent over-stratification. The proposed changes to the protocol do not impact the safety of subjects, the scope of the investigation, or significantly impact the scientific quality of the study.

- Update Table 3, Schedule of Pharmacogenetic and Pharmacodynamic Procedures.

  **Rationale:** Clarify and align with stratification adjustment.

- Update Figure 1, Study Design.

  **Rationale:** Reflect stratification adjustment.

- Update Table 12, Q-Week Schedule Dose Modifications for Dose-Limiting Hematologic Toxicity, Reduced ANC (1000 – 1499/mm$^3$) or Reduced Platelets (75,000 – 99,000/mm$^3$) on Day 1, or Cycle Delay > 7 Days due to Hematologic Toxicity.
- **Rationale**: Typographical errors.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix I.
1.0 Title Page

Clinical Study Protocol M13-694

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

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

AbbVie Investigational Product: Veliparib (ABT-888)
Date: 14 November 2016
Development Phase: 3
Study Design: This is a Phase 3, placebo-controlled, randomized study of veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in subjects with untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.
EudraCT Number: 2014-005070-11
Investigator: Multicenter Study: Site Investigator information is on file at AbbVie Inc. (AbbVie)
Sponsor: AbbVie Inc. (AbbVie)*
Collaborative Partners: This protocol was designed and developed in collaboration with the Gynecologic Oncology Group (GOG) Foundation. The study is also being conducted in collaboration with the Australia New Zealand Gynecologic Oncology Group (ANZGOG).
GOG Study Number: PROTOCOL GOG-3005
Sponsor/Emergency Contact:

Medical Monitor:

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The primary purpose of this amendment is to clarify the use of growth factors and modify the threshold for starting cycles in maintenance phase as follows:

- Add language that will allow G-CSF to be administered per institutional guidelines during the combination phase.  
  **Rationale:** *To allow investigators the flexibility to treat patients with G-CSF as per their institutional guidelines.*
- Clarify the language in Inclusion Criterion 9.  
  **Rationale:** *The intention is to be inclusive of subjects with measurable and non-measurable disease.*
- Allow subjects to start Cycle 8 and beyond with an ANC of 1,000/mm$^3$ and a platelet count of 75,000/mm$^3$ (Section 5.7.2, Veliparib/Placebo Monotherapy Dose Reductions and Delays (Cycles 7 – 36)).  
  **Rationale:** *This will potentially allow for more continuous administration of study drug in maintenance phase and adequate time for bone marrow recovery after combination phase chemotherapy. To date, few subjects have delayed the start of study drug in Cycle 8 and beyond due to neutropenia and thrombocytopenia.*
- Update Table 3, Schedule of Pharmacogenetic and Pharmacodynamic Procedures, to include the optional whole blood sample collected on Cycle 3 Day 1 from each subject who consents to provide samples for exploratory research.
**Rationale:** To align Table 3 with guidance provided in Section 5.3.1.2 subsection: Samples for Pharmacogenetic Exploratory Research.

- Change of the sponsor/emergency contact from [Redacted], MD, PhD to [Redacted] MD throughout the protocol.

**Rationale:** Personnel change.

- A general inbox [Redacted] will replace the individual medical monitor and sponsor contact inboxes.

**Rationale:** To provide sites with a single email point of contact for all medical communications, as well as an archive of all email communications.

- Update Appendix D (General Chemotherapy Guidelines) to clarify that the Fujimoto, DuBois, or institutional standard formulas may be used to calculate BSA.

**Rationale:** This will allow sites flexibility in calculating BSA.

In addition, this amendment incorporates Administrative Changes 1 and 2 as follows:

**Administrative Change 1:**

- The following changes were made in administrative change 1 and are now being incorporated in protocol amendment 3.
  - Change of the medical monitor contact to Robert Coleman, MD throughout the protocol.
    **Rationale:** Personnel change.
  - Clarify that bicarbonate should be drawn in Japan, if the test is available.
    **Rationale:** This was updated to account for practice differences in Japan.

**Administrative Change 2:**

- The following changes were made in Administrative Change 2 and are now being incorporated in protocol Amendment 3.
  - Adjust stratification factors to include germline BRCA (gBRCA) mutation status (gBRCA positive versus gBRCA negative or Unknown).
**Rationale:** During the IDMC review of the study's randomization across the treatment arms, an imbalance of BRCA positive subjects in one or more of the three treatment groups was identified. One of the suggested recommendations was to add germline BRCA (gBRCA) mutation status as a randomization stratification factor. The IDMC recommendation is to ensure that any potential treatment effect will be interpretable across the three treatment groups and will not be confounded by subjects' BRCA tumor mutation status. AbbVie agreed with the proposed IDMC's recommendation to add gBRCA as a stratification factor, and adjusted the regional stratification factor to prevent over-stratification. The proposed changes to the protocol do not impact the safety of subjects, the scope of the investigation, or significantly impact the scientific quality of the study.

- Update **Table 3**, Schedule of Pharmacogenetic and Pharmacodynamic Procedures.
  **Rationale:** Clarify and align with stratification adjustment.

- Update **Figure 1**, Study Design.
  **Rationale:** Reflect stratification adjustment.

- Update **Table 12**, Q-Week Schedule Dose Modifications for Dose-Limiting Hematologic Toxicity, Reduced ANC (1000 – 1499/mm$^3$) or Reduced Platelets (75,000 – 99,000/mm$^3$) on Day 1, or Cycle Delay > 7 Days due to Hematologic Toxicity.
  **Rationale:** Typographical errors.

An itemized list of all changes made to the protocol under this amendment can be found in **Appendix 1**.
Clinical Study Protocol M13-694

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

AbbVie Investigational Product: Veliparib (ABT-888)

Date: 24 March 2017

Development Phase: 3

Study Design: This is a Phase 3, placebo-controlled, randomized study of veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in subjects with untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.

EudraCT Number: 2014-005070-11

Investigator: Multicenter Study: Site Investigator information is on file at AbbVie Inc. (AbbVie)

Sponsor: AbbVie Inc. (AbbVie)*

Collaborative Partners: This protocol was designed and developed in collaboration with the Gynecologic Oncology Group (GOG) Foundation. The study is also being conducted in collaboration with the Australia New Zealand Gynecologic Oncology Group (ANZGOG).

GOG Study Number: PROTOCOL GOG-3005
Sponsor/Emergency Contact:

Medical Monitor:

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<td>Amendment 3</td>
<td>14 November 2016</td>
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</table>

The primary purpose of this amendment is to further clarify dose modification guidance as follows:

- Formatting changes were made to the Dose Reductions or Delays section (Section 5.7) to clarify and simplify instructions for dose limiting hematological toxicities, and the guidelines for hematological and non-hematological toxicity.
  
  **Rationale:** For clarity.

- Provide guidance on veliparib/placebo administration when subjects undergo elective surgeries (Section 5.2.3.2, Concomitant Therapy).
  
  **Rationale:** To align with guidance currently provided for veliparib/placebo administration around interval surgery.

- Update Table 2, Study Procedures for Long Term Follow-Up Phase, to include the CA-125 blood sample collection in the Long Term Follow-Up Phase.
  
  **Rationale:** To clarify and align Table 2 with Section 5.3.3.1 and RECIST 1.1 response criteria for non-target lesions.

- Clarify that subjects who discontinue veliparib/placebo during combination may restart veliparib/placebo in maintenance (Section 5.1, Overall Study Design and Plan: Description).
  
  **Rationale:** For clarity.
• Clarify the processing time for serum marker blood collection so it aligns with the lab manual (Section 5.3.1.2, Collection and Handling of Biomarker and Optional Exploratory Research Samples).

**Rationale:** *To align protocol guidance with that provided in the ICON Lab Manual.*

• Add a reference for a prophylactic regimen when an iodine contrast allergy is known.

**Rationale:** *Provide sites with guidance on treating patients with known or suspected CT contrast sensitivity.*

• Correct typographical errors and minor language or word revisions as needed throughout the document.

**Rationale:** *For clarity.*

• Specify the imaging modality required when a subject has a known contrast allergy.

**Rationale:** *Clarify the modality that should be used for the disease pathology.*

An itemized list of all changes made to the protocol under this amendment can be found in Appendix I.
Clinical Study Protocol M13-694

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Incorporating Administrative Changes 1, 2, and 3 (Japan Only) and Amendments 1, 2, 3, 4 and 5

AbbVie Investigational Product: Veliparib (ABT-888)
Date: 10 December 2018
Development Phase: 3
Study Design: This is a Phase 3, placebo-controlled, randomized study of veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in subjects with untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.
EudraCT Number: 2014-005070-11
Investigator: Multicenter Study: Site Investigator information is on file at AbbVie Inc. (AbbVie)
Sponsor: AbbVie Inc. (AbbVie)*
Collaborative Partners: This protocol was designed and developed in collaboration with the Gynecologic Oncology Group (GOG) Foundation. The study is also being conducted in collaboration with the Australia New Zealand Gynecologic Oncology Group (ANZGOG).
GOG Study Number: PROTOCOL GOG-3005
Sponsor/Emergency Contact:

Medical Monitor:

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

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

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.
1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

<table>
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<tr>
<th>Protocol</th>
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<tr>
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<td>24 March 2017</td>
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<td>Administrative Change 3 (Japan Only)</td>
<td>17 May 2018</td>
</tr>
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</table>

The primary purpose of this amendment is to add further subgroup analysis to the protocol:

- Incorporate analysis of the Homologous Recombination Deficient (HRD) population; update efficacy endpoints and statistical methods used to evaluate efficacy endpoints throughout the protocol
  **Rationale:** Expand analysis to investigate whether homologous recombination deficiency, in addition to BRCA deficiencies, yields improved outcomes with or without the addition of veliparib in combination with chemotherapy and in maintenance.

- Update Long Term Follow Up Phase section, and Table 2, Study Procedures for Long Term Follow Up Phase, to remove the requirement for Chemistry and Hematology Labs in the Long Term Follow Up Phase
  **Rationale:** These laboratory values are not needed in this phase in order to reduce patient burden.

- Clarify PRO collection schedule in Long Term Follow Up and Survival Phases
  **Rationale:** Provide clarity to these sections to improve compliance with study assessments.

- Clarify the terminology of somatic BRCA and sBRCA to tissue-based BRCA and tBRCA throughout the protocol.
**Rationale:** The BRCA testing done on the tissue samples identifies deleterious or suspected deleterious mutations in BRCA1 or BRCA2 using centralized testing. Somatic BRCA and sBRCA were modified to tissue-based BRCA and tBRCA, respectively, for accuracy. The assay used in this study evaluates tissue-based BRCA, and not somatic BRCA mutations.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix I.
Clinical Study Protocol M13-694

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Incorporating Administrative Changes 1, 2, and 3 (Japan Only) and Amendments 1, 2, 3, 4, 5 and 6

AbbVie Investigational Product: Veliparib (ABT-888)

Date: 24 April 2019

Development Phase: 3

Study Design: This is a Phase 3, placebo-controlled, randomized study of veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in subjects with untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.

EudraCT Number: 2014-005070-11

Investigator: Multicenter Study: Site Investigator information is on file at AbbVie Inc. (AbbVie)

Sponsor: AbbVie Inc. (AbbVie)*

Collaborative Partners: This protocol was designed and developed in collaboration with the Gynecologic Oncology Group (GOG) Foundation. The study is also being conducted in collaboration with the Australia New Zealand Gynecologic Oncology Group (ANZGOG).

GOG Study Number: PROTOCOL GOG-3005
*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

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

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.
1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

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<td>10 December 2018</td>
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The purpose of this amendment is to:

- Provide estimated number of events needed in treatment Arms 1 and 3 to trigger the primary analyses of PFS in the BRCA-deficient, HRD, and whole populations. Provide power calculations for the comparison of two treatment arms for PFS using 391 events in the whole population (Section 8.3, Table 18 and Table 19).

**Rationale:** Section 8.3 language in protocol Amendment 5 did not explicitly specify the threshold of events sufficient to trigger the primary analysis. Modified language provides clarification on estimated number of events needed to trigger the primary analyses in the BRCA-deficient, HRD, and whole populations. Triggering the primary PFS analysis with 391 progression events in the whole population is based on review of original estimates, recently observed decrease in event accrual, and determination of enough events in the whole population that would retain at least 90% power to detect a hazard ratio of 0.70 in all testing scenarios. Table 18 and Table 19 are updated to show power for the comparison of two treatment arms with 391 PFS events in the whole population and Section 8.2 provides further rationale. These changes are also finalized in the statistical analysis plan and made before database lock and availability of results. The proposed changes
have no impact to the number of subjects enrolled and study activities. The minor change in power to the whole population will have no significant impact on proposed primary or secondary statistical analyses, study conduct, benefit-risk assessment, nor overall scientific validity of the study.

- Clarify that blinded independent central review of tumor assessment imaging will be performed as a sensitivity analysis as described in the statistical analysis plan (Section 5.3.1.1).

  **Rationale:** Updated for consistency with current procedures.

- Clarify the following statistical methods in Section 8.1: secondary efficacy endpoints regarding PFS comparison between treatment Arms 1 and 2 (Section 8.1.2.2), PFS2 definition (Section 8.1.2.3), and DRS scores in Table 17 (Section 8.1.4).

  **Rationale:** Secondary endpoints of PFS between treatment Arms 1 and 2 for all populations was inadvertently deleted from Section 8.1.2.2 in protocol Amendment 5, though it was retained in synopsis and other sections of protocol; this is added back for clarity. PFS2 definition updated to be consistent with current regulatory guidance documents. Clarify in Table 17 that DRS scores will be tested as a secondary endpoint but will not be in the formal testing hierarchy.

- Clarify that additional statistical details regarding the primary and secondary analyses will be documented in the SAP

  **Rationale:** Clarification that SAP will be primary document for statistical analyses and this will be finalized prior to unblinding.

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

<table>
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<tr>
<th>AbbVie Inc.</th>
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<tr>
<td>Name of Study Drug: Veliparib (ABT-888)</td>
<td>Phase of Development: 3</td>
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<tr>
<td>Name of Active Ingredient: Veliparib</td>
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**Protocol Title:** A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

**Objectives:**
The primary objective of the study is to evaluate whether progression-free survival (PFS) is prolonged when veliparib is added to carboplatin/paclitaxel and then continued as maintenance. Progression-free survival as the primary study endpoint will be evaluated in three populations: the BRCA-deficient (gBRCA and/or tBRCA), homologous recombination deficient (HRD), and whole population, as multiple primary endpoints. Secondary objectives include PFS with veliparib in combination with chemotherapy versus chemotherapy alone, overall survival (OS), safety of all three arms, and disease related symptom (DRS) scores in the BRCA-deficient, HRD, and whole population.

**Investigator:** Multicenter

**Study Sites:** Approximately 300 sites

**Study Population:** Female subjects with previously untreated Stage III or IV high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.

**Number of Subjects to be Enrolled:** Approximately 1100

**Methodology:**
This is a Phase 3, randomized, placebo-controlled study to evaluate the efficacy and tolerability of veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in the above stated study population. The study will consist of five phases: the Pre-Therapy Phase (Screening), a Combination Therapy Phase, a Maintenance Therapy Phase, a Long-Term Follow-Up Phase, and a Survival Phase.

Pre-therapy (screening) procedures will be performed within 28 days prior to randomization and Cycle 1 Day 1. A computerized tomography (CT) of the abdomen and pelvis (and chest if metastases are present) will be used by Investigators to evaluate disease status per RECIST 1.1. In addition to being reviewed by the Investigator and/or qualified site staff, radiographic scans will be sent to a central imaging center. During the Pre-Therapy Phase, Investigators will be allowed the choice of either carboplatin AUC 6 in combination with weekly paclitaxel (Q-week) or carboplatin AUC 6 in combination with every 3 weeks paclitaxel (Q3-weeks). Either of these chemotherapy regimens will be administered with either primary or interval cytoreductive surgery. The Investigator's treatment decision will be documented prior to proceeding to randomization.
Methodology (Continued):

Once pre-therapy procedures are complete and eligibility is confirmed, subjects will be randomized 1:1:1 to one of the following three arms. Subjects will be stratified by stage of disease (Stage III versus IV), residual disease and choice of regimen, region of the world (Japan versus North America or Rest of World), and gBRCA mutation status (gBRCA positive versus gBRCA negative or Unknown).

Arm 1: Carboplatin/paclitaxel plus placebo for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;

Arm 2: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;

Arm 3: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by veliparib maintenance therapy for 30 additional 21-day cycles.

During the Combination Therapy Phase, subjects will receive veliparib/placebo orally (PO) twice daily (BID) in combination with intravenous (IV) carboplatin/paclitaxel for six cycles (Cycle 1 through Cycle 6).

Subjects who complete the Combination Therapy Phase and who have not progressed will receive single-agent veliparib/placebo for an additional 30 cycles (Cycles 7 – 36) starting at 300 mg BID. If the subject tolerates 300 mg BID for 2 weeks, veliparib/placebo should be increased to 400 mg BID during the Maintenance Phase. Prior to increasing the dose of veliparib/placebo, at a minimum, vital signs and adverse event(s) must be assessed if escalation occurs outside of a routine study visit. A Therapy Completion Visit will be performed for all subjects upon completion of the Maintenance Phase, when therapy is discontinued, or if the subject is discontinued prior to therapy completion. All subjects will have one Follow-Up Visit approximately 30 days after the Therapy Completion Visit. After the Therapy Completion Visit, subjects will enter the Long-Term Follow-Up Phase.

Long Term Follow-Up assessments are conducted as follows:

Subjects who have not progressed but have discontinued or completed study therapy will remain on study. Subject status will be monitored via the collection of assessments as described in Section 5.3.1.1 and Table 2 of the protocol. Post-therapy information will be assessed every 3 months and new onset malignancy will be assessed every 6 months (or as requested by the sponsor).

Post baseline tumor assessments for all subjects randomized who have not progressed will be collected every 9 weeks, then at the end of the Combination Phase, then every 12 weeks for 2 years, then every 6 months for up to 3 years, then annually until disease progression per RECIST 1.1.

Once a subject meets an event of progression, survival and post therapy information will be collected at 3 month intervals and new-onset malignancy will be collected at 6 month intervals (or as requested by the sponsor) until the endpoint of death, the subject is lost to follow-up or until study termination by AbbVie.

Post baseline PRO assessments for all subjects will be collected according to the schedule of procedures for up to 2 years from C1D1 or until disease progression per RECIST 1.1, whichever is later.

Subjects will be followed for up to 10 years for collection of new onset malignancy.

Pharmacogenetic and Pharmacodynamic samples will be collected for biomarker research and exploratory research at designated time points throughout the study.

A detailed description of the study visits and procedures are provided in the protocol.
Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:
1. Subjects with a histologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, International Federation of Gynecology and Obstetrics (FIGO) Stage III or IV with appropriate tissue available for histologic evaluation.
2. Subjects will be required to have high-grade serous adenocarcinoma to be eligible.
3. Subject is willing to undergo testing for \( \text{gBRCA} \).
4. Subject must have adequate hematologic, renal, and hepatic function as follows:
   - Hemoglobin ≥ 9.5 g/dL (5.89 mmol/L);
   - Absolute neutrophil count greater than or equal to 1,500/µL;
   - Platelet count greater than or equal to 100,000/µL;
   - Serum creatinine ≤ 1.0 × ULN range; subjects with a serum creatinine > 1.0 × ULN range must have a creatinine clearance ≥ 60 mL/min (according to the Cockcroft-Gault equation);
   - Total bilirubin ≤ 1.5 × ULN. Subjects with Gilbert's Syndrome may have a bilirubin ≥ 1.5 × the ULN range if no evidence of biliary obstruction exists;
   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase must be less than or equal to 2.5 × ULN;
   - Albumin ≥ 3.0 g/dL.
5. Subjects with neuropathy (sensory and motor) less than or equal to Grade 1.
6. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
7. Subject is able to swallow and retain oral medication and does not have uncontrolled emesis.
8. Subjects who undergo primary cytoreductive surgery must be randomized between 1 and 12 weeks after surgery. Subjects undergoing interval surgery must have a tumor sample confirming the histological diagnosis prior to enrollment.
9. Subjects with measurable disease or non-measurable disease are eligible. Subjects may or may not have cancer-related symptoms.
10. Subject has one of the following available for PD analyses including tissue-based \( \text{BRCA} \) testing:
   - Archived diagnostic formalin-fixed paraffin embedded (FFPE) tumor tissue; or tumor tissue biopsy collected prior to Cycle 1 Day 1.
Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

1. Subjects with the following histologic cell types are ineligible: endometrioid adenocarcinoma, carcinosarcoma, undifferentiated carcinoma, mixed epithelial adenocarcinoma, adenocarcinoma not otherwise specified, mucinous adenocarcinoma, clear cell adenocarcinoma, low-grade serous adenocarcinoma, or malignant Brenner's tumor.

2. Subjects with synchronous primary endometrial cancer, or a past history of endometrial cancer unless all of the following conditions are met: endometrial cancer stage not greater than IA, no vascular or lymphatic invasion, no poorly differentiated subtypes including serous, clear cell, or other FIGO grade 3 lesions.

3. Subjects with any evidence of other invasive malignancy being present within the last 3 years (with the exception of non-melanoma skin cancer). Subjects are also excluded if their previous cancer treatment contraindictates this protocol's therapy.
   - Subjects may not receive any non-protocol specified anti-cancer therapy during the study, including maintenance therapy or hormonal therapy for breast cancer. Subjects receiving hormonal therapy (such as tamoxifen or aromatase inhibitors) will require a 7 day (1 week) washout prior to randomization.

4. Subjects who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded.

5. Subjects who have received prior chemotherapy for any abdominal or pelvic tumor are excluded.

6. Subject has a clinically significant uncontrolled condition(s), including but not limited to:
   - Uncontrolled seizure disorder, or focal or generalized seizure within the last 12 months;
   - Active infection that requires parenteral antibiotics;
   - Known active hepatitis B or hepatitis C with abnormal liver function test or organ dysfunction;
   - Symptomatic congestive heart failure; unstable angina pectoris; serious ventricular cardiac arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or serious cardiac arrhythmia requiring medication (this does not include asymptomatic atrial fibrillation with controlled ventricular rate); or myocardial infarction within the last 6 months;
   - Uncontrolled hypertension (sustained systolic blood pressure > 150 mmHg or diastolic pressure > 100 mmHg despite optimal medical management);
   - Bowel obstruction or gastric outlet obstruction. **Note:** Subjects requiring drainage gastrostomy tube and/or parenteral hydration and/or nutrition are not eligible;
   - Psychiatric illness/social situations that would limit compliance with study requirements;
   - Any medical condition which in the opinion of the Investigator places the subject at an unacceptably high risk for toxicities.

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

8. Subjects with history or evidence upon physical examination of central nervous system (CNS) disease, including primary brain tumor, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) within 6 months of Cycle 1 Day 1.

9. Subjects under the age of 18.
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<th>Veliparib (ABT-888) 50 mg or 100 mg</th>
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<td>Doses:</td>
<td>Veliparib 150 mg BID with carboplatin/paclitaxel for six 21-day cycles. Starting dose of 300 mg BID Days 1 through 21 of 21-day cycle as maintenance therapy, if tolerated, escalate to 400 mg BID (Cycle 7 through Cycle 36)</td>
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<tr>
<td>Mode of Administration:</td>
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<tr>
<td>Reference Therapy:</td>
<td>Placebo (matching 50 mg or 100 mg)</td>
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<tr>
<td>Doses:</td>
<td>Placebo BID with carboplatin/paclitaxel for six 21-day cycles. Placebo BID maintenance therapy for up to 30 additional 21-day cycles</td>
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<tr>
<td>Mode of Administration:</td>
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<tr>
<td>Duration of Treatment:</td>
<td>Subjects will receive veliparib/placebo PO BID in combination with carboplatin/paclitaxel for six 21-day cycles of therapy. Subjects who have not progressed per RECIST 1.1 will then receive maintenance therapy with veliparib/placebo PO BID for a maximum of an additional thirty 21-day cycles.</td>
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<td>Criteria for Evaluation:</td>
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<tr>
<td>Efficacy:</td>
<td>The primary objective of the study is to evaluate whether PFS is prolonged when veliparib is added to carboplatin/paclitaxel and then continued as maintenance (Arm 3 versus Arm 1). PFS as the primary study endpoint will be evaluated in three populations: the BRCA-deficient (gBRCA and/or tBRCA), HRD, and whole population, as multiple primary objectives. Secondary objectives include PFS with veliparib in combination with chemotherapy versus chemotherapy alone (no maintenance; Arm 2 versus 1), OS (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), safety of all three arms, and DRS scores (Arm 3 versus Arm 1 and Arm 2 versus Arm 1) in the BRCA-deficient, HRD, and whole populations.</td>
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<tr>
<td>Pharmacokinetic:</td>
<td>Sparse pharmacokinetic (PK) samples will be collected for the estimate of population PK parameters of veliparib such as apparent oral clearance (CL/F) and volume of distribution (V/F).</td>
</tr>
<tr>
<td>Pharmacodynamic:</td>
<td>All subjects must have a pre-therapy tumor biopsy (archived or fresh biopsy) for inclusion in the study. Genetic analysis to determine BRCA mutation status will be conducted using tissue and blood specimens to support efficacy endpoints. Biospecimens will be collected at designated time points throughout the study to conduct research with the intent of identifying biomarkers associated with subject outcome or to better characterize the disease.</td>
</tr>
<tr>
<td>Safety:</td>
<td>AbbVie will assess adverse events, laboratory data, ECGs and vital signs throughout the study. Adverse events intensity and laboratory evaluation changes will be assessed by utilizing National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.</td>
</tr>
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</table>
Statistical Methods:

Efficacy:

Primary Efficacy Endpoint
The primary efficacy endpoint is progression-free survival (PFS). PFS will be defined as the number of days from the date that the subject was randomized to the date the subject experiences an event of disease progression, according to RECIST criteria version 1.1 (as determined by the Investigator) or to the date of death (all causes of mortality) if disease progression is not reached. All 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. However, if a disease progression event occurs after a subject misses two or more consecutive disease progression assessments this subject will be censored at the last disease progression assessment prior to the missing disease progression assessments. All events of death will be included for subjects who had not experienced disease progression provided the death occurred within a time window defined according to the underlying disease assessment interval. If the subject does not have an event of disease progression nor has the subject died, the subject's data will be censored at the date of the subject's last disease assessment.

The primary efficacy analyses are defined by comparing PFS in Arm 3 versus Arm 1 in the BRCA-deficient, HRD, and whole population.

Secondary Efficacy Endpoints

Overall Survival
Overall survival (OS) 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.

The secondary efficacy analyses for OS are defined by comparing OS in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the BRCA-deficient, HRD, and whole population.

PFS will also be compared between Arm 2 and Arm 1 as a secondary analysis.

Disease Related Symptoms
The overall mean change from baseline for the DRS scores measured at each assessment point up to 2 years or disease progression will be a secondary endpoint of the study. The overall mean change from baseline for the total DRS scores between the treatment groups will be compared using a longitudinal repeated measures model that takes into account the DRS scores measured at each assessment point up to 2 years. This analysis will include all available data, from baseline out to 2 years or disease progression.
Statistical Methods (Continued)

Efficacy (Continued):

Interim Analyses
For OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the BRCA-deficient population and HRD population, two efficacy interims will be performed. The first interim analysis will occur at the time of the final PFS analysis (~Month 36) with a nominal alpha of 0.0001, and the second interim analysis will occur at the time of the OS analysis for the whole population (~Month 58) with a nominal alpha of 0.0001, so that the final OS analyses (~Month 77) have a nominal alpha of 0.0248 to have the overall alpha controlled at 0.025.

For OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the whole population, one efficacy interim will be performed at the time of the final PFS analysis (~Month 36) with a nominal alpha of 0.0001, so that the final OS analyses (~Month 58) have a nominal alpha of 0.0248.

Sample Size Calculation
The trial will enroll approximately 1100 subjects (with 1:1:1 randomization ratio for Arm 1:Arm 2:Arm 3) in the whole population, including approximately 264 subjects with BRCA-deficient status (assuming 24% of the subjects in the whole population are BRCA deficient) to power the hypotheses specified in the whole and BRCA-deficient populations. Detailed sample size calculation information for each endpoint of the BRCA-deficient, HRD, and whole populations is provided in Section 8.2.

Multiplicity Control
Multiple testing strategies and multiplicity control are detailed in Section 8.1.4.
1.3 List of Abbreviations and Definition of Terms

**Abbreviations**

- **ALT** alanine aminotransferase
- **ANC** absolute neutrophil count
- **ASCO** American Society of Clinical Oncology
- **AST** aspartate aminotransferase
- **ATEMS** AbbVie Temperature Excursion Management System
- **AUC** area under the plasma concentration-time curve
- **BCS** Biopharmaceutics Classification System
- **BID** twice daily
- **BMI** body mass index
- **BRCA1/2** breast cancer genes 1 and 2
- **BRCA-deficient** germline or tissue-based mutation in **BRCA1** or **BRCA2**
- **BSA** Body Surface Area
- **C1D1** Cycle 1 Day 1
- **C3D1** Cycle 3 Day 1
- **C5D1** Cycle 5 Day 1
- **CL/F** oral clearance
- **C_{max}** maximum observed plasma concentration
- **CNS** central nervous system
- **CT** computed tomography
- **CTCAE** Common Terminology Criteria for Adverse Events
- **CTEP** Cancer Therapy Evaluation Program
- **CVA** cerebrovascular accident
- **CYP** cytochrome P450
- **DLT** dose-limiting toxicity
- **DNA** Deoxyribonucleic acid
- **DRS** disease-related symptoms
- **ECG** Electrocardiogram
- **ECOG** Eastern Cooperative Oncology Group
- **eCRF** electronic case report form
- **EQ-5D-5L** EuroQOL five dimensions, five levels
- **ESMO** European Society for Medical Oncology
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<td>FACT</td>
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<tr>
<td>FIGO</td>
<td>International Federation of Gynecology and Obstetrics</td>
</tr>
<tr>
<td>gBRCA</td>
<td>germline <strong>BRCA1</strong> or <strong>BRCA2</strong> mutation</td>
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<tr>
<td>G-CSF</td>
<td>granulocyte colony-stimulating factor</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>granulocyte macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>GOG</td>
<td>Gynecologic Oncology Group Foundation</td>
</tr>
<tr>
<td>GPRD</td>
<td>Global Pharmaceutical Research &amp; Development</td>
</tr>
<tr>
<td>HDPE</td>
<td>high-density polyethylene</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>HRD</td>
<td>Homologous Recombination Deficiency</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>INR</td>
<td>international normalized ratio</td>
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<td>IP</td>
<td>intraperitoneal</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>IRT</td>
<td>Interactive Response Technology</td>
</tr>
<tr>
<td>ITT</td>
<td>intent-to-treat</td>
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<tr>
<td>IUD</td>
<td>intra-uterine device</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous or intravenously</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<td>MTD</td>
<td>maximum tolerated dose</td>
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<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
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<td>NFOSI-18</td>
<td>NCCN FACT Ovarian Symptom Index-18</td>
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<td>OS</td>
<td>Overall Survival</td>
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<tr>
<td>PARP</td>
<td>poly-(ADP-ribose)-polymerase</td>
</tr>
<tr>
<td>PARPi</td>
<td>PARP inhibitor</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>PFS</td>
<td>progression-free survival</td>
</tr>
<tr>
<td>PLT</td>
<td>platelet</td>
</tr>
<tr>
<td>PO</td>
<td>by mouth</td>
</tr>
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<td>POR</td>
<td>Proof of Receipt</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
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<tr>
<td>PRO</td>
<td>patient-reported outcome</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>partial thromboplastin time</td>
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<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria In Solid Tumors</td>
</tr>
<tr>
<td>SGOT</td>
<td>serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>serum glutamic pyruvic transaminase</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TA MD</td>
<td>Therapeutic Area Medical Director</td>
</tr>
<tr>
<td>tBRCA</td>
<td>tissue-based BRCA1 or BRCA2 mutation</td>
</tr>
<tr>
<td>TCGA</td>
<td>The Cancer Genome Atlas</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>T_{max}</td>
<td>time to maximum observed plasma concentration</td>
</tr>
<tr>
<td>TTFST</td>
<td>time to the first subsequent therapy</td>
</tr>
<tr>
<td>TTSST</td>
<td>time to the second subsequent therapy</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analog scale</td>
</tr>
<tr>
<td>V/F</td>
<td>volume of distribution</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
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3.0 Introduction

This Phase 3 study is designed to test whether the integration of concurrent and continuation maintenance veliparib (ABT-888), a poly-(ADP-ribose)-polymerase (PARP) inhibitor, with carboplatin/paclitaxel chemotherapy for high grade serous epithelial, ovarian, fallopian tube, or primary peritoneal cancer will improve clinical outcomes.

In this context, it is important to recognize that the potential mechanisms of PARP inhibition differ when directly integrated with platinum-based chemotherapy (enhanced cytotoxicity or therapeutic synergy) compared to use as a single agent after completion of chemotherapy (synthetic lethality in tumors with defective homologous deoxyribonucleic acid [DNA] repair). This Phase 3 study incorporates both of these approaches in the experimental arms.

While significant strides have been made to tailor the primary treatment of ovarian cancer to improve efficacy and tolerability, the mortality of advanced-stage ovarian cancer has not changed, and additional improvements are needed. The discovery and development of new molecular targeted agents may lead to more effective combination regimens and improved outcomes for patients. Currently, the standard of care for the primary treatment of ovarian, fallopian tube, or primary peritoneal cancer is a combination of platinum and taxane chemotherapy.\(^1\,^2\) For patients with early-stage disease, as well as advanced suboptimal Stage III and Stage IV disease, intravenous (IV) carboplatin and paclitaxel is given on an every-3-week (Q3-weeks) cycle for 6 cycles. Weekly administration of paclitaxel has shown a survival benefit compared to every-3-weeks paclitaxel administration for patients with Stage II – IV disease.\(^3\) For Stage II/III patients with small-volume (optimal) residual disease after primary cytoreductive surgery, a regimen combining intraperitoneal (IP) cisplatin and paclitaxel with IV paclitaxel is often used.\(^2\) Despite the majority of patients entering a clinical complete remission following initial cytoreductive surgery and chemotherapy, most recur and eventually develop treatment resistant disease.
The clinical development of PARP inhibitors offers promising activity in both breast cancer genes 1 and 2 (BRCA1/2) mutation carriers and sporadic ovarian cancer patients. The Cancer Genome Atlas (TCGA) project has identified that approximately 50% of high grade serous ovarian cancers exhibit defects in homologous recombination and DNA repair pathways and many of these defects could be susceptible to targeting with PARP inhibition. In addition, groups have looked at ways to identify homologous recombination-repair-deficient (HRD) tumors using primary cultures from ascites or genomic profiles of loss of heterozygosity to identify subgroups of ovarian cancer patients who may be more responsive to chemotherapy and PARP inhibitors. Homologous recombination deficiency assays have been evaluated in clinical trials of the PARP inhibitors rucaparib and niraparib. This Phase 3 study incorporates this new knowledge regarding the biological subtypes of ovarian, fallopian tube, and primary peritoneal cancer and concepts of synthetic lethality and therapeutic synergy to improve the outcomes for women with high-grade serous ovarian cancer.

**PARP Inhibitors**

PARP-1 and PARP-2 are nuclear enzymes that recognize DNA damage and facilitate DNA repair. Activation of PARP-1 and PARP-2 enzymes is an essential step in the recognition of DNA damage that results in the poly(ADP-ribose)lation of many nuclear target proteins, including those that facilitate DNA repair. Preclinical and clinical data indicate that PARP inhibitors enhance and prolong the effects of DNA-damaging therapies such as carboplatin (enhanced cytotoxicity or therapeutic synergy) and that tumors with DNA-repair deficiencies are particularly sensitive to PARP inhibition, even in the absence of any other DNA-damaging insults (synthetic lethality).

**Therapeutic Synergy: Combination with Cytotoxic Chemotherapy**

In a variety of preclinical tumor models, including melanoma, prostate, colon, glioma, and BRCA-mutated breast and pancreatic carcinoma, veliparib significantly enhanced the antitumor activity when dosed on a schedule that overlapped the administration of a DNA-damaging agent. Significant inhibition of tumor PARP levels at doses similar to
Those with antitumor effect was observed, which is consistent with veliparib potentiation of DNA-damaging agents being mediated through mechanistic inhibition of PARP.

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. 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. In particular, tumor cells with BRCA1 or BRCA2 deficiencies are exquisitely sensitive to PARP inhibition, even in the absence of any other insults. Deficiencies in homologous recombination, caused by low expression of BRCA1 have also been observed in tumors not associated with germline BRCA deficiency (e.g., ovarian cancer, non-small cell lung cancer [NSCLC], and gastric cancer). These tumors would be expected to be sensitive to PARP inhibition.

Platinum agents such as carboplatin and cisplatin cause DNA damage through the formation of interstrand crosslinks. These crosslinks initially cause single-strand DNA breaks that lead to the recruitment and activation of PARP1 and PARP2 to facilitate DNA repair. Thus, PARP inhibitors can augment the DNA damage caused by carboplatin leading to greater tumor cell death, in both BRCA-proficient and BRCA-deficient tumors. This is further supported by the Phase 2 study in women with platinum sensitive recurrent serous ovarian cancer receiving either olaparib (200 mg BID) in combination with carboplatin (area under the plasma concentration-time curve [AUC] 4) and paclitaxel followed by olaparib monotherapy maintenance (400 mg BID) versus carboplatin (AUC 6) and paclitaxel with no further therapy in which the olaparib arm showed an improvement in PFS (HR = 0.51, 95% CI 0.34 – 0.77; \( P = 0.0012 \); median PFS 12.2 versus 9.6 months).
Comparative data from a placebo-controlled, randomized, double-blind Phase 2 study in subjects with advanced NSCLC (Study M10-898) further support the concept of therapeutic synergy in a DNA-repair proficient population. In this study, veliparib 120 mg BID on Days 1 to 7 added to standard therapy (carboplatin AUC 6 and paclitaxel 200 mg/m^2 on Day 3 on 21-day cycles) improved the median PFS by approximately 1.6 months (HR 0.737; \( P = 0.14 \)) and improved median OS by approximately 2 months (HR 0.769; \( P = 0.229 \)). Comparative safety data demonstrated a modest increase in neutropenia and leukopenia in the veliparib arm without other remarkable differences in treatment toxicity. Leukopenia (all grades) was increased in frequency by < 15% for veliparib- versus placebo-treated subjects, and neutropenia (all grades) was increased in frequency by < 10% for veliparib- versus placebo-treated subjects. No other adverse event was increased by > 5%. Adverse events led to reduction or discontinuation of backbone therapies at similar rates (± 3%) with or without veliparib. These data support the tolerability of the combination and are consistent with a toxicity profile similar in nature to that anticipated for the backbone regimen, with some increase in hematological toxicities and hematological toxicities being the most commonly observed dose limiting toxicity.

Approximately 375 subjects with advanced cancer have been treated with veliparib in combination with carboplatin and paclitaxel in Phase 1 and Phase 2 studies to date. The most commonly observed toxicities in these studies (> 30% of subjects) have included anemia (49.2%), nausea (42.9%), fatigue (40.9%), decreased neutrophil count/neutropenia (40.9% and 20.1%, respectively), decreased white blood cell count (35.8%), alopecia (32.7%), and decreased platelet count (30.3%). Less frequent, but potentially serious events included fever (6.3%), embolism (4.3%), allergic reaction (drug hypersensitivity 3.5%; hypersensitivity 3.1%), and febrile neutropenia (2.8%).

To best elucidate the dose in the intended Phase 3 study population, the GOG has conducted an ongoing Phase 1 dose-escalation study to evaluate the safety and maximum tolerated dose (MTD) of the combination of carboplatin (AUC 6, Q3-weeks), paclitaxel (175 mg/m^2 Q3-weeks or 80 mg/m^2 weekly [Q-week]), and bevacizumab (15 mg/kg,
Q3 weeks; initiated in Cycle 2 followed by bevacizumab maintenance) with escalating
doses of either intermittent or continuous veliparib (Study GOG 9923; N = 300). The
most common toxicities in all subjects to date (veliparib 30 – 400 mg BID) have been
those commonly observed with the backbone therapy and include myelosuppression
(anemia, decreased white blood cell count, neutrophil count, and platelet count (96.3%
each); fatigue (81.5%); alopecia (77.8%); nausea (59.3%); constipation and diarrhea
(55.6% each); peripheral sensory neuropathy (51.9%); hypertension (40.7%); headache
(37.0%), and dyspnea and epistaxis (33.3% each). As expected for carboplatin and
paclitaxel, myelosuppression has also been the most commonly observed Grade 3 and 4
toxicities.

With consideration that subjects in the Phase 3 Study M13-694 will have untreated
disease, Study GOG 9923 includes a stringent tolerability assessment in the expansion
cohorts, with feasibility determined based upon DLTs through 4 cycles in a minimum of
17 subjects at the recommended dose that confirms the ability to deliver multiple cycles of
chemotherapy per standard of care. Veliparib 150 mg BID continuous is the
recommended dose in combination with both the Q3-weeks paclitaxel and carboplatin and
the Q-week paclitaxel and carboplatin regimens. Seventeen evaluable subjects were
treated at this dose level in combination with Q3-weeks paclitaxel and carboplatin with
2 DLTs (Grade 3 febrile neutropenia and Grade 3 hyponatremia). One DLT (Grade 3
headache) was observed in the 17 evaluable subjects treated with Q-week paclitaxel and
carboplatin at this dose level. The dose for this Phase 3 study is veliparib 150 mg BID
administered continuously on Days 1 to 21 of a 21 day cycle for both regimens.

**Synthetic Lethality: Single-Agent Therapy**

The TCGA project has identified that at least 50% of high-grade serous ovarian tumors
exhibit defects in homologous recombination pathways that may result in increased
sensitivity to PARP inhibitors. This includes approximately 15% to 20% of high-grade
serous epithelial ovarian cancers with gBRCA and an estimated additional 7% with
tBRCA. Defects in homologous repair secondary to mutations in the BRCA genes result in
DNA repair via more error prone mechanisms. The combination of defective homologous
recombination due to mutations in $BRCA_1/2$ and suppressed base excision repair due to PARP inhibition results in targeted cell death in the tumor cells, and has been called "synthetic lethality." Durable responses have been observed with veliparib monotherapy in both $gBRCA$ advanced breast cancer and $gBRCA$ recurrent ovarian cancer supporting the mechanism of synthetic lethality in $BRCA_1/2$-mutated tumors.

**Monotherapy Studies**

Studies showing responses to monotherapy with PARP inhibitors in ovarian cancer have been presented and/or published with veliparib, olaparib, niraparib, and talazoparib. In the initial Phase 1 study of olaparib, a cohort of $BRCA$ mutation carriers and patients with a strong family history had a favorable response rate of 28%. Olaparib was studied further in the $BRCA$ population in a Phase 2 dose-finding proof-of-concept study of 100 mg twice daily (BID) and 400 mg BID. Again, a 33% response rate was seen at the 400 mg BID dose, but only one third of that was seen at the 100 mg BID dose. This is interesting in light of the pharmacodynamic data from the Phase 1 study that showed that 90% inhibition of the PARP enzyme was reached at 100 mg BID. Inhibition did not seem to increase further with higher doses when studying peripheral blood mononuclear cells as a surrogate tissue.

Olaparib has also been studied as monotherapy in a group of recurrent high-grade serous ovarian cancer patients or triple-negative breast cancer patients, stratified by whether they had a $BRCA_1$ or $BRCA_2$ mutation or not. Of the subjects with ovarian cancer, an objective response rate of 41% (7/17; 95% confidence interval [CI] 22 – 64%) was observed in those with a $BRCA_1/BRCA_2$ mutation and of 24% (11/46; 95% CI 14 – 38%) in those without, supporting that underlying defects in DNA damage repair occur in ovarian tumors in the absence of $BRCA_1/BRCA_2$ mutations and that these lead to sensitivity to PARP inhibitor single-agent therapy. Similarly, in a randomized, placebo controlled Phase 2 study evaluating olaparib maintenance monotherapy after carboplatin and paclitaxel treatment for platinum-sensitive recurrent serous ovarian cancer, PFS was significantly longer in the olaparib-treated group compared to placebo (hazard ratio [HR] = 0.35; 95% CI 0.25 – 0.49; $P < 0.00001$; median 8.4 versus 4.8 months) with
clinical benefit observed in BRCA-deficient patients (HR = 0.18, \( P < 0.00001 \)) and in patients without a BRCA mutation (BRCA wild type) (HR = 0.54, \( P = 0.0075 \)).

