



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, 2, and 3 (Japan Only) and Amendments 1, 2, 3, 4, 5, 6, 7, and 8

AbbVie	
Investigational Product:	Veliparib (ABT-888)
Date:	08 March 2021
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

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

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

Protocol	Date
Original	18 December 2014
Amendment 1	26 May 2016
Administrative Change 1	30 June 2016
Administrative Change 2	13 September 2016
Amendment 2	21 September 2016
Amendment 3	14 November 2016
Amendment 4	24 March 2017
Administrative Change 3 (Japan Only)	17 May 2018
Amendment 5	10 December 2018
Amendment 6	24 April 2019
Amendment 7	01 May 2020

The purpose of this amendment is to:

- Add benefits and risks evaluation information and updated study procedures in the context of the ongoing COVID-19 pandemic (Section 3.2, Section 9.2, and Section 9.3).

Rationale: *To confirm that the current pandemic situation does not change the benefit risk of study participation as COVID-19 related risks are not expected to differ substantially between trial participants and the broader population of subjects being treated for Ovarian, Fallopian or Peritoneal cancer, as well as allow for procedure modification in response to the COVID-19 pandemic (including local labs, Adverse Event reporting and consent procedures).*

- Remove select study procedures for patients in survival and long-term follow-up (Table 2, Section 5.1, and Section 5.3.1.1)

Rationale: *Primary analysis has already been completed. Removal of select procedures allows for reduced burden on subjects and sites.*

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- Remove the requirement to send scans performed after the primary analysis cut-off date to the central imaging vendor (Table 2 and Section 5.3.1.1)
Rationale: Concordance between central imaging vendor and site was shown to be high at the primary analysis, which has already been completed. Removal of this requirement allows for reduced burden on sites.
 - Indicate that unblinding requests can be confirmed by either the TA MD or TA SD
Rationale: To reflect staffing changes on the trial
 - Update study contact information (Section 1.0, Section 6.6.3 and Section 7.0)
Rationale: To reflect changes in staffing and contact information
 - Added language indicating that the stated months at which endpoints will mature are estimates (Section 8.2.1)
Rationale: For clarity
 - Added language indicating that the final OS analyses will occur when required OS events have accrued in all populations (Section 8.3)
Rationale: For clarity

1.2 Synopsis

AbbVie Inc.	Protocol Number: M13-694
Name of Study Drug: Veliparib (ABT-888)	Phase of Development: 3
Name of Active Ingredient: Veliparib	Date of Protocol Synopsis: 08 March 2021
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 <i>BRCA</i> -deficient (<i>gBRCA</i> and/or <i>tBRCA</i>), 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 <i>BRCA</i> -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 <u>prior to</u> 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 CID1 or until disease progression per RECIST 1.1, whichever is later. Following the primary analysis and implementation of Protocol Amendment 8, PRO collection will no longer be required.

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 *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/ μ L;
 - Platelet count greater than or equal to 100,000/ μ L;
 - Serum creatinine $\leq 1.0 \times$ ULN range; subjects with a serum creatinine $> 1.0 \times$ ULN range must have a creatinine clearance ≥ 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 ≥ 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 *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 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 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 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 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)
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:	
<p>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 <i>BRCA</i>-deficient (<i>gBRCA</i> and/or <i>tBRCA</i>), HRD, and whole population, as multiple primary objectives.</p> <p>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 <i>BRCA</i>-deficient, HRD, and whole populations.</p>	
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:	
<p>All subjects must have a pre-therapy tumor biopsy (archived or fresh biopsy) for inclusion in the study. Genetic analysis to determine <i>BRCA</i> mutation status will be conducted using tissue and blood specimens to support efficacy endpoints.</p> <p>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.</p>	
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 4.03.	

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 the OS hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the *BRCA*-deficient population, the HRD population, and the whole population, at least one efficacy interim analyses will be performed. The first interim analysis will occur at the time of the final PFS analysis. The alpha of the final OS analyses will depend on prior interim analyses as described in the statistical analysis plan (SAP). Additional details regarding the secondary analyses, including any interim efficacy analyses (e.g., at the request of a regulatory agency), will be specified in the SAP.