In Cancer Therapy Evaluation Program (CTEP) Study 8282, a Phase 1 study in subjects with gBRCA-mutated cancer (germline BRCA1 or BRCA2 mutation), platinum refractory ovarian, fallopian tube, primary peritoneal cancer, or basal-like cancer, the recommended Phase 2 dose was 400 mg BID, with 500 mg BID declared intolerable due to nausea and fatigue. Dose limiting toxicities included Grade 3 nausea and vomiting (400 mg BID) and Grade 2 seizures (400 mg BID and 500 mg BID). Most common all-grade toxicities included fatigue, nausea, and lymphopenia. Durable responses have been observed in the highest dose levels (300 to 500 mg BID) and enrollment in the expansion cohort is ongoing.

In GOG 280, a Phase 2 study evaluating veliparib 400 mg BID in gBRCA subjects with recurrent high-grade serous ovarian cancer and a maximum of 3 prior therapies, demonstrated two confirmed complete responses, 11 confirmed partial responses, and 24 subjects with stable disease (N = 50). The most notable toxicities have been gastrointestinal, with 18 subjects experiencing Grade 1 nausea, 23 subjects experiencing Grade 2 nausea, and 2 subjects experiencing Grade 3 nausea (50 subjects evaluable for toxicity). These toxicities, although not severe, were a common reason for dose delay and dose reduction. Grade 3 and 4 treatment-emergent adverse events that occurred in more than 2 or more subjects (\( \geq 3\% \)) included nausea (4%), small intestinal obstruction (8%), fatigue (6%), decreased lymphocyte count (4%), and hyponatremia (4%).

In total, approximately 400 subjects have been treated with veliparib monotherapy to date, either as single-agent therapy or as maintenance therapy, and the most common toxicities across these studies included nausea, fatigue, anemia, vomiting, decreased white blood cell count, and lymphocyte count. In subjects receiving veliparib for greater than 6 months, no increase in toxicity is observed over time. The safety and efficacy of monotherapy with veliparib from these studies support the further evaluation of maintenance therapy (400 mg BID continuous) in subjects with previously untreated high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.
3.1 Differences Statement

This is the first randomized, Phase 3 study evaluating the addition of veliparib to standard therapy in subjects with previously untreated high-grade serous epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer.

Other Phase 3 veliparib studies include:

- Study M12-914: A Phase 3 Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel with or without the PARP Inhibitor Veliparib (ABT-888) in HER2-Negative Metastatic or Locally Advanced Unresectable BRCA-Associated Breast Cancer.

3.2 Benefits and Risks

Preclinical data demonstrated two areas that warrant caution in the design and execution of human clinical trials: 1) as monotherapy, veliparib induced seizures in beagle dogs at exposures approximately 4-fold above anticipated efficacious clinical exposures at the MTD for veliparib in combination with platinum/paclitaxel (150 mg BID); and 2) in rats, veliparib administration resulted in a reversible and non-lethal exacerbation of temozolomide hematologic toxicity at doses that, in previous studies, resulted in exposures that were similar to or greater than the maximally efficacious exposure (AUC) in the melanoma murine model. In addition to these two risk areas, a trend towards QTc prolongation was observed in anesthetized dogs, albeit at concentrations > 10-fold the
anticipated human efficacious maximum observed plasma concentration ($C_{\text{max}}$). As anticipated, hematological toxicity has been the dose-limiting toxicity for veliparib in combination with cytotoxic chemotherapy in the clinic, occurring at doses and exposures well below those at which seizures have been observed.

Multiple clinical studies are currently evaluating veliparib in combination with cytotoxic chemotherapy in subjects with various solid tumors. The main toxicities observed in these studies are consistent with those known for each background therapy, with myelosuppression being the most common dose-limiting toxicities. Subjects who participate in Study M13-694 will be monitored for hematologic toxicities as well as for potentiation of any toxicity in combination therapy.

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

To date, over 3,000 subjects have been treated with veliparib and uncommon events of seizure have been observed. The majority of cases have occurred with various confounding factors, primarily associated with underlying malignancy. In this study, subjects with an uncontrolled seizure disorder or brain metastases will be excluded.

Best supportive care and treatment will be given as appropriate to each subject. Specifically, biologic response modifiers for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) and colony-stimulating factors (e.g., neulasta, G-CSF, GM CSF, etc.) may be administered according to institutional or clinical practice guidelines (e.g., American Society of Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO]). Prophylactic antiemetics may also be given per National Comprehensive Cancer Network (NCCN), ESMO, or institutional practice guidelines.
The lack of significant interaction with major cytochrome P450 (CYP) enzymes (either inhibition or induction), suggests that potential pharmacokinetic drug interactions with veliparib are unlikely. For this reason, the Phase 3 study does not limit use of other medications on the basis of their CYP interactions. As a Biopharmaceutics Classification System (BCS) Class 1 compound, veliparib exhibits rapid absorption and high solubility. In addition, food does not have a significant effect on veliparib bioavailability. The administration of a high-fat meal had no significant effect on AUC and only caused a slight decrease in veliparib $C_{\text{max}}$ (17%) and a delay of approximately 1 hour in time to $C_{\text{max}}$ (peak time, $T_{\text{max}}$). For these reasons, veliparib may be administered with or without food. As veliparib is predicted to be predominately excreted in urine, the Phase 3 study will be limited to subjects with adequate renal function (e.g., creatinine clearance $\geq 60 \text{ mL/min}$).

In summary, veliparib is an orally available PARP inhibitor that has been shown to significantly potentiate the effects of platinum/paclitaxel in multiple preclinical models of tumor progression. Potential risks, as identified above, will be minimized by careful patient selection and monitoring to mitigate potential risks to subjects with previously untreated ovarian cancer. The above scientific rationale supports the initiation of the proposed Phase 3 study of veliparib in combination with standard therapy.

4.0 Study Objective

The primary objective of the study is to evaluate whether PFS is prolonged with the addition of veliparib to standard platinum-based chemotherapy (carboplatin/paclitaxel) and then continued as maintenance therapy when compared to chemotherapy alone. This will be evaluated in the $BRCA$-deficient, HRD, and whole populations. The $BRCA$-deficient population will be defined as subjects with either a germ-line ($gBRCA$) and/or tissue-based ($tBRCA$) deleterious or suspected deleterious mutation in $BRCA1$ or $BRCA2$ using centralized testing. The HRD population will be defined as subjects with homologous recombination deficiency based on HRD score or presence of a deleterious or suspected deleterious mutation in $BRCA1$ or $BRCA2$ as determined using centralized testing.
Secondary objectives include evaluations of PFS (Arm 2 versus Arm 1), OS (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), safety of all three arms, and Disease Related Symptom (DRS) scores (Arm 3 versus Arm 1 and Arm 2 versus Arm 1) in the BRCA-deficient, HRD, and whole population.

The tertiary objectives include PFS to the second objective radiographic progression (PFS2), time to first subsequent therapy (TTFST), time to second subsequent therapy (TTSST), and other PRO endpoints (which will be specified in a separate analysis plan).

5.0 Investigational Plan

This protocol was designed in collaboration between AbbVie and the Gynecologic Oncology Group Foundation.

5.1 Overall Study Design and Plan: Description

This is a randomized, placebo-controlled, double-blind, stratified, multicenter, multi-country Phase 3 study designed to evaluate if PFS is prolonged when veliparib is added to carboplatin/paclitaxel and continued as maintenance therapy in subjects with previously untreated high-grade serous ovarian epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Approximately 1100 subjects at approximately 300 sites will be randomized to receive oral veliparib 150 mg/placebo BID in combination with standard first-line chemotherapy (paclitaxel and carboplatin) followed by oral veliparib/placebo BID maintenance therapy (Figure 1). The study was designed to enroll 1100 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.
The study will consist of five phases: a Pre-Therapy Phase (Screening), a Combination Therapy Phase, a Maintenance Therapy Phase, a Long-Term Follow-Up Phase, and a Survival Phase. An overview of the study design is shown in Figure 2 followed by a description of each phase.

Study visits and procedures are detailed in Table 1, Table 2 and Section 5.3.1.1.
Figure 2. Overall Study Design

Pre-therapy Phase (Screening)
- Primary cytoreductive surgery with: Carboplatin and Q-week paclitaxel
- OR Carboplatin and Q3-weeks paclitaxel

Physician's Choice
- Interval cytoreductive surgery with: Carboplatin and Q-week paclitaxel
- OR Carboplatin and Q3-weeks paclitaxel

Eligible Population
- High-Grade Serous, Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
- FIGO Stage III or IV
- No prior systemic therapy
- ECOG 0 to 2
- No CNS metastases

Combination Phase
- Arm 1: Placebo with carboplatin/paclitaxel (Cycle 1-6)*
- Arm 2: Veliparib with carboplatin/paclitaxel (Cycle 1-6)*
- Arm 3: Veliparib with carboplatin/paclitaxel (Cycle 1-6)*

Maintenance Phase
- Placebo** (Cycle 7-36)
- Placebo** (Cycle 7-36)
- Veliparib** (Cycle 7-36)

Long-term Follow-up/Study Endpoints
- Primary: Progression Free Survival (PFS)*
- Secondary: Overall Survival & Disease Related Symptom Scores
- Tertiary: Time to 2nd subsequent therapy

Subjects on study, off treatment, no progression:
- SOC assessments, post-therapy information, tumor assessments

Subjects off study, off treatment, progressed:
- Survival and post-therapy information

All subjects: PROs for up to 2 years or until progression, whichever is later

All subjects: Collection of new onset malignancy information for up to 10 years

LEGEND:
- Q-week schedule = carboplatin AUC 6 + paclitaxel 80 mg/m² weekly;
- Q3-weeks schedule = carboplatin AUC 6 + paclitaxel 175 mg/m² every 3 weeks;
- Veliparib 150 mg/Placebo PO Bid, Cycle 1-6 (21 out of 21 days)
- Veliparib 300 mg/Placebo PO Bid, Cycle 7-36 (21 out of 23 days)
- PFS will be evaluated in the BRCA-deficient population, HRD population, and whole patient population.
- Every 3 months beginning on date of progression

LEGEND (Commons):
- Residual disease and choice of regimen:
  - Q3-weeks carboplatin/paclitaxel, no residual disease
  - Q3-weeks carboplatin/paclitaxel, any residual disease
  - Q-week carboplatin/paclitaxel, no residual disease
  - Q-week carboplatin/paclitaxel, any residual disease
  - Interval cytoreductive surgery, Q3-weeks carboplatin/paclitaxel
  - Interval cytoreductive surgery, Q-week carboplatin/paclitaxel
Pre-Therapy Phase

During the Pre-Therapy Phase, Investigators will be allowed the choice of either carboplatin AUC 6 in combination with weekly paclitaxel (Q-week) or carboplatin AUC 6 in combination with paclitaxel every 3 weeks (Q3-weeks). Either of these chemotherapy regimens will be administered with primary or interval cytoreductive surgery such that there are the following treatment choices prior to randomization:

1. Primary cytoreductive surgery with carboplatin AUC 6 and weekly paclitaxel;
2. Carboplatin AUC 6 and weekly paclitaxel with interval cytoreductive surgery between Cycle 3 and Cycle 4;
3. Primary cytoreductive surgery with carboplatin AUC 6 and every 3 weeks paclitaxel;
4. Carboplatin AUC 6 and every 3 weeks paclitaxel with interval cytoreductive surgery between Cycle 3 and Cycle 4.

The Investigator's treatment decision will be documented prior to proceeding to randomization.

Pre-therapy (screening) procedures will be performed within 28 days prior to randomization and Cycle 1 Day 1, except where noted in Table 1 and Section 5.3.1.1.

For subjects undergoing primary cytoreductive surgery, surgical outcomes including residual disease following primary cytoreductive surgery will be recorded on electronic case report forms (eCRFs).

Subjects must be willing (and consent) to undergo BRCA1/BRCA2 testing in order to participate on the study. Both germline and tissue-based BRCA mutation status will be documented for all subjects by the central laboratory (Myriad).

Once pre-therapy procedures are complete and eligibility is confirmed, subjects will be randomized 1:1:1 to one of the following three arms. Subjects will be stratified by stage...
of disease (Stage III versus Stage IV), residual disease and choice of regimen, region of
the world (Japan versus North America or Rest of World), and gBRCA mutation status
(gBRCA positive versus gBRCA negative or Unknown). Subject randomization is detailed
in Section 8.4.

Arm 1: Carboplatin/paclitaxel plus placebo for six 21-day cycles followed by
placebo maintenance therapy for 30 additional 21-day cycles;

Arm 2: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by
placebo maintenance therapy for 30 additional 21-day cycles;

Arm 3: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by
veliparib BID maintenance therapy for 30 additional 21-day cycles.

Combination Therapy and Maintenance Phases

During the Combination Therapy Phase, subjects will receive veliparib/placebo by mouth
(PO) in combination with intravenous (IV) carboplatin and paclitaxel (Q-week or
Q3-weeks) for 6 cycles. Subjects will self-administer veliparib 150 mg/placebo PO BID
(approximately 8 to 12 hours apart; with or without food) continuously (Days 1 – 21)
within each cycle of Cycles 1 – 6. The morning dose of veliparib/placebo should be
administered in the clinic prior to carboplatin and paclitaxel on C1D1, C2D1, C3D1 and
C4D1 to facilitate pre-dose PK sampling.

Q-Week Paclitaxel Dosing Schedule:

• Paclitaxel 80 mg/m² IV over approximately 1-hour on Days 1 (prior to
carboplatin), 8, and 15;

• Carboplatin AUC 6 IV over approximately 30 minutes on Day 1;

• Veliparib 150 mg/Placebo PO BID, continuously on Days 1 – 21.

Q3-Weeks Paclitaxel Dosing Schedule:

• Paclitaxel 175 mg/m² IV over approximately 3 hours on Day 1 prior to
Carboplatin;

• Carboplatin AUC 6 IV over approximately 30 minutes on Day 1;
• Veliparib 150 mg/Placebo PO BID, continuously on Days 1 – 21.

Subjects who complete the Combination Therapy Phase and who have not progressed per RECIST 1.1 will receive single-agent veliparib/placebo for an additional 30 cycles (Cycles 7 – 36) starting at 300 mg BID. If the subject tolerates 300 mg BID for 2 weeks, veliparib/placebo may be increased to 400 mg BID at the Investigator's discretion during the Maintenance Phase. Prior to increasing the dose of veliparib/placebo, at a minimum, vital signs and adverse event(s) must be assessed if escalation occurs outside of a routine study visit.

If subjects have discontinued veliparib/placebo during the Combination Therapy Phase, veliparib/placebo may be reinitiated at 300 mg to begin the Maintenance Phase once all therapy related toxicities have resolved to ≤ Grade 1 or baseline.

A Therapy Completion Visit will be conducted when the subject completes the Combination and the Maintenance Therapy Phase or when the Investigator determines a subject should discontinue all study treatments. All subjects will have one Follow-Up Visit approximately 30 days after the Therapy Completion Visit.

Additional details regarding dosing with veliparib/placebo, carboplatin, and paclitaxel are provided in Section 5.5.1, Appendix D and Appendix E. Guidelines for dose reductions or delays and toxicity management are provided in Section 5.7.

Subjects Undergoing Interval Cytoreductive Surgery

After adequate tissue biopsy to establish diagnosis, subjects will receive 3 cycles of therapy with interval cytoreductive surgery between Cycle 3 and Cycle 4, followed by 3 additional cycles of therapy. The specimen obtained to establish diagnosis must be processed locally as formalin-fixed paraffin embedded (FFPE) tissue. Before sending to the central laboratory the tissue must be confirmed as adequate (at least 20% tumor content with a minimum of 80% nucleated cellular content) for planned analyses prior to enrollment. To ensure sufficient viable tumor tissue is obtained, image-guided biopsies
should be achieved with 14 to 18 gauge cutting needles to provide 1 to 2 cores measuring 1 to 1.5 cm in length. Biopsy must be of solid tumor tissues; ascites is not acceptable for inclusion.

Veliparib/placebo should be discontinued 3 – 4 days prior to surgery. Surgery must be performed after the third course of therapy, as soon as nadir counts permit, but within 6 weeks after the completion of the third cycle. The fourth cycle of therapy should be administered as soon as possible, but no more than 6 weeks after surgery. Subjects may restart veliparib/placebo once recovered from surgery, with adequate hematological counts (ANC ≥ 1,500, PLT ≥ 100,000). Hematological parameters must be assessed at a minimum of every 4 weeks if the monotherapy extends longer than this prior to resuming chemotherapy.

Cytoreductive surgery should be performed in accordance with the surgical procedures outlined in Appendix C. Surgical outcomes including residual disease following interval cytoreductive surgery will be recorded on the eCRF.

**Long-Term Follow-Up Phase**

Subjects who have not progressed, but have discontinued or completed study therapy will remain on study and will continue to be followed for standard of care assessments, PROs, and tumor assessments per the protocol schedule. Further details surrounding the assessments and activities in the Long Term Follow-Up Phase can be found in Table 2 and Section 5.3.1.1.

**Survival Phase**

Once a subject meets an event of progression, survival and post therapy information (subsequent therapy and progression/PFS2) will be collected at 3 month intervals and new-onset malignancy will be collected at 6 month intervals (or as requested by the sponsor) until the endpoint of death, the subject is lost to follow-up or until study termination by AbbVie.
Subjects will be followed for up to 10 years for collection of new onset malignancy.

5.2 Selection of Study Population

Women 18 years of age and older with previously untreated (no prior systemic therapy), International Federation of Gynecology and Obstetrics (FIGO) Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

Subjects must also have had or be willing to undergo radiographic imaging within 28 days prior to randomization and Cycle 1 Day 1 (baseline).

5.2.1 Inclusion Criteria

1. Subjects with a histologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, FIGO Stage III or IV with appropriate tissue available for histologic evaluation. FIGO staging is outlined in Appendix F.

2. Subjects will be required to have high-grade serous adenocarcinoma to be eligible. Guidance for identifying high grade serous carcinoma is provided in Appendix G.

3. Subject is willing to undergo testing for gBRCA.

4. Subjects must have adequate hematologic, renal, and hepatic function as follows:
   - Hemoglobin ≥ 9.5 g/dL (5.89 mmol/L);
   - Absolute neutrophil count (ANC) greater than or equal to 1500/µL;
   - Platelet count greater than or equal to 100,000/µL;
   - Serum creatinine ≤ 1.0 × ULN range; subjects with a serum creatinine >1.0 × ULN range must have a creatinine clearance ≥ 60 mL/min (according to the Cockcroft-Gault equation);
   - Total bilirubin ≤ 1.5 × ULN. Subjects with Gilbert's Syndrome may have a bilirubin ≥ 1.5 × the ULN range if no evidence of biliary obstruction exists;
   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase must be less than or equal to 2.5 × ULN;
● Albumin ≥ 3.0 g/dL.

5. Subjects with neuropathy (sensory and motor) less than or equal to Grade 1.

6. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

7. Subject is able to swallow and retain oral medication and does not have uncontrolled emesis.

8. Subjects who undergo primary cytoreductive surgery must be randomized between 1 and 12 weeks after surgery. Subjects undergoing interval cytoreductive surgery must have a tumor tissue sample confirming histological diagnosis prior to enrollment.

9. Subjects with measurable disease or non-measurable disease are eligible. Subjects may or may not have cancer-related symptoms.

10. Subject has one of the following available for PD analyses including tissue-based BRCA testing:
   ● Archived diagnostic formalin-fixed paraffin embedded (FFPE) tumor tissue; or
   ● Tumor tissue biopsy collected prior to Cycle 1 Day 1.

11. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to initiation of study drug/placebo and a negative urine pregnancy test at Cycle 1 Day 1 and agree to use adequate contraception (one of the bullet points listed below) prior to study entry, and until permanently surgically sterile. Women not of childbearing potential (permanently surgically sterile or postmenopausal defined as amenorrheic for at least 12 months without an alternative medical cause) at Screening do not require pregnancy testing:
   ● Total abstinence from sexual intercourse as the preferred lifestyle of the subject;
   ● Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream);
   ● Intra-uterine device (IUD).
● Vasectomized male partner of a female subject, provided the partner is sole sexual partner.

12. Subject is 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.

Rationale for Inclusion Criteria

1 – 2, 5, 8 – 10 To select the subject population with appropriate disease severity for the evaluation
3 – 4, 6 – 7 For the safety of the subjects
11 The impact of veliparib and carboplatin or paclitaxel on pregnancies or breastfeeding is unknown
12 In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. Subjects with the following histologic cell types are ineligible: endometrioid adenocarcinoma, carcinosarcoma, undifferentiated carcinoma, mixed epithelial adenocarcinoma, adenocarcinoma not otherwise specified, mucinous adenocarcinoma, clear cell adenocarcinoma, low-grade serous adenocarcinoma, transitional cell carcinoma, or malignant Brenner's tumor.

2. Subjects with synchronous primary endometrial cancer, or a past history of endometrial cancer unless all of the following conditions are met: endometrial cancer stage not greater than IA, no vascular or lymphatic invasion, no poorly differentiated subtypes including serous, clear cell, or other FIGO grade 3 lesions.

3. Subjects with any evidence of other invasive malignancy being present within the last 3 years (with the exception of non-melanoma skin cancer). Subjects are also excluded if their previous cancer treatment contraindicates this protocol's therapy.
Subjects may not receive any non-protocol specified anti-cancer therapy during the study, including maintenance therapy or hormonal therapy for breast cancer. Subjects receiving hormonal therapy (such as tamoxifen or aromatase inhibitors) will require a 7 day (1 week) washout period prior to randomization.

4. Subjects who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded.

5. Subjects who have received prior chemotherapy for any abdominal or pelvic tumor are excluded.

6. Subject has a clinically significant uncontrolled condition(s), including but not limited to:
   - Uncontrolled seizure disorder, or focal or generalized seizure within the last 12 months;
   - Active infection that requires parenteral antibiotics;
   - Known active hepatitis B or hepatitis C with abnormal liver function test or organ dysfunction;
   - Symptomatic congestive heart failure; unstable angina pectoris; serious ventricular cardiac arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or serious cardiac arrhythmia requiring medication (this does not include asymptomatic atrial fibrillation with controlled ventricular rate); or myocardial infarction within the last 6 months;
   - Uncontrolled hypertension (sustained systolic blood pressure > 150 mmHg or diastolic pressure > 100 mmHg despite optimal medical management);
   - Bowel obstruction or gastric outlet obstruction. **Note:** Subjects requiring drainage gastrostomy tube and/or parental hydration and/or nutrition are not eligible;
   - Psychiatric illness/social situations that would limit compliance with study requirements;
   - Any medical condition which in the opinion of the Investigator places the subject at an unacceptably high risk for toxicities.
7. Known history of allergic reaction to Cremophor-paclitaxel, carboplatin, Azo-Colourant Tartrazine (also known as FD&C Yellow 5 or E102), Azo-Colourant Orange Yellow-S (also known as FD&C Yellow 6 or E110) or known contraindications to any study supplied drug.

8. Subjects with history or evidence upon physical examination of central nervous system (CNS) disease, including primary brain tumor, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) within 6 months of Cycle 1 Day 1.

9. Subjects who are pregnant or nursing.

10. Subjects under the age of 18.

11. In the opinion of the Investigator, the subject is an unsuitable candidate to receive veliparib or combination therapy.

Rationale for Exclusion Criteria

1 – 5, 10 To select the subject population with appropriate severity for the evaluation

6 – 9, 11 For the safety of the subjects

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements), except medications administered during primary or interval cytoreductive surgery (e.g., anesthesia), that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapies.
5.2.3.1 Prior Therapy

For the purposes of this protocol, prior 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 prior chemotherapy for any abdominal or pelvic tumor.

Radiation: Subject must have received no prior radiotherapy to any portion of the abdominal cavity or pelvis.

5.2.3.2 Concomitant Therapy

Premedication: Refer to Section 5.5.1.2.

Anticancer Agents: Any anti-cancer therapy including chemotherapy or biological therapy (maintenance therapy) will not be allowed until an event of disease progression per RECIST 1.1 has occurred, with the exception of docetaxel as noted in Section 5.7.1.2. Subjects receiving hormonal therapy such as tamoxifen will require a 7 day (1 week) washout prior to randomization.

Supportive Care: Best supportive care and treatment will be given as appropriate to each subject (antibiotics, transfusions, nutritional support, non-radiation palliative treatment for pain) according to institutional guidelines or ASCO or NCCN guidelines.

An antiemetic treatment for chemotherapy induced nausea and vomiting and veliparib/placebo monotherapy is outlined in Section 5.7.1.1 and Section 5.7.2.

Growth Factors: Guidelines for the use of hematopoietic cytokines are outlined in Section 5.7.1.1.

Radiation: Concomitant radiation therapy will not be allowed.
Surgery: If the subject requires surgery during the study other than that specified by protocol, then this needs to be discussed with the AbbVie TA MD. Generally, veliparib/placebo should be discontinued 3 days prior to surgery, and subjects may restart veliparib/placebo once the subject has adequate hematological counts (ANC ≥ 1,500, PLT ≥ 100,000) and the investigator determines the subject has recovered from surgery.

Secondary Surgery: The performance of non-emergent abdominal surgery, other than that specified by protocol (such as interval or secondary cytoreductive surgery or second look surgery), prior to documentation of disease progression is not permitted. Non-emergent surgery for other indications, such as ostomy reversal, should be discussed with the AbbVie TA MD.

Alternative Therapy: No anti-cancer 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 Pharmacokinetic, Pharmacodynamic Pharmacogenetic and Safety Measurements Assessed and Flow Chart

The study visit and procedure schedule is outlined in Table 1 and Table 2. The schedule for pharmacogenetic and pharmacodynamic sampling (translational research) and pharmacokinetic sampling is presented in Table 3 and Table 4 respectively.
## Table 1. Study Procedures for Pre-Therapy, Combination and Maintenance Phases

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pre-Therapy Phase (Screening)</th>
<th>Combination Phase (Cycles 1 – 6)</th>
<th>Maintenance Phase (Cycles 7 – 36)</th>
<th>Therapy Completion Visit</th>
<th>Follow-Up Visit</th>
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<td>C1D1 Day 8 and Day 15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cycle 2 – Cycle 6</td>
<td>Every 9 Weeks from C1D1 then End of the Combination Phase&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Urinalysis&lt;sup&gt;j&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>PT/INR, PTT&lt;sup&gt;m&lt;/sup&gt;</td>
<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
</tr>
<tr>
<td>CA-125 Blood Draw&lt;sup&gt;n&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Randomization&lt;sup&gt;v&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Tumor Assessment&lt;sup&gt;p&lt;/sup&gt;</td>
<td>X&lt;sup&gt;q&lt;/sup&gt;</td>
<td></td>
<td>X&lt;sup&gt;r&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Chest X-Ray</td>
<td>X&lt;sup&gt;t&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>NFOSI-18&lt;sup&gt;h,v&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>EQ-5D-5L&lt;sup&gt;h,v&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Table 1. Study Procedures for Pre-Therapy, Combination and Maintenance Phases (Continued)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pre-Therapy Phase (Screening)</th>
<th>Combination Phase (Cycles 1 – 6)</th>
<th>Maintenance Phase (Cycles 7 – 36)</th>
<th>Therapy Completion Visit</th>
<th>Follow-Up Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review Subject Calendar</td>
<td></td>
<td>Day 8 and Day 15</td>
<td>Every 9 Weeks from C1D1 then End of the Combination Phase</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Veliparib/Placebo Dispensing</td>
<td>X^w</td>
<td>X^w</td>
<td>Every Other Cycle (C7, C9, C11, etc.)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Monitor AEs</td>
<td>X</td>
<td>X</td>
<td>Study Drug Evaluation^a</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Prior and Concomitant Medication Assessment</td>
<td>X</td>
<td>X</td>
<td>Every 12 Weeks for 2 Years, then Every 6 Months for 3 Years, Then Annually^c</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

PS = Performance Status; C=Cycle; AEs = Adverse Events

a. Perform within 28 days prior to randomization and Cycle 1 Day 1.

b. Procedures in this column are only required for subjects being treated with weekly paclitaxel (Cycles 1 – 6 only). If dose modification results in discontinuation of the Day 15 paclitaxel infusion, the Day 15 visit may be omitted.

c. Can be performed ± 7 days of the scheduled visit. Note, the end of Combination Therapy Phase tumor assessment scan is not required if the prior scan was completed within the last 6 weeks. Intervals are as follows: Every 9 weeks from C1D1, then end of the combination phase, then every 12 weeks for 2 years (from the start of maintenance phase), then every 6 months for 3 years (from the last scan on the every 12 week schedule), then annually.

d. Approximately 2 weeks after beginning maintenance therapy at 300 mg BID, subjects will be evaluated for escalation to 400 mg at a Study Drug Evaluation Visit. The procedures noted in this column will be performed. If the PI determines the subject is not eligible to increase veliparib/placebo to 400 mg BID at this visit, the PI may reassess the subject's tolerability at any future visit. Note, the procedures in this column will be required when determining if a subject can escalate to 400 mg BID.

e. Perform within 30 days of the Therapy Completion Visit.

f. All exams should include weight. Height is obtained at the Pre-Therapy Visit only.

g. If the physical examination is performed within 7 days prior to Cycle 1 Day 1, it is not required to repeat the exam on Cycle 1 Day 1 unless clinically indicated.
Table 1. Study Procedures for Pre-Therapy, Combination and Maintenance Phases (Continued)

h. Procedures can be performed by PI or delegated to qualified medical staff (e.g., a nurse, sub-investigator, etc.).
i. Subjects of childbearing potential: a serum pregnancy test will be performed within 7 days of Cycle 1 Day 1. A serum or urine pregnancy test should also be performed prior to randomization or Cycle 1 Day 1 if > 7 days since obtaining screening serum test results. Subjects of childbearing potential who have prolonged interruption of therapy (> 3 months), a pregnancy test (urine or serum) must be performed and confirmed to be negative prior to resuming therapy.
j. Refer to Table 5 for the complete listing of required clinical laboratory tests.
k. Must be obtained within 4 days prior to therapy. Any subject whose therapy is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met.
l. Non-Protocol Specified Surgery: Subject may restart veliparib/placebo when ANC ≥ 1,500 and PLT ≥ 100,000. Hematological parameters will be assessed as determined by the investigator.
\hspace{1cm} Interval Surgery: Subject may restart veliparib/placebo when ANC ≥ 1,500 and PLT ≥ 100,000. Hematological parameters must be assessed at a minimum of every 4 weeks if the monotherapy extends longer than this prior to resuming carboplatin/paclitaxel.
m. For subjects on prophylactic or therapeutic anticoagulation with warfarin, PT/INR should be monitored at screening and with additional assessments as clinical indicated. Therapy should be held for PT/INR of > 1.5 × ULN on prophylactic warfarin or > therapeutic range if on full dose warfarin.
n. A baseline (prior to initiating therapy) value is required. CA-125 levels should then be drawn prior to each cycle during Cycles 1 – 6 only. Additional CA-125 levels drawn over the course the study will be collected on the appropriate eCRF.
o. Randomization should occur as close as possible to Cycle 1 Day 1.
p. 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. Tumor assessments may also be done as clinically indicated at any time based on symptoms or physical signs suggestive of progressive disease. All scan dates should be calculated from Cycle 1 Day 1. In addition to being reviewed by the Investigator, imaging scans should be sent within 5 business days of imaging acquisition to the central imaging vendor.
q. Primary surgery subjects: The post-operative baseline scan must be performed within 28 days prior to randomization and Cycle 1 Day 1. Interval surgery subjects: A baseline scan (prior to initiating therapy) must be completed within 28 days prior to randomization and Cycle 1 Day 1.
r. Interval surgery subjects: Pre-operative scan data will be collected after the completion of Cycle 3 on the appropriate eCRF to evaluate disease per RECIST 1.1. A scan of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease prior to re-starting therapy on C4D1. The post-operative scan should be performed as close as possible to resuming therapy at C4D1 and no more than 4 weeks prior to C4D1.
s. For subjects who discontinue therapy for reasons other than progression, a tumor scan will not be required at the time of discontinuation if completed within 4 weeks prior to the Therapy Completion Visit.
### Table 1. Study Procedures for Pre-Therapy, Combination and Maintenance Phases (Continued)

- **t.** Not required if CT of chest already performed at screening.
- **u.** PRO questionnaires administered at the Screening visit are considered baseline. PROs do not need to be repeated at C1D1 if completed ≤ 7 days prior to C1D1. Subsequent administration of the PROs to continue at odd numbered cycles, after the baseline PRO has been completed.
- **v.** Complete the NFOSI-18 first followed by the EQ-5D-5L. Both questionnaires should be administered before discussing imaging scan results or disease status changes with the subject.
- **w.** Review each subject's calendar and document compliance with veliparib/placebo prior to the start of each cycle.
- **x.** Perform weekly for subjects receiving weekly paclitaxel. Weekly AE assessments can be performed by the PI or delegated to qualified medical staff (e.g., a nurse, sub-investigator).

**Note:** For procedures performed during the Pre-Therapy Phase (screening) and repeated, the later procedure performed prior to dosing will serve as a baseline for clinical assessment. For C1D1 and subsequent study procedures (excluding tumor assessments), assessments should be performed within 4 days prior to the scheduled study visit.
Table 2. Study Procedures for Long Term Follow-Up and Survival Phase

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Completion or Discontinuation of Therapy Without Disease Progression (Long Term Follow-Up Phase)</th>
<th>Discontinuation of Therapy due to Disease Progression (Survival Phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Every 9 Weeks Until the End of Combination, then Every 12 Weeks for 2 Years, then Every 6 Months for 3 Years, then Annually, Until Disease Progression</td>
<td>At Least Every 3 Months Until Disease Progression</td>
</tr>
<tr>
<td>Physical Exam</td>
<td></td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vital Signs</td>
<td></td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CA-125 Blood Draw</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tumor Assessment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NFOSI-18&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EQ-5D-5L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Monitor AEs</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Survival Information&lt;sup&gt;c,f&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Post-Therapy Information&lt;sup&gt;c,f&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Review for New Onset Malignancy&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

a. Assessments (except for PROs) may be performed according to standard of care or every 3 months for up to 3 years (from C1D1).
b. Both PROs will be completed for up to 2 years from C1D1, or until disease progression, whichever is later. If disease progression occurs prior to 2 years from C1D1, both PROs should continue to be collected until 2 years from C1D1. Complete the NFOSI-18 first followed by the EQ-5D-5L. Both questionnaires should be administered before discussing imaging scan results or disease status changes with the subject.
c. Every 12 weeks for 2 years (from the start of maintenance phase), then every 6 months for 3 years (from the last scan on the every 12 week schedule), then annually.
Table 2. Study Procedures for Long Term Follow-Up and Survival Phase (Continued)

d. Subjects will be monitored for SAEs only per Section 6.5.

e. Survival information and post-therapy information will be collected every 3 months (i.e., 3, 6, 9, 12 etc.) or as requested by the Sponsor to support data analysis, beginning on the date of disease progression per RECIST 1.1 until the endpoint of death, or until the subject becomes lost to follow-up, or until study termination by AbbVie.

f. Section 5.3.1.1 outlines the data being collected for survival and post-therapy information.

g. New onset malignancy will be assessed every 6 months for up to 10 years.

h. 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. Tumor assessments may also be done as clinically indicated at any time based on symptoms or physical signs suggestive of progressive disease. All scan dates should be calculated from Cycle 1 Day 1. In addition to being reviewed by the Investigator, imaging scans should be sent within 5 business days of imaging acquisition to the central imaging vendor.
Table 3. Schedule of Pharmacogenetic and Pharmacodynamic Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Visit Schedule</th>
<th>Timing of Sample Collection</th>
<th>Sampling Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optional Pharmacogenomic Sample</td>
<td>C1D1, C3D1</td>
<td>Prior to Dosing</td>
<td>Blood</td>
</tr>
<tr>
<td>BRCA Sequencing: Bridging Sample</td>
<td>C1D1</td>
<td>Prior to Dosing</td>
<td>Blood</td>
</tr>
<tr>
<td>Germline BRCA Sample</td>
<td>Screening</td>
<td>Prior to Dosing</td>
<td>Blood</td>
</tr>
<tr>
<td>Plasma Markers&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C1D1, C3D1, C5D1</td>
<td>Prior to Dosing</td>
<td>Blood → Plasma&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum Markers</td>
<td>C1D1, C3D1, C5D1</td>
<td>Anytime during the clinic visit</td>
<td>Frozen –20°C or colder</td>
</tr>
<tr>
<td>Therapy Completion Visit</td>
<td></td>
<td></td>
<td>Blood → Serum&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pre-therapy tumor biopsy sample (Required):</td>
<td>Pre-therapy Phase&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Pre-Study Treatment FFPE tissue blocks (Room Temperature or Refrigerated-FFPE)</td>
</tr>
<tr>
<td>Archival Tissue or Newly Collected Biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optional tissue sample</td>
<td>C1D1 – Therapy Completion Visit&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Anytime over the course of the study, including the Therapy Completion Visit</td>
<td>Archived FFPE tissue blocks (Room Temperature or Refrigerated-FFPE)</td>
</tr>
</tbody>
</table>

---

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

b. Plasma and serum samples should be sent to the central lab within 4 weeks. Samples that require storage longer than 4 weeks should be stored in –70 degree Celsius.

c. All subjects must have a pre-therapy tumor biopsy for inclusion on the study.

d. Post-therapy biopsy can be taken from any consenting subjects at any time over the course of the study, including at the Therapy Completion Visit. The collection of this tissue sample does not require a separate biopsy procedure and may be collected during routine procedures including interval surgery or during a biopsy at the time disease progression is suspected.

Note: If a drug interruption is needed, the subject will continue to have study visits as planned; however, the above samples will not be drawn during the time of study drug interruption.
Table 4. Schedule of Pharmacokinetic Sampling

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Visit Schedule</th>
<th>Before Drug Administration</th>
<th>After Veliparib AM Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sampling Plan</th>
<th>Specimen Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib PK Sampling</td>
<td>C1D1</td>
<td>0-hour&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1, 2, 3 hours</td>
<td>Blood → Plasma</td>
<td>Frozen –20°C or colder</td>
</tr>
<tr>
<td>Veliparib PK Sampling</td>
<td>C2D1, C3D1,</td>
<td>0-hour&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>Blood → Plasma</td>
<td>Frozen –20°C or colder</td>
</tr>
<tr>
<td></td>
<td>C4D1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The Veliparib PK sampling draws may be completed within a window of ± 10%.

<sup>b</sup> Before the administration of the morning dose of veliparib/placebo. The morning dose of veliparib/placebo should be dosed in clinic prior to carboplatin and paclitaxel on C1D1, C2D1, C3D1 and C4D1.

Notes: If a drug interruption is needed, the subject will continue to have study visits as planned; however PK samples will not be drawn during the time of study drug interruption.

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

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

The study procedures outlined in Table 1 and Table 2 are discussed in further detail in this section, with the exception of prior and concomitant therapy (Section 5.2.3), tumor assessment criteria (RECIST 1.1; Section 5.3.3.1), administration of veliparib/placebo (Section 5.5.1.1), the monitoring of treatment compliance (Section 5.5.6) and adverse event information (Section 6.1.1). All study data will be recorded on electronic case report forms (eCRFs) with supporting source documentation.

Pre-Therapy, Combination, Maintenance, and Long-Term Follow-Up Phases

Study Visits

For procedures performed during the Pre-Therapy Phase (screening) and repeated, the later procedure performed prior to dosing on Cycle 1 Day 1 will serve as a baseline for clinical assessment. Assessments obtained as standard practice for management of the underlying disease may be accepted for eligibility, provided the assessments were collected within the specified eligibility window. Please refer to Table 1 for specified windows. Cycle 1 Day 1 and subsequent study procedures (excluding tumor assessments) should be performed within 4 days prior to the scheduled study visit date.

During the Combination Phase (Cycles 1 – 6), the frequency of study visits will vary depending on the dosing schedule chosen for paclitaxel. Subjects receiving weekly paclitaxel will have weekly study visits. Subjects receiving Q3-weeks paclitaxel will have study visits on Day 1 of every cycle.

During the Maintenance Therapy Phase, all subjects will have study visits on Day 1 of every other cycle except for the Study Drug Evaluation visit (conducted approximately 2 weeks after starting maintenance therapy). At this visit, the PI or designated qualified staff will evaluate whether a subject is tolerating therapy at 300 mg BID and is suitable to escalate veliparib/placebo to 400 mg BID. If the PI determines a subject is not suitable to escalate to 400 mg BID at the Study Drug Evaluation visit, the PI may reassess the
subject's tolerability at any future visit. Procedures for the Study Drug Evaluation visit and any future visits where escalation is considered, are outlined in Table 1.

Baseline scans for primary and interval cytoreductive surgery are discussed in this section under the Tumor Assessment subheading. All post-baseline tumor assessments can be performed ± 7 days of the scheduled visit.

**Informed Consent**

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent will be required for the optional research tests. 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 a study-specific procedure has been performed (e.g., local laboratories drawn), but subject does not randomize into the study. The reason for screen failure will be documented in the source documents and will be captured in the eCRF.

**Medical History**

A complete medical history includes documentation of any clinically significant medical condition(s); history of tobacco and alcohol use; presence and severity of any symptoms/conditions associated with ovarian cancer and detailed ovarian oncology history (histology, tumor staging, residual disease at the completion of surgery [if applicable], date of diagnosis, tumor burden, metastatic sites, any previous BRCA status testing (US only) and results of tumor molecular analysis/profiling, if available).

On Cycle 1 Day 1 any changes observed from the pre-therapy procedures (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

Physical examinations, including body weight, will be performed per Table 1 and Table 2. If the pre therapy physical examination is performed within 7 days of Cycle 1 Day 1, it is not required to repeat the exam on Cycle 1 Day 1 unless clinically indicated. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events.

Height will be measured at the Pre-Therapy Visit only. For height and weight, subject should not wear shoes.

Vital Signs

Vital signs will be performed per Table 1 and Table 2. Vital sign determinations include sitting blood pressure, heart rate and body temperature. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

Weekly Paclitaxel Dosing Schedule: During weekly study visits, vital signs can be performed by PI or delegated to qualified medical staff (e.g., a nurse, sub-investigator, etc.).

Adverse Event Assessment

AE assessments will be performed per Table 1 and Table 2.

Weekly Paclitaxel Dosing Schedule: During weekly study visits, AE assessments can be performed by the PI or delegated to qualified medical staff (e.g., a nurse, sub-investigator, etc.).

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed per Table 1. 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.

**ECOG Performance Status**

The ECOG performance status will be assessed per Table 1 and Table 2 as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully Active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>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.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>

**Pregnancy Test (In Women of Childbearing Potential)**

For female subjects of childbearing potential, a serum pregnancy test will be performed within 7 days of Cycle 1 Day 1. A serum or urine pregnancy test at day of randomization should also be performed and reviewed prior to randomization, if a serum pregnancy test is completed more than 7 days prior to randomization. If a serum pregnancy test is performed on the day of randomization, a urine pregnancy test does not need to be completed. Pregnancy tests may also be repeated during the study according to country requirements.

If pregnancy results are equivocal (e.g., false positive due to B-hCG being a tumor marker) in subjects with evidence to support lack of pregnancy (e.g., surgically sterile), the results should be discussed with the AbbVie TA MD and the Investigator's interpretation along with supporting information documented in the source documents.
The urine or serum pregnancy test results must be reviewed and determined to be negative prior to randomization. If the urine pregnancy test is positive, it should be confirmed by a serum pregnancy test or additional testing and dosing should be delayed.

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

Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately (Section 6.7).

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile) at Screening do not require pregnancy testing.

**Clinical Laboratory Tests**

Samples for chemistry, hematology, and urinalysis will be collected per Table 1 and Table 2 using a certified local laboratory. Specific laboratory tests are outlined in Table 5.

All laboratory samples will be assessed using a certified local reference laboratory and these data will be used for all data analysis. The appropriate certifications will be collected from the local laboratories, as needed.

Qualified medical staff at the site will review, initial and date all local laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.1.1.
### Table 5. Clinical Laboratory Tests

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Clinical Chemistry</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Blood urea nitrogen (BUN)</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Serum creatinine</td>
<td>Ketones</td>
</tr>
<tr>
<td>Red blood cell (RBC) count</td>
<td>Total bilirubin</td>
<td>pH</td>
</tr>
<tr>
<td>White blood cell (WBC) count</td>
<td>Serum glutamic-pyruvic transaminase (SGPT/ALT)</td>
<td>Protein</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Serum glutamic-oxaloacetic transaminase (SGOT/AST)</td>
<td>Blood</td>
</tr>
<tr>
<td>Bands (if indicated)</td>
<td>Alkaline phosphatase</td>
<td>Glucose</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>Basophils (if indicated)</td>
<td>Calcium</td>
<td></td>
</tr>
<tr>
<td>Eosinophils (if indicated)</td>
<td>Inorganic phosphorus</td>
<td>Serum Pregnancy Tests</td>
</tr>
<tr>
<td>Platelet count (estimate not acceptable)</td>
<td>Total protein</td>
<td>Human Chorionic Gonadotropin (hCG)</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration</td>
<td>Albumin</td>
<td></td>
</tr>
<tr>
<td>RBC distribution width</td>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bicarbonate (if available, Japan only)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coagulation</th>
<th>Special Chemistry</th>
<th>Tumor Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Partial Thromboplastin Time (aPTT)¹</td>
<td><strong>BRCA1 and BRCA2 germline mutation³</strong></td>
<td>CA-125</td>
</tr>
<tr>
<td>International Normalized Ratio (INR)¹</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

1. Collected per Table 1.
2. Not required on Day 8 and Day 15 assessments during Cycles 1 – 6 for subjects receiving carboplatin and weekly paclitaxel.
3. Collected during screening.
4. Collected and reviewed prior to Randomization.

### Tumor Assessments

Tumor assessments will be performed per Table 1 and Table 2. A CT scan of the abdomen and pelvis (and chest, if metastases are present) using RECIST 1.1 will be used in the evaluation of tumor responses, as appropriate. Subjects will continue to be monitored by the same diagnostic method as outlined in Section 5.3.3.1 (Methods for Evaluation of Disease).
**Primary surgical subjects:** The post-operative (baseline) scan must be performed within 28 days **prior** to randomization and Cycle 1 Day 1.

**Interval surgery subjects:** A pre-therapy (screening) baseline scan is required to be performed on interval surgery subjects within 28 days prior to randomization and Cycle 1 Day 1. Pre-operative scan data will be collected after the completion of Cycle 3 on the appropriate eCRF to evaluate disease per RECIST 1.1. A scan of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of disease evaluation prior to re-starting therapy on Cycle 4 Day 1. The post-operative scan should be performed as close as possible to resuming therapy at Cycle 4 Day 1 and no more than 4 weeks prior to Cycle 4 Day 1.

Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. The end of Combination Therapy Phase tumor assessment scan is not required if the prior scan was completed within the last 6 weeks. Subjects who discontinue therapy for reasons other than disease progression will continue to be followed as per the scheduled tumor assessments to determine the extent of tumor burden, until disease progression occurs.

In addition to being reviewed by the Investigator and/or qualified medical site staff, imaging scans should be sent within 5 business days of imaging acquisition to an independent central imaging vendor. AbbVie may discontinue this requirement at any time during the course of the study. The central imaging vendor will provide instructions regarding the preparation and shipment of the images. Imaging scans will be assessed for quality by the central imaging vendor and archived. Interpretations from the central imaging vendor will not be sent to the study site. Blinded independent central reviews will be performed as a sensitivity analysis as described in the SAP.

**Randomization and Subject Number Assignment**

Interactive Response Technology (IRT) will be utilized to register (screen and randomize) subjects on study. The site will contact the IRT to obtain a screening (subject) number.
once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., labs are 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 meet the eligibility criteria, agree to participate, and complete all pre-therapy (screening) procedures will proceed to randomization. Randomization is to occur as close as possible to Cycle 1 Day 1. The site will need to also access the IRT system and a unique randomization number will be provided. During the randomization process, subjects will be randomized in a 1:1:1 ratio to one of 3 treatment arms:

Arm 1: Carboplatin/paclitaxel plus placebo for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles.

Arm 2: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles.

Arm 3: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by veliparib maintenance therapy for 30 additional 21-day cycles.

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 IRT vendor.

**Dispensing Study Drug**

Randomized subjects will receive sufficient quantities of veliparib/placebo for 21 days in each 21 day cycle during the Combination Phase, and 42 days for 2 cycles, during the Maintenance Phase. The IRT will assign every bottle of veliparib/placebo to be dispensed to a subject. Prior to each cycle (per Table 1), site personnel must contact IRT for the next bottle number assignment. Veliparib/Placebo cannot be dispensed without contacting the IRT. AbbVie or designee will provide specific instructions on the use of IRT. During the combination and maintenance phase, IRT will allow additional kits to be dispensed during scheduled clinic visits, if needed.
Trained site personnel will administer IV carboplatin and paclitaxel. Subjects will be supervised at the time of the infusion.

Subjects will be provided with veliparib/placebo self-administration instructions and subject dosing cards. Subjects will be instructed to store veliparib/placebo according to specific directions included in Section 5.5.2.3. Subjects should return bottles of veliparib or placebo (empty, partially filled, or full) to the study site prior to each cycle and at the Therapy Completion Visit.

**Disease Related Symptom Scores**

Two PRO questionnaires will be administered (per Table 1 and Table 2): the NCCN Functional Assessment of Cancer Therapy (FACT) Ovarian Symptom Index-18 (NFOSI-18) questionnaire, and the EQ-5D-5L/VAS.\textsuperscript{34,35}

The NFOSI-18 consists of 18 items and separates disease related symptoms from treatment related side effects. Four subscale scores will be constructed: a 9-item based disease related symptoms (DRS) score, a 1-item based disease related emotional well-being (DRS-E) score, a 5-item based treatment side effect (TSE) subscale, and a 3-item based functional well-being (FWB) subscale score.\textsuperscript{36} The DRS score will be used as a secondary endpoint of the study.

The EuroQol 5 Dimensions (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations. The EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health.

**Order of Administration**

Subjects will be asked to complete the NFOSI-18 first, followed by the EQ-5D-5L. To minimize response bias, the questionnaires should be administered before discussing
imaging scan results or disease related clinical changes with the subject. Subjects should be encouraged to respond to all of the questions. Clarification can be given regarding the intention of each question even when the question(s) do not seem relevant to their situation. While the subject is still at the site, the Investigator or a designee will need to check the forms returned by the subject for completeness. If a subject is unable to a complete form(s) for any reason, it should be documented in the source.

Subjects Who Cannot Come to the Site

In the event a subject is unable to come to the site (e.g., physical condition is a barrier) or have moved to long-term follow-up, the questionnaires may be sent (e.g., mail, courier, email, electronically, etc.) with a request to complete them and return to the site as instructed by site staff.

Questionnaires collected outside the clinic should be reviewed by qualified site staff for missing information and follow-up with subject may be required per investigator's discretion.

Long-Term Follow-Up Phase

Completion or Discontinuation of Study-Therapy without Progression:

Subjects who have not progressed, but have discontinued or completed study therapy will remain on-study. In addition to standard of care assessments and PROs, these subjects are followed for tumor assessments until unequivocal progression per RECIST 1.1. Subjects will be monitored for SAEs according to Section 6.5. Assessments will be completed in the following timeframes:

- PRO questionnaires will be collected every 3 months for 2 years from C1D1 or until disease progression, whichever is later. If disease progression occurs prior to 2 years from C1D1, both PROs should continue to be collected until 2 years from C1D1. PRO time points are calculated from Cycle 1 Day 1.
- Tumor assessments will be collected every 9 weeks from C1D1, then end of the combination phase, then every 12 weeks for 2 years (from the start of
maintenance phase), then every 6 months for 3 years (from the last scan on the every 12 week schedule), then annually, until progression is noted. Tumor assessment timepoints are calculated from Cycle 1 Day 1.

- Subject status will be monitored via the collection of standard of care assessments, including physical exam, vital signs, and ECOG. The assessments will be completed per a standard of care schedule or every 3 months (whichever is sooner), for a maximum of 3 years from C1D1 and documented on the appropriate eCRF.
- All subsequent therapies will be documented on the appropriate eCRF.
- New onset malignancy will be assessed every 6 months for up to 10 years.

**Discontinuation of Study-Therapy due to Progression**

- Survival and post-therapy information will be assessed every 3 months.
- New onset malignancy will be assessed every 6 months for up to 10 years.

**Assessment for New Onset Malignancy**

All subjects will be followed for any occurrence and outcome of a second primary cancer, including myelodysplastic syndrome or acute myeloid leukemia. New onset malignancy may be spontaneously reported at any time.

**Survival Information and Post-Therapy Information**

Once an event of progression occurs, subjects will be registered as "off-study" in IRT and will continue to be followed for survival, post-therapy information, including date of progression on first and second subsequent therapy, PROs (as applicable), and new onset malignancy, per Table 2.

Survival (i.e., the date and cause of death) and post-therapy information will be collected on the appropriate eCRF at 3-month intervals (or as requested by sponsor to support data analysis) beginning on the date of disease progression and continuing either until the endpoint of death, until the subject is lost to follow-up, or until the study termination by
AbbVie. If the subject withdraws from survival 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.

The following will be collected for post-therapy information:

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

Subject must request to be withdrawn specifically from survival follow-up; this request must be documented in the subject's medical record and signed by the investigator. If the subject withdraws from survival follow-up, the site staff may use a public information source (such as county records) to obtain information about survival status only, as appropriate per local regulations.

5.3.1.2 Collection and Handling of Biomarker and Optional Exploratory Research Samples

Blood, plasma, serum, and tumor tissue will be collected and may be utilized to evaluate known and/or novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status, related conditions or to evaluate the association with pharmacokinetics, safety or efficacy. The biomarker rationale will be discussed in the Biomarker Research Variables Section (Section 5.3.6).

All samples should be labeled and shipped as outlined in the study-specific laboratory manual.

AbbVie (or people or companies working with AbbVie) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on veliparib (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion, or per local
requirement. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

**Biomarker Samples (Mandatory Sampling)**

Blood and tumor tissue will be used to determine germline and tissue-based BRCA mutation status respectively. Other exploratory pharmacodynamic correlative studies will be performed. Serum, plasma and tissue specimens may be utilized to evaluate known and novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status. Pharmacodynamic variables will be further discussed in Section 5.3.6.

**Germline BRCA Sample (gBRCA)**

Each subject will have blood collected (7 mL) as described in Table 3 for gBRCA testing. The gBRCA status of each patient will be determined using the sponsor core laboratory. Genetic risk assessment and counseling should proceed per NCCN guidelines or the standard policy of the institution.

**BRCA Sequencing 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 (7 mL per tube) must be obtained from all subjects per Table 3 to be tested at a future date.

**Blood Collection for Plasma Markers**

Approximately 12 mL (Cycle 1 Day 1 and Therapy Completion Visit) or 6 mL (Cycle 3 Day 1 and Cycle 5 Day 1) of blood will be collected pre-dose by venipuncture at time points outlined in conjunction with PK samples, if possible, as outlined in Table 4. The collection, processing and storage should be performed as described in the study-specific laboratory manual. The complete process of centrifugation, transfer to cryovial and freezing should be accomplished in less than 1 hour from the time of blood draw.
Blood Collection for Serum Markers

Approximately 5 mL of blood will be collected pre-dose by venipuncture as outlined in Table 3. The collection should be performed as described in the study-specific laboratory manual. The complete process of clot formation, centrifugation, transfer to cryovials and freezing should be accomplished in less than 2 hours from the time of blood draw.

Tumor Biopsy Tissue Collection

Pre-Therapy Tumor Biopsy Sample (Archived or Newly Collected Biopsy) (Required for Randomization)

Subjects must consent to provide available archival tissue. A portion of this biopsy will be used to assess BRCA status therefore all subjects must have a pre-therapy biopsy for inclusion on the study. Only one of the following forms of pre-therapy tumor tissue (archived tissue or newly collected biopsy) is required:

- **Archived biopsy:** The most recent archived biopsy is preferred and should be obtained during Screening, if possible. If no archived material is available, a fresh biopsy should be collected from subjects according to institutional procedures for subjects willing to participate on study.

- **Newly Collected biopsy:** Sample should be collected during Screening period, and fixed in formalin and embedded in paraffin according to institutional procedures. Tumor samples should be stored according to Institutional procedures until shipment to AbbVie or an AbbVie-designated contract research organization (CRO). AbbVie or a designated CRO will prepare the samples for analysis.

While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study-specific laboratory manual.
Exploratory Research Samples (Optional Sampling)

Subjects will have the option to provide samples for exploratory research. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research.

Samples for Pharmacogenetic Exploratory Research

An optional whole blood sample for DNA isolation will be collected on Cycle 1 Day 1 and Cycle 3 Day 1 from each subject who consents to provide samples for exploratory research.

Samples will be shipped frozen to AbbVie or a designated laboratory for DNA extraction and long-term storage. Instructions for the preparation and shipment of the pharmacogenetic exploratory research samples will be provided in a laboratory manual.

Samples for Biomarker Exploratory Research

For subjects who consent, additional samples may be collected for exploratory research to potentially help identify biomarkers associated with subjects' response to the study drug or to better characterize the disease. All subjects will have the following samples collected as described in the Table 3:

- An optional post-therapy tumor tissue biopsy should be collected at the time point outlined in Table 3 from subjects who are willing to consent. Institutional procedures should be followed to fix and embed the collected biopsy in paraffin. While tissue blocks are preferred, slides prepared by the local pathology laboratory are acceptable, and should be prepared as described in the study-specific laboratory manual.

Optional Tissue Sample Collection

An optional post-therapy tumor tissue biopsy should be collected at the time point outlined in Table 3 from subjects who are willing to consent. Collection of this tissue sample does not require a separate biopsy procedure and may be collected during routine
procedures including interval surgery or during progression. Institutional procedures should be followed to fix and embed the collected biopsy in paraffin. While tissue blocks are preferred, slides prepared by the local pathology laboratory are acceptable, and should be prepared as described in the study-specific laboratory manual.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Veliparib Pharmacokinetic Specimen Collection

Approximately 3 mL of blood will be collected by venipuncture for veliparib concentrations at 0 hours (just before morning dose of veliparib) and other time points as specified per Table 4. The date/time of collection of each blood sample and the last two doses of veliparib/placebo taken prior to the blood sample collection will be recorded.

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

Refer to the study-specific laboratory manual for detailed instructions on sample collection, processing and shipment.

5.3.2.2 Measurement Methods

Plasma concentrations of veliparib will be determined using validated method in the Drug Analysis Department at AbbVie. Plasma concentrations of veliparib metabolite(s) may be determined using validated or non-validated methods.

5.3.3 Efficacy Variables

The primary efficacy endpoint is PFS. The secondary efficacy endpoints are OS and DRS. The tertiary efficacy endpoints are PFS2, time from randomization to
first subsequent therapy or death (TTFST), and time from randomization to second subsequent therapy or death (TTSST), and additional PRO endpoints.

5.3.3.1 RECIST 1.1 for Disease Status

Overall tumor assessment will be assessed using RECIST 1.1. Changes in the overall tumor assessment over the course of therapy must be evaluated using the criteria listed below:

Eligibility

Subjects with measurable or non-measurable disease prior to cytoreductive surgery are eligible. Subjects with measurable disease will have objective tumor response evaluated by RECIST 1.1. Measurable disease is defined by the presence of at least one measurable lesion. All subjects will be followed to determine the overall assessment according to RECIST 1.1, including subjects with no radiographically evaluable disease following cytoreductive surgery.

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, lymphangitic involvement of skin or lung and also 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 $\geq 15$ 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 $\geq 10$ to $< 15$ mm short axis.

### Special Considerations Regarding Lesion Measurability

**Bone lesions**

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as MRI/CT can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

**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 as measurable lesions, if they meet the definition of measurability described above.

However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

**Lesions with prior local treatment**

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

### Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed.
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 $\geq 10$ mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Conventional CT should be performed with cuts of 5 mm or less in slice thickness contiguously. This applies to tumors of the chest and abdomen. A scale should be incorporated into all radiographic measurements. MRI can be performed if required by local law, but should have sponsor approval.

If prior to enrollment, it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, MRI may be substituted. Alternatively, a contrast dye preparation protocol may be used in consultation with the AbbVie TA MD. The use of non-contrast CTs, which may affect how tumor progression is evaluated, is discouraged. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be made based upon discussion with the AbbVie TA MD.

For accurate objective response evaluation, PET scans and ultrasound (US) 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 partial response (PR) and complete response (CR) in rare cases.

**Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
CA-125 levels: CA-125 alone cannot be used to assess response. If CA-125 is initially above the upper normal limit, it must normalize for a subject to be considered in complete response.

**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. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

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 must meet the criterion of a short axis of $\geq 15$ 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 if a node is involved by solid tumor. Nodal size is normally reported as two 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 $20 \text{ mm} \times 30 \text{ mm}$ has a short axis of $20 \text{ mm}$ and qualifies as a malignant, measurable node. In this example, $20 \text{ mm}$ should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq 10 \text{ mm}$ but $< 15 \text{ mm}$) should be considered non-target lesions. Nodes that have a short axis $< 10 \text{ mm}$ 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 SOD. If lymph nodes are to be included in the sum, then as noted above, only
the short axis is added into the sum. The baseline SOD will be used as reference by which
to characterize the objective tumor response.

All other lesions (or sites of disease) including pathological lymph nodes 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.

**Re-Baseline for Interval Surgery Subjects**

Interval surgery subjects will have a second baseline timepoint with imaging.
Post-surgical imaging should be performed as close as possible to resuming therapy at
Cycle 4 Day 1 and no more than 4 weeks prior to Cycle 4 Day 1. The post-surgical scan
is considered a re-baseline for the subject. Overall tumor response assessments will be
determined by comparing follow-up visit scans to the post-surgical baseline (re-baseline)
scan and/or post-surgery nadir. Adequate assessment of tumor persistence and resection
should be made during interval surgery.

**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 SOD of target lesions,
  taking as reference the baseline SOD.

- **Progressive Disease (PD):** At least a 20% increase in the SOD 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 lesion is believed to be 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.

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).

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 will therefore be extremely rare.

In the absence of radiographic or clinical evidence of progressive disease, a rise in CA-125 alone is not sufficient to declare progression.

**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 finding thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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

**Overall Response:**

If a patient has neither measurable nor non-measurable lesions evident on the baseline (post-surgical) tumor assessment, the overall responses for post base-line scan should be PD, Non-PD, or not evaluable, as follows.
Table 6. Calculating Final Response for Subjects with No Radiographic or Clinical Evidence of Disease (ND) on the Post-Surgical Baseline Tumor Assessment

<table>
<thead>
<tr>
<th>New Lesion</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (Absent)</td>
<td>nonPD (No disease)</td>
</tr>
<tr>
<td>Yes (Present)</td>
<td>PD (Progressive Disease)</td>
</tr>
<tr>
<td>Not Evaluated</td>
<td>NE*</td>
</tr>
</tbody>
</table>

* NE will be used in exceptional cases where insufficient data exist, unless progressive disease is identified.

The overall assessment of the tumor burden will include assessment of target (for subjects with measurable disease) and non-target lesion as follows:

Calculating Final Response:

<table>
<thead>
<tr>
<th>Overall Response for Subjects with Measurable Disease at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Lesion</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Not all evaluated</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Any</td>
</tr>
</tbody>
</table>

* Equivocal new lesions will not allow for CR but will otherwise not impact the overall response.
Calculating Final Response for Non-Measurable Disease:

<table>
<thead>
<tr>
<th>Non-Target Lesion</th>
<th>New Lesion</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>Non-CR/Non-PD</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>Unequivocal PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

Note: If CA-125 is initially above the upper normal limit, it must normalize for a subject to be considered in complete response.

### 5.3.4 Safety Variables

AbbVie will assess adverse events, laboratory data, and vital signs throughout the study. Adverse events intensity and laboratory evaluation changes will be assessed by utilizing National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).

During the conduct of the study, the AbbVie medical and safety team will be monitoring blinded, subject laboratory results and serious adverse event data as they are reported.

### 5.3.5 Pharmacokinetic Variables

A nonlinear mixed effect modeling analysis will be conducted to estimate the population pharmacokinetic parameters of veliparib such as apparent oral clearance (CL/F) and volume of distribution (V/F). The results of pharmacokinetic analyses may be reported in a separate report.

AbbVie or a designated laboratory will store the pharmacokinetic 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 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.
5.3.6 Biomarker and Optional Exploratory Research Variables

Biomarker (blood, plasma, serum, and tissue) and optional pharmacogenetic samples will be collected to investigate and conduct exploratory analyses of biomarkers including, but not limited to, nucleic acids, proteins, lipids or metabolites.

Biomarker and pharmacogenetic research samples may be analyzed with the intent of identifying potential associations with subject outcome or to better characterize the disease. These characterizations may include genetic and non-genetic assessment of DNA repair pathways, pathway(s) targeted by the study drug (veliparib/placebo) or those believed to be related to the disease or to drug response. Specifically, biomarker samples will be used to determine germline and tissue-based BRCA status. Additional analysis aimed at identifying underlying defects in the homologous recombination pathway, regardless of etiology, may be performed and associated with response. The information learned from analyzing biomarker and pharmacogenetic samples may be used to investigate factors influencing response to treatment, scientific questions related to cancer, and/or in the development of new therapies and diagnostic tests. The results of biomarker and pharmacogenetic testing may not be included with the study summary.

Biomarker and exploratory research samples may be anonymized and used for diagnostic test development.

5.3.7 Pharmacogenetic Variables

Biomarker (blood, plasma, serum, and tissue) and optional pharmacogenetic samples will be collected to investigate and conduct exploratory analyses of biomarkers including, but not limited to, nucleic acids, proteins, lipids or metabolites.

Biomarker and pharmacogenetic research samples may be analyzed with the intent of identifying potential associations with subject outcome or to better characterize the disease. These characterizations may include genetic and non-genetic assessment of DNA repair pathways, pathway(s) targeted by the study drug (veliparib/placebo) or those believed to be related to the disease or to drug response. Specifically, biomarker samples
will be used to determine germline and tissue-based BRCA status. Additional analysis aimed at identifying underlying defects in the homologous recombination pathway, regardless of etiology, may be performed and associated with response. The information learned from analyzing biomarker and pharmacogenetic samples may be used to investigate factors influencing response to treatment, scientific questions related to cancer, and/or in the development of new therapies and diagnostic tests. The results of biomarker and pharmacogenetic testing may not be included with the study summary.

Biomarker and exploratory research 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.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will receive therapy until disease progression according to Section 5.3.3.1, RECIST 1.1., completion of therapy, or unmanageable toxicity (per discussion with the AbbVie TA MD). Subjects who discontinue therapy for reasons other than disease progression will continue to be followed as per the schedule of assessments in Table 2, until disease progression occurs.

Each subject also has the right to withdraw from therapy at any time. Additionally, the Investigator may discontinue a subject from therapy at any time for any reason if he/she considers it necessary, including the occurrence of noncompliance with the protocol.

Each subject will discontinue therapy (as applicable) if any of the following occur:

- The subject experiences an unmanageable toxicity or requires an alternate anticancer agent(s) that is not specified in the protocol.
- Subject requires cancer-directed radiotherapy or surgery related to clinical disease progression.
● Subject is suspected to be pregnant; pregnancy is confirmed or begins breastfeeding during the combination and maintenance therapy phases of the study.

● The subject or subject's legally acceptable representative decides to withdraw consent for any reason.

● Any other medical reason that AbbVie or the study Investigator deems appropriate.

Discontinued subjects will not be replaced.

A Therapy Completion Visit will be conducted for all subjects when therapy is discontinued. All subjects will have one Follow-Up Visit approximately 30 days after the Therapy Completion Visit. Subjects starting any new cancer therapy within the 30 days after the last dose of study drug (veliparib/placebo) must complete the 30-day follow-up assessments in advance of starting any anti-cancer therapy. This Follow-Up Visit does not need to be performed for subjects who have had a Therapy Completion Visit conducted ≥ 30 days after the last dose of study drug (veliparib/placebo). For subjects who discontinue therapy for reasons other than progression, a tumor scan will not be required if completed within 4 weeks prior to the Therapy Completion Visit.

Once an event of progression occurs, subjects will be registered as "off-study" within IRT and continue to be followed during the Long-Term Follow-Up Phase (per Table 2 and Section 5.3.1.1).

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

In the event that a subject becomes pregnant during the study, the administration of study drugs to that subject must be discontinued immediately. The site must report the pregnancy by telephone within 24 hours to one of the AbbVie representatives listed in Section 7.0.
5.4.2 Discontinuation of Carboplatin/Paclitaxel and Veliparib/Placebo

Carboplatin, paclitaxel, and veliparib/placebo, dose reductions or delays and discontinuation will occur as outlined in Section 5.7.

5.4.3 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/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 due to safety concerns.

The following procedures for study discontinuation will be followed:

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

5.5 Treatments

5.5.1 Treatments Administered

Subjects will receive the following:

- Carboplatin/Paclitaxel plus placebo PO BID for six 21-day cycles, followed by maintenance therapy with placebo PO BID for up to an additional thirty 21-day cycles;
● Carboplatin/Paclitaxel plus veliparib 150 mg PO BID for six 21-day cycles, followed by maintenance therapy with placebo PO BID for up to an additional thirty 21-day cycles; or

● Carboplatin/Paclitaxel plus veliparib 150 mg PO BID for six 21-day cycles, followed by maintenance therapy with veliparib 400 mg PO BID for up to an additional thirty 21-day cycles.

● For subjects switching to docetaxel due to discontinuation of paclitaxel, following the 7-day washout period of veliparib, docetaxel in combination with carboplatin is to be administered per institutional guidelines, including modifications for toxicity.

General chemotherapy guidelines are found in Appendix D.

5.5.1.1 Administration of Veliparib/Placebo

Subjects will self-administer the morning dose of veliparib/placebo and the evening doses of veliparib/placebo approximately 8 to 12 hours after the morning dose with or without food in the same calendar day, starting on Day 1 of each cycle. Veliparib/placebo will be taken 1 hour prior to paclitaxel for Day 1 of Cycle 1, 2, 3, and 4 and in the case of veliparib/placebo interruptions during the Combination Phase.

During the maintenance phase (Cycles 7 – 36) standard anti emetic therapy may be administered as appropriate, including a combination of standard antiemetics (i.e., 5-HT3 receptor antagonists, steroids, and prochlorperazine, and/or promethazine).

It is recommended that if a subject misses a scheduled dose of veliparib/placebo and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. 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 veliparib/placebo, another dose will be administered. The dose may only be repeated once. If more than 15 minutes has passed from the time of oral dosing then no additional doses will be taken.

5.5.1.2 Administration of Carboplatin/Paclitaxel

Investigators should evaluate subjects for carboplatin and paclitaxel treatment per the locally approved product label, local practice, or applicable SmPC. Due to the risk of immediate hypersensitivity reaction, paclitaxel should always be administered before carboplatin.

Best supportive care and treatment for nausea and vomiting can be provided according to institutional guidelines or American Society of Clinical Oncology (ASCO) or NCCN guidelines.

For example, 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-HT\textsubscript{3} receptor antagonists may be used, preferably ondansetron or granisetron. ASCO dosing guidelines are as follows:

- Palonosetron 0.25 mg IV OR 0.50 mg oral, Day 1 only
- Dexamethasone 8 mg (IV or oral), Days 1 to 3

NK1 antagonist 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 or Fosaprepitant 150 mg IV Day 1
- 5-HT\textsubscript{3} receptor antagonist dosing

Dexamethasone: 12 mg (IV or oral) on Day 1 and 8 mg (IV or oral) Days 2 and 3 or Days 2 – 4 (with aprepitant) or Dexamethasone: 12 mg (IV or oral) on Day 1 and 8 mg
(IV or oral) on Day 2 and 8 mg (IV or oral) twice per day on Days 3 and 4 (with fosaprepitant).³⁸

5.5.1.2.1 Paclitaxel

Pre-Medication for Paclitaxel

To reduce the severity of hypersensitivity reactions due to treatment with paclitaxel, manage according to institutional guidelines, the locally approved product label, local practice, or applicable Summary of Product Characteristics (SmPC, i.e., premedication with corticosteroids, diphenhydramine, and H₂ antagonists). Pre-medications are to be documented in the appropriate forms in EDC.

Weekly Paclitaxel

For subjects receiving paclitaxel 80 mg/m², paclitaxel will be administered over approximately 1-hour as an IV infusion on Days 1, 8, and 15 of each 21-day cycle × 6 cycles.

Every 3-Weeks Paclitaxel

For subjects receiving paclitaxel 175 mg/m², paclitaxel will be administered as an IV infusion over approximately 3 hours on Day 1 of each 21-day cycle × 6 cycles.

5.5.1.2.2 Carboplatin

Carboplatin AUC 6 will be administered as a 30-minute IV infusion, following paclitaxel administration on Day 1 of each 21-day cycle × 6 cycles. Carboplatin dose calculation instructions can be found in Appendix E.

5.5.2 Identity of Investigational Products

Information regarding the veliparib formulation to be used in this study is presented in Table 7.
Table 7. Identity of Investigational Product

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Dosage Form</th>
<th>Strength</th>
<th>Route of Administration</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib (ABT-888)</td>
<td>Capsule</td>
<td>50 mg or 100 mg</td>
<td>Oral</td>
<td>AbbVie</td>
</tr>
<tr>
<td>Placebo</td>
<td>Capsule</td>
<td>Placebo to match 50 mg and 100 mg</td>
<td>Oral</td>
<td>AbbVie</td>
</tr>
</tbody>
</table>

5.5.2.1 Standard of Care Medicinal Products

Information regarding carboplatin, paclitaxel, and docetaxel to be used in this study is presented in Table 8.

Table 8. Standard of Care Medicinal Products

<table>
<thead>
<tr>
<th>Standard of Care Products</th>
<th>Dosage Form</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin (commercially available)*</td>
<td>Solution in a vial</td>
<td>Intravenously</td>
</tr>
<tr>
<td>Paclitaxel (commercially available)*</td>
<td>Solution in a vial</td>
<td>Intravenously</td>
</tr>
<tr>
<td>Docetaxel (commercially available)*</td>
<td>Solution in a vial</td>
<td>Intravenously</td>
</tr>
</tbody>
</table>

* Carboplatin, docetaxel and paclitaxel formulations may vary based on the source. Each investigational site will be responsible for tracking the lot numbers for all non-investigational medicinal products (e.g., carboplatin, paclitaxel and docetaxel) dispensed.

Note: AbbVie will not be providing carboplatin, paclitaxel, or docetaxel during the study.

5.5.2.2 Packaging and Labeling

Veliparib (ABT-888) will be packaged in high-density polyethylene (HDPE) bottles containing either 50 mg, 100 mg, or matching placebo capsules. Bottles of 50 mg and matching placebo will contain 44 capsules (this includes 2 additional capsules in each bottle dispensed per cycle to cover loss, spillage or replacement due to vomiting within 15 minutes). Bottles of 100 mg and matching placebo will contain 44 capsules (this includes 2 additional capsules in each bottle dispensed per cycle to cover loss, spillage or replacement due to vomiting within 15 minutes). Each bottle label will include all
information as required by local regulations and must remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

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

### 5.5.2.3 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 9, until they are dispensed for subject use or are returned to AbbVie.

#### Table 9. Study Drug Storage Conditions

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Country</th>
<th>Storage Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib (ABT-888) or placebo</td>
<td>All countries, except Australia/New Zealand</td>
<td>Store at 15° to 25°C (59° to 77°F)</td>
</tr>
<tr>
<td>Veliparib (ABT-888) or placebo</td>
<td>Australia/New Zealand</td>
<td>Store below 25°C</td>
</tr>
</tbody>
</table>

Investigational products are for investigational use only, and are to be used only within the context of this study. The clinical supplies for this study must be maintained under adequate security and stored under conditions specified on the label.

The controlled storage area should have a temperature recording device. A storage temperature log is to be maintained to document proper storage conditions. The room temperature storage must be recorded each business day to document proper function.

Malfunctions or temperature excursions outside the specified storage range for veliparib or matching placebo must be reported to the sponsor immediately. Sites should use the AbbVie Temperature Excursion Management System (ATEMS) module via IRT, if available, or fax copies of the temperature log indicating the extent of the excursion (time, duration of the temperature excursion, min/max values and study drugs affected) to AbbVie Global Drug Supply Management including the Storage Temperature Excursion Reporting Form.
This information will be used to determine the continued acceptability of the drug.

In case of a temperature excursion, study medication should be quarantined and not dispensed until AbbVie Global Pharmaceutical Research & Development (GPRD) or ATEMS deems the medication as acceptable.

**Storage and Disposition of Carboplatin and Paclitaxel**

**Paclitaxel**

Vials must be stored between 15° to 25°C (59° to 77°F) (or per locally approved label or SmPC) in the provided cartons to protect from light.

**Carboplatin**

Vials must be stored between 15° to 25°C (59° to 77°F) (or per locally approved label or SmPC) in the provided cartons to protect from light.

### 5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects in the study will be randomized using an IRT. Before the study is initiated, directions for the IRT will be provided to each site. The site will contact the IRT to obtain a Screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., laboratory samples 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. For others, the site will access the system and a unique randomization number will be provided. Note: The Investigator's treatment decision must be documented prior to accessing the IRT for subject randomization.

The IRT will randomize subjects into the 3 treatment arms in a 1:1:1 ratio. Subject randomization will be stratified by stage of disease (III versus IV), residual disease and choice of regimen, and region of the world (Japan versus North America or Rest of the World), and germline \(BRCA\) mutation status (\(gBRCA\) positive versus \(gBRCA\) negative or
Unknown). The stratification factors used for the randomization should be the last values on the date of randomization and should be consistent with those on the eCRF.

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 IRT vendor.

5.5.4 Selection and Timing of Dose for Each Subject

All randomized subjects will receive veliparib 150 mg/placebo PO BID in combination with chemotherapy (carboplatin/paclitaxel) for 6 cycles. Subjects who complete the Combination Therapy Phase and who have not progressed will receive single-agent veliparib/placebo for an additional 30 cycles (Cycles 7 – 36) starting at 300 mg BID. If the subject tolerates 300 mg BID, veliparib/placebo should be increased to 400 mg BID during the Maintenance Phase. Veliparib/placebo will be dosed starting on Day 1 of each cycle and dosed continuously (21/21 days). One dose will be taken in the morning and the second dose will be taken in the evening. The morning dose of veliparib/placebo should be dosed in clinic prior to carboplatin and paclitaxel on Day 1 of Cycles 1, 2, 3, and 4 for PK sampling purposes.

All randomized subjects will also receive carboplatin (AUC 6) on Day 1 of each cycle and paclitaxel (80 mg/m² on Days 1, 8, and 15 of each cycle, or 175 mg/m² on Day 1 of each cycle) (unless a delay is required per locally approved product labels or SmPCs). The paclitaxel infusion should be given first.

5.5.5 Blinding

AbbVie (with the exception of AbbVie Drug Supply Management), the Investigator, the study site personnel and subject will remain blinded to each subject's therapy with veliparib or placebo throughout the course of the study.

All subjects will be treated with open-label carboplatin and paclitaxel.
The IRT will provide access to blinded subject therapy information during the double blind period.

AbbVie must be notified before the blind is broken unless identification of the investigational product is required for medical emergency, i.e., situation in which the knowledge of the specific blinded therapy will affect the immediate management of the subject's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

5.5.5.1 Blinding of Investigational Product

The IRT will provide access to blinded subject therapy 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 treatment is required, every effort must be made to contact the AbbVie TA MD (listed in Section 6.7) prior to contacting the IRT for 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.

5.5.5.2 Blinding of Data for Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will review safety data for this study in an un-blinded fashion approximately 12 months and 24 months from the date the first subject is randomized. Details of the IDMC review will be outlined in the IDMC Charter. Aggregate clinical safety data will be reviewed on a real-time basis throughout the course of the study.
5.5.5.2.1 Requested Unblinding Following Progression for Subsequent Treatment

For subjects who have completed Study M13-694 and for whom the treatment assignment is necessary for immediate patient management and treatment decisions, unblinding may be considered on a case-by-case basis. Unequivocal disease progression per RECIST 1.1 must be documented and the data must be complete prior to unblinding the case, to ensure that the data integrity is maintained. In addition, these requests would be anticipated to be either consistent with the indication for PARP inhibitors or for patients for whom this information is necessary for participation in other clinical studies.

Patients who undergo optional treatment unblinding and are found to have been randomized to "placebo" will not continue to receive veliparib.

a. Criteria for Requested Unblinding:

The unblinding procedure applies to patients who experience progression as defined in Section 5.3.3.1. It is vital to properly apply the protocol specified definition of progression. In addition, the treatment assignment must be needed for immediate treatment decisions. If any questions arise with regard to progression for a patient, please contact the AbbVie TA MD.

Prior to unblinding, a separate document requesting unblinding with rationale must be submitted and processed. The AbbVie TA MD will provide written confirmation to the site that the patient has an adequately documented progression. This documentation must be archived properly in the appropriate site files.

b. Unblinding Procedures

Patients who meet the criteria for requested unblinding will be unblinded by AbbVie and the treatment assignment provided to the site. Please allow 3 – 5 days for unblinding.
5.5.6 **Treatment Compliance**

The Investigator or his/her designated and qualified representatives will administer/dispense study drugs only to subjects enrolled in the study in accordance with the protocol. The study drugs must not be used for reasons other than that described in the protocol.

Veliparib/Placebo should be taken as directed by the Investigator. Carboplatin and paclitaxel will be administered intravenously by trained site personnel.

Subjects will be instructed to return all veliparib/placebo bottles (empty, partially filled or full) to the study site personnel prior to each cycle and at the Therapy Completion Visit. The site staff will document the bottles returned and the number of capsules per bottle on the appropriate form.

Upon completion or termination of the study, all original bottles/cartons containing unused veliparib/placebo (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 bottles will be performed at the site.

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

5.5.7 **Drug Accountability**

The site will record the dose of carboplatin and paclitaxel (and docetaxel, if applicable) given to each subject in the source documents and on the eCRF. As the Investigator will obtain carboplatin, paclitaxel and docetaxel commercially, site inventory and accountability of carboplatin, paclitaxel and docetaxel will not be performed, and drug accountability forms will not be provided. Each investigational site will be responsible for tracking the lot numbers for all non-investigational medicinal products (e.g., carboplatin, paclitaxel and docetaxel) dispensed.
Upon receipt of a shipment of veliparib/placebo, the representative at each site will 1) open and inspect the shipment; 2) verify that the veliparib/placebo 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; 4) register the shipment as received via the IRT. 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 IRT.

An overall accountability of the study drugs will be performed and verified by the site monitor throughout the study and at the study site closeout visit. An accurate running inventory of veliparib/placebo will be maintained utilizing the IRT drug accountability module and, if required, according to your institutional policy and will include the lot number, POR number(s), the bottle/kit numbers, and the date veliparib/placebo was dispensed for each subject.

Upon completion or termination of the study, all original containers containing unused study drug (veliparib/placebo, empty containers will be defaced and discarded on site) will be returned to a destruction facility according to instructions from AbbVie or if prearranged between the sponsor and site, destruction of used and unused veliparib/placebo in bottles will be performed at the site.

The study Investigator or his/her designated representative agrees not to supply study medication to any persons not enrolled in the study or not named as a sub-investigator listed on the FDA 1572 or Investigator Information and Agreement (IIA) form.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The proposed Phase 3 study will evaluate the efficacy and tolerability of veliparib in combination with standard chemotherapy compared to chemotherapy alone in women with previously untreated, Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Treating physicians will be allowed the choice of
treating with either paclitaxel on a weekly schedule or every 3 weeks schedule in combination with carboplatin AUC 6 such that there are the following treatment choices prior to randomization:

1. Primary cytoreductive surgery with carboplatin and weekly paclitaxel (21-day cycle)
2. Carboplatin and weekly paclitaxel (21-day cycle) with interval cytoreductive surgery after Cycle 3
3. Primary cytoreductive surgery with carboplatin and Q3-weeks paclitaxel (21-day cycle)
4. Carboplatin and Q3-weeks paclitaxel (21-day cycle) with interval cytoreductive surgery after Cycle 3

Following the Investigator's choice of therapy, subjects will be randomized in a 1:1:1 ratio to one of the following:

- Carboplatin/paclitaxel plus placebo for 6 cycles followed by placebo maintenance therapy for up to an additional 30 cycles (Cycles 7 – 36)
- Carboplatin/paclitaxel plus veliparib for 6 cycles followed by placebo maintenance therapy for up to an additional 30 cycles (Cycles 7 – 36)
- Carboplatin/paclitaxel plus veliparib for 6 cycles followed by veliparib maintenance therapy for up to an additional 30 cycles (Cycles 7 – 36)

These regimens are supported as category 1 level of evidence by NCCN guidelines and consistent with current standard of care. This design will allow the effect of adding veliparib to standard chemotherapy to be assessed separately from the effect of adding veliparib as induction therapy and maintenance therapy. A pre-specified alpha allocation rule is used to control the overall type I error rate.
5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be used in this study.

The efficacy measurements in this study are standard and validated. Progression-free survival is a widely accepted endpoint of clinical importance for the evaluation of subjects with previously untreated ovarian cancer. Additionally, RECIST 1.1 is a validated guideline for the measurement of responses in subjects with advanced or metastatic solid tumors.

5.6.3 Suitability of Subject Population

The proposed Phase 3 study will evaluate the efficacy and tolerability of veliparib in combination with standard chemotherapy compared to chemotherapy alone in subjects with previously untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. The study will enroll subjects ≥ 18 years of age with a histologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma FIGO Stage III or IV, with appropriate tissue available for histologic evaluation. The proposed inclusion and exclusion criteria are anticipated to result in a study subject population representative of ovarian cancer patients who are receiving front line systemic therapy with carboplatin and paclitaxel according to current practice guidelines.

5.6.4 Selection of Doses in the Study

The doses of standard chemotherapy (carboplatin and paclitaxel) are identical to those used as standard first-line therapy for the treatment of ovarian cancer and to those used in the GOG 9923 study. The dose of veliparib in combination with carboplatin and paclitaxel is based upon the GOG 9923 study in subjects with newly diagnosed ovarian cancer in which the recommended dose of veliparib in combination with carboplatin and paclitaxel was determined to be 150 mg PO BID, and as verified by assessment of tolerability beyond Cycle 1 during the expansion phase. This Phase 3 study will allow subjects to receive veliparib 300 – 400 mg PO BID maintenance therapy following the
completion of 6 cycles of chemotherapy with veliparib/placebo. This dose has been
selected based upon the recommended Phase 2 dose (CTEP 8282) and additional safety
and efficacy data in Phase 2 studies in gBRCA breast cancer (CTEP 8264) and ovarian
cancer (GOG 280) in which durable responses were observed to single-agent therapy.40

The maximum dose of veliparib for any subject in this study is 150 mg BID in
combination with carboplatin and paclitaxel for 21 of 21 days per cycle over 6 cycles and
400 mg BID as single-agent therapy for 21 of 21 days per cycle over 30 cycles.

5.7 Dose Reductions or Delays

In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable
efforts will be made to minimize dose reduction and therapy delays as specified. Any
subject whose therapy is delayed must be evaluated on a weekly basis until adequate
hematologic and non-hematologic parameters have been met. The therapy schedule will
then proceed in the usual sequence. For the purposes of this section, therapy refers to
veliparib/placebo and chemotherapy.

Dose-Limiting Hematologic Toxicities

Dose-limiting hematological toxicities will include only those listed in Table 10. Dose-
limiting toxicities will be handled according to Table 11 (Q3-weeks) and Table 12
(Q-week).