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
AEMS	AbbVie Temperature Excursion Management System
AUC	area under the plasma concentration-time curve
BCS	Biopharmaceutics Classification System
BID	twice daily
BMI	body mass index
<i>BRCA1/2</i>	breast cancer genes 1 and 2
<i>BRCA</i> -deficient	germline or tissue-based mutation in <i>BRCA1</i> or <i>BRCA2</i>
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

FACT	Functional Assessment of Cancer Therapy
FDA	US Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FIGO	International Federation of Gynecology and Obstetrics
<i>gBRCA</i>	germline <i>BRCA1</i> or <i>BRCA2</i> 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
HRD	Homologous Recombination Deficiency
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
PLT	platelet
PO	by mouth
POR	Proof of Receipt
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria In Solid Tumors
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TA SD	Therapeutic Area Scientific Director
tBRCA	tissue-based <i>BRCA1</i> or <i>BRCA2</i> mutation
TCGA	The Cancer Genome Atlas
TIA	transient ischemic attack
T _{max}	time to maximum observed plasma concentration
TTFST	time to the first subsequent therapy
TTSST	time to the second subsequent therapy
ULN	upper limit of normal
VAS	visual analog scale
V/F	volume of distribution
WBC	white blood cell

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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.⁴⁻¹¹ 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.¹² 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.^{13,14} Homologous recombination deficiency assays have been evaluated in clinical trials of the PARP inhibitors rucaparib and niraparib.¹⁵⁻¹⁷ 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.¹⁸ 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 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.¹⁹ 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.²⁰ In particular, tumor cells with *BRCA1* or *BRCA2* deficiencies are exquisitely sensitive to PARP inhibition, even in the absence of any other insults.²¹ 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).²²⁻²⁴ 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.^{18,25} 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).¹¹

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/m² 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).²⁶ 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 (\pm 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/m² Q3-weeks or 80 mg/m² 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.¹² 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 *BRCA1/2* and suppressed base excision repair due to PARP inhibition results in targeted cell death in the tumor cells,¹² and has been called "synthetic lethality."^{28,29} Durable responses have been observed with veliparib monotherapy in both *gBRCA* advanced breast cancer³⁰ and *gBRCA* recurrent ovarian cancer³¹ supporting the mechanism of synthetic lethality in *BRCA1/2*-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%.⁴ 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.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 *BRCA1* or *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 *BRCA1/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 *BRCA1/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 *BRCA*-deficient patients (HR = 0.18, $P < 0.00001$) and in patients without a *BRCA* mutation (*BRCA* wild type) (HR = 0.54, $P = 0.0075$).³²

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).³¹ 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 M11-089: Randomized, Double-Blind, Multicenter, Phase 3 Study Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Previously Untreated Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC).
- Study M14-011: A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study Evaluating Safety and Efficacy of the Addition of Veliparib Plus Carboplatin Versus the Addition of Carboplatin to Standard Neoadjuvant Chemotherapy Versus Standard Neoadjuvant Chemotherapy in Subjects with Early Stage Triple Negative Breast Cancer (TNBC).
- 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_{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_{\max} (17%) and a delay of approximately 1 hour in time to C_{\max} (peak time, T_{\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 ≥ 60 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.

The benefits and risks of study participation have been evaluated in the context of the ongoing COVID-19 pandemic. No data are available to characterize the risk of participation in this trial specific to COVID-19. COVID-19-related risks are not expected to differ substantially between trial participants and the broader population of individuals receiving treatment for untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. In consideration of the life-threatening nature of the disease under study, the benefit/risk balance for participation in this trial is not changed.

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.

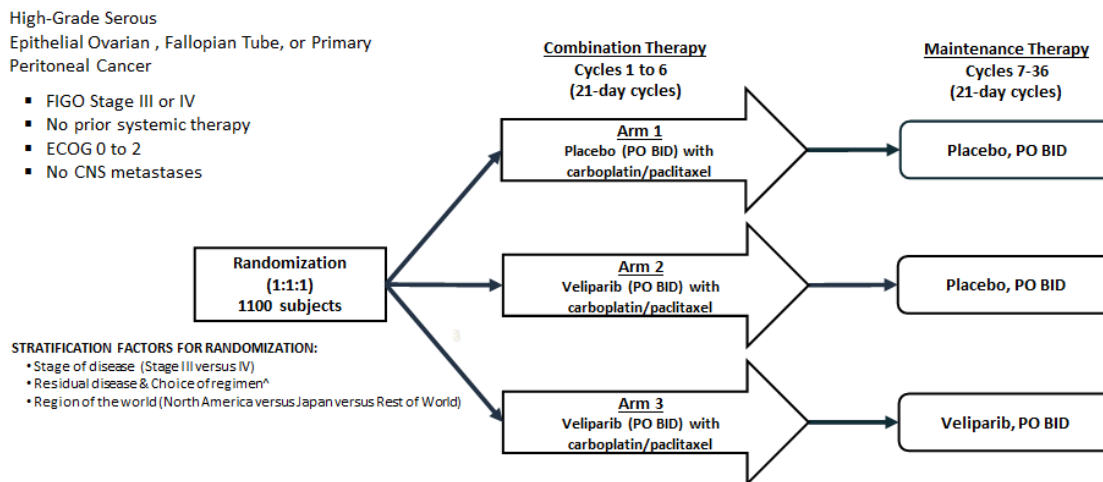
5.1 Overall Study Design and Plan: Description

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.