Table 10. Dose Limiting Hematological Toxicities

Febrile neutropenia
Prolonged Grade 4 neutropenia persisting for greater than 7 days
Grade 4 thrombocytopenia (< 25,000/mm$^3$)
Bleeding associated with Grade 3 thrombocytopenia (25,000 to < 50,000/mm$^3$)
Grade 4 neutropenia with severe infection

No dose modifications will be made for anemia. Subjects may receive red blood cell
transfusions and/or erythropoiesis stimulating agents using standard supportive care
guidelines. In cases of profound anemia where additional intervention or dose modification may be considered appropriate please contact the AbbVie TA MD.

For dose-limiting hematological toxicity the cycle should be delayed until the ANC recovers to \( \geq 1,000 \text{ cells/mm}^3 \) and the platelet count recovers to \( \geq 75,000/\text{mm}^3 \) (Grade 1).

For dose-limiting neutropenia, veliparib/placebo should be held until the ANC recovers to \( \geq 1,000 \text{ cells/mm}^3 \). For dose-limiting thrombocytopenia, veliparib/placebo should be held until the platelet count recovers to \( \geq 75,000/\text{mm}^3 \). Once veliparib/placebo is reinstituted, the dose will remain the same.

Unless required per the Investigator, there should be no modifications for uncomplicated Grade 4 neutropenia lasting \( \leq 7 \) days or for uncomplicated Grade 3 thrombocytopenia.

### 5.7.1 Dose Reductions or Delays for Carboplatin and Paclitaxel with Placebo/Veliparib (Cycles 1 – 6)

If a subject experiences an adverse event that results in a delay in starting a cycle or requires that therapy be delayed or interrupted during a cycle, the subject will complete the planned activities per Table 1 and Section 5.3.1.1. For subjects receiving carboplatin and paclitaxel with veliparib/placebo (Cycles 1 – 6), re-escalation of the dose following dose reductions is not allowed.

### 5.7.1.1 Guidelines for Hematologic Toxicity During Combination Phase

Initial therapy modifications may consist of cycle delay and/or dose reduction. Treatment decisions will be based on the ANC rather than the total white cell count.

Administration of chemotherapy in Cycles 1 – 6 should not begin until the ANC is \( \geq 1000 \text{ cells/mm}^3 \) and the platelet count is \( \geq 75,000/\text{mm}^3 \). While subjects with an ANC 1000 – 1499/\text{mm}^3 or platelet count 75,000 – 99,000/\text{mm}^3 may be able to proceed with therapy; recommended dose modifications are outlined in Table 11 and Table 12.
For the weekly regimen, the Day 8 and 15 weekly paclitaxel doses should not be given unless the ANC ≥ 500 cells/mm³ and the platelet count ≥ 50,000 cells/mm³. For subjects with an ANC < 500 cells/mm³ or platelets < 50,000 cells/mm³, the dose should be omitted and dose reductions should be used for the following cycle. Day 8 and/or Day 15 cycle days should be omitted in their entirety in the event of delays due to hematological toxicity. Within a given cycle, if the Day 8 dose is held and the counts recover by Day 15, the Day 15 dose may be given.

**During the Combination Phase in the event of chemotherapy delays/interruptions veliparib/placebo is continued in the absence of a dose-limiting toxicity as part of the same cycle.** A new cycle (subsequent cycle) is started when chemotherapy is restarted.

Guidelines for dose modifications and delays for hematological toxicity during the Combination Phase are summarized as follows:
| Table 10 | Dose Limiting Hematological Toxicities | Hold study therapy until recovered (including veliparib/placebo) Dose modification per Table 11 or Table 12 | If a subject experiences both a DLT and a delay for the same hematologic parameter (i.e., ANC) within a given cycle, only one dose modification is indicated |
| Table 11 | Q3-Week Dose Modifications for Dose Limiting Hematologic Toxicity, Reduced ANC or Platelets on D1, or Cycle Delay > 7 Days due to Hematologic Toxicity | Modifications should occur for the following: 1. Dose limiting hematological toxicities (Table 10) 2. Reduced ANC or Platelets on Day 1 • Delay of cycle Day 1 therapy if ANC < 1000/mm³ or Platelets < 75,000/mm³; • If ANC 1001 – 1499/mm³ or Platelets 75,000 – 99,000/mm³, the patient can be immediately treated with a dose reduction OR treatment can be delayed 1 week, to allow for hematologic recovery, and treatment resumed without dose reduction (per the investigator's discretion). 3. Delayed hematological recovery for > 7 days. | If ANC recovers to ≥ 1500/mm³ and Platelets recover to ≥ 100,000/mm³ within 7 days, no dose modification may be needed and cycle Day 1 can be reattempted. Veliparib/Placebo is continued despite chemotherapy delays in the absence of a DLT. Following a DLT, veliparib/placebo may be restarted when the ANC ≥ 1000/mm³ and Platelets ≥ 75,000/mm³ |
| Table 12 | Q-Week Dose Modifications for Dose-Limiting Hematologic Toxicity, Reduced ANC Platelets on D1, or Cycle Delay > 7 Days due to Hematologic Toxicity | Modifications should occur for the following: 1. Dose limiting hematological toxicities (Table 10) 2. Reduced ANC or Platelets on Day 1 • Delay of cycle Day 1 therapy if ANC < 1000/mm³ or Platelets < 75,000/mm³; • Dose reduce OR delay therapy if ANC 1001 – 1499/mm³ or Platelets 75,000 – 99,000/mm³ (per the Investigator's discretion); • Delayed hematological recovery for > 7 days. | If ANC recovers to ≥ 1500/mm³ and Platelets recover to ≥ 100,000/mm³ within 7 days, no dose modification may be needed and cycle Day 1 can be reattempted. Veliparib/Placebo is continued despite chemotherapy delays in the absence of a DLT. Following a DLT, veliparib/placebo may be restarted when the ANC ≥ 1000/mm³ and Platelets ≥ 75,000/mm³ |
| Table 13 | Q-Week Dose Modifications for Hematologic Toxicity on Day 8 or 15 | Day 8 and/or Day 15 paclitaxel should be omitted when ANC or platelets are not adequate ’on that day’ for treatment. | Not applicable |
Table 11.  Q3-Week Schedule Dose Modifications for Dose Limiting Hematologic Toxicity, Reduced ANC (1000 – 1499/mm$^3$) or Reduced Platelets (75,000 – 99,000/mm$^3$) on Day 1, or Cycle Delay > 7 Days due to Hematologic Toxicity

<table>
<thead>
<tr>
<th>ANC</th>
<th>PLT</th>
<th>First Occurrence*</th>
<th>Second Occurrence</th>
<th>Third Occurrence**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF</td>
<td>Reduce carboplatin one AUC unit (AUC 4)</td>
<td>Discontinue veliparib/placebo and notify AbbVie TA MD</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF</td>
<td>Reduce carboplatin one AUC unit (AUC 4)</td>
<td>Discontinue veliparib/placebo and notify AbbVie TA MD</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5)</td>
<td>Reduce carboplatin one AUC unit (AUC 4)</td>
<td>Discontinue veliparib/placebo and notify AbbVie TA MD</td>
</tr>
</tbody>
</table>

* GCSF should continue through the end of the Combination Phase, once initiated. Refer to the Guidelines for the Use of Hematopoietic Cytokines.

** If the subject has recovered within 7 days, dose modifications may not be needed and veliparib/placebo can be continued. Following recovery, Day 1 of the cycle is reattempted.

Note: For cycle delays > 21 days, notify the AbbVie TA MD.

Table 12.  Q-Week Schedule Dose Modifications for Dose-Limiting Hematologic Toxicity, Reduced ANC (1000 – 1499/mm$^3$) or Reduced Platelets (75,000 – 99,000/mm$^3$) on Day 1, or Cycle Delay > 7 Days due to Hematologic Toxicity

<table>
<thead>
<tr>
<th>ANC</th>
<th>PLT</th>
<th>First Occurrence*</th>
<th>Second Occurrence</th>
<th>Third Occurrence**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF</td>
<td>Discontinue Day 15 paclitaxel dose</td>
<td>Discontinue veliparib/placebo and notify AbbVie TA MD</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF</td>
<td>Reduce carboplatin one AUC unit (AUC 4) and discontinue Day 15 paclitaxel dose</td>
<td>Discontinue veliparib/placebo and notify AbbVie TA MD</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5)</td>
<td>Reduce carboplatin one AUC unit (AUC 4)</td>
<td>Discontinue veliparib/placebo and notify AbbVie TA MD</td>
</tr>
</tbody>
</table>

* GCSF should continue through the end of the Combination Phase, once initiated. Refer to the Guidelines for the Use of Hematopoietic Cytokines.

** If the subject has recovered within 7 days, dose modifications may not be needed and veliparib/placebo can be continued. Following recovery, Day 1 of the cycle is reattempted.
Table 12. Q-Week Schedule Dose Modifications for Dose-Limiting Hematologic Toxicity, Reduced ANC (1000 – 1499/mm$^3$) or Reduced Platelets (75,000 – 99,000/mm$^3$) on Day 1, or Cycle Delay > 7 Days due to Hematologic Toxicity (Continued)

Note: For cycle delays > 21 days, notify the AbbVie TA MD. For subjects who have had 2 dose reductions for reduced ANC, and then develop reduced platelets, an additional dose modification is allowed but should be discussed with the AbbVie TA MD. Alternatively, for subjects who have had 2 dose reductions for reduced platelets, and then develop reduced ANC, an additional dose modification is allowed but should be discussed with the AbbVie TA MD.

Table 13. Q-Week Dosing Schedule Modifications for Hematologic Toxicity on Day 8 or 15

<table>
<thead>
<tr>
<th>ANC &lt; 500</th>
<th>PLT &lt; 50</th>
<th>First Occurrence*</th>
<th>Second Occurrence</th>
<th>Third Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF with the next cycle</td>
<td>Discontinue Day 15 paclitaxel dose with the next cycle</td>
<td>Discontinue veliparib/placebo and notify AbbVie TA MD</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5) and add G-CSF with the next cycle</td>
<td>Reduce carboplatin one AUC unit (AUC 4) and discontinue Day 15 paclitaxel dose with the next cycle</td>
<td>Discontinue veliparib/placebo and notify AbbVie TA MD</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Reduce carboplatin one AUC unit (AUC 5) with the next cycle</td>
<td>Reduce carboplatin one AUC unit (AUC 4) with the next cycle</td>
<td>Discontinue veliparib/placebo and notify AbbVie TA MD</td>
</tr>
</tbody>
</table>

* GCSF should continue through the end of the Combination Phase, once initiated. Refer to the Guidelines for the Use of Hematopoietic Cytokines.

Note: Day 8 and/or Day 15 cycle days should be omitted in their entirety in the event of delays due to hematological toxicity.

For subjects who have had 2 dose reductions for reduced ANC, and then develop reduced platelets, an additional dose modification is allowed but should be discussed with the AbbVie TA MD. Alternatively, for subjects who have had 2 dose reductions for reduced platelets, and then develop reduced ANC, an additional dose modification is allowed but should be discussed with the AbbVie TA MD.

Modifications for Delayed Hematologic Recovery:

Dose modifications noted in Table 11 (Q3-weeks) and Table 12 (Q-week) should be considered for management of cycle Day 1 delays > 7 days for hematologic recovery (delays ≤ 7 days may not need a dose modification). Delay on the basis of neutropenia is
defined if the ANC is < 1000 cells/mm$^3$ within 24 hours prior to Day 1 of each cycle of scheduled therapy.

Delay on the basis of thrombocytopenia is defined if the platelet count is < 75,000/mm$^3$ within 24 hours prior to Day 1 of each cycle of scheduled therapy.

If a subject experiences delays for the same hematologic parameter within a given cycle, these are considered to be one occurrence and only one dose modification is indicated. If a subject experiences both a DLT and a delay for the same hematologic parameter (i.e., ANC) within a given cycle, only one dose modification is indicated.

**Guidelines for the Use of Hematopoietic Cytokines**

The use of hematopoietic cytokines is restricted as noted:

In general, subjects will NOT receive prophylactic filgrastim (G-CSF), PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless they experience therapy delays, dose omissions, or neutropenic complications as specified. In particular, hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, subjects may receive growth factors for the management of neutropenic complications in accordance with ASCO or institutional guidelines. Subjects who may be at increased risk of febrile neutropenia for whom prophylactic growth factors may be indicated (such as age 65 or older) should be discussed with the AbbVie TA MD prior to randomization.

If needed per dose modifications guidelines, it is recommended that filgrastim (dosed according to institutional standard) be administered daily subcutaneously, separated from chemotherapy by at least 24 hours. Pegfilgrastim should not be used for subjects receiving Day 15 paclitaxel as they do not have a 2-week chemotherapy-free interval. For subjects receiving Day 15 paclitaxel who require the addition of filgrastim per dose modification guidelines, it is recommended that doses be given daily on Days 16 – 18 of the cycle. If institutional guidelines allow for G-CSF to be administered at another time
during a cycle, this may be allowed per investigator discretion as long as it is given 24 hours apart from chemotherapy.

Growth factors as part of a dose modification should continue and be given on the same cycle days through the end of the Combination Phase, once initiated.

Subjects will NOT receive prophylactic thrombopoietic agents.

Subjects may receive erythropoietin, iron supplements, and/or transfusions as clinically indicated for management of anemia.

Treating physicians should be aware of the prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in subjects with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.

Subjects may NOT receive amifostine or other protective reagents.

5.7.1.2 Guidelines for Non-Hematologic Toxicity

Management of therapy related Grade 3 or Grade 4 non-hematological toxicity (excluding fatigue, nausea, vomiting, constipation, diarrhea, hypokalemia, hypomagnesemia, hypocalcemia, hyponatremia, and hypophosphatemia) should consider the dose level modifications as indicated specifically in this section. Table 14 below provides guidance on the dose levels for modifications related to non-hematologic toxicity. Dose modifications can be made for one drug at a time and do not require reducing all three drugs at once.
Table 14. Dose Levels for Modifications for Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen –2 Level</th>
<th>Regimen –1 Level</th>
<th>Regimen Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (Q3-week)</td>
<td>110 mg/m² Day 1</td>
<td>135 mg/m² Day 1</td>
<td>175 mg/m² Day 1</td>
</tr>
<tr>
<td>Paclitaxel (Q-week)</td>
<td>60 mg/m² Days 1, 8</td>
<td>80 mg/m² Days 1, 8</td>
<td>80 mg/m² Days 1, 8, 15</td>
</tr>
<tr>
<td>Carboplatin (Q-week and Q3-week)</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Veliparib/Placebo</td>
<td>50 mg BID</td>
<td>100 mg BID</td>
<td>150 mg BID</td>
</tr>
</tbody>
</table>

Note: Refer to the text below to determine which study drug(s) should be modified.

**Peripheral Neuropathy**

For grade 2 (or greater) peripheral neuropathy, paclitaxel should be reduced one dose level (both dosing schedules) and chemotherapy can be delayed for a maximum of three weeks until recovered to Grade 1.

**Veliparib/Placebo is continued despite chemotherapy delays in the absence of a dose-limiting toxicity.**

If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due, the AbbVie TA MD should be contacted. If Grade 2 (or greater) neuropathy recurs after 2 dose reductions of paclitaxel, the AbbVie TA MD should be contacted. Docetaxel may be substituted if neuropathy results in discontinuation of paclitaxel. **A washout of 7 days from veliparib/placebo is required before starting docetaxel. Veliparib/Placebo is not permitted in combination with docetaxel.**

Subjects requiring a switch to docetaxel during Cycles 1 – 6 will be allowed to proceed with veliparib/placebo monotherapy beginning in Cycle 7.

**Seizures**

Any event of seizure, regardless of grade or attribution requires discontinuation of veliparib/placebo and discussion with the AbbVie TA MD regarding the decision to resume treatment.
**Renal Toxicity**

Renal toxicity (associated with reduction in glomerular filtration rate [GFR]) is not expected from carboplatin as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule of the regimen. As such, there are no specific dose modifications for renal toxicity. However, the target AUC dose of carboplatin must be recalculated each cycle in any subject who develops renal insufficiency, defined by serum creatinine $>1.5 \times$ ULN, Grade $\geq 2$.

**Hepatic Toxicity**

Hepatic toxicity is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel and delay in subsequent therapy for a maximum of three weeks until recovered to $\leq$ Grade 1. If Grade 3 (or greater) elevations do not recover within three weeks or recur despite dose modification, the AbbVie TA MD should be contacted.

**Hypersensitivity Reaction**

In general, the occurrence of a hypersensitivity reaction to carboplatin or paclitaxel is not considered a dose-limiting toxicity. Subjects may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made. However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the subject will discontinue this agent. Severe hypersensitivity reactions to paclitaxel do not have to proceed with a rechallenge. Docetaxel may be substituted for paclitaxel. A washout of 7 days from veliparib/placebo is required before starting docetaxel. **Veliparib/Placebo is not permitted in combination with docetaxel.** Subjects requiring a switch to docetaxel during Cycles 1 – 6 will be allowed to proceed with veliparib/placebo monotherapy beginning in Cycle 7.
Subjects receiving docetaxel who experience either febrile neutropenia, neutrophils $<500$ cells/mm$^3$ for more than 7 days or severe or cumulative cutaneous reactions during docetaxel therapy should have the docetaxel dose reduced. If the subject continues to experience these reactions, the dosage should be discontinued. Conversely, subjects who do not experience febrile neutropenia, neutrophils $<500$ cells/mm$^3$ for more than 7 days, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during docetaxel therapy may be able to tolerate higher doses at the Investigator's discretion and careful monitoring. Those subjects who experience grade 3 or greater peripheral neuropathy should discontinue docetaxel therapy.

**Other Toxicity**

There will be no dose modifications for alopecia, nausea, constipation, diarrhea, hypokalemia, hypocalcemia, hypomagnesemia, hyponatremia, hyponatremia, or hypophosphatemia. It is recommended that routine medical measures be employed to manage nausea, constipation, diarrhea, and electrolyte abnormalities.

**Nausea, Vomiting, or Fatigue**

Nausea, vomiting, or fatigue $\geq$ Grade 3 which persists despite supportive medications with symptoms thought to be secondary to veliparib/placebo and not related to carboplatin, paclitaxel, or disease progression, veliparib/placebo should be held until symptoms resolve to $\leq$ Grade 1. These cases should be discussed with the AbbVie TA MD, as it is unlikely for veliparib to be the predominant cause of nausea, vomiting, or fatigue during the combination phase. Veliparib/Placebo should then be restarted at the next lower dose level. No more than 2 dose reductions are allowed prior to discontinuation of veliparib/placebo.

If veliparib/placebo is discontinued during Cycles 1 – 6, the subject will resume veliparib/placebo dosing with Cycle 7 (the maintenance phase) if therapy toxicity resolves to $\leq$ Grade 1.

Dose modifications for other non-hematologic toxicities will occur as follows:
- For any Grade 3 non-hematologic adverse event (except controllable nausea/vomiting, constipation, diarrhea, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, or hyponatremia) considered to be related to study treatment, therapy should be held until symptoms resolve to ≤ Grade 1 or to baseline and reduce the dose of the drug(s) most likely to have caused the toxicity by one dose level. If a Grade 3 adverse event persists for > three weeks or recurs after resumption of therapy, the subject may be taken off therapy after discussing with the AbbVie TA MD.

- Any Grade 4 non-hematologic adverse event (except controllable nausea/vomiting, constipation, diarrhea, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, or hyponatremia) considered to be related to therapy should be discussed with the AbbVie TA MD and the subject may either be taken off therapy or dose reductions implemented.

5.7.2 Veliparib/Placebo Monotherapy Dose Reductions and Delays (Cycles 7 – 36)

Subjects who complete six cycles of carboplatin and paclitaxel and who have not progressed will receive single-agent, blinded veliparib/placebo starting at 300 mg. If subjects have discontinued veliparib/placebo during the Combination Phase, veliparib/placebo may be reinitiated at 300 mg during the Maintenance Phase once therapy related toxicity resolve to ≤ Grade 1 or baseline.

Subjects should have an ANC ≥ 1,000/mm$^3$ and a platelet count ≥ 75,000/mm$^3$ prior to initiating all cycles during maintenance.

If the subject tolerates 300 mg BID, veliparib/placebo should be increased to 400 mg BID during the Maintenance Phase. If the subject is not tolerating 300 mg BID, the AbbVie TA MD should be contacted. Additionally, the following are guidelines for dose reductions, delays and discontinuation of veliparib/placebo monotherapy as needed for toxicities thought to be related to veliparib/placebo. Subjects will follow the schedule of procedures outlined in Table 1.
For any subject who experiences Grade 3 or 4 toxicity despite optimal supportive care (with the exception of anemia and non-treatment related clinically insignificant laboratory abnormalities), and the toxicity is not attributable to underlying disease, the veliparib/placebo dose will be held until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 is present at the time of study entry.

Interruptions of study drug for events that are clearly not related to therapy (e.g., underlying cancer, planned surgical procedures, or acute viral illnesses), do not necessitate a dose reduction.

The timing of the dose resumption should be at the Investigator's discretion. In the cases of delays, tumor assessments should continue per Table 1.

The dose of veliparib/placebo may be reduced by one dose level (per Table 15) for subjects experiencing the following toxicities if attributed to veliparib/placebo:

**Hematological Toxicities**

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

**Non-Hematological Toxicities**

- Any CTCAE ≥ Grade 3 toxicity that represents at least 2 grade increase from baseline with the following clarifications:
  - Excludes nausea, vomiting, diarrhea, and tumor pain that have not received optimal treatment with antiemetics, antidiarrheals, or analgesics.
  - A rise in creatinine to Grade 3, only if not corrected to Grade 1 or baseline within 24 hours with IV fluids.
  - Metabolic toxicities, only if unable to be corrected to Grade 2 or less within 24 hours (such as glucose changes, hypokalemia, hypomagnesemia, hyperuricemia, hypophosphatemia, and hyponatremia). Grade 4 metabolic...
toxicities that are symptomatic will result in dose reduction regardless of duration or ability to correct.

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

Re-escalation may be permitted if toxicity has resolved to Grade 1 or lower and can be maintained with optimal supportive care. In addition, temporary dose reductions or interruptions may be allowed for Grade 1 or 2 nausea or vomiting that remain intolerable despite optimal treatment. This should be discussed with the AbbVie TA MD.

Table 15. Veliparib/Placebo Monotherapy Dose Levels

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Veliparib/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose Level</td>
<td>300 mg BID (if unable to escalate dose due to toxicity then continue current dose)</td>
</tr>
<tr>
<td>Dose Level +1</td>
<td>400 mg BID</td>
</tr>
<tr>
<td>Dose Level –1</td>
<td>300 mg BID</td>
</tr>
<tr>
<td>Dose Level –2</td>
<td>250 mg BID*</td>
</tr>
</tbody>
</table>

* If veliparib 250 mg/placebo BID is not tolerable, veliparib/placebo will be interrupted or discontinued. There will be no dose reductions below the 250 mg BID dose.

**Gastrointestinal Toxicities: Nausea or Vomiting**

Gastrointestinal toxicities, predominantly nausea and vomiting, are observed with veliparib as single-agent therapy (300 – 400 mg BID). These toxicities most commonly occur within first few days or weeks of treatment and are most often Grade 2 or lesser severity. In Phase 1 and Phase 2 studies, approximately 5% of subjects have experienced Grade 3 nausea during the first 4 weeks of treatment at 400 mg BID veliparib, and approximately 15% dose reduce, 2% discontinue and 5% delay or interrupt dosing due to nausea at 300 – 400 mg BID dose levels.

To optimize dose intensity and maintain subject quality of life, early initiation or prophylactic management with scheduled anti-emetic therapy (5HT-3 antagonists,
metoclopramide, prochlorperazine) and/or lorazepam should be considered when subjects begin the maintenance phase. In addition, management should include counseling regarding these toxicities and may include brief interruption of dosing or dose modification. As this is based upon a retrospective review of Phase 1 and 2 data, investigators should also rely on standard clinical practice and guidelines for nausea management.

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 the study drugs, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with 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. Worsening in severity of a reported adverse event should be reported as a new 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 6.8 regarding toxicity management]) and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a 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. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

All protocol-related nonserious AEs must be collected from the signing of the study specific informed consent until therapy administration. In addition, adverse events with onset or worsening reported by a subject from the time that the first dose of study drug (veliparib or placebo) is administered until 30 days have elapsed following discontinuation of study drug administration will be considered as treatment-emergent adverse events.

6.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie 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.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-Threatening</td>
<td>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.</td>
</tr>
<tr>
<td>Hospitalization or Prolongation of Hospitalization</td>
<td>An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility hospitalization for respite care, or hospitalization due solely to progression of the underlying cancer.</td>
</tr>
<tr>
<td>Congenital Anomaly</td>
<td>An anomaly detected at or after birth, or any anomaly that results in fetal loss.</td>
</tr>
<tr>
<td>Persistent or Significant Disability/Incapacity</td>
<td>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).</td>
</tr>
<tr>
<td>Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome</td>
<td>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). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. 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.</td>
</tr>
</tbody>
</table>

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 Events Expected Due to Ovarian, Fallopian Tube, or Primary Peritoneal Cancer or Progression of Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Events that are clearly consistent with ovarian cancer or the expected progression of ovarian cancer, including but not limited to abdominal pain, abdominal distension, ascites, intestinal obstruction, colonic obstruction, small intestinal obstruction, pleural effusion, and constipation should be considered as expected. A list of expected adverse events is presented in Appendix H of the protocol. These adverse events may occur alone or in various combinations and are considered expected adverse events in ovarian subjects.

6.3 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 Published: May 28, 2009 (v4.03: June 14, 2010).

For adverse events not captured by the NCI CTCAE Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010), 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.

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 eCRFs also need to be updated and need to include the new AE serial number.

### 6.4 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study therapies (for the purpose of this section, therapy is considered veliparib/placebo plus carboplatin/paclitaxel):

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

The Investigator will assess the relationship of each adverse event to veliparib, to carboplatin, to paclitaxel, and to ovarian cancer. Most events will be reasonably related to one treatment or to ovarian cancer, though some events may be reasonably related to more than one or to none. For causality assessments, events assessed as having a reasonable possibility of being related to veliparib will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the Investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of no reasonable possibility of being related to veliparib, to carboplatin, to paclitaxel, and to ovarian cancer is given, an Other cause of event must be provided by the Investigator for the serious adverse event.

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

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

Adverse event information will be collected as shown in Figure 3.

**Figure 3. Adverse Event Collection**

<table>
<thead>
<tr>
<th>Protocol-Related SAEs* &amp; AEs**</th>
<th>SAEs and Nonserious AEs Elicited and/or Spontaneously Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Signed Study Drug Start</td>
<td>Study Drug Stopped After Study Drug Stopped</td>
</tr>
</tbody>
</table>

* SAEs and AEs will be reported 30 days following the completion of veliparib/placebo and/or carboplatin/paclitaxel (whichever treatment occurs last). Significant AEs (Grade 3/4) and SAEs considered by the Investigator as having a reasonable possibility of being related to veliparib/placebo and carboplatin/paclitaxel should be reported to AbbVie during the Long term Follow-up Period after the subject experiences progression, at the Investigator's discretion.

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

### 6.6 Adverse Event Reporting

#### 6.6.1 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (Section 6.5) that are more likely related to disease progression will therefore be an expected adverse event and will not be an expedited report.
Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms, or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

6.6.2 Lack of Efficacy or Worsening of Disease

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

6.6.3 Reporting Serious Adverse Events

In the event of a serious adverse event, whether associated with therapy 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 EDC system (RAVE®). Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE® is not operable should use the SAE Non-CRF paper forms and send them to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Serious adverse events which are considered expected due to the underlying ovarian, fallopian tube, or primary peritoneal cancer as described in Section 6.2 would not be expedited as individual safety case reports to regulatory authorities.
For safety concerns, contact the Therapeutic Area Safety Team at:

Oncology Safety Team
1 North Waukegan Road
North Chicago, IL 60064

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

Medical Monitor:
Primary Therapeutic Area Medical Director:

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:**

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 reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure for veliparib or SmPC for carboplatin and paclitaxel.

In Japan, the principal investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

### 6.7 Pregnancy

In the event of a positive pregnancy test, subjects must immediately discontinue study drugs and must be discontinued from the study. The Investigator must report the positive
pregnancy test to the appropriate contact listed in protocol Section 6.6 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 therapy (veliparib/placebo). 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.

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.

6.8 Toxicity Management

Management of toxicity should be performed by Investigators according to standard medical practice and according to local label for toxicity due to carboplatin or paclitaxel. Guidelines for carboplatin, paclitaxel, and veliparib/placebo dose reductions and delays are provided in Section 5.7.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and the following AbbVie Clinical Monitors:
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.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.
8.0 **Statistical Methods and Determination of Sample Size**

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a one-sided $P$ value $\leq 0.025$.

The date of randomization (enrollment) is defined as the date that the Interactive Response Technology (IRT) issues a randomization number.

The primary, secondary, and exploratory efficacy analyses will be performed on the intent-to-treat (ITT) population.

All subjects who receive at least one dose of veliparib/placebo will be included in the safety analysis.

**8.1 Statistical and Analytical Plans**

**8.1.1 Baseline Characteristics**

All baseline summary statistics and analyses will be based on characteristics obtained prior to randomization. Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to randomization.

Baseline characteristic data will be summarized with all randomized subjects for Arms 1, 2, and 3 of the study separately.

**8.1.1.1 Demographics**

Continuous demographic variables such as age, height, and weight will be summarized with means, standard deviation and range. Frequencies and percentages will be computed for the categorical parameters such as race, gender, $BRCA$-deficiency status, stage of the disease, residual disease, choice of regimen, and region.

**8.1.1.2 Medical History**

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 endpoint is progression-free survival (PFS). PFS will be defined as the number of days from the date that the subject was randomized to the date the subject experiences an event of disease progression, according to RECIST criteria version 1.1 (as determined by the investigator) or to the date of death (all causes of mortality) if disease progression is not reached. All events of disease progression (as determined by the investigator) will be included, regardless of whether the event occurred while the subject was still taking study drug (veliparib or placebo containing regimen) or had previously discontinued study drug. However, if a disease progression event occurs after a subject misses two or more consecutive disease progression assessments this subject will be censored at the last disease progression assessment prior to the missing disease progression assessments. All events of death will be included for subjects who had not experienced disease progression provided the death occurred within the expected time windows defined according to the underlying disease assessment interval (every 9 weeks, then at the end of the Combination Phase, then every 12 weeks for 2 years, then every 6 months for 3 years, and then annually). If the subject does not have an event of disease progression (as determined by the investigator) nor has the subject died, the subject's data will be censored at the date of the subject's last disease assessment.

The primary efficacy analyses are defined by comparing PFS in Arm 3 versus Arm 1 in the BRCA-deficient population, HRD population and whole population. The study will be successful if the first analysis in the multiplicity testing procedure described in Section 8.1.4 (comparison of PFS [Arm 3 vs. Arm 1] in the BRCA-deficient population) is statistically significant. If this comparison is statistically significant, the other primary endpoints will be analyzed for statistical significance in the specified order.

The distribution of PFS will be estimated for each treatment arm using Kaplan-Meier methodology. For the whole population, PFS will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease
and BRCA-deficient status. For the BRCA-deficient population and HRD population, PFS will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease.

Median PFS time will be estimated and 95% confidence interval for the estimated median PFS time will be presented for each treatment arm.

Additional details regarding the primary analyses including the final list of stratification factors to be used will be specified in the final SAP prior to unblinding of the data.

8.1.2.2 Secondary EfficacyEndpoints

8.1.2.2.1 Progression Free Survival (PFS)

PFS will also be compared between Arm 2 and Arm 1 as a secondary analysis, following the same methodology as the primary analysis.

8.1.2.2.2 Overall Survival (OS)

OS 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 (veliparib or placebo containing regimen), 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.

The secondary efficacy analyses for OS are defined by comparing OS in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the BRCA-deficient, HRD, and whole population.

The distribution of OS will be estimated for each treatment arm using Kaplan-Meier methodology. For the whole population, OS will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and BRCA-deficient status. For the BRCA-deficient population and HRD population, OS will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease.
Median OS time will be estimated and 95% confidence interval for the estimated median OS time will be presented for each treatment arm.

8.1.2.2.3 Patient Reported Outcomes

**Disease Related Symptoms (DRS) Score**

The overall mean change from baseline for the NFOSI-18 DRS scores measured at each assessment point up to 2 years or disease progression will be a secondary endpoint of the study. The overall mean change from baseline for the total DRS scores between the treatment groups will be compared using a longitudinal repeated measures model that takes into account the DRS scores measured at each assessment point up to 2 years or disease progression with analysis of appropriate timepoints as indicated.

8.1.2.3 Tertiary Efficacy Endpoints

8.1.2.3.1 PFS2, TTFST, and TTSST

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

Time to the first subsequent therapy (TTFST) will be defined as the number of days from the day the subject is randomized to the start of the first subsequent therapy or death of any cause. If the subject does not have an event of TTFST, the subject's data will be censored at the date of the subject's last visit or survival follow-up.

Time to the second subsequent therapy (TTSST) will be defined as the number of days from the day the subject is randomized to the start of the second subsequent therapy or death of any cause. If the subject does not have an event of TTSST, the subject's data will be censored at the date of the subject's last visit or survival follow-up.
PFS2, TTFST, and TTSST will be summarized and analyzed using the same methodologies as PFS.

### 8.1.2.3.2 Additional PRO Endpoints

Additional analyses based on other PRO endpoints will be specified either in the SAP or in a separate PRO analysis plan.

### 8.1.3 Interim Efficacy Analyses for OS

Overall survival is expected to mature at month 58 in the whole population and at month 77 for the *BRCA*-deficient and HRD populations.

For the OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the *BRCA*-deficient population and the HRD population, two efficacy interim analyses will be performed. The first interim analysis will occur at the time of the final PFS analysis (~Month 36) with a nominal alpha of 0.0001, and the second interim analysis will occur at the time of the OS analysis for the whole population (~Month 58) with a nominal alpha of 0.0001, so that the final OS analyses in each population (~Month 77) have a nominal alpha of 0.0248 if all null hypotheses tested at the time of the primary analysis are rejected.

For the OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the whole population, one efficacy interim analysis will be performed at the time of the final PFS analysis (~Month 36) with a nominal alpha of 0.0001, so that the final OS analyses (~Month 58) have a nominal alpha of 0.0248 if all null hypotheses tested at the time of the Primary Analysis and the OS hypotheses (Arm 3 versus Arm 1) in the *BRCA*-deficient population and HRD population are rejected.

The nominal alpha of the final OS analyses may be slightly different as the timings of the interims are rough estimates. Additional details regarding the secondary analyses including the interim efficacy analyses for OS will be specified in the final SAP prior to unblinding of the data.
8.1.4 Multiplicity Adjustment

This is a three-arm, randomized, placebo-controlled Phase 3 clinical trial. All of the subjects will receive six cycles of carboplatin and paclitaxel. In addition to the chemotherapy, subjects will be randomly allotted to receive either placebo or veliparib. While 6 cycles of chemotherapy are planned, the randomized treatment (placebo or veliparib) will be continued during a maintenance phase of treatment for a maximum of 36 total cycles of veliparib/placebo.

Table 16. Study Treatment Arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: C/P + placebo → placebo</td>
<td>Reference regimen</td>
</tr>
<tr>
<td>Arm 2: C/P + veliparib → placebo</td>
<td>Veliparib administered in the combination therapy phase only</td>
</tr>
<tr>
<td>Arm 3: C/P + veliparib → veliparib</td>
<td>Veliparib administered in both combination therapy and maintenance therapy phases</td>
</tr>
</tbody>
</table>

Note: [+ ] indicates 'concurrent with;' [→ ] indicates 'followed by;' [C/P] indicates 'backbone chemotherapy' (i.e., carboplatin/paclitaxel).

There are three populations of interest: the BRCA-deficient population, HRD population, and whole population.

In each population, the hypotheses of interest are listed below in Table 17.

Table 17. The Null Hypotheses of Interest in Each Population

<table>
<thead>
<tr>
<th>PFS (Arm 3 versus Arm 1)</th>
<th>PFS (Arm 2 versus Arm 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (Arm 3 versus Arm 1)</td>
<td>OS (Arm 2 versus Arm 1)</td>
</tr>
<tr>
<td>DRS (Arm 3 versus Arm 1)*</td>
<td>DRS (Arm 2 versus Arm 1)*</td>
</tr>
</tbody>
</table>

PFS = Progression Free Survival; OS = Overall Survival; DRS = Disease Related Symptom

* No alpha allocation on this test.

Note: PFS (Arm 3 versus Arm 1) denotes the null hypothesis: Arm 3 (C/P + veliparib → veliparib) does not increase PFS compared to Arm 1 (C/P + placebo → placebo). Other PFS and OS notations in this table are defined similarly. DRS (Arm 3 versus Arm 1) denotes the null hypothesis of no difference in DRS scores between Arm 3 and Arm 1. DRS (Arm 2 versus Arm 1) is defined similarly.
The expected proportion of *BRCA*-deficient subjects is approximately 24% in the whole population. Test results will be available for all subjects during the trial.

*BRCA* testing data available as of July 2018 suggest that the final proportion of subjects with *BRCA*-deficient status will be approximately 25%, thus meeting the criteria under the original protocol to include the *BRCA*-deficient population in the testing sequence. Therefore, an alternate testing sequence scenario to account for a low (< 18%) proportion of *BRCA*-deficient subjects, as proposed in the original protocol, will not be needed for the analyses.

Emerging data during the course of this trial has supported the increasing use of PARP inhibitors in patients with ovarian, fallopian tube, and primary peritoneal cancer. In 2017, niraparib maintenance therapy was shown to provide improvement in outcomes (PFS) for all patients with platinum-sensitive, recurrent ovarian cancer. While the largest improvement was seen in patients with *gBRCA* mutations (HR = 0.27, 95% CI = 0.17 - 0.41), a significant benefit was also observed in the HRD population (HR = 0.30, 95% CI = 0.22 - 0.41). Similarly, rucaparib has also demonstrated benefit in patients with high loss of heterozygosity (LOH) scores (HR = 0.32, 95% CI = 0.24 - 0.42). The addition of a third subgroup analysis (HRD population) to the primary endpoint was thus incorporated into the study design to test the hypothesis that veliparib would also benefit patients with *BRCA*-like mutations.

Since subject randomization was not prospectively stratified by HRD status, two testing scenarios are proposed below dependent on the level of the balance of treatment arms within the HRD population:

- If there is little to no evidence of a severe treatment imbalance in the HRD population, then the fixed sequential testing sequence will be applied as outlined in Scenario 1 below.
- If there is severe treatment imbalance in the HRD population, the truncated Hochberg multiplicity adjustment will be applied as outlined in Scenario 2 below.
The criteria to determine if a severe treatment imbalance is present will be outlined in the SAP and this criterion will be finalized prior to any unblinding for the primary PFS analysis. The use of either Scenario 1 or Scenario 2 will be made after unblinding, using the pre-determined criteria for imbalance.

**Figure 4. Testing Procedures Under Scenario 1**
Scenario 1: Testing sequence if there is no treatment imbalance in the HRD population

- A fixed-sequence testing procedure will be used to control the Type I error rate at 0.05 from the primary efficacy endpoint sequentially through the secondary efficacy endpoints. Each of the comparisons in this sequence will be tested at a 1-sided 0.025 level (approximately, due to spending 0.0001 on analyses of OS). There will be no multiplicity adjustment on the DRS scores or the tertiary efficacy endpoints.

At month 36 (alpha = 0.0249),
1. Test PFS (Arm 3 versus Arm 1) in \textit{BRCA}\textendash deficient population,
2. Test PFS (Arm 3 versus Arm 1) in HRD population,
3. Test PFS (Arm 3 versus Arm 1) in whole population
   - In parallel, alpha = 0.0001 will be spent on interim OS analyses
At month 58 when OS matures in the whole population, alpha = 0.0001 will be spent on second interim OS analyses for \textit{BRCA}\textendash deficient and HRD populations.
At month 77 (alpha = 0.0248, provided all preceding null hypotheses in the hierarchical testing sequence at month 36 are rejected)
1. Test OS (Arm 3 versus Arm 1) in \textit{BRCA}\textendash deficient population,
2. Test OS (Arm 3 versus Arm 1) in HRD population,
3. Test OS (Arm 3 versus Arm 1) in whole population (based on data from month 58)
4. Test PFS (Arm 2 versus Arm 1) in \textit{BRCA}\textendash deficient population (based on data from month 36),
5. Test PFS (Arm 2 versus Arm 1) in HRD population (based on data from month 36),
6. Test PFS (Arm 2 versus Arm 1) in whole population (based on data from month 36)
7. Test OS (Arm 2 versus Arm 1) in \textit{BRCA}\textendash deficient population (based on data from month 77),
8. Test OS (Arm 2 versus Arm 1) in HRD population (based on data from month 77),
9. Test OS (Arm 2 versus Arm 1) in whole population (based on data from month 58)
Scenario 2: Testing Sequence if there is treatment imbalance in the HRD population

- The entire one-sided type I error of 0.025 (approximately, due to spending 0.0001 on analyses of OS) will be allocated to the below testing sequence:

1. In the BRCA-deficient population, test PFS (Arm 3 versus Arm 1) at level 0.0249,
   - If it is rejected, proceed to Step 2,
   - Otherwise, stop and accept subsequent hypotheses.

2. Test PFS (Arm 3 versus Arm 1) in both the HRD (hypothesis 1, H₁) and whole populations (hypothesis 2, H₂) using a truncated Hochberg procedure (with gamma = 0.8) at level α = 0.0249 as follows: Order the two P values from H₁ and H₂ such that \( P(1) < P(2) \). Denote the ordered hypotheses as H(1) and H(2).
   - If \( P(2) \leq 0.02241 \) then reject both hypotheses and proceed to Step 3,
   - Otherwise, if \( P(1) \leq 0.01245 \), then reject only H(1) and proceed to Step 3,
   - Otherwise, stop and accept H(1) and H(2), and all subsequent hypotheses

3. At month 77, the same hierarchical testing strategy that is described in Scenario 1 will be applied at alpha = 0.0248 if both null hypotheses in Step 2 above are rejected, and at alpha = 0.00239 if only one null hypothesis is rejected. If only one null hypothesis in Step 2 is rejected, then the population for which the hypothesis was not rejected will not be included in the testing sequence.

For the truncated Hochberg Procedure, the following formulas are used to calculate the two alphas used to test the two hypotheses:

\[
\alpha_1 = (\alpha/2)
\]
\[
\alpha_2 = (\gamma)(\alpha) + (1 - \gamma)(\alpha/2)
\]
Here, $0 \leq \gamma \leq 1$; such that using $\gamma = 0$ results in Bonferroni method, and using $\gamma = 1$ results in full Hochberg Procedure. With total $\alpha = 0.0249$, choosing $\gamma = 0.8$ gives an $\alpha_1 = 0.01245$ and $\alpha_2 = 0.02241$. If $P(2) \leq \alpha_2$, then both hypotheses are rejected and the full alpha is passed to subsequent hypotheses. If $P(2) > \alpha_2$ and $P(1) \leq \alpha_1$, then only $H(1)$ is rejected and the reduced $\alpha_r = (\alpha - \alpha_2) = 0.00249$ is passed to subsequent hypotheses. Spending 0.0001 alpha on OS analyses at month 58 yields a final alpha = 0.00239 on hypotheses in the testing sequence. This controls the overall type I error rate at one-sided 0.025 level.

The criteria to determine the final multiple testing procedure will be specified in the final statistical analysis plan (SAP) before the database is locked. Once the data are unblinded, the treatment balance in the HRD population will be tested and either Scenario 1 or Scenario 2 will be chosen based solely on the pre-specified criteria. The algorithm to determine the final testing procedure will only utilize results of HRD testing and treatment allocation, and will not utilize any efficacy or safety data, so no bias or inflation of type I error is expected.

### 8.1.5 Safety

The safety of veliparib 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 were randomized but did not receive study drug (veliparib or placebo containing regime) will not be included in the analyses of safety.

#### 8.1.5.1 Duration of Study Drug

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

#### 8.1.5.2 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 summarized by preferred terms within a System and Organ Class according to the most current Medical Dictionary for Regulatory Activities (MedDRA) dictionary. In addition, the percentage of subjects experiencing an adverse event at a NCI CTCAE Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010) toxicity grade, and relationship to study drug will be provided. The percentages of subjects experiencing an adverse event will be compared between Arm 2 and 3 versus Arm 1 using Fisher's exact test.

The frequencies and percentages of subjects experiencing a treatment-emergent Grade 3 or Grade 4 peripheral neuropathy will be summarized and compared between the treatment arms using CMH test stratified by the stratification factors.

8.1.5.3 Serious Adverse Events

Serious adverse events will be summarized using the same methods as Adverse Events described above.

8.1.5.4 Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of the last dose of study drug, (2) for deaths occurring more than 30 days of 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.

8.1.5.5 Analyses of Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, then an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after
the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. Comparisons of the differences in mean changes from baseline for Arm 2 and 3 versus Arm 1 will be made using ANOVA with treatment group as the factor for each post-baseline visit.

8.1.5.6 Analyses of Laboratory Data Using NCI CTCAE

Where applicable, blood chemistry and hematology determinations will be categorized according to NCI CTCAE version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010), and shifts from baseline NCI CTCAE 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 last post-baseline measurement collected no more than 30 days after the last dose of study drug.

The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post baseline grades of 3 to 4 will be compared between Arm 2 and 3 and Arm 1 using Fisher's exact test.

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.

8.1.6 Pharmacokinetic Analysis

The pharmacokinetic parameters of rate of absorption (Ka), apparent volume of distribution (V/F) and oral clearance (CL/F) for veliparib may be estimated using a nonlinear mixed-effect population modeling approach with NONMEM software and reported in a separate pharmacokinetic report.
8.2 Determination of Sample Size

The study originally aimed to power for the PFS and OS endpoints in both the whole and the *BRCA*-deficient populations. The update to the multiplicity adjustment will change the power as described under the original protocol, particularly in the whole population. Hence, fewer events will be required for the primary analysis in the whole population as compared to original estimates (391 versus 446).

8.2.1 Total Sample Size

The trial will enroll approximately 1100 subjects (with 1:1:1 randomization ratio for Arm 1:Arm 2:Arm 3) in the whole population, including approximately 264 subjects with *BRCA*-deficient status (assuming 24% of the subjects in the whole population are *BRCA*-deficient) to power the hypotheses specified in the whole and *BRCA*-deficient populations. Detailed sample size calculation information for each endpoint of the *BRCA*-deficient, HRD, and whole populations is provided in Table 18 and Table 19.

8.2.2 For the Hypotheses in the Whole Population

**PFS (Arm 3 Versus Arm 1):**

Testing of PFS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the whole population. According to the original protocol, the power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a PFS hazard ratio of 0.7 in Arm 3 versus Arm 1, up to a total of 446 events would be needed for the test to have 94% power to detect a statistically significant treatment effect. Assuming a median PFS of 15.5 months in Arm 1 and an enrollment period of 18 months, and taking into account a dropout rate of 10%, approximately 367 subjects were needed per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) in order to have a matured PFS endpoint at around 36 months.

Based on the revised testing procedures (Figure 4 [Scenario 1] and Figure 5 [Scenario 2]), and keeping all other assumptions above the same, the power based on the log-rank test at
a one-sided alpha level of 0.025 (Scenario 1), 0.0224, and 0.0125 (Scenario 2) are 96.5%, 96.1%, 93.6%, respectively. The actual alpha level will depend on the testing scenario, and the ordering of the p-values between the HRD population and the Whole population if under Scenario 2. Power calculations based on 391 events are provided in Table 18 and Table 19.

**PFS (Arm 2 Versus Arm 1):**

Testing of PFS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo→ placebo) in the whole population. The original protocol specified that this hypothesis would be assessed with the stratified log-rank test at a one sided alpha level of 0.00625 or 0.0125 based on the Hochberg procedure. The power calculation for this hypothesis was based on the log-rank test at a one-sided alpha level of 0.00625. Assuming a PFS hazard ratio of 0.7 in Arm 2 versus Arm 1, up to a total of 446 events would be needed for the test to have 90% power to detect a statistically significant treatment effect based on the alpha level of 0.00625. Assuming median PFS of 15.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10%, approximately 367 subjects were needed per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) to have a mature PFS endpoint at around 36 months.

Based on the revised testing procedures (Figure 4 [Scenario 1] and Figure 5 [Scenario 2]), and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.025 is 96.5%. Using a one-sided alpha level of 0.0024, the power is 83.1%. The actual alpha level will depend on the Testing Scenario, and on the outcome of testing PFS of 3vs1 in the HRD and Whole populations if under Scenario 2. Power calculations based on 391 events are provided in Table 18 and Table 19.

**OS (Arm 3 Versus Arm 1):**

Testing of OS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the OS event rate relative to reference
regimen in Arm 1 (C/P + placebo → placebo) in the whole population. According to the original protocol, this hypothesis would be assessed with the stratified log-rank test at a one sided alpha level of 0.00625 or 0.0125. The power calculation for this hypothesis was based on the log-rank test at a one-sided alpha level of 0.00625. Assuming an OS hazard ratio of 0.7 in Arm 3 versus Arm 1, up to a total of 350 events would be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming a median OS of 41.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10% and an efficacy interim analysis that occurs at the time of the PFS analysis, approximately 367 subjects were needed per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) to have a mature OS endpoint at around 58 months.

Based on the revised testing procedures (Figure 4 [Scenario 1] and Figure 5 [Scenario 2]), and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.025 is 91.5%. Using a one-sided alpha level of 0.0024, the power is 70%. The actual alpha level will depend on the outcomes of the preceding tests in the testing sequence.

**OS (Arm 2 Versus Arm 1):**

Testing of OS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the whole population. According to the original protocol, the power calculation for this hypothesis was based on the log-rank test at a one-sided alpha level of 0.0125. Assuming an OS hazard ratio of 0.7 in Arm 2 versus Arm 1, up to a total of 350 events would be needed for the test to have 86% power to detect a statistically significant treatment effect. Assuming a median OS of 41.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10% and an efficacy interim analysis that occurs at the time of the PFS analysis, approximately 367 subjects were needed per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) to have a mature OS endpoint at around 58 months.
Based on the revised testing procedures (Figure 4 [Scenario 1] and Figure 5 [Scenario 2]), and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.025 is 91.5%. Using a one-sided alpha level of 0.0024, the power is 70%. The actual alpha level will depend on the outcomes of the preceding tests in the testing sequence.

8.2.3 For the Hypotheses in the BRCA-Deficient Population

**PFS (Arm 3 Versus Arm 1):**

Testing of PFS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. According to the original protocol, the power calculation for this hypothesis was based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a hazard ratio for PFS of 0.5 in Arm 3 versus Arm 1, up to a total of 79 events would be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming median PFS of 21 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) were needed to have a matured PFS endpoint at around 36 months taking into account of a dropout rate of 10%.

Based on the revised testing procedures (Figure 4 [Scenario 1] and Figure 5 [Scenario 2]), and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.025 is 87%.

**PFS (Arm 2 Versus Arm 1):**

Testing of PFS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. According to the original protocol, the power calculation for this hypothesis was based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a hazard ratio for PFS of 0.5 in Arm 2 versus Arm 1, up to a total of 79 events would be needed for the test to have
80% power to detect a statistically significant treatment effect. Assuming median PFS of 21 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) were needed to have a matured PFS endpoint at around 36 months taking into account of a dropout rate of 10%.

Based on the revised testing procedures (Figure 4 [Scenario 1] and Figure 5 [Scenario 2]), and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.0248 is 87%. If under Scenario 2, only one of HRD or Whole is significant, then the power based on the log-rank test at a one-sided alpha level of 0.0024 is 61%.

**OS (Arm 3 Versus Arm 1):**

Testing of OS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the *BRCA*-deficient population.

According to the original protocol, the power calculation for this hypothesis was based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a hazard ratio for OS of 0.5 in Arm 3 versus Arm 1, up to a total of 79 events would be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming median OS of 53 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) were needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the PFS analysis and OS analysis for the whole population.

Based on the revised testing procedures (Figure 4 [Scenario 1] and Figure 5 [Scenario 2]), and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.0248 is 87%. Using a one-sided alpha level of 0.0024, the power is 61%. The actual alpha level will depend on the outcomes of the preceding tests in the testing sequence.
OS (Arm 2 Versus Arm 1):

Testing of OS (Arm 2 versus Arm 1) evaluates whether the veliparib containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. According to the original protocol, the power calculation for this hypothesis was based on the log-rank test at a one-sided alpha level of 0.0125. Assuming a hazard ratio for OS of 0.5 in Arm 2 versus Arm 1, up to a total of 79 events would be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming median OS of 53 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) were needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the PFS analysis and OS analysis for the whole population.

Based on the revised testing procedures (Figure 4 [Scenario 1] and Figure 5 [Scenario 2]), and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.0248 is 87%. Using a one-sided alpha level of 0.0024, the power is 61%. The actual alpha level will depend on the outcomes of the preceding tests in the testing sequence.

8.2.4 For the Hypotheses in the HRD Population

PFS (Arm 3 Versus Arm 1):

Testing of PFS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the HRD population. According to Scenario 1 (Figure 4) of the revised testing procedure, the power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.025. It is currently estimated that at the time of achieving the latter of 646 PFS events in the Whole Population and 109 in the BRCA deficient population, that at least 242 total events will accrue in the HRD population. Assuming a HR = 0.60, we can expect a total of
170 events in Arm 3 and Arm 1 combined. Assuming a hazard ratio for PFS of 0.6 in Arm 3 versus Arm 1, 242 events will provide 91.5% power to detect a statistically significant treatment effect. Assuming a median PFS of 18 months in Arm 1 and an enrollment period of 18 months, approximately 160 subjects per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) are needed to have a matured PFS endpoint at around 36 months taking into account of a dropout rate of 10%.

Based on Scenario 2 (Figure 5) of the revised testing procedures, and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.0224 and 0.0125 is 90.8% and 86%, respectively.

**PFS (Arm 2 Versus Arm 1):**

Testing of PFS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the HRD population. According to Scenario 1 of the revised testing procedure, the power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.025. It is currently estimated that at the time of achieving the latter of 646 PFS events in the Whole Population and 109 in the BRCA deficient population, that at least 242 total events will accrue in the HRD population. Assuming a HR = 0.60, we can expect a total of 170 events in Arm 2 and Arm 1 combined. Assuming a hazard ratio for PFS of 0.6 in Arm 2 versus Arm 1, 242 events will provide 91.5% power to detect a statistically significant treatment effect. Assuming a median PFS of 18 months in Arm 1 and an enrollment period of 18 months, approximately 160 subjects per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) are needed to have a matured PFS endpoint at around 36 months taking into account of a dropout rate of 10%.

Based on Scenario 2 (Figure 5) of the revised testing procedures, and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.0024 is 70%.
OS (Arm 3 Versus Arm 1):

Testing of OS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the HRD population. According to Scenario 1 (Figure 4) of the revised testing procedure, the power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.025. Assuming a hazard ratio for OS of 0.6 in Arm 3 versus Arm 1, up to a total of 166 events will be needed for the test to have 90% power to detect a statistically significant treatment effect. Assuming median OS of 47 months in Arm 1 and an enrollment period of 18 months, approximately 160 subjects per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) are needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the PFS analysis and OS analysis for the whole population.

Based on Scenario 2 (Figure 5) of the revised testing procedures, and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.0024, the power is 68.6%. The actual alpha level will depend on the outcomes of the preceding tests in the testing sequence.

OS (Arm 2 Versus Arm 1):

Testing of OS (Arm 2 versus Arm 1) evaluates whether the veliparib containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the HRD population. Based on Scenario 1 (Figure 4) of the revised testing procedure, the power calculation for this hypothesis is based on the log-rank test at a one-sided alpha level of 0.025. Assuming a hazard ratio for OS of 0.6 in Arm 2 versus Arm 1, up to a total of 166 events will be needed for the test to have 90% power to detect a statistically significant treatment effect. Assuming median OS of 47 months in Arm 1 and an enrollment period of 18 months, approximately 160 subjects per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) are needed to have a matured OS endpoint at around 77 months, taking into account of a
dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the PFS analysis and OS analysis for the whole population.

Based on Scenario 2 (Figure 5) the revised testing procedures, and keeping all other assumptions above the same, the power based on the log-rank test at a one-sided alpha level of 0.0024, the power is 68.6%. The actual alpha level will depend on the outcomes of the preceding tests in the testing sequence.
Table 18. Power and Sample Size Calculation for Testing Scenario 1

<table>
<thead>
<tr>
<th>Type I Error</th>
<th>Population</th>
<th>No. of Subjects per Arm (N)</th>
<th>Power</th>
<th>Expected Hazard Ratio</th>
<th>No. of Events for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
<th>Power</th>
<th>Expected Hazard Ratio</th>
<th>No. of Events for 2 Arm Comparison</th>
<th>Projected Endpoint mature Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha = 0.025</td>
<td>BRCA-deficient</td>
<td>88</td>
<td>87%</td>
<td>0.50</td>
<td>79</td>
<td>36</td>
<td>87%(^a)</td>
<td>0.50</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>HRD</td>
<td>160</td>
<td>91.5%</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>90%(^a)</td>
<td>0.60</td>
<td>166</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Whole</td>
<td>367</td>
<td>94.1%</td>
<td>0.70</td>
<td>391</td>
<td>36</td>
<td>91.5%(^b)</td>
<td>0.70</td>
<td>350</td>
<td>58</td>
</tr>
</tbody>
</table>

PFS = progression-free survival; OS = overall survival

a. Assumes 2 efficacy interim analyses (at month 36 and month 58, respectively) with alpha spending of 0.0001 at each of the 2 interim analyses. The multiplicity adjusted alpha for the final analysis at month 77 is 0.0248, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.

b. Assumes an efficacy interim analysis at month 36 with alpha spending of 0.0001. The nominal alpha for the final analysis at month 58 is 0.0248. The multiplicity adjusted alpha for the analysis at month 77 is 0.0248, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.

Note: All calculations take into account a 10% dropout rate. An enrollment period of 18 months with linear enrollment rate is assumed. The actual endpoint mature time may vary depending on the true enrollment pattern.
Table 19. Power and Sample Size Calculation for Testing Scenario 2

<table>
<thead>
<tr>
<th>Type I Error</th>
<th>Population</th>
<th>No. of Subjects per Arm (N)</th>
<th>Power</th>
<th>Expected Hazard Ratio</th>
<th>No. of Events for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
<th>Power</th>
<th>Expected Hazard Ratio</th>
<th>No. of Events for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha = 0.025</td>
<td>BRCA-deficient</td>
<td>88</td>
<td>87%</td>
<td>0.50</td>
<td>79</td>
<td>36</td>
<td>87%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.50</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>HRD</td>
<td>160</td>
<td>91.5%</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>90%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.60</td>
<td>166</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Whole</td>
<td>367</td>
<td>94.1%</td>
<td>0.70</td>
<td>391</td>
<td>36</td>
<td>91.5%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.70</td>
<td>350</td>
<td>58</td>
</tr>
<tr>
<td>alpha = 0.0224</td>
<td>HRD</td>
<td>160</td>
<td>90.8%</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Whole</td>
<td>367</td>
<td>93.6%</td>
<td>0.70</td>
<td>391</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>alpha = 0.0125</td>
<td>HRD</td>
<td>160</td>
<td>86.2%</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Whole</td>
<td>367</td>
<td>90.1%</td>
<td>0.70</td>
<td>391</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>alpha = 0.0024</td>
<td>HRD</td>
<td>160</td>
<td>70%</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>68.6%</td>
<td>0.60</td>
<td>166</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Whole</td>
<td>367</td>
<td>76%</td>
<td>0.70</td>
<td>391</td>
<td>36</td>
<td>70%</td>
<td>0.70</td>
<td>350</td>
<td>58</td>
</tr>
</tbody>
</table>

PFS = progression-free survival; OS = overall survival

a. Assumes 2 efficacy interim analyses (at month 36 and month 58, respectively) with alpha spending of 0.0001 at each of the 2 interim analyses. The multiplicity adjusted alpha for the final analysis at month 77 is 0.0248, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.

b. Assumes an efficacy interim analysis at month 36 with alpha spending of 0.0001. The nominal alpha for the final analysis at month 58 is 0.0248. The multiplicity adjusted alpha for the analysis at month 77 is 0.0248, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.

Note: All calculations take into account a 10% dropout rate. An enrollment period of 18 months with linear enrollment rate is assumed. The actual endpoint mature time may vary depending on the true enrollment pattern.
8.3 Timing for Analyses and Unblinding of the Study

As shown in Table 18 and Table 19, the estimated PFS endpoint mature time is approximately 36 months for both the whole and the BRCA-deficient population, as well as the HRD population, and the estimated OS endpoint mature time is approximately 58 months for the whole population and 77 months for the BRCA-deficient and HRD populations. AbbVie will unblind the data to perform the primary analyses when required numbers of PFS endpoints are accrued in the BRCA-deficient, HRD, and whole populations. The data cutoff date for the primary analyses of PFS will be determined when the total number of PFS events in Arms 1 and 3 combined have reached at least 79 in the BRCA-deficient population, at least 170 in the HRD population, and at least 391 in the whole population. Since this is a blinded study involving 3 arms, an independent statistical data analysis center will inform the sponsor when all criteria specified above have been met. Subsequently all subjects will be followed as planned for survival and investigators and subjects will remain blinded to reduce bias. The subsequent OS analyses will occur when the required numbers of OS endpoints are accrued. Additional analyses of efficacy and safety may be performed in Japanese subjects after the primary analyses to meet the Japanese regulatory requirements. Additional details on these analyses will be specified in a separate SAP for the Japanese subjects.

8.4 Randomization Methods

An Interactive Response Technology (IRT) system will be utilized to randomize subjects. Before the study is initiated, directions for the IRT will be provided to each site. The investigational site will contact the IRT on or prior the subject's Cycle 1 Day 1 visit and a unique randomization number will be provided.

Subject randomization will be stratified into 48 groups as defined by combining categories of the four randomization stratification factors listed as below:

1. Stage of the disease:
2. Residual disease and choice of regimen:
   - Q3-weeks carboplatin/paclitaxel, no residual disease
   - Q3-weeks carboplatin/paclitaxel, any residual disease
   - Q-week carboplatin/paclitaxel, no residual disease
   - Q-week carboplatin/paclitaxel, any residual disease
   - Interval cytoreductive surgery, Q3-weeks carboplatin/paclitaxel
   - Interval cytoreductive surgery, Q-weeks carboplatin/paclitaxel

3. Region:
   - Japan
   - North America or Rest of World

4. Germline BRCA mutation status
   - gBRCA positive
   - gBRCA negative or unknown

Cancer stage at diagnosis, maximal residual disease, and BRCA mutation status are major prognostic factors of survival. Complete (no visible residual disease) and optimal (residual disease < 1 cm) primary surgical cytoreduction is also associated with prolonged survival in advanced epithelial ovarian cancer.\(^{40,42}\) To control for these known prognostic factors, randomization will be stratified by (Stage III versus IV), residual disease (any residual disease versus no visual residual disease) following initial cytoreductive surgery and germline BRCA mutation status (positive versus negative or unknown). Residual disease following interval cytoreduction will be captured and recorded on electronic case report forms (eCRFs) for subjects receiving treatment with carboplatin and paclitaxel as the data will not be available at randomization but could still influence outcomes/prognosis. Randomization will also be stratified by choice of therapy to minimize the impact of potential heterogeneity between these regimens and for region to account for regional differences in treatment decisions and surgical practices.
During randomization, subjects within each of the 48 stratification groups will be randomized in a 1:1:1 ratio to treatment Arms 1, 2 and 3, respectively.

The stratification factors used for the randomization should be the last values on or prior to the date of randomization and should be consistent with those on the eCRF.

Randomization to Arms 1, 2, and 3 will occur until the required number of subjects is enrolled as defined in Section 8.2.

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 Conference 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, International Conference on Harmonization (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 and 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 main study 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.

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

In the event a subject withdraws from the main study, stored biomarker and optional exploratory research samples will continue to be stored and analyzed unless the subject specifically withdraws consent for these samples (samples will not be stored for more than 20 years). If consent is withdrawn for the biomarker and optional sampling, the subject
must inform their study doctor, and once AbbVie is informed, the samples will be destroyed. In the event that destruction is not possible, they will no longer be linked to the subject. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating 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 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 principal 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

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

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

12.1 Publication

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

13.0 Completion of the Study

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

The Investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

The global end-of-study is defined as the date of the last subject's last visit, or the date of the last subject's last follow-up contact, whichever is later. The sponsor may also end the study upon confirmation that the primary endpoint was statistically met.
14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for veliparib and the product labeling for carboplatin and paclitaxel.

2. I have read this protocol and agree that the study is ethical.

3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.

4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Protocol Date: 24 April 2019

________________________________________  _________________________
Signature of Principal Investigator Date

________________________________________
Name of Principal Investigator (printed or typed)
15.0 Reference List


32. Ledermann et al. ASCO. 2013.


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

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Functional Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td></td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical Program Development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statistics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statistics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pharmacokinetics</td>
</tr>
</tbody>
</table>
Appendix C. Ovarian Surgical Procedure

Purpose: To obtain an accurate staging of ovarian cancer; to perform maximum resection of ovarian cancer; to optimize the selection of postoperative therapy.

Indications: All cases of ovarian cancer, including borderline tumors of the ovary.

Contraindications: Poor surgical risk.

Content of Procedure

1. The procedure's exposure must be adequate to explore the entire abdominal cavity and allow safe cytoreductive surgery. A vertical incision is recommended for celiotomy. Endoscopic approaches should not compromise disease assessment nor feasibility of resection. The goal for any resection attempt is no visible tumor residuum, or R0 resection.

2. The volume of any free peritoneal fluid should be estimated. Free peritoneal fluid is to be aspirated for cytology. If no free peritoneal fluid is present, separate peritoneal washings will be obtained from the pelvis, paracolic gutters and infradiaphragmatic area. These may be submitted separately or as a single specimen. Subjects with Stage III or IV disease do not require cytologic assessment.

3. All peritoneal surfaces including the undersurface of both diaphragms and the serosa and mesentery of the entire gastrointestinal tract will be visualized and palpated for evidence of metastatic disease.

4. Careful inspection of the omentum and removal if possible of at least the infracolic omentum will be accomplished. At minimum a biopsy of the omentum must be obtained.

5. If possible an extrafascial total abdominal hysterectomy and bilateral salpingo oophorectomy will be performed. If this is not possible or not indicated, a biopsy of the ovary and sampling of the endometrium must be performed. The surgery
section (§4.1) in selected ovarian cancer protocols may permit a unilateral salpingo-oophorectomy and/or subtotal hysterectomy.

6. If there is no evidence of disease beyond the ovary or pelvis, the following must be done.
   a. Peritoneal biopsies from:
      i. Cul-de-sac
      ii. Vesical peritoneum
      iii. Right and left pelvic sidewalls
      iv. Right and left paracolic gutters
   b. Biopsy or scraping of the right diaphragm
   c. Selective bilateral pelvic and periaortic lymph node sampling.
   d. Infracolic omentectomy

7. Selective pelvic and periaortic lymph node sampling must be done in the following situations:
   a. Subjects with tumor nodules outside the pelvis which are ≤ 2 cm (presumed Stage IIIB) must have bilateral pelvic and periaortic lymph node biopsies
   b. Subjects with parenchymal Stage IV disease and those with tumor nodules outside the pelvis which are greater than 2 cm do not require pelvic or periaortic lymph node biopsies unless the only nodule greater than 2 cm is a lymph node in which case it must be at least biopsied, or preferentially, resected.

8. Histologically confirmed metastatic nodal disease makes further node sampling unnecessary unless their resection would enable R0 resection.

Adequate assessment of tumor persistence and resection should be made during surgery.
Appendix D. General Chemotherapy Guidelines

- A subject will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

- It will be acceptable for individual chemotherapy doses to be delivered within a 24-hour window before and after the protocol-defined date for "Day 1" treatment. If the treatment due date is a Friday, and the subject cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (Day 3 past due).

- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.

- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately ± 5% of the calculated dose).

- Chemotherapy doses are required to be recalculated if the subject has a weight change of greater than or equal to 10%. Subjects are permitted to have chemotherapy doses recalculated for < 10% weight changes.

- The Fujimoto, DuBois, or institutional standard formulas may be used to calculate BSA.

- It is acceptable for capping BSA at 2.0 for paclitaxel dosing, if it is site's institutional practice to do so.
Appendix E. Carboplatin Dose Calculation Instructions

Dosing of Carboplatin:

1. The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

2. The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine > 1.5 × ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

3. Carboplatin doses are required to be recalculated if the subject has a weight change of greater than or equal to 10%. Subjects are permitted to have chemotherapy doses recalculated for < 10% weight changes.

4. At the time of dose modification, if the subject's age had changed (the subject has had a birthday), the site can use the current age.

5. In subjects with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a minimum value of 0.7 mg/dl. For trials where subjects enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.
CALVERT FORMULA:

Carboplatin dose (mg) = target AUC \times (GFR + 25)

**NOTE:** the GFR used in the Calvert formula should not exceed 125 ml/min. **Maximum** carboplatin dose (mg) = target AUC (mg/min) \times 150 ml/min. **The maximum allowed doses of carboplatin are:**

- AUC 6 = 900 mg
- AUC 5 = 750 mg
- AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\text{Creatinine Clearance (mL/min)} = \left(\frac{140-\text{Age (years)}}{72}\right) \times \frac{\text{Weight (kg)}}{\text{serum creatinine (mg/dl)}} \times 0.85$$

**Notes:**

1. Weight in kilograms (kg)
   a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link:
      http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm
   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25
   c. Adjusted weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**
   d. Adjusted weight calculation:
      - Ideal weight (kg) = \(((\text{Height (cm)}/2.54) - 60) \times 2.3) + 45.5
- Adjusted weight (kg) = (Actual weight – Ideal weight) × 0.40 + Ideal weight

2. The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

3. For sites in which the institutional practice is to estimate GFR using isotopic/EDTA clearance: if the calculated carboplatin dose (using Cockcroft & Gault formula) is > 10% higher than the carboplatin calculated using the EDTA-based GFR, carboplatin dose may be administered as calculated per institutional guidelines. GFR estimated using isotopic/EDTA clearance should then be used for subsequent doses and dose modifications.

At the time of a dose modification for toxicity:

If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.
Appendix F. FIGO Stage Grouping for Primary Carcinoma of the Ovary

These categories are based on findings at clinical examination and/or surgical exploration. The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspicious areas outside the pelvis.

<table>
<thead>
<tr>
<th>STAGE I: Tumor confined to ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
</tr>
<tr>
<td>IB</td>
</tr>
<tr>
<td>IC</td>
</tr>
<tr>
<td>IC1</td>
</tr>
<tr>
<td>IC2</td>
</tr>
<tr>
<td>IC3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
</tr>
<tr>
<td>IIB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastases to the retroperitoneal lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA (positive retroperitoneal lymph nodes and/or microscopic metastases beyond the pelvis)</td>
</tr>
<tr>
<td>IIIA1 (i)</td>
</tr>
<tr>
<td>IIIA1 (ii)</td>
</tr>
<tr>
<td>IIIA2</td>
</tr>
<tr>
<td>IIIA2</td>
</tr>
<tr>
<td>IIIB</td>
</tr>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>IIIC</td>
</tr>
<tr>
<td>STAGE IV:</td>
</tr>
<tr>
<td>IVA</td>
</tr>
<tr>
<td>IVB</td>
</tr>
</tbody>
</table>

Other major recommendations are as follows:

- Histologic type including grading should be designated at staging
- Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible
  - Tumors that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to Stage II if tumor cells are histologically proven to be present in the adhesions
Appendix G. Guidance for Identifying High Grade Serous Carcinoma

The following should be considered when determining a diagnosis of high grade serous carcinoma:

- Diagnosed as Grade 2 or Grade 3 serous carcinoma using Shimizu-Silverberg grading scheme.
- Wide spectrum of architectural patterns, including solid, glandular, and cribriform patterns, and patterns resembling transitional cell carcinoma. At least focal papillae and micropapillae with gaping and slit-like architectural features are present.
- Histologic variants such as transitional cell carcinoma or serous carcinoma with microcystic features.
- High nuclear grade, with extreme nuclear size variability (> 5×).
- More than 10 mitotic figures per 10 high power fields.
- Typically disseminated at presentation. WT1 expression should be sought for Stage I tumors.
- WT1, p53, and/or p16 overexpression may be sought if the differential diagnosis includes low grade serous carcinoma, endometrioid carcinoma, or clear cell carcinoma.
- Can be distinguished from serous borderline tumor by the presence of high nuclear grade if obvious stromal invasion is not identified after examination of multiple sections.
Appendix H. Adverse Events Expected Due to Ovarian, Fallopian Tube, or Primary Peritoneal Cancer or Progression of Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

<table>
<thead>
<tr>
<th>Adverse Events Expected Due to Ovarian Cancer or Progression of Ovarian Cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Abdominal distension</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
</tr>
<tr>
<td>Colonic obstruction</td>
</tr>
<tr>
<td>Small intestinal obstruction</td>
</tr>
<tr>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
</tbody>
</table>

* Coding Guidelines for MedDRA Term Selection, AbbVie Global Pharmaceutical Research and Development (GPRD), Global Pharmacovigilance and Clinical Project Team, current version on file at AbbVie.
Appendix I. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 4.0 Study Objective
Second paragraph previously read:
Secondary objectives include evaluations of OS (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), safety of all three arms, and Disease Related Symptom (DRS) scores (Arm 3 versus Arm 1 and Arm 2 versus Arm 1) in the BRCA-deficient, HRD, and whole population.

Has been changed to read:
Secondary objectives include evaluations of PFS (Arm 2 versus Arm 1), OS (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), safety of all three arms, and Disease Related Symptom (DRS) scores (Arm 3 versus Arm 1 and Arm 2 versus Arm 1) in the BRCA-deficient, HRD, and whole population.

Section 5.3.1.1 Study Procedures
Subsection Tumor Assessment
Last paragraph, last sentence previously read:
If at some time during the study a central read is requested by the sponsor, interpretations from the central imaging vendor will not be sent to the study site.

Has been changed to read:
Interpretations from the central imaging vendor will not be sent to the study site. Blinded independent central reviews will be performed as a sensitivity analysis as described in the SAP.
Section 8.1.2.1 Primary Efficacy Endpoint
Add: new last paragraph

Additional details regarding the primary analyses including the final list of stratification factors to be used will be specified in the final SAP prior to unblinding of the data.

Section 8.1.2.2.1 Progression Free Survival (PFS)
Add: new section title and text

8.1.2.2.1 Progression Free Survival (PFS)

PFS will also be compared between Arm 2 and Arm 1 as a secondary analysis, following the same methodology as the primary analysis.

Section 8.1.2.3.1 PFS2, TTFST, and TTSST
First paragraph, first sentence previously read:

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

Has been changed to read:

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

Section 8.1.3 Interim Efficacy Analyses for OS
Last paragraph
Add: new last sentence

Additional details regarding the secondary analyses including the interim efficacy analyses for OS will be specified in the final SAP prior to unblinding of the data.
Table 17. The Null Hypotheses of Interest in Each Population
"DRS (Arm 3 versus Arm 1)" and "DRS (Arm 2 versus Arm 1)" previously read:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DRS (Arm 3 versus Arm 1)</td>
<td>DRS (Arm 2 versus Arm 1)</td>
</tr>
</tbody>
</table>

Has been changed to read:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DRS (Arm 3 versus Arm 1)*</td>
<td>DRS (Arm 2 versus Arm 1)*</td>
</tr>
</tbody>
</table>

Table 17. The Null Hypotheses of Interest in Each Population
Add: new table note "*"

* No alpha allocation on this test.

Table 17. The Null Hypotheses of Interest in Each Population
Table note "Note:")
Last sentence previously read:

Other notations in this table are defined similarly.

Has been changed to read:

Other PFS and OS notations in this table are defined similarly.

Table 17. The Null Hypotheses of Interest in Each Population
Table note "Note:")
Add: new third and fourth sentence

DRS (Arm 3 versus Arm 1) denotes the null hypothesis of no difference in DRS scores between Arm 3 and Arm 1. DRS (Arm 2 versus Arm 1) is defined similarly.

Section 8.2 Determination of Sample Size
Previously read:

The study aims to power for the PFS and OS endpoints in both the whole and the BRCA-deficient populations. The update to the multiplicity adjustment will ultimately change the power as described under the original protocol, but no modification to the number of events required for the primary analysis will be made.
Has been changed to read:

The study originally aimed to power for the PFS and OS endpoints in both the whole and the BRCA-deficient populations. The update to the multiplicity adjustment will change the power as described under the original protocol, particularly in the whole population. Hence, fewer events will be required for the primary analysis in the whole population as compared to original estimates (391 versus 446).

Section 8.2.2 For the Hypotheses in the Whole Population
Subsection PFS (Arm 3 Versus Arm 1):
Last paragraph
Add: new last sentence

Power calculations based on 391 events are provided in Table 18 and Table 19.

Section 8.2.2 For the Hypotheses in the Whole Population
Subsection PFS (Arm 2 Versus Arm 1):
Last paragraph
Add: new last sentence

Power calculations based on 391 events are provided in Table 18 and Table 19.
### Table 18. Power and Sample Size Calculation for Testing Scenario 1

Previously read:

<table>
<thead>
<tr>
<th>Type I Error</th>
<th>Population</th>
<th>No. of Subjects per Arm (N)</th>
<th>Power</th>
<th>Expected Hazard Ratio</th>
<th>No. of Events Needed for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
<th>Power</th>
<th>Expected Hazard Ratio</th>
<th>No. of Events Needed for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha = 0.025</td>
<td>BRCA-deficient</td>
<td>88</td>
<td>87%</td>
<td>0.50</td>
<td>79</td>
<td>36</td>
<td>87%</td>
<td>0.50</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>HRD</td>
<td>160</td>
<td>91.5%</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>90%</td>
<td>0.60</td>
<td>166</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Whole</td>
<td>367</td>
<td>96.5%</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>91.5%</td>
<td>0.70</td>
<td>350</td>
<td>58</td>
</tr>
</tbody>
</table>

Has been changed to read:

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<th>No. of Subjects per Arm (N)</th>
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<td>160</td>
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### Table 19. Power and Sample Size Calculation for Testing Scenario 2

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<th>Projected Endpoint Mature Time (Months)</th>
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Section 8.3 Timing for Analyses and Unblinding of the Study

First, second, and third sentence previously read:

As shown in Table 18 and Table 19, the estimated PFS endpoint mature time is approximately 36 months for both the whole and the BRCA-deficient population, and the estimated OS endpoint mature time is approximately 58 months for the whole population and 77 months for the BRCA-deficient population. AbbVie will unblind the data to perform the primary analyses when required numbers of PFS endpoints are accrued in both the whole population and BRCA-deficient population. No update to the timing of this analysis will be made to account for the updated testing sequence.

Has been changed to read:

As shown in Table 18 and Table 19, the estimated PFS endpoint mature time is approximately 36 months for both the whole and the BRCA-deficient population, as well as the HRD population, and the estimated OS endpoint mature time is approximately 58 months for the whole population and 77 months for the BRCA-deficient and HRD populations. AbbVie will unblind the data to perform the primary analyses when required numbers of PFS endpoints are accrued in the BRCA-deficient, HRD, and whole populations. The data cutoff date for the primary analyses of PFS will be determined when the total number of PFS events in Arms 1 and 3 combined have reached at least 79 in the BRCA-deficient population, at least 170 in the HRD population, and at least 391 in the whole population. Since this is a blinded study involving 3 arms, an independent statistical data analysis center will inform the sponsor when all criteria specified above have been met.
Appendix B. List of Protocol Signatories
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Study M13694 - A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer - Amendment 6 - EudraCT 2014-005070-11 - 24Apr2019

<table>
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1.0 Title Page

Statistical Analysis Plan

Study M13-694

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Date: 16 January 2017
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3.0 Introduction

This statistical analysis plan (SAP) is created based on Study Protocol M13-694. Study M13-694 examines the safety and efficacy of veliparib (ABT-888) in combination with standard platinum-based chemotherapy (carboplatin/paclitaxel) and then as monotherapy in maintenance for high grade serous epithelial, ovarian, fallopian tube, or primary peritoneal cancer.

The SAP provides details to guide the analyses for baseline, efficacy, and safety variables and describes the populations and variables that will be analyzed and the statistical methods that will be used. Primary and follow-up analyses will be conducted for Study M13-694 (Analysis timing is defined in Section 4.5). Analyses will be performed using SAS® Version 9.4 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective of the study is to evaluate whether PFS is prolonged with the addition of veliparib to standard platinum-based chemotherapy (carboplatin/paclitaxel) and then continued as maintenance therapy when compared to chemotherapy alone. This will be evaluated in the whole patient population, as well as a more selective cohort of subjects with BRCA-deficient tumors. The BRCA-deficient population will be defined as subjects with either a germ-line (gBRCA) and/or somatic (sBRCA) deleterious or suspected deleterious mutation in BRCA1 or BRCA2 as determined using centralized testing.

Secondary objectives include evaluations of OS (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), safety of the 3 study arms, and Disease Related Symptom (DRS) scores (Arm 3 versus Arm 1 and Arm 2 versus Arm 1) in both the whole population and BRCA-deficient population.
The tertiary objectives include PFS to the second objective radiographic progression (PFS2), time to first subsequent therapy (TTFST), time to second subsequent therapy (TTSST), and other PRO endpoints (which will be specified in a separate analysis plan).

4.2 Design Diagram

This is a randomized, placebo-controlled, double-blind, stratified, multicenter, multi-country Phase 3 study designed to evaluate if PFS is prolonged when veliparib is added to carboplatin/paclitaxel and continued as maintenance therapy in subjects with previously untreated high-grade serous ovarian epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Subject randomization will be stratified by stage of disease, residual disease and choice of regimen, region of the world, and gBRCA mutation status. Approximately 1100 subjects will be randomized in a 1:1:1 ratio to one of the following three treatment Arms:

Arm 1: Carboplatin/paclitaxel plus placebo for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;

Arm 2: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;

Arm 3: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by veliparib BID maintenance therapy for 30 additional 21-day cycles.

The study will consist of four phases: a Pre-Therapy Phase (Screening), a Combination Therapy Phase, a Maintenance Therapy Phase, and a Long-Term Follow-Up Phase. An overview of the study design is shown in Figure 1.
Figure 1. Overall Study Design

**Pre-therapy Phase (Screening)**
- Physician's Choice: Primary cytoreductive surgery with Carboplatin and Q-week paclitaxel OR Carboplatin and Q3-weeks paclitaxel
- Interval cytoreductive surgery with Carboplatin and Q-week paclitaxel OR Carboplatin and Q3-weeks paclitaxel

**Combination Phase**
- Arm 1: Placebo with carboplatin/paclitaxel (Cycle 1-6)
- Arm 2: Veliparib with carboplatin/paclitaxel (Cycle 1-6)
- Arm 3: Veliparib with carboplatin/paclitaxel (Cycle 1-6)

**Maintenance Phase**
- Placebo** (Cycle 7-36)
- Placebo** (Cycle 7-36)
- Veliparib** (Cycle 7-36)

**Long-term Follow-up/Study Endpoints**
- Primary: Progression-Free Survival (PFS)
- Secondary: Overall Survival & Disease-Related Symptom Scores
- Tertiary: PFS2 and Time to 1st subsequent therapy
- Tertiary: Time to 2nd subsequent therapy

**Eligible Population**
- High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
- FIGO Stage II or IV
- No prior systemic therapy
- ECOG 0 to 2
- No CNS metastases

**Legend:**
- Q-week schedule = carboplatin AUC 6 + paclitaxel 80 mg/m² weekly
- Q3-weeks schedule = carboplatin AUC 6 + paclitaxel 175 mg/m² every 3 weeks
- Veliparib 150 mg/Placebo PO bid, Cycle 1-6 (21 out of 21 days)
- Veliparib 100 mg/Placebo PO bid, Cycle 7-36 (21 out of 21 days)
- PFS will be evaluated in the whole patient population (end of study) and the selective patient population (BRCA deficient).
- Every 3 months beginning on date of progression

**Legend (continued):**
- Residual disease and choice of regimen:
  - Q3-weeks carboplatin/paclitaxel, no residual disease
  - Q3-weeks carboplatin/paclitaxel, any residual disease
  - Q-week carboplatin/paclitaxel, no residual disease
  - Q-week carboplatin/paclitaxel, any residual disease
  - Interval cytoreductive surgery, Q3-weeks carboplatin/paclitaxel
  - Interval cytoreductive surgery, Q-week carboplatin/paclitaxel

All subjects: Collection of new-onset malignancy information for up to 10 years
4.3 Sample Size

The trial will enroll approximately 1100 subjects (with 1:1:1 randomization ratio for Arm 1:Arm 2:Arm 3) in the whole population, including approximately 264 subjects with \textit{BRCA}-deficient status (assuming 24\% of the subjects in the whole population are \textit{BRCA}-deficient) to power the hypotheses specified in the whole and \textit{BRCA}-deficient populations (Table 1). Detailed sample size calculations for each endpoint of the whole and \textit{BRCA}-deficient populations are described in Section 4.3.1 and Section 4.3.2.
### Table 1. Power and Sample Size Calculation

<table>
<thead>
<tr>
<th>Type I Error</th>
<th>Population</th>
<th>No. of Subjects per Arm (N)</th>
<th>Power</th>
<th>Expected Hazard Ratio</th>
<th>No. of Events Needed for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
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<th>No. of Events Needed for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
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</thead>
<tbody>
<tr>
<td>(\alpha = 0.0125): for PFS (Arm 3 versus Arm 1) in the whole population, and PFS and OS endpoint in the BRCA population</td>
<td>Whole</td>
<td>367</td>
<td>94%</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>86%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.7</td>
<td>350</td>
<td>58</td>
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<tr>
<td></td>
<td>BRCA-deficient</td>
<td>88</td>
<td>80%</td>
<td>0.5</td>
<td>79</td>
<td>36</td>
<td>80%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.5</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td>(\alpha = 0.00625): for PFS (Arm 2 versus Arm 1) and OS (Arm 3 versus Arm 1) in the whole population</td>
<td>Whole</td>
<td>367</td>
<td>90%</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>80%</td>
<td>0.7</td>
<td>350</td>
<td>58</td>
</tr>
</tbody>
</table>

PFS = progression-free survival; OS = overall survival

- a. Assumes an efficacy interim analysis at Month 36 with \(\alpha\) spending of 0.0001. The nominal \(\alpha\) for the final analysis is 0.0124.
- b. Assumes 2 efficacy interim analyses (at Month 36 and Month 58, respectively) with \(\alpha\) spending of 0.0001 at each of the 2 interim analyses. The nominal \(\alpha\) for the final analysis is 0.0124.

Note: All calculations take into account a 10% dropout rate. An enrollment period of 18 months with linear enrollment rate is assumed. The actual endpoint mature time may vary depending on the true enrollment pattern.
4.3.1 Testing of Hypotheses in the Whole Population

**PFS (Arm 3 Versus Arm 1):**

Testing of PFS (Arm 3 versus Arm 1, as shown in Figure 2 and Table 3) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the whole population. The power calculation for this hypothesis is based on the log-rank test at a one-sided α level of 0.0125. Assuming a PFS hazard ratio of 0.7 in Arm 3 versus Arm 1, up to a total of 446 events will be needed for the test to have 94% power to detect a statistically significant treatment effect. Assuming a median PFS of 15.5 months in Arm 1 and an enrollment period of 18 months, and taking into account a dropout rate of 10%, approximately 367 subjects are needed per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) in order to have a matured PFS endpoint at around 36 months.

**PFS (Arm 2 Versus Arm 1):**

Testing of PFS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the whole population. This hypothesis will be assessed with the stratified log-rank test at a one sided α level of 0.00625 or 0.0125 under the Scenario 1, based on the Hochberg procedure specified in Section 10.6. The power calculation for this hypothesis is based on the log-rank test at a one-sided α level of 0.00625. Assuming a PFS hazard ratio of 0.7 in Arm 2 versus Arm 1, up to a total of 446 events will be needed for the test to have 90% power to detect a statistically significant treatment effect based on the α level of 0.00625. Assuming median PFS of 15.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10%, approximately 367 subjects are needed per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) to have a mature PFS endpoint at around 36 months. The actual α level will be determined by the test result for OS (Arm 3 versus Arm 1) based on the Hochberg testing procedure specified in Section 10.6. The α level of
0.00625 in this power calculation is based on the conservative scenario that assumes the hypothesis for OS (Arm 3 versus Arm 1) is not rejected.

**OS (Arm 3 Versus Arm 1):**

Testing of OS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the whole population. This hypothesis will be assessed with the stratified log-rank test at a one sided α level of 0.00625 or 0.0125 under Scenario 1, based on the Hochberg procedure specified in Section 10.6. The power calculation for this hypothesis is based on the log-rank test at a one-sided α level of 0.00625. Assuming an OS hazard ratio of 0.7 in Arm 3 versus Arm 1, up to a total of 350 events will be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming a median OS of 41.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10% and an efficacy interim analysis that occurs at the time of the PFS analysis, approximately 367 subjects are needed per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) to have a mature OS endpoint at around 58 months. The actual α level will be determined by the P values for the test result of PFS (Arm 2 versus Arm 1) based on the Hochberg procedure specified in Section 10.6. The α level of 0.00625 in this power calculation is based on the conservative scenario that assumes the hypothesis for PFS (Arm 2 versus Arm 1) is not rejected.

**OS (Arm 2 Versus Arm 1):**

Testing of OS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the whole population. The power calculation for this hypothesis is based on the log-rank test at a one-sided α level of 0.0125. Assuming an OS hazard ratio of 0.7 in Arm 2 versus Arm 1, up to a total of 350 events will be needed for the test to have 86% power to detect a statistically significant treatment effect. Assuming a median OS of 41.5 months in Arm 1 and an
enrollment period of 18 months, and taking into account of a dropout rate of 10% and an
efficacy interim analysis that occurs at the time of the PFS analysis, approximately
367 subjects are needed per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) to
have a mature OS endpoint at around 58 months. OS (Arm 2 versus Arm 1) will be tested
only if all of the previous hypotheses are rejected based on the Hochberg procedure
specified in Section 10.6.

4.3.2 Testing of Hypotheses in the BRCA-Deficient Population

PFS (Arm 3 Versus Arm 1):

Testing of PFS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen
in Arm 3 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference
regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. The
power calculation for this hypothesis is based on the log-rank test at a one-sided α level of
0.0125. Assuming a hazard ratio for PFS of 0.5 in Arm 3 versus Arm 1, up to a total of
79 events will be needed for the test to have 80% power to detect a statistically significant
treatment effect. Assuming median PFS of 21 months in Arm 1 and an enrollment period
of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 3
versus Arm 1) are needed to have a matured PFS endpoint at around 36 months taking
into account of a dropout rate of 10%.

PFS (Arm 2 Versus Arm 1):

Testing of PFS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen
in Arm 2 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference
regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. The
power calculation for this hypothesis is based on the log-rank test at a one-sided α level of
0.0125. Assuming a hazard ratio for PFS of 0.5 in Arm 2 versus Arm 1, up to a total of
79 events will be needed for the test to have 80% power to detect a statistically significant
treatment effect. Assuming median PFS of 21 months in Arm 1 and an enrollment period
of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 2
versus Arm 1) are needed to have a matured PFS endpoint at around 36 months taking into account of a dropout rate of 10%.

OS (Arm 3 Versus Arm 1):

Testing of OS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. The power calculation for this hypothesis is based on the log-rank test at a one-sided α level of 0.0125. Assuming a hazard ratio for OS of 0.5 in Arm 3 versus Arm 1, up to a total of 79 events will be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming median OS of 53 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) are needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the PFS analysis and OS analysis for the whole population.

OS (Arm 2 Versus Arm 1):

Testing of OS (Arm 2 versus Arm 1) evaluates whether the veliparib containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the BRCA-deficient population. The power calculation for this hypothesis is based on the log-rank test at a one-sided α level of 0.0125. Assuming a hazard ratio for OS of 0.5 in Arm 2 versus Arm 1, up to a total of 79 events will be needed for the test to have 80% power to detect a statistically significant treatment effect. Assuming median OS of 53 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 2 versus Arm 1) are needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the PFS analysis and OS analysis for the whole population.
4.4 Interim Analysis

Interim Efficacy Analysis

For OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the whole population, one efficacy interim analysis will be performed at the time of the final PFS analyses (~Month 36) with a nominal α of 0.0001, so that the final OS analysis (~Month 58) have a nominal α of 0.0124.

For OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the BRCA-deficient population, two efficacy interim analyses will be performed. The first interim analysis will occur at the time of the corresponding PFS analyses (~Month 36) with a nominal α of 0.0001, the second interim analysis will occur at the time of the OS analysis for the whole population (~Month 58) with a nominal α of 0.0001, so that the final OS analyses (~Month 77) have a nominal α of 0.0124 to have the overall α controlled at 0.0125 in the BRCA-deficient population.

Interim Safety Analyses

An Independent Data Monitoring Committee (IDMC) will review safety data in an unblinded fashion approximately 12 months from the date the first subject is randomized. Details of the IDMC review will be outlined in the IDMC Charter. Aggregate clinical safety data will be reviewed on a real-time basis throughout the course of the study.

The first IDMC meeting reviewed safety data on July 29, 2016. The IDMC saw no concerning safety signals and recommended continuing the study. They also recommended an additional IDMC meeting in 6 months due to the fast enrollment rate. In addition, the IDMC noted a significant imbalance of gBRCA status across treatment groups, and recommended adding gBRCA status as a randomization stratification factor to potentially correct this imbalance. This recommendation was based on the expectation that BRCA status is a strong prognostic and predictive factor for patients' responses to the study regimen. AbbVie followed the IDMC’s recommendation and added the gBRCA stratification factor in September 2016.
4.5 Analysis Timing

The final analysis of the primary endpoint (PFS) will occur when the total number of accrued PFS events in all three arms reaches 646 for the whole population and 109 for the BRCA-deficient population (the later of these two milestones will trigger the final analysis of PFS). An interim analysis of OS will occur in both the whole and BRCA-deficient population at the time of the final analysis for PFS. Then there are two follow-up analyses for OS. The analyses for OS in the whole and BRCA-deficient population will occur when the total number of deaths reaches 503 and 109 in the whole and BRCA-deficient population respectively.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Three study populations will be analyzed, defined as follows:

- **Intent-To-Treat (ITT) population** (also referred as whole population) – all subjects who were randomized by IRT. The data from ITT population will be analyzed by the treatment group assignment given at the time of randomization, even if the subject takes the incorrect drugs that do not match the assigned treatment, or does not receive any treatment, or does not follow the protocol until completion.

- **BRCA-deficient population** – all randomized subjects with either a germ-line (gBRCA) and/or somatic (sBRCA) deleterious or suspected deleterious mutation in BRCA1 or BRCA2 as determined using centralized testing.

- **As Treated (AST) population** – all subjects who were randomized by IRT and took at least one dose of veliparib/placebo. The data from the AST population will be analyzed by the actual treatment that subject received.
5.2 Variables Used for Stratification of Randomization

Subject randomization will be stratified into 48 groups as defined by combining categories of the four randomization stratification factors (gBRCA was added per the IDMC's recommendation during the course of the study) that follow:

1. Stage of the disease
   a. III
   b. IV

2. Residual disease and choice of regimen
   a. Q3-weeks carboplatin/paclitaxel, no residual disease
   b. Q3-weeks carboplatin/paclitaxel, any residual disease
   c. Q-week carboplatin/paclitaxel, no residual disease
   d. Q-week carboplatin/paclitaxel, any residual disease
   e. Interval cytoreductive surgery, Q3-weeks carboplatin/paclitaxel
   f. Interval cytoreductive surgery, Q-week carboplatin/paclitaxel

3. Region
   a. Japan
   b. North America or Rest of World

4. Germline BRCA mutation status
   a. gBRCA positive (meaning with germ-line deleterious or suspected deleterious mutation in BRCA1 or BRCA2)
   b. gBRCA negative or unknown
6.0 Analysis Conventions

General Considerations

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a 2-sided $P$ value $\leq 0.05$.

The date of randomization is defined as the date that the IRT issues a randomization number.

All randomized subjects will be included in the efficacy analyses. All subjects who receive at least one dose of veliparib/placebo will be included in the safety analysis.

Definition of Study Drug

Unless otherwise specified, the study drug in this document refers to veliparib/placebo.

Definition of Study Treatment

Unless otherwise specified, the study treatment in this document refers to veliparib/placebo, carboplatin and paclitaxel.

Variables to be Adjusted for Efficacy Analyses

Residual Disease and Choice of Regimen, and $BRCA$-deficient status will be used in all stratified analyses of the efficacy endpoints for the whole population, and Residual Disease and Choice of Regimen will be used in all stratified analyses of the efficacy endpoints for the $BRCA$-deficient population. The stratification factor value under which the subject is randomized by the IRT will be used in the efficacy analyses for residual disease and choice of regimen. For $BRCA$-deficient status, the actual results from the central testing will be used for the analyses (not the $gBRCA$ status used for stratification at randomization).
Dealing with Multiple Values on the Same Day

In cases where multiple values are collected on the same day (including baseline visit and post-baseline visits), the maximum grade value will be selected as the value for that day for the shift analysis of lab parameters; the arithmetic average will be calculated and used as the value for that day for analysis of quality of life (QoL), performance status (ECOG), laboratory, and vital signs parameters.

Definition of Baseline

Unless otherwise specified, the baseline is defined as the last non-missing observation collected on or prior to the date of the first dose of study drug for treated subjects (or the date of randomization for non-treated subjects).

Definition of Final Visit

For laboratory and vital signs variables, Final Visit is defined as the last non-missing observation collected within 30 days following the last dose of study drug (veliparib/placebo). All post-baseline assessments collected more than 30 days after the last dose of study drug (veliparib/placebo) will not be included in the analyses of laboratory and vital signs variables.

Definition of Study Rx Day (Days Relative to the First Dose of Veliparib/Placebo)

Study Rx Days are calculated for each time point relative to the first dose date of study drug (veliparib/placebo). They are defined as the number of days between the day of the first dose of study drug and the specific time point. Rx days are negative values when the time point of interest is prior to the first study drug dose day. Rx days are positive values when the time point of interest is after the first study drug dose day. The day of the first dose of study drug is defined as Study Rx Day 1, while the day prior to the first study drug dose is defined as Study Rx Day –1 (there is no Study Rx Day 0).
Definition of Cycle Rx Days in Each Cycle

During the combination phase (Cycles 1 through 6), Cycle Rx Days for each cycle are calculated for each time point relative to the first dose of veliparib/placebo/carboplatin/paclitaxel in each cycle. During the maintenance phase (Cycles 7 through 30), Cycle Rx Days are calculated for each time point relative to the first dose of veliparib/placebo in each cycle.

Definition of Analysis Windows

All time points and corresponding time windows are based on Cycle Rx Days.

For visit wise longitudinal analyses such as mean change from baseline to all post-baseline assessments in ECOG, QoL, laboratory, and vital signs values, the time windows specified in Table 1 describe how the data will be assigned to the protocol specified visits. Analysis time windows are constructed using the following algorithm:

- Determine the nominal Cycle Rx Day for each scheduled visit.
- Determine the window around a specific nominal Cycle Rx Day as in Table 1.
- If more than one assessment is included in a time window, the assessment closest to the nominal day should be used. If there are two observations equally distant to the nominal day, the later one will be used in analyses.

The data will only be analyzed for visits that have at least 5 subjects' observations for each treatment group.
### Table 2. Time Windows for Visit-Wise Analysis (QoL, ECOG, Laboratory, and Vital Signs)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Cycle Rx Day</th>
<th>Time Window (Study Rx Day Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combination Phase:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 1 Day 1</td>
<td>Baseline</td>
<td>As Baseline Definition</td>
</tr>
<tr>
<td>Cycle X Day 1</td>
<td>1</td>
<td>(−3,4)</td>
</tr>
<tr>
<td><strong>Maintenance Phase:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 7 Day 1</td>
<td>1</td>
<td>(−3, 4)</td>
</tr>
<tr>
<td>Cycle 9 Day 1</td>
<td>1</td>
<td>(−3,4)</td>
</tr>
<tr>
<td>Cycle XXa Day 1</td>
<td>1</td>
<td>(−3,4)</td>
</tr>
<tr>
<td><strong>Therapy Completion Visit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Every other cycle until Cycle 30.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Determination of Censoring Dates for Overall Survival**

The overall survival censoring date for a subject will be the last assessment date from the following list of data record types:

- Vital signs
- Physical exam
- Lab variables, including SAE lab reports
- ECOG performance status
- Quality of life measures
- Study drug administration
- Tumor assessments
- Transfusions
- Electrocardiogram
- Adverse event
- PK blood draws
- Survival follow-up (last-known-alive date)
Records that indicate that the assessment was not done will not be used in determining the censoring date.

**Definition of Treatment-Emergent Adverse Events**

Adverse Events will be considered "treatment-emergent" when their onset is on or after the day of the first dose of study drug and also are at most 30 days after the last dose of study drug (veliparib/placebo).

If the onset date for an adverse event is reported with a month and year but without the day of the month, and the reported month matches that of the start of treatment with study drug, then the adverse event will be treatment-emergent. Similarly, if the reported month matches the month in which the post-treatment follow-up period ends then the adverse event will be treatment-emergent.

**7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications and Prior Oncology Therapies**

The ITT population will be used in the analyses of demographic, baseline characteristics, medical history, and previous/concomitant medication and prior oncology therapies.

All summaries and analyses will be presented by each treatment arm.

**7.1 Demographic and Baseline Characteristics**

The following demographic and baseline characteristics will be summarized:

- Country
- Geographical Region
- Race
- Gender
- Age (continuous and categorical \( \leq 65 \) years versus \( > 65 \) years)
- Height
• Weight
• *BRCA*-deficient status [deleterious or suspected deleterious germ-line or somatic mutation in *BRCA*1 and/or *BRCA*2 gene versus none]
• Stage of Disease at randomization [III vs. IV]
• Stage of Disease as confirmed by investigator after randomization [III vs. IV]
• Residual Disease and Choice of Regimen at randomization
• Residual Disease and Choice of Regimen as confirmed by investigator after randomization
• Region of the World at randomization [North America versus Japan versus Rest of World]
• Smoking history [current smoker versus past smoker versus never smoked]
• ECOG performance status [0 versus ≥ 1]

The number of subjects with missing information will also be summarized.

Categorical data will be summarized by numbers and percentages in each category.

Continuous data will be summarized by mean, standard deviation, median, minimum and maximum values.

The chi-square test will be used for testing homogeneity across 3 treatment arms for the categorical demographic and baseline characteristics data. The missing information of categorical data will not be included in the test. An ANOVA model with treatment group as the factor will be used for testing homogeneity across 3 treatment arms for the continuous demographic and baseline characteristics data.

### 7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The frequency and percentage of subjects with a particular
condition/diagnosis will be summarized for each treatment group. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system. There will be no statistical comparison for the medical history among the treatment groups.

7.3 Prior and Concomitant Medications and Prior Oncology Therapies

The frequency and percentage of subjects who took at least one dose of medication will be summarized by the generic name coded by WHO dictionary. This analysis will be performed for prior and concomitant (other than components in the study treatment) medications separately.

There will be no statistical comparison for the prior and concomitant medications among the treatment groups.

8.0 Subject Disposition

Analyses for the subject disposition will be performed on the ITT population at the time of the primary analysis and final analysis as appropriate.

The screen failure reasons will be summarized for the screen failure subjects.

The number of randomized subjects, the number of treated subjects, and final status will be summarized by treatment group and by investigator site/country.

The frequency and percentage of subjects who discontinued study, veliparib/placebo, carboplatin, or paclitaxel will be summarized for each treatment group. The reasons for discontinuation of each drug including docetaxel will be summarized by treatment group. In addition, the primary reason of discontinuation will be included in the summarization.

The treatment groups assigned by IRT will be used in the summaries of subject disposition and there will be no statistical comparison for the subject disposition.
9.0 Study Drug Exposure and Compliance

9.1 Study Treatment Exposure

The duration of exposure to each component of the study treatment will be summarized for each treatment arm in the AST population. Duration of exposure is defined as the total number of days a subject received the drug, calculated as the last date of dose minus first date of dose + 1 day for each subject.

Descriptive statistics (mean, standard deviation, median, and range) will be used to summarize duration of exposure by treatment group. An ANOVA model will be used for the comparisons of duration between the treatment arms by the two pairwise (Arm 3 versus Arm 1 and Arm 2 versus Arm 1). In addition, the frequency and percentage of subjects exposed to veliparib/placebo will be summarized for each of the following duration intervals.

- 1 to 63 days
- 64 to 126 days
- 127 to 252 days
- 253 to 378 days
- 379 to 504 days
- 505 to 630 days
- ≥ 631 days

The number of cycles that subjects are exposed to veliparib/placebo, carboplatin/placebo, paclitaxel, docetaxel (for subjects dosed with docetaxel) will also be summarized.

The frequencies and percentages of subjects having dose reduction (all treatments), interruption (study drug only), or delay (carboplatin/placebo, paclitaxel, docetaxel) will be summarized for each treatment group. If a subject has any dose reduction from the previous dose of veliparib/placebo/carboplatin/paclitaxel/docetaxel, this subject will be considered as having experienced dose reduction of
veliparib/placebo/carboplatin/paclitaxel/docetaxel, respectively. If a subject skips 1 or more consecutive days, this subject will be considered as having experienced a dose interruption of veliparib/placebo. If the difference between carboplatin dose dates of two consecutive doses is more than 27 days, then the subject will be considered as having experienced a dose delay of carboplatin. If the difference between paclitaxel dose dates of two consecutive doses is more than 13 days for paclitaxel Q-week subjects, or more than 27 days for paclitaxel Q3-week subjects, then the subject will be considered as having experienced a dose delay of paclitaxel.

10.0 Efficacy Analysis

10.1 General Considerations

Unless otherwise noted, for all statistical analysis, statistical significance will be determined by a 2-sided $P$ value $\leq 0.05$ (when rounded to three decimal places).

Efficacy analyses will be performed on the ITT population. The date of randomization is defined as the date when the randomization number is issued by IRT.

10.2 Primary Efficacy Analysis

The primary efficacy endpoint is progression-free survival (PFS). PFS will be defined as the number of days from the date that the subject was randomized to the date the subject experiences an event of disease progression, according to RECIST criteria version 1.1 (as determined by the investigator) or to the date of death (all causes of mortality) if disease progression is not reached. All events of disease progression (as determined by the investigator) will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. However, if a disease progression event occurs after a subject misses two or more consecutive disease progression assessments this subject will be censored at the last disease progression assessment prior to the missing disease progression assessments. All events of death will be included for subjects who had not experienced disease progression provided the death occurred within the expected time windows defined according to the underlying disease
assessment interval (every 9 weeks, then at the end of the Combination Phase, then every 12 weeks for 2 years, then every 6 months for 3 years, and then annually). If the subject does not have an event of disease progression (as determined by the investigator) nor has the subject died, the subject's data will be censored at the date of the subject's last disease assessment.

The primary efficacy analyses are defined by:

- comparing PFS in Arm 3 versus Arm 1 in the whole population using the log-rank test, stratified by residual disease and choice of regimen, and BRCA-deficient status at the 1-sided 0.0125 α level (or 0.025 based on the pre-specified α allocation rule in Section 10.6);
- comparing PFS in Arm 3 versus Arm 1 in the BRCA-deficient population using the log-rank test, stratified by residual disease and choice of regimen at the 1-sided 0.0125 α level (or only in the whole population based on the pre-specified α allocation rule in Section 10.6).

The distribution of PFS will be estimated for each treatment arm using Kaplan-Meier methodology. Median PFS time will be estimated and 95% confidence interval for the estimated median PFS time will be presented for each treatment arm.

### 10.3 Secondary Efficacy Analyses

#### 10.3.1 Overall Survival

OS 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.

The secondary efficacy analyses for OS are defined by:
● comparing OS in Arm 3 versus Arm 1 and Arm 2 versus Arm 1 in the whole population using the log-rank test, stratified by residual disease and choice of regimen, and BRCA-deficient status at the α level based on the pre-specified α allocation rule in Section 10.6;

● comparing OS in Arm 3 versus Arm 1 and Arm 2 versus Arm 1 in the BRCA-deficient population using the log-rank test, stratified by residual disease and choice of regimen at the α level based on the pre-specified α allocation rule in Section 10.6.

The distribution of OS will be estimated for each treatment arm using Kaplan-Meier methodology. Median OS time will be estimated and 95% confidence interval for the estimated median survival time will be presented for each treatment arm.

10.3.2 Progression-Free Survival

The secondary efficacy analyses of PFS include:

● comparing PFS in Arm 2 versus Arm 1 in the whole population using the log-rank test, stratified by residual disease and choice of regimen, and BRCA-deficient status at the α level based on the pre-specified α allocation rule in Section 10.6;

● comparing PFS in Arm 2 versus Arm 1 in the BRCA-deficient population using the log-rank test, stratified by residual disease and choice of regimen at the α level based on the pre-specified α allocation rule in Section 10.6.

10.3.3 Patient Reported Outcomes

Disease Related Symptoms

The overall mean change from baseline for the disease related symptom (DRS) scores measured at each assessment point up to 2 years or disease progression will be a secondary endpoint of the study.

The secondary efficacy analyses for DRS are defined by:
• comparing mean changes from baseline for the total DRS scores in Arm 3 vs. Arm 1 and Arm 2 vs. Arm 1 in the whole population using a longitudinal repeated measures model that takes into account the DRS scores measured at each assessment point up to 2 years from randomization or disease progression based on the pre-specified α allocation rule in Section 10.6;

• comparing mean changes from baseline for the total DRS scores Arm 3 vs. Arm 1 and Arm 2 vs. Arm 1 in the BRCA-deficient population using a longitudinal repeated measures model that takes into account the DRS scores measured at each assessment point up to 2 years or disease progression based on the pre-specified α allocation rule in Section 10.6.

10.4 Tertiary Efficacy Analyses

10.4.1 Time to the Second Objective Disease Progression

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

The tertiary efficacy analyses for PFS2 are defined by comparing PFS2 in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the whole population and the BRCA-deficient population (or only in the whole population based on the pre-specified α allocation rule). PFS2 will be also compared between Arm 2 and Arm 3 as an exploratory analysis. The distribution of PFS2 will be estimated for each treatment arm using Kaplan-Meier methodology. For the whole population, PFS2 will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen, and BRCA-deficient status. For the BRCA-deficient population, PFS2 will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen as applicable. Median PFS2 time will be estimated and 95% confidence interval for the estimated median PFS2 time will be presented for each treatment arm.
10.4.2 Time to the First Subsequent Therapy

Time to the First Subsequent Therapy (TTFST) will be defined as the number of days from the day the subject is randomized to the start of the first subsequent therapy or death of any cause. If the subject does not have an event of TTFST, the subject's data will be censored at the date of the subject's last visit or survival follow-up.

The tertiary efficacy analyses for TTFST are defined by comparing TTFST in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the whole population and the \textit{BRCA}-deficient population (or only in the whole population based on the pre-specified \(\alpha\) allocation rule). TTFST will be also compared between Arm 2 and Arm 3 as an exploratory analysis. The distribution of TTFST will be estimated for each treatment arm using Kaplan-Meier methodology. For the whole population, TTFST will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen, and \textit{BRCA}-deficient status. For the \textit{BRCA}-deficient population, TTFST will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen as applicable. Median TTFST time will be estimated and 95% confidence interval for the estimated median TTFST time will be presented for each treatment arm.

10.4.3 Time to the Second Subsequent Therapy

Time to the Second Subsequent Therapy (TTSST) will be defined as the number of days from the day the subject is randomized to the start of the second subsequent therapy or death of any cause. If the subject does not have an event of TTSST, the subject's data will be censored at the date of the subject's last visit or survival follow-up. PFS2, TTFST, and TTSST will be summarized and analyzed using the same methodologies as PFS.

The tertiary efficacy analyses for TTSST are defined by comparing TTSST in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the whole population and the \textit{BRCA}-deficient population (or only in the whole population based on the pre-specified \(\alpha\) allocation rule). TTSST will be also compared between Arm 2 and Arm 3 as an exploratory analysis. The distribution of TTSST will be estimated for each treatment arm using Kaplan-Meier
methodology. For the whole population, TTSST will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen, and BRCA-deficient status. For the BRCA-deficient population, TTSST will be compared between each of the treatment arms and the control arm using the log-rank test, stratified by residual disease and choice of regimen as applicable. Median TTSST time will be estimated and 95% confidence interval for the estimated median TTSST time will be presented for each treatment arm.

10.4.4 Additional PRO Endpoints

Additional analysis based on other PRO endpoints will be specified in a separate PRO analysis plan.

10.5 Efficacy Subgroup Analyses

Subgroup analyses will be performed for the endpoints of PFS and OS to evaluate the impact of the baseline characteristics on treatment effect. The subgroup will be (but not limited) as follows:

- BRCA-deficient status [deleterious BRCA 1/2 mutation versus no mutation]
- Stage of Disease [III vs. IV]
- Residual Disease and Choice of Regimen
- Age group [≤ 65 years versus > 65 years]
- Smoking history [current smoker versus past smoker versus never smoked]
- ECOG [0 versus ≥ 1]

10.6 Multiplicity Adjustment

The multiplicity considerations of this study include three treatment arms, two populations, and multiple endpoints.

Three treatment arms are annotated in Table 3.
Table 3. Study Treatment Arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: C/P + placebo → placebo</td>
<td>Reference regimen</td>
</tr>
<tr>
<td>Arm 2: C/P + veliparib → placebo</td>
<td>Veliparib administered in the combination therapy phase only</td>
</tr>
<tr>
<td>Arm 3: C/P + veliparib → veliparib</td>
<td>Veliparib administered in both combination therapy and maintenance therapy phases</td>
</tr>
</tbody>
</table>

Note: [+] indicates 'concurrent with;' [−] indicates 'followed by;' [C/P] indicates 'backbone chemotherapy' (i.e., carboplatin/paclitaxel).

There are two populations of interest: whole population and BRCA-deficient population.

The hypotheses of interest are listed below:

Table 4. The Null Hypotheses of Interest in the Both the Whole Population and BRCA-Deficient Population

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (Arm 3 versus Arm 1)</td>
<td>PFS (Arm 2 versus Arm 1)</td>
</tr>
<tr>
<td>OS (Arm 3 versus Arm 1)</td>
<td>OS (Arm 2 versus Arm 1)</td>
</tr>
<tr>
<td>DRS (Arm 3 versus Arm 1)</td>
<td>DRS (Arm 2 versus Arm 1)</td>
</tr>
</tbody>
</table>

PFS = Progression Free Survival; OS = Overall Survival; DRS = Disease Related Symptom

Note: PFS (Arm 3 versus Arm 1) denotes the null hypothesis: Arm 3 (C/P + veliparib → veliparib) does not increase PFS compared to Arm 1 (C/P + placebo → placebo). Other notations in this table are defined similarly.

The expected proportion of BRCA-deficient subjects is approximately 24% in the whole population. Due to the challenge of obtaining all the testing results of BRCA-deficient status prior to randomization, the test results are expected to be fully available for all subjects during the trial. A pre-specified α allocation rule is defined as below for 2 scenarios, based on the proportion of the subjects with BRCA-deficient status obtained prior to the database lock. In Scenario 1 (Figure 2), BRCA-deficient subjects account for at least 18% of the whole population; in Scenario 2 (Figure 3), BRCA-deficient subjects account for less than 18% of the population.
Figure 2. Testing Procedures for the Hypotheses in the Whole and \textit{BRCA}-Deficient Populations Under Scenario 1

\textbf{Scenario 1}

Whole population \((\alpha = 0.0125)\)

- PFS (Arm 3 vs. Arm 1) at \(\alpha\)

- Hochberg Procedure at \(\alpha\)
  - OS (Arm 3 vs Arm 1) at \(\alpha/2\) or \(\alpha\)
  - PFS (Arm 2 vs Arm 1) at \(\alpha/2\) or \(\alpha\)

  If both tests are rejected

  - OS (Arm 2 versus Arm 1) at \(\alpha\)

BRCA-deficient population \((\alpha = 0.0125)\)

- PFS (Arm 3 vs. Arm 1) at \(\alpha\)

- PFS (Arm 2 vs. Arm 1) at \(\alpha\)

- OS (Arm 3 vs Arm 1) at \(\alpha\)

- OS (Arm 2 vs. Arm 1) at \(\alpha\)

- DRS (Arm 3 vs Arm 1) at \(\alpha/2\) or \(\alpha\)

- DRS (Arm 2 vs Arm 1) at \(\alpha/2\) or \(\alpha\)

Total type I error = 0.025
Scenario 1: If the *BRCA*-deficient subjects consist of at least 18% of the whole population (Figure 2):
• The entire one-sided type I error of 0.025 will be equally allocated to the whole population and the BRCA-deficient population, or 0.0125 for each population,

• The testing procedures of the hypotheses within each population are defined as below and illustrated by the flow chart in Figure 2 as above.
  ○ For the whole population, assuming $\alpha$ (0.0125 in this case) is allocated, follow the below steps in order:

  1. Test PFS (Arm 3 versus Arm 1) at level $\alpha$,
     ● If it's rejected, proceed to Step 2,
     ● Otherwise stop and accept subsequent hypotheses,

  2. Test PFS (Arm 2 versus Arm 1) and OS (Arm 3 versus Arm 1) using a Hochberg procedure at level $\alpha$,
     ● Test PFS (Arm 2 versus Arm 1) at level $\alpha/2$ and let $P$ be the $P$ value of the test,
     ● If $P \leq \alpha/2$, reject PFS (Arm 2 versus Arm 1) and test OS (Arm 3 versus Arm 1) at level $\alpha$,
     ● If $\alpha/2 < P \leq \alpha$, test OS (Arm 3 versus Arm 1) at level $\alpha$ (reject PFS [Arm 2 versus Arm 1] if OS [Arm 3 versus Arm 1] is rejected at $\alpha$, otherwise accept both hypotheses and stop),
     ● If $P > \alpha$, accept PFS (Arm 2 versus Arm 1) and test OS (Arm 3 versus Arm 1) at level $\alpha/2$,
     ● If both PFS (Arm 2 versus Arm 1) and OS (Arm 3 versus Arm 1) are rejected, proceed to Step 3, otherwise stop and accept subsequent hypotheses,

  3. Test OS (Arm 2 versus Arm 1) at level $\alpha$,
     ● If it's rejected, proceed to Step 4, otherwise stop and accept subsequent hypotheses,

  4. Test DRS (Arm 3 versus Arm 1) and DRS (Arm 2 versus Arm 1) using a Hochberg procedure at level $\alpha$,,
○ For the BRCA-deficient population, assuming α (0.0125 in this case) is allocated, hypotheses will be tested by a fixed-sequence procedure in the following testing order:
   5. (Arm 3 versus Arm 1),
   6. PFS (Arm 2 versus Arm 1),
   7. OS (Arm 3 versus Arm 1),
   8. OS (Arm 2 versus Arm 1),
   9. DRS (Arm 3 versus Arm 1),
   10. DRS (Arm 2 versus Arm 1).

Scenario 2: If BRCA-deficient subjects account for less than 18% of the whole population (Figure 3):

- The entire one-sided type I error of 0.025 will be allocated to the whole population only and the hypotheses in the BRCA-deficient population will not be formally tested, but will be analyzed as exploratory analyses.

For Scenario 1, between the two populations (whole population and BRCA-deficient population), a one-sided α of 0.0125 is allocated to each population based on the Bonferroni adjustment so that the total one-sided α is 0.025; within each population, a gate-keeping procedure is used to control the type I error rate at 0.0125. Therefore, the overall type I error is controlled at one-sided 0.025 level.

For Scenario 2, only the whole population will be formally tested and a gate-keeping procedure is used to test all of the hypotheses within the whole population, so the overall type I error rate is controlled at one-sided 0.025 level.

The final testing procedure will be either Scenario 1 or Scenario 2, depending on the proportion of BRCA-deficient subjects in the whole population, which will be based on the BRCA-deficient test results obtained prior to the database lock. If the proportion of
the \textit{BRCA}-deficient subjects is below the target of 24\% under Scenario 1, considerations may be given to increase the sample size in the whole population or follow the subjects for longer duration to ensure sufficient power to test the primary objective in the \textit{BRCA}-deficient population. Details of the potential increase in sample size will be determined prior to completion of enrollment and included in a final statistical analysis plan prior to the database lock.

The final multiple testing procedure will be based on the pre-specified rules as above, and will be determined in a blinded fashion before the database is locked. It will be also specified in the statistical final analysis plan (SAP) before the database is locked. The algorithm to determine the final testing procedure only utilizes the testing results of the \textit{BRCA}-deficient status of the subjects during the study, and does not utilize any efficacy or safety data, so no bias or inflation of type I error is expected.

\section*{11.0 Safety Analysis}

\subsection*{11.1 General Considerations}

Safety analyses will be performed on the AST population. All subjects who took at least one dose of veliparib/placebo will be included. Treatment groups in the safety summaries will be based on the actual treatment the subject receives. For the visit wise safety analyses, the analysis visit windows are described in Table 1.

Summaries involving docetaxel will only be performed on subjects who were dosed with docetaxel.

Only \( P \) values \( \leq 0.100 \) when rounded to three digits will be presented.

\subsection*{11.2 Analysis of Adverse Events}

Analyses of adverse events will include only "treatment-emergent" events. "Treatment-emergent adverse events" are defined as any adverse events that first occur on or after the date of first dosing and with an onset date no more than 30 days after the last dose of veliparib/placebo. Treatment-emergent adverse events will be summarized by
preferred terms within a System and Organ Class according to the MedDRA adverse event coding dictionary. The frequencies and percentages of subjects experiencing an adverse event at a NCI CTCAE Version 4.0 terminology grade, and relationship to veliparib/placebo, carboplatin, paclitaxel, docetaxel will be provided. Serious adverse events, adverse events leading to study discontinuation, adverse events leading to veliparib/placebo, carboplatin, paclitaxel, docetaxel interruption, adverse events leading to veliparib/placebo, carboplatin, paclitaxel, docetaxel dose reduction, and adverse events leading to veliparib/placebo, carboplatin, paclitaxel, docetaxel dose delay will be summarized. Comparisons of the rates of subjects experiencing an adverse event between Arm 2 versus Arm 1 and Arm 3 versus Arm 1 using Fisher's exact test.

The frequencies and percentages of subjects experiencing a treatment-emergent grade 3 or 4 peripheral neuropathy will be summarized and compared between the treatment arms by the two pairwise comparisons (Arm 2 versus Arm 1 and Arm 3 versus Arm 1) using CMH test stratified by the stratification factors.

In summary, the frequencies and percentages of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event categories:

- Any treatment-emergent adverse event*
- Any treatment-emergent adverse event with number broken down by maximum NCI terminology grade*
- Any treatment-emergent adverse event with number broken down by maximum relationship to each of: veliparib/placebo, carboplatin, paclitaxel, docetaxel
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to each of: veliparib/placebo, carboplatin, paclitaxel, docetaxel
- Any treatment-emergent NCI terminology grade 3, 4 or 5 adverse event
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to each of: veliparib/placebo,
carboplatin, paclitaxel, docetaxel with NCI terminology grade 3, 4 or 5 adverse event

- Any treatment-emergent NCI terminology grade 3 or 4 adverse event
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to each of: veliparib/placebo, carboplatin, paclitaxel, docetaxel with NCI terminology grade 3 or 4 adverse event
- Any treatment-emergent serious adverse event
- Any treatment-emergent serious adverse event with number broken down by maximum NCI terminology grade
- Any treatment-emergent serious adverse event with number broken down by maximum relationship to veliparib/placebo, carboplatin, paclitaxel, docetaxel
- Any treatment-emergent serious adverse event that is rated by the investigator as a reasonable possibility of being related to each of: veliparib/placebo, carboplatin, paclitaxel, docetaxel
- Any treatment-emergent NCI terminology grade 3, 4 or 5 serious adverse event
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to veliparib/placebo, carboplatin, paclitaxel, docetaxel with NCI terminology grade 3, 4 or 5 serious adverse event
- Any treatment-emergent NCI terminology grade 3 or 4 serious adverse event
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to veliparib/placebo, carboplatin, paclitaxel, docetaxel with NCI terminology grade 3 or 4 serious adverse event
- Any treatment-emergent adverse event leading to discontinuation of veliparib/placebo, carboplatin, paclitaxel, docetaxel
- Any treatment-emergent adverse event leading to veliparib/placebo interruption or reduction
- Any treatment-emergent adverse event leading to veliparib/placebo interruption
• Any treatment-emergent adverse event leading to veliparib/placebo dose reduction
• Any treatment-emergent adverse event leading to dose reduction or delay of each of carboplatin, paclitaxel, docetaxel
• Any treatment-emergent adverse event leading to carboplatin, paclitaxel, docetaxel dose reduction
• Any treatment-emergent adverse event leading to carboplatin, paclitaxel, docetaxel dose delay
• Any treatment-emergent adverse event leading to death
• Any treatment-emergent adverse event leading to death rated by the investigator as a reasonable possibility of being related to veliparib/placebo

* Analyses will also be summarized by the following groups: Q-week carbo/pac, Q3-week carbo/pac, docetaxel dosed, interval surgery, primary surgery, combination period (Cycles 1 through 6), and maintenance period (Cycles 7 through 30).

Adverse Events of Special Interest

Treatment-emergent adverse events and serious adverse events of special interest based on Standardized (SMQ-s) or Company (CMQ-s) MedDRA Queries, will also be summarized. The search criteria for each event is located in Table 5. The rates of these events will be summarized by MedDRA system organ class and preferred term. An overview summary for each event, and summaries of all treatment-emergent adverse events, grade 3 and 4 events, and serious adverse events, will be produced.
Table 5. Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Adverse Event of Special Interest</th>
<th>Search Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Nausea and vomiting preferred terms</td>
</tr>
<tr>
<td>Seizures</td>
<td>SMQ 20000079 (query for convulsions) [broad search]</td>
</tr>
<tr>
<td>Hematopoietic cytopenias</td>
<td>SMQ 20000027 (all such events) [broad search] and SMQ 20000028 (events affecting more than one type of cell) [broad search]</td>
</tr>
<tr>
<td>Hematopoietic Erythropenia</td>
<td>SMQ 20000029 [broad search]</td>
</tr>
<tr>
<td>Hematopoietic Leukopenia</td>
<td>SMQ 20000030 [broad search]</td>
</tr>
<tr>
<td>Hematopoietic Thrombocytopenia</td>
<td>SMQ 20000031 [broad search]</td>
</tr>
<tr>
<td>Hematological Toxicities</td>
<td>CMQ 'Hematological Toxicity – Neutropenia' and CMQ 'Hematological Toxicity – Lymphopenia'</td>
</tr>
<tr>
<td>Changes in reproductive organ function</td>
<td>SMQ 20000210 (fertility disorders)</td>
</tr>
<tr>
<td>Secondary Malignancies</td>
<td>SMQ 20000194 and SMQ 20000195</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome</td>
<td>SMQ 20000217</td>
</tr>
</tbody>
</table>

11.3 Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of the last dose of study drug, (2) for deaths occurring more than 30 days of the last dose of study drug and (3) for all deaths in this study regardless of the number of days relative to the last dose of study drug. There will be no statistical test for above analyses.

11.4 Analysis of Laboratory and Vital Signs Data

Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, then an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline...
measurement or do not have any post-baseline measurements will not be included. Comparisons of the differences in mean changes from baseline for Arm 2 and 3 versus Arm 1 will be made using ANOVA with treatment group as the factor for each post-baseline visit.

**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 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 last post-baseline measurement collected no more than 30 days after the last dose of study drug. The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post baseline grades of 3 to 4 will be compared between Arm 2 and 3 and Arm 1 using Fisher's exact test.

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 veliparib/placebo, will be included in these listings.

The tables will contain a cross-tabulation of frequency of categorized baseline grades versus maximum post-baseline grades. The categories in the cross-tabulation include terminology grades 0 to 4, no grade (e.g., a laboratory variable value that is high with respect to the normal range is not assigned a grade when the toxicity criteria are for low laboratory values), and missing value. Grade 0 is defined as the value within the normal range. The maximum post-baseline grade for each subject is based on the graded values (0 to 4). All treated subjects will be included in the cross tabulation regardless whether baseline or post-baseline measurements are collected.
11.5 Analyses of Vital Signs Using Criteria for Potentially Clinically Significant Vital Sign Values

Vital signs values will be assessed for potential clinical significance through the application of criteria developed at AbbVie as detailed in Table 6 below.

**Table 6. Potential Clinical Significance Criteria for Vital Signs**

<table>
<thead>
<tr>
<th>Vital Sign</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td>&gt; 150 mmHg and &gt; 20 mmHg higher than baseline</td>
</tr>
<tr>
<td></td>
<td>&lt; 70 mmHg and a decrease of ≥ 30 mmHg from baseline</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>&gt; 100 mmHg and higher than baseline</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 mmHg and a decrease of ≥ 20 mmHg from baseline</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>&gt; 120 bpm and an increase of ≥ 30 bpm from baseline</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 bpm and a decrease of ≥ 30 bpm from baseline</td>
</tr>
<tr>
<td>Temperature</td>
<td>≥ 38.9°C</td>
</tr>
<tr>
<td></td>
<td>≤ 35.6°C</td>
</tr>
</tbody>
</table>

The frequency and percentage of subjects with post-baseline values meeting Criteria for Potentially Clinically Significant Vital Signs values will be summarized. A subject who has at least one post-baseline measurement will be included in the summary. If a subject does not have vital signs measurement at baseline but has post-baseline measurement which met the above criteria for blood pressure and pulse rate, this subject is considered as meeting the potentially clinically significant vital signs values for the measurement. If a subject has both baseline and post-baseline measurements, the post-baseline value must also be more extreme than baseline value for blood pressures and pulse rates. A separate listing will be provided that presents all of the subjects and values that meeting the criteria. The comparisons of the rates of subjects met the above criteria between Arm 2 versus Arm 1 and Arm 3 versus Arm 1 will be performed using Fisher's exact test.
### Signed by:

<table>
<thead>
<tr>
<th>Date</th>
<th>Meaning Of Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-Jan-2017 05:48:27 PM</td>
<td>Approver</td>
</tr>
<tr>
<td>16-Jan-2017 06:01:50 PM</td>
<td>Approver</td>
</tr>
<tr>
<td>16-Jan-2017 06:09:03 PM</td>
<td>Approver</td>
</tr>
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<td>16-Jan-2017 08:21:12 PM</td>
<td>Approver</td>
</tr>
<tr>
<td>17-Jan-2017 03:58:21 PM</td>
<td>Author</td>
</tr>
</tbody>
</table>
1.0 Title Page

Statistical Analysis Plan

Study M13-694

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP inhibitor) in Subjects with Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Date: 09 May 2019

Version 2.0
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3.0 Introduction

This statistical analysis plan (SAP) is created based on Study Protocol M13-694, incorporating Amendments 1, 2, 3, 4 and 5. Study M13-694 examines the safety and efficacy of veliparib (ABT-888) in combination with standard platinum-based chemotherapy (carboplatin/paclitaxel) and then as monotherapy in maintenance for high grade serous epithelial, ovarian, fallopian tube, or primary peritoneal cancer.

This SAP provides details to guide the analyses for baseline, efficacy, and safety variables and describes the populations and variables that will be analyzed and the statistical methods that will be used for primary and follow-up analyses for Study M13-694 (Analysis timing is defined in Section 4.5). Analyses will be performed using SAS® Version 9.4 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective of the study is to evaluate whether PFS is prolonged with the addition of veliparib to standard platinum-based chemotherapy (carboplatin/paclitaxel) and then continued as maintenance therapy when compared to chemotherapy alone (Arm 3 versus Arm 1). This will be evaluated in three nested cohorts defined in Section 5.1: subjects with BRCA-deficient tumors, subjects with homologous recombination deficient (HRD) tumors, and the whole patient population.

Secondary objectives include evaluations of OS (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), PFS (Arm 2 versus Arm 1), Disease Related Symptom (DRS) scores (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), and safety of the 3 study arms. These will be evaluated within the three patient populations.

The tertiary objectives include progression free survival 2 (PFS2), time to first subsequent therapy (TTFST), time to second subsequent therapy (TTSST), and other PRO endpoints.
(which will be specified in a separate analysis plan). These will also be evaluated by comparing Arms 3 and 2 with Arm 1, within the three patient populations.

### 4.2 Design Diagram

This is a randomized, placebo-controlled, double-blind, stratified, multicenter, multi-country Phase 3 study designed to evaluate if PFS is prolonged when veliparib is added to carboplatin/paclitaxel and continued as maintenance therapy when compared to chemotherapy alone in subjects with previously untreated high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Subject randomization was stratified by stage of disease, residual disease and choice of regimen, region of the world, and \( gBRCA \) mutation status (\( gBRCA \) was added during the course of the study). Approximately 1100 subjects were planned for enrollment, and 1140 subjects were randomized in a 1:1:1 ratio to one of the following three treatment Arms:

- **Arm 1:** Carboplatin/paclitaxel plus placebo for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;
- **Arm 2:** Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;
- **Arm 3:** Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by veliparib BID maintenance therapy for 30 additional 21-day cycles.

Subjects that were found not to tolerate paclitaxel, could instead receive docetaxel but had to temporarily discontinue veliparib due to lack of safety data for this combination. Subjects were allowed to restart veliparib in the maintenance phase once treatment with docetaxel had ended.

The study consists of five phases: a Pre-Therapy Phase (Screening), a Combination Therapy Phase, a Maintenance Therapy Phase, a Long-Term Follow-Up Phase, and a Survival Phase. An overview of the study design is shown in Figure 1.
Figure 1. Overall Study Design

- Pre-treatment Phase (Screening):
  - Primary cytoreductive surgery with Carboplatin and Q3-weeks paclitaxel OR Carboplatin and Q3-weeks paclitaxel
  - Internal cytoreductive surgery with Carboplatin and Q3-weeks paclitaxel OR Carboplatin and Q3-weeks paclitaxel

- Randomisation:
  - High-grade Serious Epithelial Ovarian, Rhabdoid, Tubal, or Primary Peritoneal Cancer
  - FIGO Stage III or IV
  - No prior systemic therapy
  - ECOG 0 or 1
  - No CNS metastases

- Eligible Population:

- Combination Phase:
  - Arm 1: Placebo with Carboplatin/paclitaxel (Cycle 1-8)**
  - Arm 2: Veliparib with Carboplatin/paclitaxel (Cycle 1-8)**
  - Arm 3: Veliparib with Carboplatin/paclitaxel (Cycle 1-8)**

- Maintenance Phase:
  - Primary: Progression-Free Survival (PFS)**
  - Secondary: Overall Survival & Disease-Related Symptom Scores

- Long-term follow-up/Study Endpoints:
  - Tertiary: PFS2 and Time to 2nd subsequent therapy
  - Tertiary: Time to 2nd subsequent therapy
4.3 Sample Size

The trial was planned to enroll approximately 1100 subjects (with 1:1:1 randomization ratio for Arm 1:Arm 2:Arm 3) in the whole population, including approximately 264 subjects with BRCA-deficient status (assuming 24% of the subjects in the whole population are BRCA-deficient) to power the hypotheses specified in the BRCA-deficient and whole populations (Table 1 and Table 2). Detailed sample size calculations for the PFS and OS endpoints of the BRCA-deficient, HRD and whole populations are described in Section 4.3.1 – Section 4.3.2.

In order to calculate the needed number of subjects in each of the 3 arms, the same statistical assumptions were used to power both the comparisons of PFS and OS between Arm 3 versus Arm 1 [3vs1], and between Arm 2 versus Arm 1 [2vs1], within each population.

The associated power for the alpha level and population can be found in Table 1 and Table 2.

Throughout the SAP, Month 36 is used as the 'surrogate' for the time of primary analysis of PFS for all three populations; Month 58 is used as the 'surrogate' for the time of final analysis of OS in Whole population; and Month 77 is used as the 'surrogate' for the time of final analysis of OS in both BRCA-deficient and HRD populations.
### Table 1. Power and Sample Size Calculation for Testing Scenario 1

<table>
<thead>
<tr>
<th>Type I Error</th>
<th>Population</th>
<th>No. of Subjects per Arm (N)</th>
<th>Power</th>
<th>Median PFS in Arm 1</th>
<th>Hazard Ratio</th>
<th>No. of Events for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
<th>Power</th>
<th>Median OS in Arm 1</th>
<th>Hazard Ratio</th>
<th>No. of Events for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha = 0.025</td>
<td>BRCA-deficient</td>
<td>88</td>
<td>87%</td>
<td>21</td>
<td>0.50</td>
<td>79</td>
<td>36</td>
<td>87%*</td>
<td>53</td>
<td>0.50</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>HRD</td>
<td>160</td>
<td>91.5%</td>
<td>18</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>90%*</td>
<td>47</td>
<td>0.60</td>
<td>166</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Whole</td>
<td>367</td>
<td>96.5%</td>
<td>15.5</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>91.5%*</td>
<td>41.5</td>
<td>0.70</td>
<td>350</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>94.1%</td>
<td>15.5</td>
<td>0.7</td>
<td>391</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS = progression-free survival; OS = overall survival

- **a.** Assumes 2 efficacy interim analyses (at month 36 and Month 58, respectively) with alpha spending of 0.000001 at each of the 2 interim analyses. The multiplicity adjusted alpha for the final analysis at Month 77 is 0.025, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.

- **b.** Assumes an efficacy interim analysis at Month 36 with alpha spending of 0.000001. The nominal alpha for the final analysis at Month 58 is 0.025. The multiplicity adjusted alpha for the analysis at Month 77 is 0.025, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.

**Note:** All calculations take into account a 10% dropout rate. An enrollment period of 18 months with linear enrollment rate is assumed. The actual endpoint mature time may vary depending on the true enrollment pattern.
### Table 2. Power and Sample Size Calculation for Testing Scenario 2

<table>
<thead>
<tr>
<th>Type I Error Population</th>
<th>No. of Subjects per Arm (N)</th>
<th>Power</th>
<th>Median PFS in Arm 1</th>
<th>Hazard Ratio</th>
<th>No. of Events for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
<th>Power</th>
<th>Median OS in Arm 1</th>
<th>Hazard Ratio</th>
<th>No. of Events for 2 Arm Comparison</th>
<th>Projected Endpoint Mature Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha = 0.025 BRCA-deficient</td>
<td>88</td>
<td>87%</td>
<td>21</td>
<td>0.50</td>
<td>79</td>
<td>36</td>
<td>87%</td>
<td>53</td>
<td>0.50</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>HRD</td>
<td>160</td>
<td>91.5%</td>
<td>18</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>90%</td>
<td>47</td>
<td>0.60</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>Whole</td>
<td>367</td>
<td>96.5%</td>
<td>15.5</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>91.5%</td>
<td>41.5</td>
<td>0.70</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>alpha = 0.0225 HRD</td>
<td>160</td>
<td>90.8%</td>
<td>18</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Whole</td>
<td>367</td>
<td>96.1%</td>
<td>15.5</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>alpha = 0.0125c HRD</td>
<td>160</td>
<td>86.2%</td>
<td>18</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Whole</td>
<td>367</td>
<td>93.6%</td>
<td>15.5</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>alpha = 0.0025d HRD</td>
<td>160</td>
<td>70%</td>
<td>18</td>
<td>0.60</td>
<td>170</td>
<td>36</td>
<td>68.6%</td>
<td>47</td>
<td>0.60</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>Whole</td>
<td>367</td>
<td>83.1%</td>
<td>15.5</td>
<td>0.70</td>
<td>446</td>
<td>36</td>
<td>70%</td>
<td>41.5</td>
<td>0.70</td>
<td>350</td>
<td></td>
</tr>
</tbody>
</table>

PFS = progression-free survival; OS = overall survival

a. Assumes 2 efficacy interim analyses (at Month 36 and month 58, respectively) with alpha spending of 0.000001 at each of the 2 interim analyses. The multiplicity adjusted alpha for the final analysis at Month 77 is 0.025, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.
Table 2. Power and Sample Size Calculation for Testing Scenario 2 (Continued)

b. Assumes an efficacy interim analysis at Month 36 with alpha spending of 0.000001. The nominal alpha for the final analysis at Month 58 is 0.025. The multiplicity adjusted alpha for the analysis at Month 77 is 0.025, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.

c. Calculations under these alpha values are only relevant for the comparison of PFS between Arm 3 and Arm 1.

d. PFS Calculations under this alpha value is only relevant for comparison of PFS between Arm 2 and Arm 1. OS calculations are applicable for both Arm 3 and Arm 2 versus Arm 1.

Note: All calculations take into account a 10% dropout rate. An enrollment period of 18 months with linear enrollment rate is assumed. The actual endpoint mature time may vary depending on the true enrollment pattern.
4.3.1 Hypotheses related to PFS

**PFS (Arm 3 versus Arm 1, and Arm 2 versus Arm 1):**

Testing of PFS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the population of interest.

Testing of PFS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the population of interest.

**BRCA-deficient Population:** A total of 79 events would provide 87% power for a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in PFS assuming a true hazard ratio of 0.5 (between Arm 3 and Arm 1, or between Arm 2 and Arm 1).

Assuming a median PFS of 21 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 3:Arm 1 and Arm 2:Arm 1) were needed to have a matured PFS endpoint at around 36 months taking into account a dropout rate of 10%.

**HRD Population:** This population was not in the original protocol design consideration. Assuming a HR = 0.6 between Arm 3 and Arm 1, or Arm 2 and Arm 1, we can expect at least a total of 170 PFS events in Arm 3 and Arm 1 combined, and Arm 2 and Arm 1 combined at the time of primary analyses of PFS in BRCA-deficient and Whole populations. A total of 170 events would provide 91.5% power with a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in PFS assuming a true hazard ratio of 0.6 (between Arm 3 and Arm 1, and Arm 2 and Arm 1).

Assuming a median PFS of 18 months in Arm 1 and an enrollment period of 18 months, approximately 160 subjects per arm in a 1:1 randomization ratio (Arm 3:Arm 1, and Arm 2:Arm 1) are needed to have a matured PFS endpoint at around 36 months taking into account of a dropout rate of 10%.
**Whole Population:** A total of events between 391 and 446 would provide power between 94.1% and 96.5%, with a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in PFS assuming a true hazard ratio of 0.7 (between Arm 3 and Arm 1, or between Arm 2 and Arm 1). Assuming a median PFS of 15.5 months in Arm 1 and an enrollment period of 18 months, and taking into account a dropout rate of 10%, approximately 367 subjects were needed per arm in a 1:1 randomization ratio (Arm 3:Arm 1, and Arm 2:Arm 1) in order to have a matured PFS endpoint at around 36 months.

**4.3.2 Hypotheses related to OS**

**OS (Arm 3 versus Arm 1, and Arm 2 versus Arm 1):**

Testing of OS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the population of interest.

Testing of OS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the population of interest.

**BRCA-deficient Population:** A total of 79 events would provide 87% power with a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in OS, assuming a true hazard ratio of 0.5 (between Arm 3 and Arm 1, or between Arm 2 and Arm 1). Assuming a median OS of 53 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 3:Arm 1, and Arm 2:Arm 1) were needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the primary analyses of PFS and final analysis of OS analysis for the whole population.
HRD Population: A total of 166 events would provide 90% power with a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in OS, assuming a true hazard ratio of 0.6 (between Arm 3 and Arm 1, and Arm 2 and Arm 1).

Assuming a median OS of 47 months in Arm 1 and an enrollment period of 18 months, approximately 160 subjects per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) are needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the primary PFS and final analysis of OS for the whole population.

Whole Population: Under the design considerations in the original protocol, a total of 350 events would provide 91.5% power for a 1-sided log-rank test at a 0.025 significance level, respectively, to detect a statistically significant improvement in OS assuming a true hazard ratio of 0.7 (between Arm 3 and Arm 1, or between Arm 2 and Arm 1).

Assuming a median OS of 41.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10% and an efficacy interim analysis that occurs at the time of the PFS analysis, approximately 367 subjects were needed per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) to have a mature OS endpoint at around 58 months.

4.4 Interim Analysis

Interim Efficacy Analyses for Overall Survival

Overall survival is expected to mature at Month 58 in the whole population and at Month 77 for the BRCA-deficient and HRD populations.

For the OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the BRCA-deficient population and the HRD population, two efficacy interim analyses will be performed. The first interim analysis will occur at the time of the primary analyses of PFS analyses (~Month 36) with a nominal alpha of 0.000001, and the second interim
analysis will occur at the time of the final analysis of OS for the whole population (~Month 58) with a nominal alpha of 0.000001, so that the final analyses of OS in each population (~Month 77) have a nominal alpha of 0.025 if all null hypotheses tested previously according to the testing sequence are rejected.

For the OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the whole population, one efficacy interim analysis will be performed at the time of the primary analyses of PFS analyses (~Month 36) with a nominal alpha of 0.000001, so that the final analyses of OS (~Month 58) have a nominal alpha of 0.025 if all null hypotheses tested at the time of the primary analyses of PFS and the OS hypotheses (Arm 3 versus Arm 1) in the BRCA-deficient and HRD populations are rejected at the time of the final analyses of OS.

Depending on the outcome of the primary analysis and the OS event accrual, the sponsor may decide not to spend any alpha for the analysis of immature OS data in BRCA-deficient and HRD populations at the time when OS data matures in Whole population (i.e., when the targeted number of OS data is achieved in the Whole population) and the nominal alphas for the final analyses will be adjusted accordingly. The final analysis for Whole Population, planned to be performed along with the analyses of mature OS data in BRCA-deficient and HRD populations, will still be based on the data from the time when the targeted number of OS data was achieved in the Whole Population.

Interim Safety Analyses

An Independent Data Monitoring Committee (IDMC) will review safety data in an unblinded fashion approximately 12 months from the date the first subject is randomized. Details of the IDMC review will be outlined in the IDMC Charter. Aggregate clinical safety data will be reviewed on a real-time basis throughout the course of the study.

The first IDMC meeting reviewed safety data on July 29, 2016. The IDMC saw no concerning safety signals and recommended continuing the study. They also recommended an additional IDMC meeting in 6 months due to the fast enrollment rate. In
addition, the IDMC noted a significant imbalance of g\textit{BRCA} status across treatment groups, and recommended adding g\textit{BRCA} status as a randomization stratification factor to potentially correct this imbalance. This recommendation was based on the expectation that \textit{BRCA} status is a strong prognostic and predictive factor for patients' responses to the study regimen. AbbVie followed the IDMC's recommendation and added the g\textit{BRCA} stratification factor in September 2016.

The study proceeded to have three subsequent IDMC meetings to review safety data, on January 17, 2017, July 31, 2017, and May 04, 2018. No further IDMC meetings are scheduled at the time of finalization of this SAP.

\textbf{4.5 Analysis Timing}

The 'data cutoff date' for the primary analyses of PFS will be determined when the total number of PFS events in Arms 1 and 3 combined have reached 79 in the \textit{BRCA}-deficient population, 170 in the HRD population, and 391 in the whole population. Since this is a blinded study involving 3 arms, an independent statistical data analysis center will be used to confirm that the above stated criteria for the total number of PFS events between Arms 1 and 3 have been reached.

The 'data cutoff date' is finalized as May 3\textsuperscript{rd}, 2019.

An interim analysis of OS will occur in the \textit{BRCA}-deficient, HRD and whole populations at the time of the primary analyses for PFS.

For the whole population, the final analysis of OS will occur after the total number of deaths between Arms 1 and 3 reached 350. At the time of the final analysis of OS for the whole population, interim analysis of OS will be performed for \textit{BRCA}-deficient and HRD populations.

For the \textit{BRCA}-deficient and HRD populations, final analyses of OS will occur after the total number of deaths in Arms 1 and 3 reaches 79 in the \textit{BRCA}-deficient population and 166 in the HRD population.
5.0 Analysis Populations

5.1 Definition for Analysis Populations

The study populations are defined as follows:

- **Whole population (ITT population)** – all subjects randomized by IRT.
- **BRCA-deficient population** – all subjects in the ITT population with either a germline (gBRCA) and/or tissue (tBRCA) deleterious or suspected deleterious mutation in BRCA1 or BRCA2 as determined using centralized testing.
- **HRD population** – all subjects in the BRCA-deficient population as well as those determined as having homologous repair deficiency tumors based on HRD score as determined using centralized testing.
- **As Treated (AST) population** – all subjects who were randomized by IRT and took at least one dose of veliparib/placebo. The data from the AST population will be analyzed by the actual treatment that subject received.

For all efficacy analyses, subjects in the Whole population, BRCA-deficient population, and HRD population will be analyzed by the treatment group assignment given at the time of randomization, regardless of actual treatment received, or failure to follow the protocol until completion.

5.2 Variables Used for Stratification of Randomization

Subject randomization was stratified into 48 groups as defined by combining categories of the four randomization stratification factors (gBRCA was added per the IDMC’s recommendation during the course of the study) that follow:

1. Stage of the disease
   a. III
   b. IV
2. Residual disease and choice of regimen
   a. Q3-weeks carboplatin/paclitaxel, no residual disease
b. Q3-weeks carboplatin/paclitaxel, any residual disease

c. Q-week carboplatin/paclitaxel, no residual disease

d. Q-week carboplatin/paclitaxel, any residual disease

e. Interval cytoreductive surgery, Q3-weeks carboplatin/paclitaxel

f. Interval cytoreductive surgery, Q-week carboplatin/paclitaxel

3. Region

a. Japan

b. North America or Rest of World

4. Germline \textit{BRCA} mutation status

a. \textit{gBRCA} positive (germline deleterious or suspected deleterious mutation in \textit{BRCA1} or \textit{BRCA2})

b. \textit{gBRCA} negative (wildtype or unknown)

Stratification factors to be used in stratified efficacy analyses are described below in Section 6.0.

\textbf{6.0 Analysis Conventions}

\textbf{General Considerations}

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a 2-sided $P$ value $\leq 0.05$.

The date of randomization is defined as the date that the IRT issues a randomization number.

All randomized subjects will be included in the efficacy analyses. All subjects who receive at least one dose of veliparib/placebo will be included in the safety analysis.
Data Cutoff Date

Only data occurring on or before the 'data cutoff date' will be used in all analyses and summaries of safety and efficacy data. The 'data cutoff date' is the data cleaning cutoff date for the database versioning for the primary PFS analysis. Data occurring after the cutoff date may be used in determining end dates for calculation of exposure (e.g., exposure or adverse event duration) or last known alive dates.

The 'data cutoff date' is finalized as May 3rd, 2019.

Definition of Study Drug

Unless otherwise specified, the study drug in this document refers to veliparib/placebo.

Definition of Study Treatment

Unless otherwise specified, the study treatment in this document refers to veliparib/placebo, carboplatin, paclitaxel, and as applicable, docetaxel.

Stratification Variables to be Adjusted for in Stratified Efficacy Analyses

Due to suspected sparseness of data in some strata observed through blinded summaries, a subset of the randomization stratification factors will be used for all stratified efficacy analyses. The subset was chosen based on the differences observed between the stratification levels in the efficacy data (pooled across three treatment groups). Additionally, based on the pooled data, Residual Disease was further collapsed as the Interval Surgery and Any Residual Disease after Primary Surgery showed similar efficacy.

Whole population:  Primary Plan: Residual Disease (2 levels: No Residual Disease after Primary Surgery versus Any Residual Disease after Primary Surgery or Interval Surgery), Stage of Disease (Stage III versus Stage IV), Choice of Paclitaxel Dosing Regimen (Q-weekly versus Q3-weekly) and BRCA-deficient status (BRCA-deficient versus BRCA wildtype or unknown) will be used in all stratified analyses of the efficacy endpoints for
the whole population. However, if any of the 16 stratum cells due to the above strategy result in 0 PFS events for Arms 1 and 3 combined, then Choice of Paclitaxel Dosing Regimen will be dropped from the set of factors. The set of factors will be consistent among all stratified efficacy analyses based on the whole population (unless specified otherwise).

BRCA-deficient and HRD populations: Residual Disease (2 levels: No Residual Disease after Primary Surgery versus Any Residual Disease after Primary Surgery or Interval Surgery) and Stage of Disease (Stage III versus Stage IV) will be used in all stratified analyses of the efficacy endpoints for the BRCA-deficient and HRD populations.

The stratification factor value under which the subject is randomized by the IRT will be used in the efficacy analyses for all factors except BRCA-deficient status. Since tissue BRCA status was not a randomization factor, and not all subjects were randomized by germline BRCA status, the actual results from the central testing will be used for the analyses (i.e., not the gBRCA status used for stratification at randomization).

**Dealing with Multiple Values on the Same Day**

In cases where multiple values are collected on the same day (including baseline visit and post-baseline visits), the maximum grade value will be selected as the value for that day for the shift analysis of lab parameters; the worst score calculated for that day will be used for analysis of quality of life (QoL), and performance status (ECOG).

**Definition of Baseline**

Unless otherwise specified, the baseline is defined as the last non-missing observation collected on or prior to the date of the first dose of study treatment for treated subjects (or the date of randomization for non-treated subjects).

**Definition of Final Visit**

For laboratory and vital signs variables, Final Visit is defined as the last non-missing observation collected within 30 days following the last dose of study treatment. All post-
baseline assessments collected more than 30 days after the last dose of study treatment will not be included in the analyses of laboratory and vital signs variables.

**Definition of Study Rx Day (Days Relative to the First Dose of Study Treatment)**

Study Rx Days are calculated for each time point relative to the first dose date of any component of study treatment. They are defined as the number of days between the day of the first dose of study treatment and the specific time point. Rx days are negative values when the time point of interest is prior to the first study treatment dose day. Rx days are positive values when the time point of interest is after the first study treatment dose day. The day of the first dose of study treatment is defined as Study Rx Day 1, while the day prior to the first study treatment dose is defined as Study Rx Day –1 (there is no Study Rx Day 0).

**Definition of Cycle Rx Days in Each Cycle**

During the combination phase (Cycles 1 through 6), Cycle Rx Days for each cycle are calculated for each time point relative to the first dose of veliparib/placebo/carboplatin/paclitaxel/docetaxel in each cycle.

During the maintenance phase (Cycles 7 through 36), Cycle Rx Days are calculated for each time point relative to the first dose of veliparib/placebo in each cycle.

Subjects that have discontinued study therapy and are in the Long Term Follow Up without Disease Progression Phase will still have QoL data summarized as treatment cycles. Cycle Rx Days will be calculated by taking the last available Cycle start date while on treatment, and iteratively adding 21 days to define the nominal day of each Cycle Rx Day up until Cycle 36.

**Definition of Analysis Windows for DRS**

All time points and corresponding time windows are based on Cycle Rx Days.
For visit wise longitudinal analyses such as mean change from baseline to all post-baseline assessments in DRS, the time windows specified in describe how the data will be assigned to the protocol specified visits. Analysis time windows are constructed using the following algorithm:

Determine the nominal Cycle Rx Day for each scheduled visit.
Determine the window around a specific nominal Cycle Rx Day as in Table 3.
If more than one assessment is included in a time window, the assessment closest to the nominal day should be used. If there are two observations equally distant to the nominal day, the later one will be used in analyses.

The data will only be analyzed for visits that have at least 5 subjects' observations for each treatment group.

### Table 3. Time Windows for Visit-Wise Analysis of DRS

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Cycle Rx Day</th>
<th>Time Window while On Study Therapy (Study Rx Day Range)</th>
<th>Time Window when Off Study Therapy (Study Rx Day Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination Phase:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 1</td>
<td>Baseline</td>
<td>As Baseline Definition</td>
<td>As Baseline Definition</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>1</td>
<td>(−3, 4)</td>
<td>(−21, 21)</td>
</tr>
<tr>
<td>Cycle 5</td>
<td>1</td>
<td>(−3, 4)</td>
<td>(−21, 21)</td>
</tr>
<tr>
<td>Maintenance Phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 7</td>
<td>1</td>
<td>(−3, 4)</td>
<td>(−21, 21)</td>
</tr>
<tr>
<td>Cycle 9</td>
<td>1</td>
<td>(−3, 4)</td>
<td>(−21, 21)</td>
</tr>
<tr>
<td>Cycle XX&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>(−3, 4)</td>
<td>(−21, 21)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Every other cycle until Cycle 35.

**Determination of Censoring Dates for OS, TTFST, and TTSST**

The censoring date for overall survival, time to first subsequent therapy and time to second subsequent therapy for a subject will be the last assessment date from the following list of data record types:

- Vital signs
● Physical exam
● Lab variables, including SAE lab reports
● ECOG performance status
● Quality of life measures
● Study drug administration
● Tumor assessments scan date
● Transfusions
● Electrocardiogram
● Adverse event
● PK blood draws
● Date of Cytoreductive Surgery
● Concomitant Medications
● Post treatment therapy
● Survival follow-up (last-known-alive date)
● Randomization Date

Records that indicate that the assessment was not done will not be used in determining the censoring date.

**Partial Dates**

The following rules will apply for partial start dates:

- Missing day will be imputed as the first day of the month
- Missing month and day will be imputed as January 1st
- For partial adverse event start dates: if the first dose date is available, and the adverse event end date is missing or after the first dose date, then the imputed start date would be the maximum of the first dose date and the imputed value under the above two criteria.

The following rules will apply for partial end dates:
Missing day will be imputed as the last day of the month
Missing month and day will be imputed as December 31st
For partial adverse event end dates: the imputed value can never be set later than the subject death date, when the death date is available.

For partial exposure end dates:
For veliparib records, missing day will be imputed as the maximum of the first day of the month and the exposure record start date
For veliparib records, missing month and day will be imputed as the maximum of January 1st of the provided year and the exposure record start date
For chemotherapy, if any part of the date is missing, the end date will be imputed as the record start date
For all study treatment, if the end date is completely missing, then the end date will be imputed as the exposure record start date

**Definition of Treatment-Emergent Adverse Events**

Adverse Events will be considered "treatment-emergent" when their onset is on or after the day of the first dose of study treatment and also are at most 30 days after the last dose of any study treatment (including docetaxel if applicable).

If the onset date for an adverse event is reported with a month and year but without the day of the month, and the reported month matches that of the start of study treatment, then the adverse event will be treatment-emergent. If the reported month matches the month in which the 30 day follow-up period ends then the adverse event will be treatment-emergent. If an onset or end date for an adverse event is reported with a year only in such a way that it cannot be determined definitively if the adverse event is treatment-emergent by comparing with dosing data, the adverse event will be considered treatment-emergent.

**NCI Grades for Laboratory Variables**

Laboratory variable values will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 Published:
May 28, 2009 (v4.03: June 14, 2010)\(^1\) for some analyses. Criteria are specified for the assignment of grades with values between 1 and 4. The criteria are unidirectional: any one set of criteria constitute a screening either for low or high values of potential clinical significance.

For laboratory tests for which a normal range limit is one end of the grade 1 range then values that are either within the normal range or outside it in the direction opposite to the test will be classified as grade 0 values. For other tests, values outside the grade 1 range in the direction opposite to that of the test will be classified as grade 0.

There can be instances in which the criteria for more than one grade apply to a lab test value. In those instances the highest applicable grade will be assigned to the value.

**Definition of Safety Subgroups for Adverse Event and Laboratory Summaries**

Adverse Events and Laboratory values may be summarized according to the following clinically important safety subgroups.

- **Combination Period:** defined as the first dose date of veliparib/carboplatin/paclitaxel to the day before the first dose date veliparib during Cycle 7. For subjects not dosed after Cycle 6, the Combination Period is defined as the first dose date of veliparib/carboplatin/paclitaxel to the last dose date of any component of the study treatment + 30 days.

- **Maintenance Period:** defined as the first dose date of veliparib that occurs after the end of Cycle 6 to the last dose date of veliparib + 30 days. Only subjects that were dosed with veliparib after the end of Cycle 6 will be included in safety summaries regarding Maintenance Period.

- **Q-weekly Dosing:** for AE and Lab summaries by choice of dosing schedule, the actual dosing schedule the subject was under will be used (not necessarily what the subject was randomized as).

- **Q3-weekly Dosing:** for AE and Lab summaries by choice of dosing schedule, the actual dosing schedule the subject was under will be used (not necessarily what the subject was randomized as).
Subjects Dosed With Docetaxel: All subjects that received at least one dose of docetaxel.

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications and Prior Oncology Therapies

The ITT population will be used in the analyses of demographic, baseline characteristics, medical history, and previous/concomitant medication. Prior oncology therapies will only be summarized for subjects with a history of another cancer.

All summaries and analyses will be presented by each treatment arm, and may also be summarized separately for the BRCA-deficient and HRD populations.

7.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Country
- Region (as randomized) [North America vs. Japan vs. Rest of World].
- Region (confirmed post randomization) [North America vs. Japan vs. Rest of World]
- Race
- Age (continuous and categorical [< 65 years vs. ≥ 65 years])
- Height
- Weight
- Type of Ovarian Cancer [High-grade serous epithelial ovarian vs. High-grade serous epithelial fallopian tube vs. High-grade serous epithelial primary peritoneal]
- History of Other Cancer [History vs. No History]
- CA-125 level [≤ ULN vs. > ULN]
- Germline BRCA status (as randomized) [gBRCA Positive vs. gBRCA Negative vs. Unknown vs. Not randomized by gBRCA]
• Germline BRCA status (central testing) [BRCA1/2 mutation vs. BRCA1/2 wildtype]
• Tissue BRCA status [BRCA1/2 mutation vs. BRCA1/2 wildtype]
• BRCA-deficient status [germline or tissue BRCA1/2 mutation vs. BRCA1/2 wildtype]
• Type of BRCA-deficiency [germline BRCA1/2 mutation vs. tissue BRCA1/2 mutation and germline BRCA1/2 wildtype vs. BRCA1/2 wildtype]
• Type of BRCA1/2 mutation [BRCA1 vs. BRCA2 vs. BRCA1 and BRCA2 vs. BRCA1/2 wildtype]
• HRD status [HRD vs. non-HRD]
• HRD and BRCA-deficient status [HRD and BRCA1/2 mutation vs. HRD and BRCA1/2 wildtype vs. non-HRD]
• Stage of Disease at randomization [III vs. IV]
• Stage of Disease as confirmed by investigator after randomization [III vs. IV]
• Residual Disease and Choice of Regimen at randomization
  ○ Q3-weekly paclitaxel, no residual disease
  ○ Q3-weekly paclitaxel, any residual disease
  ○ Q-weekly paclitaxel, no residual disease
  ○ Q-weekly paclitaxel, any residual disease
  ○ Interval cytoreductive surgery, Q3-weekly paclitaxel
  ○ Interval cytoreductive surgery, Q-weekly paclitaxel
• Residual Disease and Choice of Regimen as confirmed by investigator after randomization (categories as above; where microscopic or any macroscopic residual disease is classified as any residual disease and no residual disease is classified as no residual disease)
• Choice of Surgery at randomization [primary vs. interval]
• Choice of Surgery as confirmed by investigator after randomization [primary vs. interval vs. no surgery received]
• Residual Disease at randomization [no residual disease vs. any residual disease vs. interval surgery]
● Residual Disease after primary surgery, as confirmed by investigator after randomization [no residual disease vs. microscopic residual disease only vs. any macroscopic residual disease]
● Residual Disease after interval surgery [no residual disease vs. microscopic residual disease only vs. any macroscopic residual disease]
● Choice of Dosing Regimen at randomization [Q-weekly vs. Q3-weekly]
● Choice of Dosing Regimen as confirmed by investigator after randomization [Q-weekly vs. Q3-weekly]
● Smoking history [current smoker vs. past smoker vs. never smoked vs unknown]
● Alcohol history [current user vs. past user vs. never vs. unknown]
● ECOG performance status [0, 1, vs. 2]

The number of subjects with missing information will also be summarized.

Categorical data will be summarized by numbers and percentages in each category.

Continuous data will be summarized by mean, standard deviation, median, IQR, minimum and maximum values.

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The frequency and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment group. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system. There will be no statistical comparison for the medical history among the treatment groups.
7.3 Prior and Concomitant Medications and Prior Oncology Therapies

The frequency and percentage of subjects who took at least one dose of medication other than study treatment will be summarized by the generic name coded by WHO dictionary. This analysis will be performed for prior and concomitant medications separately. Any medication initiated before the first day of treatment with study therapy is a prior treatment. Medications initiated during the study from the first day of study treatment, or else initiated before study treatment and continued into the study treatment period, are concomitant medications. Prior Oncology Therapies will be presented in a separate summary for subjects treated for another type of cancer prior to entering the study.

There will be no statistical comparison for the prior and concomitant medications among the treatment groups.

8.0 Subject Disposition

Analyses for the subject disposition will be performed on the ITT population at the time of the primary analysis and final analysis as appropriate. The treatment groups assigned by IRT will be used in the summaries of subject disposition and there will be no statistical comparison for the subject disposition.

The screen failure reasons will be summarized for the screen failure subjects.

The number of randomized subjects, the number of treated subjects, and final status will be summarized by treatment group and by investigator site/country.

The frequency and percentage of subjects who discontinued study, veliparib/placebo, carboplatin, or paclitaxel will be summarized for each treatment group. All reasons for discontinuation and the primary reason for discontinuation of each drug (including docetaxel) will be summarized by treatment group.

The frequency and percentage of subjects who underwent primary or interval surgery will be summarized by randomized surgery type. For subjects that did not undergo surgery,
the reasons may be summarized and a subject listing may be provided containing additional details.

9.0 Study Drug Exposure and Compliance

9.1 Study Treatment Exposure

Analyses for the exposure to study treatment will be performed on the AST population.

The number of cycles that subjects are exposed to veliparib/placebo, carboplatin, paclitaxel, and docetaxel (for subjects dosed with docetaxel) will be summarized by treatment group. Frequencies and percentages of the maximum cycle dosed will be displayed for each component of study treatment by treatment group.

In addition, the following will be summarized for veliparib/placebo only:

**Days exposed to study drug (days)** is defined as the total number of individual days a subject received study drug.

**Days exposed to study drug (intervals):** the frequency and percentage of subjects exposed to veliparib/placebo will be summarized for each of the following duration intervals.

- 1 to 63 days \([\leq 3 \text{ cycles}]\)
- 64 to 126 days \([3 < \text{ cycles} \leq 6]\)
- 127 to 252 days \([6 < \text{ cycles} \leq 12]\)
- 253 to 378 days \([12 < \text{ cycles} \leq 18]\)
- 379 to 504 days \([18 < \text{ cycles} \leq 24]\)
- 505 to 630 days \([24 < \text{ cycles} \leq 30]\)
- \(\geq 631 \text{ days} [> 30 \text{ cycles}]\)
Average dosed days per cycle of study drug is defined as the total number of days a subject received study drug divided by the number of cycles that the subject is exposed to study drug.

For all summaries of all components of the study treatment, descriptive statistics (mean, standard deviation, median, and range) will be used to summarize duration of exposure and number of cycles exposed by treatment group.

9.1.1 Dose Reductions, Interruptions, Delays and Intensity

The frequencies and percentages of subjects having dose reduction (all treatments), interruption (veliparib/placebo only), or delay (carboplatin, paclitaxel, docetaxel) will be summarized for each treatment group. Summaries of veliparib will be done for the entire treatment period, and will also be separated by combination period (Cycle 1 through Cycle 6) and maintenance (Cycle 7 through Cycle 36).

Dose Reductions

Carboplatin/paclitaxel/docetaxel: If a subject has any dose reduction from the previous dose of carboplatin/paclitaxel/docetaxel, this subject will be considered as having experienced dose reduction of carboplatin/paclitaxel/docetaxel, respectively. For carboplatin, this is calculated using the AUC. For paclitaxel and docetaxel, this calculation is done using the investigator-selected dose level (mg/m^2).

Veliparib: The data entry guidelines for BID dosing for veliparib instructs that each skipped dose is recorded into EDC. To only summarize true dose reductions and not days when only a single dose was taken, the following convention will be used: Dose reductions for veliparib will be calculated by first finding the maximum total daily dose per cycle. If a subject has a reduction from the previous cycle's maximum total daily dose, then this subject will be considered as having experienced a dose reduction of veliparib.
**Dose Interruptions**

Dose interruptions are defined for veliparib/placebo only. If a subject skips 1 or more consecutive days, this subject will be considered as having experienced a dose interruption of veliparib/placebo.

By definition, all interval surgery subjects that undergo surgery will have a dose interruption of veliparib. Therefore, the summary of dose interruptions will also be divided into primary versus interval surgery subjects, according to the surgery type the subject actually received.

**Dose Delays**

Dose delays are defined for carboplatin, paclitaxel and docetaxel.

For carboplatin, Q3-weekly dosing of paclitaxel, and docetaxel, a dose delay is defined as more than 27 days between consecutive dose dates of the respective therapy. For Q-weekly dosing of paclitaxel, a dose delay is more than 13 days between consecutive dose dates.

**Dose Intensity for Chemotherapy**

Dose intensity will be calculated for carboplatin and paclitaxel per Table 4. For paclitaxel, intensities will be summarized by actual dosing schedule (weekly versus Q3 weekly). There is no planned dose level of docetaxel, and so will not be summarized for subjects that switched to docetaxel.
Table 4. Dose Intensity for Carboplatin and Paclitaxel

<table>
<thead>
<tr>
<th></th>
<th>Actual Total Dose (ATD)</th>
<th>Planned Total Dose (PTD)</th>
<th>Actual Dosing Days (ADD)*</th>
<th>Ideal Dosing Days (IDD)*</th>
<th>Dose Intensity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carboplatin</strong></td>
<td>Actual total dose AUC</td>
<td>AUC 6 mg/mL/min * total number of administrations of carboplatin</td>
<td>Last dose date + 21 – first dose date</td>
<td>Number of administrations * 21</td>
<td>100* (ATD/PTD) * (IDD/ADD)</td>
</tr>
<tr>
<td></td>
<td>(mg/mL/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td>Actual total dose (mg/m2)</td>
<td>80 mg/m2 * total number of administrations of paclitaxel</td>
<td>Last dose date + 7 – first dose date</td>
<td>Number of administrations * 7</td>
<td>100* (ATD/PTD) * (IDD/ADD)</td>
</tr>
<tr>
<td>(weekly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td>Actual total dose (mg/m2)</td>
<td>175 mg/m2 * total number of administrations of paclitaxel</td>
<td>Last dose date + 21 – first dose date</td>
<td>Number of administrations * 21</td>
<td>100* (ATD/PTD) * (IDD/ADD)</td>
</tr>
<tr>
<td>(Q3 weekly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. For interval surgery subjects, ADD and IDD will be calculated for Cycles 1 - 3 and 4 - 6 separately, and summed together to get a final total value of dosing days.

10.0 Efficacy Analysis

10.1 General Considerations

Unless otherwise noted, for all statistical analysis, statistical significance will be determined by a 2-sided $P$ value $\leq 0.05$ (when rounded to three decimal places).

Efficacy analyses will be performed on all randomized subjects within the whole population, $BRCA$-deficient population and HRD populations. The date of randomization is defined as the date when the randomization number is issued by IRT.

For analyses performed at the time of the final primary PFS analysis the 'data cutoff date' is defined in Section 6.0, and this same date will be used for all three patient populations.
For the final analyses of OS, the 'data cutoff date' will be the data cleaning cutoff dates for the database versioning corresponding to when data mature (~58 months for whole population, ~77 months for BRCA-deficient and HRD populations).

All data occurring on or before the 'data cutoff date' will be included in all efficacy analyses. Data occurring after the 'data cutoff date' will be excluded for PFS, PFS2 and DRS. For OS, TTFST and TTSST, it will be used in determining the censoring date (as described in Section 10.3.1, Section 10.4.2, and Section 10.4.3).

For all time to event analyses (PFS, PFS2, OS, TTFST, TTSST), the following conventions will used:

- The distribution of the endpoint will be estimated for each treatment arm using Kaplan-Meier methodology.
- For both the BRCA-deficient population and the HRD population, the endpoint will be compared between each of the treatment arms (Arm 3 or Arm 2) and the control arm (Arm 1) using the log-rank test, stratified by the factors described in Section 6.0.
- For the whole population, the endpoint will be compared between each of the treatment arms (Arm 3 or Arm 2) and the control arm (Arm 1) using the log-rank test, stratified by the factors described in Section 6.0.
- The Cox Proportional Hazard Model will be used to estimate the hazard ratio and 95% confidence interval comparing each of the treatment arms (Arm 3 or Arm 2) and the control arm (Arm 1) within each population, stratified by the factors described in Section 6.0.
- For all endpoints, the median time and its 95% confidence interval will be estimated for each treatment arm within each population.

### 10.2 Primary Efficacy Analysis

The primary efficacy endpoint is progression-free survival (PFS). PFS will be defined as the number of days from the date that the subject was randomized to the date the subject experiences an event of disease progression, according to RECIST criteria version 1.1 (as
determined by the investigator) or to the date of death (all causes of mortality) if disease progression is not reached. If the subject does not have an event of disease progression according to RECIST criteria versions 1.1 (as determined by the investigator) nor has the subject died, the subject's data will be censored at the date of the subject's last evaluable disease assessment. Data for subjects without any post-baseline radiographic assessments and that did not die within 89 days (12 weeks + 5 days) of randomization, will be censored at the date of random assignment.

**Handling of Intercurrent Events**

- The following events of PD/death will be included:
  - Events that occur after a subject discontinues or completes study treatment
  - Events that occur after a subject starts a new therapy (so long as the subject has not withdrawn consent from protocol tumor assessments)
- The following events of PD/death will be censored
  - Events that occur after too much time has passed since the last valid radiologic assessment according to the below table

**Disease Progression or Death after too much time between scans**

Per the protocol, the scan schedule is as follows: (every 9 weeks, then at the end of the Combination Phase, then every 12 weeks for 2 years, then every 6 months for 3 years, and then annually). Due to the complexity of this scan schedule and to prevent the gap between valid assessments prior to PD from getting too wide for the later time periods, the following programming conventions are implemented:
Randomization ≤ last evaluable scan prior to PD/Death Date < 2.5 years* 2.5 ≤ last evaluable scan prior to PD/Death Date < 5.5 years* 5.5 ≤ last evaluable scan prior to PD/Death Date

<table>
<thead>
<tr>
<th>Definition of Interval</th>
<th>Randomization ≤ last evaluable scan prior to PD/Death Date &lt; 2.5 years*</th>
<th>2.5 ≤ last evaluable scan prior to PD/Death Date &lt; 5.5 years*</th>
<th>5.5 ≤ last evaluable scan prior to PD/Death Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Intervals allowed missing prior to PD before event is censored</td>
<td>2</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Skipped intervals prior to PD</td>
<td>24 weeks (168 days + 5 days)</td>
<td>9 months (270 days + 5 days)</td>
<td>18 months (548 days + 5 days)</td>
</tr>
<tr>
<td>Number of Intervals allowed missing prior to death before event is censored</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Skipped interval Prior to death</td>
<td>12 weeks + 5 days</td>
<td>6 months (182 days + 5 days)</td>
<td>12 months (365 days + 5 days)</td>
</tr>
</tbody>
</table>

* 2.5 years = 913.125 days; 5.5 years = 2,008.875 days.

The three primary efficacy analyses are defined by:

- comparing PFS in Arm 3 versus Arm 1 in the BRCA-deficient population using the log-rank test, stratified by factors defined in Section 6.0, at the 1-sided 0.025 α level;
- comparing PFS in Arm 3 versus Arm 1 in the HRD population using the log-rank test, stratified by factors defined in Section 6.0, at the 1-sided α level as specified in Section 10.7;
- comparing PFS in Arm 3 versus Arm 1 in the whole population using the log-rank test, stratified by factors defined in Section 6.0, at the 1-sided α level as specified in Section 10.7.

The distribution of PFS will be summarized per considerations in Section 10.1.

The study will be successful if the first analysis in the multiplicity testing procedure described in Section 10.7 (comparison of PFS [Arm 3 v Arm 1] in the BRCA-deficient
population) is statistically significant. If this comparison is statistically significant, the other two primary endpoints will be analyzed for statistical significance in the specified order.

10.3 Secondary Efficacy Analyses

10.3.1 Overall Survival

OS 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, using the data as specified in Section 6.0. However, if a subject is known to either be alive or have had died after the 'data cutoff date,' then the subject's data will be censored at the 'data cutoff date'.

The six secondary efficacy analyses for OS include comparing OS in Arm 3 versus Arm 1 and Arm 2 versus Arm 1 in the BRCA-deficient population, the HRD population, and the whole population. Each comparison will be tested using the log-rank test, stratified by factors defined in Section 6.0, at the α level as specified in Section 10.7;

The distribution of OS will be summarized per considerations in Section 10.1.

10.3.2 Progression-Free Survival

The three secondary efficacy analyses of PFS include comparing PFS in Arm 2 versus Arm 1 in the BRCA-deficient population, the HRD population, and the whole population. Each comparison will be tested using the log-rank test, stratified by factors defined in Section 6.0, at the α level based on the pre-specified α allocation rule in Section 10.7.

The analyses of PFS will be performed per Section 10.1.
10.3.3 Patient Reported Outcomes

Disease Related Symptoms

The overall mean change from baseline for the disease related symptom physical (DRS) scores measured at each assessment point up to disease progression or 2 years if progression has not been reached will be a secondary endpoint of the study. No alpha will be spent on these endpoints.

DRS scores are collected at odd numbered cycles, and will be summarized through Cycle 35, which is approximately 2 years of study therapy assuming no interruptions. The visits windows are detailed in Section 6.0.

The secondary efficacy analyses for DRS are defined by the following comparisons, which will be performed in the BRCA-deficient population, HRD population and the whole population:

- The comparison of mean changes from baseline in total DRS score to each scheduled assessment until disease progression or death, for up to 2 years, between Arm 3 and Arm 1, and Arm 2 and Arm 1 using a mixed-model for repeated measures (MMRM) model with observed DRS score.

A separate MMRM model will be used for each of the three populations. Only subjects with a baseline and at least one post-baseline assessment will be included in the model. Each model will include the fixed categorical effects of treatment group, stratification factors (as specified per population in Section 6.0), time point (each scheduled assessment up to 2 years), and treatment group-by-time point interaction, and the continuous fixed covariate of baseline DRS score. The REPEATED statement will be used for time point in PROC MIXED with blocks in the covariance matrix identified by subject nested within treatment group. Restricted maximum likelihood estimation will be utilized and an unstructured covariance structure will be used to model the within-subject error. In the event that the model does not converge with unstructured covariance, AR(1) will be used.
If AR(1) does not converge, compound symmetry structure will be used. If convergence has still not been met, then a simple summary of ANCOVA by visit will be produced.

**Calculation of DRS at each timepoint**

The score range of the FOSI-DRS Score is 0 – 36, where a high score is considered good and a score of 0 would be a severely symptomatic subject.

**Individual Item Scores:**

Item Codes GP1, GP4, GP6, 03, HI7, Cx6 and O1 are considered "reverse" items and the subject's item response will be subtracted from 4 to correct for the direction as follows

\[
\text{Individual Item Score} = (4 - \text{Item Response})
\]

For Item Codes C3 and GF5, no correction to the subject's item response is necessary:

\[
\text{Individual Item Score} = \text{Item Response}
\]

**DRS Score**

FOSI-DRS score = (Sum of Individual Item Scores × 9)/(number of items answered).

**10.4 Tertiary Efficacy Analyses**

**10.4.1 Progression-Free Survival 2 (PFS2)**

Progression-Free Survival 2 (PFS2) is defined as the number of days from the day the subject is randomized to the earliest date of disease progression reported on any line of subsequent therapy or death by any cause. This is regardless of the subject having a documented PD for the primary PFS analysis prior to starting a subsequent therapy. Therefore, the same event of progression may be used for both the primary PFS analysis and the analysis of PFS2, provided the subject has not withdrawn consent from the protocol tumor assessments. Additionally, an event of PFS2 may be either radiographic or clinical progression, such as increase in CA-125, and will be documented by the
investigator. Any death that occurs prior to either a documented first progression, or a
documented second progression, will be considered as an event of PFS2.

In summary, the following will be considered PFS2 events:

- The earliest event of progression (of any type), as determined by the
  investigator, that occurs after the initiation of a subsequent therapy
- Any death that occurs prior to the subject achieving the above described event
  of progressive disease, regardless if the subject started a subsequent therapy

If the subject does not have an event of PFS2, the following censoring rules will apply:

- If the subject is still being followed per protocol scan schedule for a primary
  PFS event, PFS2 will be censored at the same date as for the primary PFS
  analysis.
- If the subject is no longer being followed for primary PFS (for any reason),
  PFS2 will be censored at the subject's most recent post-treatment therapy start
  date or end date as applicable

The tertiary efficacy analyses for PFS2 are defined by comparing PFS2 in Arm 3 versus
Arm 1 and Arm 2 versus Arm 1, in the BRCA-deficient population, HRD population and
the whole population. PFS2 may also be compared between Arm 2 and Arm 3 as an
exploratory analysis.

The efficacy analyses of PFS2 will be summarized per guidelines in Section 10.1.

**10.4.2 Time to the First Subsequent Therapy**

Time to the First Subsequent Therapy (TTFST) will be defined as the number of days
from the day the subject is randomized to the start of the first subsequent therapy (after
discontinuation of protocol study treatment) or death of any cause. If the subject does not
have an event of TTFST, the subject's data will be censored at the date the subject was last
known to be alive and not have received subsequent therapy, i.e., the subject's last visit
(including on therapy study visit, long-term follow-up without disease progression visit)
or survival follow-up. If the subject is known to have an event of TTFST after the 'data
cutoff date,' or the subject is known to be alive and without an event of TTFST after the
cutoff, then the subject's data will be censored at the 'data cutoff date.' See Section 6.0 for
more censoring details.

The tertiary efficacy analyses for TTFST are defined by comparing TTFST in Arm 3
versus Arm 1 and Arm 2 versus Arm 1, in the BRCA-deficient population, the HRD
population, and the whole population. TTFST may also be compared between Arm 2 and
Arm 3 as an exploratory analysis.

The efficacy analyses of TTFST will be summarized and analyzed per guidelines in
Section 10.1.

10.4.3 Time to the Second Subsequent Therapy

Time to the Second Subsequent Therapy (TTSST) will be defined as the number of days
from the day the subject is randomized to the start of the second subsequent therapy or
death of any cause. If the subject does not have an event of TTSST, the subject's data will
be censored at the date the subject was last known to be alive and not have received a
second subsequent therapy, i.e., the subject's last visit (including on therapy study visit,
long-term follow-up without disease progression visit) or survival follow-up. If the
subject is known to have an event of TTSST after the 'data cutoff date,' or the subject is
known to be alive and without an event of TTSST after the cutoff, then the subject's data
will be censored at the 'data cutoff date'. See Section 6.0 for more censoring details.

The tertiary efficacy analyses for TTSST are defined by comparing TTSST in Arm 3
versus Arm 1 and Arm 2 versus Arm 1, in the BRCA-deficient population, the HRD
population, and the whole population. TTSST may also be compared between Arm 2 and
Arm 3 as an exploratory analysis.

The efficacy analyses of TTSST will be summarized and analyzed per guidelines in
Section 10.1.
10.4.4 Additional PRO Endpoints

Additional analysis based on other PRO endpoints will be specified in a separate PRO analysis plan.

10.5 Additional Efficacy Analyses

In addition to the stratified log-rank test for the primary and secondary efficacy endpoints, the following analyses may be performed for the comparison of PFS, and OS, between the two treatment groups, and within the three analysis populations.

- Un-stratified log-rank test and the Cox proportional hazards model for PFS, OS.
- Modified PFS endpoint to examine sensitivity to different censoring methods, described in detail below under Supplemental Analyses for PFS Endpoint.
- Modified efficacy endpoint OS to censor at the date of subject's initiation of other post anti-cancer therapies.
- Landmark analyses of PFS at end of Combination Phase (at 4.5 months), at 10 months (~6 months after the end of chemotherapy), and at 24 months.
- PFS per central review based on central review of tumor assessments for all subjects, and analyzed following the same methodology as for the primary endpoint of PFS.
- Concordance of the investigator and central review evaluation of progression may also be summarized.

Supplemental Analyses for PFS Endpoint

In addition to the Primary PFS analysis, modified PFS analyses will be performed to examine the sensitivity to various censoring methods. A summary of these are in the following table.
<table>
<thead>
<tr>
<th>Type of Censoring</th>
<th>Name for Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Post-Treatment Anti-Cancer Therapy</td>
<td>Primary</td>
</tr>
<tr>
<td>Death window implementation</td>
<td>No</td>
</tr>
<tr>
<td>Blind Break</td>
<td>Censor</td>
</tr>
<tr>
<td>Missing Scans prior to PD</td>
<td>Censor</td>
</tr>
</tbody>
</table>

No means do not censor for the event.

First Post-Treatment Anti-Cancer Therapy: PFS will be censored at the last evaluable tumor assessment prior to the date of subject's initiation of other anti-cancer therapies.

Blind Break: PFS will be censored at the last evaluable tumor assessment prior to the date of investigator blind break.

**Tumor Marker CA-125**

CA-125 values will be presented as cross-tabulations of baseline versus maximum on treatment value within each of the cycle windows as follow: Cycles 1 – 3 (not including value used as baseline), Cycles 4 – 6, Cycles 7 – 12, Cycles 13 – 18, Cycles 19 – 24, Cycles 25 – 30, Cycles 31 – 36. The first dose date of the cycle defines the start of the window, and 1 day prior to the start date of the next cycle window defines the end of the cycle window. Within each cycle window, the maximum CA-125 value will be categorized into 1 of 3 categories: ≤ ULN, > ULN & < 2 × ULN, or ≥ 2 × ULN. Summaries will be presented within the BRCA-deficient, HRD, and whole populations.

**10.6 Efficacy Subgroup Analyses**

Subgroup analyses will be performed for the endpoints of PFS and OS within each efficacy analysis population (BRCA-deficient, HRD, and whole, as appropriate) to evaluate the impact of the baseline characteristics on treatment effect. Analyses performed in the whole population will be stratified by BRCA-deficient status. Analyses performed within BRCA-deficient and HRD populations will be unstratified.

The subgroups will be (but not limited) as follows:

- BRCA-deficient status [BRCA1/2 mutation vs. BRCA1/2 wildtype] (central testing)
• Type of BRCA-deficiency [germline BRCA1/2 mutation vs. tissue BRCA1/2 mutation and germline BRCA1/2 wildtype vs. BRCA1/2 wildtype].
• Type of BRCA1/2 mutation [BRCA1 vs. BRCA2 vs. BRCA1 and BRCA2 vs. BRCA wildtype].
• HRD status [HRD vs. non-HRD]
• HRD and BRCA-deficient status [HRD and BRCA1/2 mutation vs. BRCA1/2 wildtype vs. non-HRD vs. HRD].
• Race [White, Black, Other]
• Region [North America vs. Japan vs. Rest of World].
• Stage of Disease [III vs. IV] (as randomized)
• Residual Disease and Choice of Regimen (as randomized)
• Residual Disease post Interval Surgery [No Disease (post interval surgery) vs. Any Disease (post interval surgery)]
  ○ note: this only includes interval surgery subjects
• Residual Disease (Efficacy Stratification Factor) [No Residual Disease After Primary Surgery vs. Any Residual Disease After Primary Surgery or Interval Surgery].
• Age group [< 65 years vs. ≥ 65 years]
• Smoking history [current smoker vs. past smoker vs. never smoked]
• ECOG [0 vs. ≥ 1]

10.7 Multiplicity Adjustment

The multiplicity considerations of this study include three treatment arms, (two pairwise comparisons), three populations, and multiple endpoints.

Three treatment arms are annotated in Table 5.
### Table 5. Study Treatment Arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: C/P + placebo → placebo</td>
<td>Reference regimen</td>
</tr>
<tr>
<td>Arm 2: C/P + veliparib → placebo</td>
<td>Veliparib administered in the combination therapy phase only</td>
</tr>
<tr>
<td>Arm 3: C/P + veliparib → veliparib</td>
<td>Veliparib administered in both combination therapy and maintenance therapy phases</td>
</tr>
</tbody>
</table>

Note: [+ ] indicates 'concurrent with;' [→] indicates 'followed by;' [C/P] indicates 'backbone chemotherapy' (i.e., carboplatin/paclitaxel).

There are three populations of interest: *BRCA*-deficient population, HRD population, and whole population.

The hypotheses of interest are listed below:

### Table 6. The Null Hypotheses of Interest in each Population

<table>
<thead>
<tr>
<th>PFS (Arm 3 versus Arm 1)</th>
<th>PFS (Arm 2 versus Arm 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (Arm 3 versus Arm 1)</td>
<td>OS (Arm 2 versus Arm 1)</td>
</tr>
<tr>
<td>DRS (Arm 3 versus Arm 1)</td>
<td>DRS (Arm 2 versus Arm 1)</td>
</tr>
</tbody>
</table>

PFS = Progression Free Survival; OS = Overall Survival; DRS = Disease Related Symptom

Note: PFS (Arm 3 versus Arm 1) denotes the null hypothesis: Arm 3 (C/P + veliparib → veliparib) does not increase PFS compared to Arm 1 (C/P + placebo → placebo). Other PFS and OS notations in this table are defined similarly. DRS (Arm 3 versus Arm 1) denotes the null hypothesis of no difference in DRS scores between Arm 3 and Arm 1. DRS (Arm 2 versus Arm 1) is defined similarly. Note that no alpha will be spent on DRS analyses.

### Criteria to Determine Testing Sequence

Since subject randomization was not prospectively stratified by HRD status, two testing scenarios will be available dependent on only the balance of treatment arms within the HRD population:

- If there is little to no evidence of a severe treatment imbalance between Arm 3 and Arm 1 in the HRD population, then the fixed sequential testing sequence will be applied as outlined in Scenario 1 below.
If there is evidence of severe treatment imbalance between Arm 3 and Arm 1 in the HRD population, the Truncated Hochberg multiplicity adjustment will be applied as outlined in Scenario 2 below.

The strategy for determining severe treatment imbalance is to ensure at least 85% power to detect a statistically significant improvement in PFS between Arm 3 and Arm 1, assuming a true hazard ratio of 0.6 in the HRD population with 170 PFS events.

<table>
<thead>
<tr>
<th>HR</th>
<th># events</th>
<th>power</th>
<th>alpha</th>
<th>Treatment ratio (3vs1) as Either Arm 3:A1 or A1:Arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>170</td>
<td>91.4%</td>
<td>0.025</td>
<td>1:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85%</td>
<td>0.025</td>
<td>2.53:1</td>
</tr>
</tbody>
</table>

With 170 PFS events, if the treatment ratio between Arm 3 and Arm 1 (Arm 3: Arm 1 or Arm 1:Arm 3) is greater than 2.53:1, the power of testing for a treatment effect in the HRD population will be less than 85% in the fixed sequential testing sequence (Scenario 1). Therefore, in the presence of this severe treatment imbalance (i.e., if the treatment ratio is 2.53:1 or more), the truncated Hochberg multiplicity adjustment (Scenario 2) will be used for the HRD and whole populations. If this threshold is not met (i.e., if the treatment ratio is less than 2.53:1), then Scenario 1 will be followed.

Once the data are unblinded, the treatment ratio between Arm 3 and Arm 1 in the HRD population will be calculated and either Scenario 1 or Scenario 2 will be chosen based solely on this pre-specified criteria. The algorithm to determine the final testing procedure will only utilize results of HRD testing and treatment allocation, and will not utilize any efficacy or safety data, so no bias or inflation of type I error is expected.
Figure 2. Testing Procedures Under Scenario 1

- Total 1-sided alpha = 0.025
- Test PFS 3vs1 in BRCA population at level 0.025
- Test PFS 3vs1 in HR-D population at level 0.025
- Test PFS 3vs1 in Whole population at level 0.025
- Test OS 3vs1 in BRCA population at level 0.025
- Test OS 3vs1 in HR-D population at level 0.025
- Test OS 3vs1 in Whole population at level 0.025
- Test PFS 2vs1 in BRCA population at level 0.025
- Test PFS 2vs1 in HR-D population at level 0.025
- Test PFS 2vs1 in Whole population at level 0.025
- Test OS 2vs1 in BRCA population at level 0.025
- Test OS 2vs1 in HR-D population at level 0.025
- Test OS 2vs1 in Whole population at level 0.025
Scenario 1: Testing sequence if there is no treatment imbalance in the HRD population

- A fixed-sequence testing procedure will be used to control the Type I error rate at 0.05 from the primary efficacy endpoint sequentially through the secondary efficacy endpoints. Each of the comparisons in this sequence will be tested at
a 1-sided 0.025 level. There will be no multiplicity adjustment on the DRS scores or the tertiary efficacy endpoints.

At Month 36 (alpha = 0.025),

1. Test PFS (Arm 3 versus Arm 1) in BRCA-deficient population,
2. Test PFS (Arm 3 versus Arm 1) in HRD population,
3. Test PFS (Arm 3 versus Arm 1) in whole population
   ● In parallel, alpha = 0.000001 to be spent on interim OS analyses

At Month 58 when OS matures in the whole population, alpha = 0.000001 to be spent on second interim OS analyses for BRCA-deficient and HRD populations.

At Month 77 (alpha = 0.025, provided all preceding null hypotheses in the hierarchical testing sequence at Month 36 are rejected)

4. Test OS (Arm 3 versus Arm 1) in BRCA-deficient population,
5. Test OS (Arm 3 versus Arm 1) in HRD population,
6. Test OS (Arm 3 versus Arm 1) in whole population (based on data from Month 58)
7. Test PFS (Arm 2 versus Arm 1) in BRCA-deficient population (based on data from Month 36),
8. Test PFS (Arm 2 versus Arm 1) in HRD population (based on data from Month 36),
9. Test PFS (Arm 2 versus Arm 1) in whole population (based on data from Month 36)
10. Test OS (Arm 2 versus Arm 1) in BRCA-deficient population (based on data from Month 77),
11. Test OS (Arm 2 versus Arm 1) in HRD population (based on data from Month 77),

12. Test OS (Arm 2 versus Arm 1) in whole population (based on data from Month 58)

Scenario 2: Testing Sequence if there is treatment imbalance in the HRD population

- The entire one-sided type I error of 0.025 will be equally allocated to the below testing sequence:
  1. In the \( BRCA4 \)-deficient population, test PFS (Arm 3 versus Arm 1) at level 0.025,
  - If it is rejected, proceed to Step 2,
  - Otherwise, stop and accept subsequent hypotheses.
  2. Test PFS (Arm 3 versus Arm 1) in both the HRD (hypothesis 1, \( H_1 \)) and whole populations (hypothesis 2, \( H_2 \)) using a Truncated Hochberg procedure (with gamma = 0.8) at level \( \alpha = 0.025 \) as follows: Order the two \( P \) values from \( H_1 \) and \( H_2 \) such that \( P(1) < P(2) \). Denote the ordered hypotheses as \( H_1(1) \) and \( H_2(2) \).
    - If \( P(2) \leq 0.0225 \) then reject both hypotheses and proceed to Step 3,
    - Otherwise, test \( H(1) \) and if \( P(1) \leq 0.0125 \), then reject only \( H(1) \) and proceed to Step 3,
    - Otherwise, stop and accept \( H(1) \) and \( H(2) \), and all subsequent hypotheses
  3. At Month 77, the same hierarchical testing strategy that is described in Scenario 1 will be applied at alpha = 0.025 if both null hypotheses in Step 2 above are rejected, and at alpha = 0.0025. If only one null hypothesis in Step 2 is rejected, then the population for which the hypothesis was not rejected will not be included in the testing sequence.
For the Truncated Hochberg Procedure, the following formulas are used to calculate the two alphas used to test the two hypotheses:

\[ \alpha_1 = \left( \frac{\alpha}{2} \right) \]

\[ \alpha_2 = (\gamma)(\alpha) + (1 - \gamma)(\frac{\alpha}{2}) \]

Here, \( 0 \leq \gamma \leq 1 \); such that using \( \gamma = 0 \) results in Bonferroni method, and using \( \gamma = 1 \) results in full Hochberg Procedure. With total alpha = 0.025, choosing \( \gamma = 0.8 \) gives \( \alpha_1 = 0.0125 \) and \( \alpha_2 = 0.0225 \). If \( P_{(2)} \leq \alpha_2 \), then both hypotheses are rejected and the full alpha is passed to subsequent hypotheses. If \( P_{(2)} > \alpha_2 \) and \( P_{(1)} \leq \alpha_1 \), then only \( H_{(1)} \) is rejected and the reduced alpha \( \alpha_r = (\alpha - \alpha_2) = 0.0025 \) is passed to subsequent hypotheses. Spending 0.000001 alpha on OS analyses at month 58 yields a final alpha = 0.0025 on hypotheses in the testing sequence. This controls the overall type I error rate at one-sided 0.025 level.

### 11.0 Safety Analysis

#### 11.1 General Considerations

Safety analyses will be performed on the AST population. All subjects who took at least one dose of veliparib/placebo will be included. Treatment groups in the safety summaries will be based on the actual treatment the subject receives.

Summaries involving docetaxel will only be performed on subjects who were dosed with docetaxel.

Where applicable, only \( P \) values \( \leq 0.100 \) when rounded to three digits will be presented.

#### 11.2 Analysis of Adverse Events

Analyses of adverse events will include only "treatment-emergent" events and are defined in Section 6.0. Treatment-emergent adverse events will be summarized by preferred terms within a System and Organ Class according to the MedDRA adverse event coding.
dictionary. Grading of treatment-emergent adverse events will be according to NCI CTCAE Version 4.0 terminology grade provided by the investigator.

11.2.1 Adverse Event Overview

An overview of treatment emergent adverse events will be presented for each treatment arm consisting of the number and percentage of subjects experiencing at least one event for the following adverse event categories:

- Any adverse event
- Any adverse event that is rated by the investigator as a reasonable possibility of being related to each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel*
- Any NCI terminology grade 3 or grade 4 adverse event
- Any NCI terminology grade 3, grade 4, or grade 5 adverse event**
- Any serious adverse event.
- Any adverse event leading to discontinuation of each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel.
- Any adverse event leading to discontinuation of each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel due to disease progression.
- Any adverse event leading to discontinuation of each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel not due to disease progression.
- Any adverse event leading to interruption or reduction of veliparib/placebo
- Any adverse event leading to dose interruption of veliparib/placebo
- Any adverse event leading to dose reduction of each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel
- Any adverse event leading to dose reduction or delay of each of: carboplatin, paclitaxel, and docetaxel
- Any adverse event leading to dose delay of each of: carboplatin, paclitaxel, and docetaxel
- Any adverse event of special interest (as listed in Table 7)
- Any adverse event leading to death
Any adverse event leading to death with a reasonable possibility of being related to veliparib by the investigator

All deaths.

* Only summaries for veliparib/placebo will be presented in the SOC/PT tables.

** No summary will be presented in the SOC/PT tables.

11.2.2 Adverse Event by SOC and PT

In addition to the AE categories listed under Adverse Event Overview (unless noted otherwise), the numbers and percentages of subjects experiencing treatment-emergent adverse events will be summarized by treatment group for the following adverse event categories:

- Any adverse event with number broken down by maximum NCI terminology grade.
- Any adverse event that is rated by the investigator as a reasonable possibility of being related to veliparib/placebo with NCI terminology grade 3 or grade 4 adverse event
- Any adverse event leading to discontinuation of veliparib/placebo with a reasonable possibility of being related to veliparib (as rated by investigator)
- Any serious adverse event leading to discontinuation of veliparib/placebo with a reasonable possibility of being related to veliparib (as rated by investigator)
- Any serious adverse event with number broken down by maximum NCI terminology grade.
- Any NCI terminology grade 3 or grade 4 serious adverse event
- Any serious adverse event that is rated by the investigator as a reasonable possibility of being related to veliparib/placebo
- Any serious adverse event that is rated by the investigator as a reasonable possibility of being related to veliparib/placebo with NCI terminology grade 3 or grade 4 serious adverse event

For all adverse event summaries, the number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to SOC and PT for each
treatment arm. Subjects reporting more than one AE for a given PT will only be counted once for that term. Subjects reporting more than one adverse event within an SOC will only be counted once for that SOC. Subjects reporting more than one AE will only be counted once in the overall total. The SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC.

11.2.3 Adverse Event by Frequency

The number and percentage of subjects experiencing treatment-emergent adverse events and treatment-emergent serious adverse events will be tabulated according to preferred term and sorted by overall frequency. For adverse events with a frequency greater than 10% in any treatment group, comparisons of the rates of subjects experiencing an adverse event will be done between Arm 3 versus Arm 1 and Arm 2 versus Arm 1 using Fisher's exact test. For testing the rates of AEs experienced in the maintenance phase, a 5% cutoff will be applied.

11.2.4 Adverse Events of Special Interest

Treatment-emergent adverse events and serious adverse events of special interest based on Standardized (SMQ-s) or Company (CMQ-s) MedDRA Queries, will be summarized. The search criteria for each event is located in Table 7. The rates of these events will be summarized by MedDRA system organ class and preferred term. The same overview summary as for TEAE, and listing of subjects' data, will be provided for each AESI.
<table>
<thead>
<tr>
<th>Adverse Event of Special Interest</th>
<th>Search Criteria</th>
<th>Event Definition/Medical Concept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Nausea and vomiting preferred terms MedDRA preferred terms (PT code 10028813, 10047700)</td>
<td>Treatment-emergent adverse events coded to either of those two MedDRA preferred terms</td>
</tr>
<tr>
<td>Seizures</td>
<td>Convulsions SMQ 20000079 (query for convulsions)</td>
<td>Treatment-emergent adverse events coded to MedDRA preferred terms on the broad search list.</td>
</tr>
<tr>
<td>Anemia</td>
<td>Haematopoietic erythropenia SMQ 20000029</td>
<td>Treatment-emergent adverse events coded to MedDRA preferred terms on the broad search list.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Haematopoietic thrombocytopenia SMQ 20000031</td>
<td>Treatment-emergent adverse events coded to MedDRA preferred terms on the broad search list.</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Hematological Toxicity-Neutropenia CMQ 80000154</td>
<td>Treatment-emergent adverse events coded to MedDRA preferred terms on the broad search list.</td>
</tr>
<tr>
<td>Infection events within 14 days after neutropenia events</td>
<td>Infections CMQ 80000018 and hematological toxicity-neutropenia CMQ 80000154</td>
<td>Treatment-emergent adverse events from the MedDRA preferred terms on the broad search list.</td>
</tr>
<tr>
<td>Myelodysplastic Syndromes (MDS)</td>
<td>Myelodysplastic syndrome SMQ (Narrow) 20000217</td>
<td>Treatment-emergent adverse events from the MedDRA terms on the search list.</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia (AML)</td>
<td>Acute myeloid leukaemia PT (10000880)</td>
<td>Treatment-emergent adverse events from the MedDRA terms on the search list.</td>
</tr>
<tr>
<td>Haemorrhages events within 14 days after thrombocytopenia</td>
<td>Haemorrhage terms (excl laboratory terms) SMQ 20000039 and haematopoietic thrombocytopenia SMQ 20000031</td>
<td>Treatment-emergent adverse events from the MedDRA terms on the broad search list.</td>
</tr>
<tr>
<td>Second/Secondary Malignancies</td>
<td>Secondary Malignancies SMQs, 20000194 and 20000195</td>
<td>Treatment-emergent adverse events from the MedDRA terms on the narrow search list for malignancies are used as a starting point for medical review to search for secondary malignancies.</td>
</tr>
<tr>
<td>Changes in reproductive organ function</td>
<td>SMQ 20000210 (fertility disorders)</td>
<td>Treatment-emergent adverse events from the MedDRA terms on the search list.</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td></td>
<td>Pregnancies and outcomes will be analyzed individually as they occur.</td>
</tr>
</tbody>
</table>
11.2.4.1 Time to Onset of AESI

Summary statistics (N, mean, standard deviation, median, minimum, and maximum) will be generated for the time from first dose to onset (in days) using the first AESI event for each subject.

11.2.4.2 Prevalence and Incidence Rates of AESI

Prevalence and incidence of AESI for each PT, each SOC, and overall will be provided for time periods in groups of 3 cycles, relative to the first dose of any study treatment: Cycles 1 - 3, 4 - 6, 7 - 9, 10 - 12, 13 - 15, 16 - 18, 19 - 21, 22 - 24, 25 - 27, 28 - 30, 31 - 33, and 34 - 36. The 30 day safety window will be applied and grouped into the last cycle for each subject. For each time period, the incidence for any given PT will be calculated as follows:

- The numerator for each time period will be the number of subjects who had the first occurrence of an adverse event in that time period and are included in the denominator.
- The denominator for each time period will be the number of subjects who took at least one dose of study treatment in the time period and did not experience an event within any previous period.
- Incidence for each time period = numerator/denominator.

The numerator and the corresponding incidence for each PT will be presented for each of the time periods.

For each time period, the prevalence for any given PT will be calculated as follows:

- The numerator for each time period will be the number of subjects who had an occurrence of an adverse event in that time period or in a previous time period and that was ongoing in the current time period and are included in the denominator.
- The denominator for each time period will be the number of subjects who took at least one dose of study treatment in the time period.
● Prevalence for each time period = numerator/denominator.

The numerator and the corresponding prevalence for the PT will be presented for each of the time periods.

11.2.5 Adverse Event Subgroup Assessments

The incidence of treatment emergent adverse events overview, TEAE by SOC and by PT of all treatment-emergent adverse events, grade 3 and 4 events, serious adverse events, leading to veliparib discontinuation, AEs leading to death, and AEs of special interest will be assessed for the subgroups defined below:

● Age categories [< 65 years, ≥ 65 years]
● Region [US, Japan, Rest of World]
● Combination Period (Cycles 1 through 6),
● Maintenance Period (Cycles 7 through 36),
● Q-weekly Dosing,
● Q3-weekly Dosing
● Subjects Dosed with Docetaxel.

Refer to Section 6.0 for more details on defining the latter 5 groups.

11.3 Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of the last dose of study drug, (2) for deaths occurring more than 30 days of the last dose of study drug and (3) for all deaths in this study regardless of the number of days relative to the last dose of study drug. There will be no statistical test for above analyses.

11.4 Analysis of Laboratory and Vital Signs Data

All of the below summaries will be summarized by for the entire AST population, as well as the following subgroups described in detail in Section 6.0: Combination Period
(Cycles 1 through 6), Maintenance Period (Cycles 7 through 36), Q-weekly Dosing, Q3-weekly Dosing, and Subjects Dosed with Docetaxel.

See Section 6.0 for additional information regarding laboratory data conventions.

**Analyses of Laboratory Data Using NCI CTCAE**

For hematology and chemistry variables for which NCI CTCAE Version 4 (v4.03) criteria exist, baseline and post-baseline hematology and chemistry variable observations will be categorized as grade 0 to grade 4.

The percentage of subjects experiencing a shift from baseline to the maximum value post-baseline, and from baseline to the final value, according to the categories below will be presented:

- Grade 0 or unknown at baseline, to Grade 1 to Grade 4 post-baseline, or worsened from an abnormal baseline value by at least one grade post-baseline
- Grade 0 or unknown to Grade 2 at baseline, to Grade 3 or Grade 4 post-baseline and from Grade 3 at baseline to Grade 4 post-baseline

Cross-tabulation of the frequency of categorized baseline grades versus maximum post-baseline grades and baseline grades versus final value will be presented. All treated subjects will be included in the cross tabulation regardless whether baseline or post-baseline measurements are collected.

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 veliparib/placebo, will be included in these listings.

**Drug-Induced Liver Injury**

Elevations relative to the upper limit of normal (ULN) in alanine transaminase (ALT), AST, total bilirubin, and alkaline phosphatase as outlined in the FDA Guidance for
Industry pertaining to premarketing clinical evaluations for drug-induced liver injury (DILI) will be summarized using the maximum post-baseline values:

- ALT: $> 3 \times –, > 5 \times –, > 10 \times –, \text{ or } > 20 \times \text{ULN}$
- AST: $> 3 \times –, > 5 \times –, > 10 \times –, \text{ or } > 20 \times \text{ULN}$
- Total bilirubin $> 2 \times \text{ULN}$
- Alkaline phosphatase $> 1.5 \times \text{ULN}$
- ALT or AST ($> 3 \times \text{ULN}$) accompanied by total bilirubin ($> 2 \times \text{ULN}$) at the same visit (potential Hy's Law criteria 3)

Plots will be generated for total bilirubin vs. ALT values and total bilirubin vs. AST values in the eDISH format. For each subject, the visit with the maximum total bilirubin value relative to the ULN, then the maximum ALT (or AST) value relative to the ULN will be used in the plot. A listing of lab data for subjects meeting potential Hy's law criteria will be provided.
Table 8. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

<table>
<thead>
<tr>
<th>Test</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>&gt; ULN – 3 × ULN</td>
<td>&gt; 3 – 5 × ULN</td>
<td>&gt; 5 – 20 × ULN</td>
<td>&gt; 20 × ULN</td>
<td>Death</td>
</tr>
<tr>
<td>AST</td>
<td>&gt; ULN – 3 × ULN</td>
<td>&gt; 3 – 5 × ULN</td>
<td>&gt; 5 – 20 × ULN</td>
<td>&gt; 20 × ULN</td>
<td>Death</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>&gt; ULN – 2.5 × ULN</td>
<td>&gt; 2.5 – 5 × ULN</td>
<td>&gt; 5 – 20 × ULN</td>
<td>&gt; 20 × ULN</td>
<td>Death</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>&gt; ULN – 1.5 × ULN</td>
<td>&gt; 1.5 – 3 × ULN</td>
<td>&gt; 3 – 10 × ULN</td>
<td>&gt; 10 × ULN</td>
<td>Death</td>
</tr>
<tr>
<td>Hemoglobin (low)</td>
<td>&lt; LLN – 100 g/L</td>
<td>&lt; 100 – 80 g/L</td>
<td>&lt; 80 g/L</td>
<td>--</td>
<td>Death</td>
</tr>
<tr>
<td>Hemoglobin (high)</td>
<td>CH &gt; 0.0 – 20.0 g/L</td>
<td>CH &gt; 20.0 – 40.0 g/L</td>
<td>CH &gt; 40.0 g/L</td>
<td>--</td>
<td>Death</td>
</tr>
<tr>
<td>White blood cells</td>
<td>&lt; LLN – 3.0 × 10⁹/L</td>
<td>&lt; 3.0 – 2.0 × 10⁹/L</td>
<td>&lt; 2.0 – 1.0 × 10⁹/L</td>
<td>&lt; 1.0 × 10⁹/L</td>
<td>Death</td>
</tr>
<tr>
<td>Absolute Neutrophil Count</td>
<td>&lt; LLN – 1.5 × 10⁹/L</td>
<td>&lt; 1.5 – 1.0 × 10⁹/L</td>
<td>&lt; 1.0 – 0.5 × 10⁹/L</td>
<td>&lt; 0.5 × 10⁹/L</td>
<td>Death</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt; LLN – 75.0 × 10⁹/L</td>
<td>&lt; 75.0 – 50.0 × 10⁹/L</td>
<td>&lt; 50.0 – 25.0 × 10⁹/L</td>
<td>&lt; 25.0 × 10⁹/L</td>
<td>Death</td>
</tr>
<tr>
<td>Glucose (high)</td>
<td>&gt; ULN – 8.9 mmol/L</td>
<td>&gt; 8.9 – 13.9 mmol/L</td>
<td>&gt; 13.9 – 27.8 mmol/L</td>
<td>&gt; 27.8 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>Glucose (low)</td>
<td>&lt; LLN – 3.0 mmol/L</td>
<td>&lt; 3.0 – 2.2 mmol/L</td>
<td>&lt; 2.2 – 1.7 mmol/L</td>
<td>&lt; 1.7 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt; ULN – 1.5 × ULN</td>
<td>&gt; 1.5 – 3 × ULN</td>
<td>&gt; 3 – 6 × ULN</td>
<td>&gt; 6 × ULN</td>
<td>Death</td>
</tr>
<tr>
<td>Uric acid</td>
<td>&gt; ULN – 590 mcmol/L</td>
<td>--</td>
<td>--</td>
<td>&gt; 590 mcmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td>&lt; LLN – 0.8 mmol/L</td>
<td>&lt; 0.8 – 0.6 mmol/L</td>
<td>&lt; 0.6 – 0.3 mmol/L</td>
<td>&lt; 0.3 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>Calcium (low)</td>
<td>&lt; LLN – 2.0 mmol/L</td>
<td>&lt; 2.0 – 1.75 mmol/L</td>
<td>&lt; 1.75 – 1.5 mmol/L</td>
<td>&lt; 1.5 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>Calcium (high)</td>
<td>&gt; ULN – 2.9 mmol/L</td>
<td>&gt; 2.9 – 3.1 mmol/L</td>
<td>&gt; 3.1 – 3.4 mmol/L</td>
<td>&gt; 3.4 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt; LLN – 30 g/L</td>
<td>&lt; 30 – 20 g/L</td>
<td>&lt; 20 g/L</td>
<td>--</td>
<td>Death</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>&lt; LLN – 0.8 × 10⁹/L</td>
<td>&lt; 0.8 – 0.5 × 10⁹/L</td>
<td>&lt; 0.5 – 0.2 × 10⁹/L</td>
<td>&lt; 0.2 × 10⁹/L</td>
<td>Death</td>
</tr>
</tbody>
</table>
Table 8. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values (Continued)

<table>
<thead>
<tr>
<th>Test</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>&lt; LLN – 130 mmol/L</td>
<td>--</td>
<td>&lt; 130 – 120 mmol/L</td>
<td>&lt; 120 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>(low)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>&gt; ULN – 150 mmol/L</td>
<td>&gt; 150 – 155 mmol/L</td>
<td>&gt; 155 – 160 mmol/L</td>
<td>&gt; 160 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>(high)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>&lt; LLN – 3.0 mmol/L</td>
<td>--</td>
<td>&lt; 3.0 – 2.5 mmol/L</td>
<td>&lt; 2.5 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>(low)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>&gt; ULN – 5.5 mmol/L</td>
<td>&gt; 5.5 – 6.0 mmol/L</td>
<td>&gt; 6.0 – 7.0 mmol/L</td>
<td>&gt; 7.0 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>(high)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>&lt; LLN – 0.5 mmol/L</td>
<td>&lt; 0.5 – 0.4 mmol/L</td>
<td>&lt; 0.4 – 0.3 mmol/L</td>
<td>&lt; 0.3 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>(low)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>&gt; ULN – 1.23 mmol/L</td>
<td>--</td>
<td>&gt; 1.23 – 3.30 mmol/L</td>
<td>&gt; 3.30 mmol/L</td>
<td>Death</td>
</tr>
<tr>
<td>(high)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>&lt; LLN – 16 mmol/L</td>
<td>&lt; 16 – 11 mmol/L</td>
<td>&lt; 11 – 8 mmol/L</td>
<td>&lt; 8 mmol/L</td>
<td>Death</td>
</tr>
</tbody>
</table>

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

Vital signs values will be assessed for potential clinical significance through the application of criteria developed at AbbVie as detailed in Table 9 below.

Table 9. Potential Clinical Significance Criteria for Vital Signs

<table>
<thead>
<tr>
<th>Vital Sign</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td>&gt; 150 mmHg and &gt; 20 mmHg higher than baseline</td>
</tr>
<tr>
<td></td>
<td>&lt; 70 mmHg and a decrease of ≥ 30 mmHg from baseline</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>&gt; 100 mmHg and higher than baseline</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 mmHg and a decrease of ≥ 20 mmHg from baseline</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>&gt; 120 bpm and an increase of ≥ 30 bpm from baseline</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 bpm and a decrease of ≥ 30 bpm from baseline</td>
</tr>
<tr>
<td>Temperature</td>
<td>≥ 38.9°C</td>
</tr>
<tr>
<td></td>
<td>≤ 35.6°C</td>
</tr>
<tr>
<td>Weight</td>
<td>&gt; 10% decrease from baseline</td>
</tr>
</tbody>
</table>
The frequency and percentage of subjects with post-baseline values meeting Criteria for Potentially Clinically Significant Vital Signs values will be summarized. All subjects who have at least one post-baseline measurement will be included in the summary. If a subject does not have vital signs recorded at baseline, but has a post-baseline value which met the above criteria for blood pressure and pulse rate, this subject is considered as meeting the potentially clinically significant vital signs values for the measurement. A separate listing will be provided that presents all of the subjects and values that meet the criteria.

12.0 References

## Document Approval

Study M13694 - Statistical Analysis Plan Version 2 - 09May2019 (E3 16.1.9)

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<th>Date:</th>
<th>Meaning Of Signature:</th>
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SUMMARY OF CHANGES MADE FROM SAP V.1 TO SAP V.2

Section 3.0: Incorporating Study Protocol Amendments 1-5.

Section 4.1: HRD population was added to cohorts. Secondary objectives include PFS (Arm 2 vs Arm 1).

Section 4.2: Added “subjects found not to tolerate paclitaxel could instead receive docetaxel.” Study consists of five phases with an added Survival Phase.

Section 4.3: Detailed explanation of surrogate timepoints at Month 36, Month 58, and Month 77. Added HRD population and updated the alpha and power values. Separated power and sample size calculations for Testing Scenario 1 and Testing Scenario 2. Added PFS and OS hypotheses for HRD population.

Section 4.4: Added HRD population, updated alpha for OS, added IDMC meetings in 2017-2018.

Section 4.5: Added HRD population to analysis timing and finalized a data cutoff date of May 3, 2019.

Section 5.0: Defined the HRD population.

Section 6.0: Data cutoff date of May 3, 2019. Sparseness of data noted in some strata and residual disease was further collapsed.

For multiple values on same day, the worst score (instead of the average) will be used for QoL/ECOG.

Study Rx days are relative to any component of study treatment. Maintenance phase is up to 36 cycles.

Docetaxel added to definition of cycle Rx days, and explanation of subjects who discontinued study therapy and in Long Term Follow Up. DRS added to definition of analysis window (replaced ECOG, QoL, laboratory, and vital signs).

Determination of censoring includes date of cytoreductive surgery, concomitant medications, post treatment therapy, and randomization date. Rules for partial dates were added.

Added sections on NCI grades for laboratory variables and safety subgroups for AE and lab summaries.

Section 7.0: Prior oncology therapies only to be summarized for subjects with history of another cancer. Summaries may be separated for BRCA-deficient and HRD populations.

Section 7.1: BRCA status, residual disease and choice of regimen were detailed more clearly; gender was removed; added HRD, type of ovarian cancer, CA-125 level, alcohol history. Removed chi-square and ANOVA test.

Section 7.3: Prior and concomitant medications were defined.

Section 8.0: Details added for subjects who underwent surgery.

Section 9.1: Added docetaxel and described ANOVA model. Defined dose reductions, interruptions, delays, and intensity (Table 4).
Section 10.1: Description of Cox Proportional Hazard Model, handling of intercurrent events and if too much time between scans.

Section 10.3: Added HRD population analyses and a description of MMRM model for DRS.

Section 10.4: Added the clinical progression per CA-125 and more detailed censoring rules.

Section 10.5: Details for log-rank test, supplemental analyses for PFS (censoring table), and CA-125 values were added.

Section 10.6: Added subgroups for HRD population, race, and region.

Section 10.7: Criteria to determine testing sequence were added. Figures for scenarios 1 and 2 were updated with alpha and surrogate months. Formula for the Truncated Hochberg Procedure was added.

Section 11.2: New section with Adverse Event by SOC, PT, and Frequency. Updated Adverse Events of Special Interest with infections, haemorrhages, AML, and teratogenicity. Added AESI time to onset, prevalence, and incidence. Added sub-section on AE subgroup assessments.

Section 11.4: Specified the laboratory values for drug-induced liver injury and toxicity grades 1,2,3,4 (new Table 8 and Table 9).

Section 11.5: Weight criteria added for vital signs.

Section 12.0: Added reference for CTCAE version 4.0.