Figure 1. Study Design



Endpoints: Endpoints will be evaluated in the BRCA-deficient population, HRD population, and whole patient population 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:

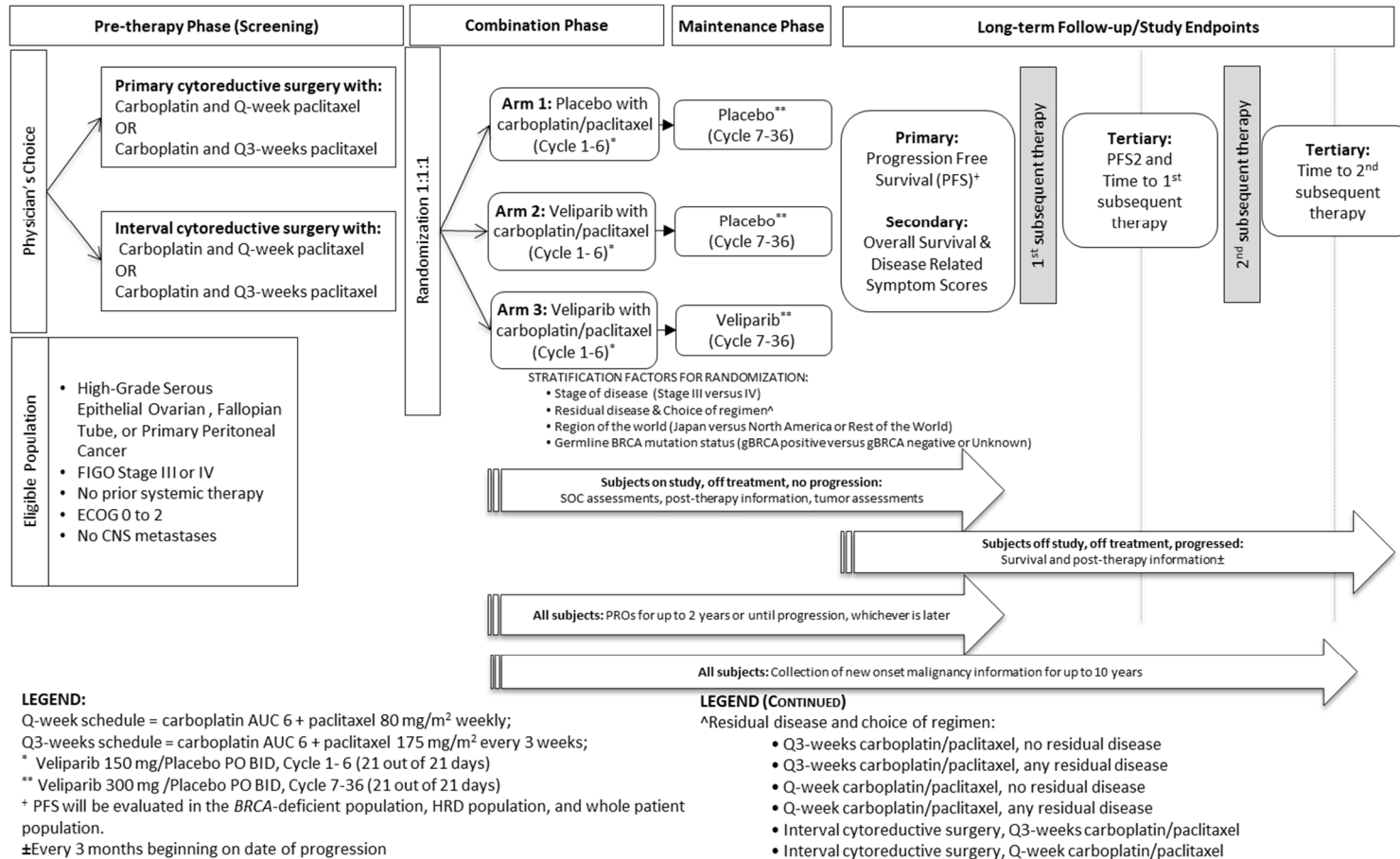
- Carboplatin AUC 6 Q3-weeks plus
- Paclitaxel Q-week (80 mg/m²), OR Paclitaxel Q3-weeks (175 mg/m²)
- Surgery
 - Primary cytoreductive, OR
 - Interval cytoreductive

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; DRS = Disease Related Symptoms, Q-week = weekly; Q3-weeks = every 3 weeks

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

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 \leq 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 \geq 1,500, PLT \geq 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](#). Subsequent to the primary analysis and implementation of Protocol Amendment 8, PROs and some standard of care assessments are no longer required. This is detailed 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/ μ L;
 - Platelet count greater than or equal to 100,000/ μ L;
 - Serum creatinine $\leq 1.0 \times$ ULN range; subjects with a serum creatinine $>1.0 \times$ ULN range must have a creatinine clearance ≥ 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 ≥ 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:
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- 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);

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- 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. 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 \geq 1,500, PLT \geq 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

Procedure	Pre-Therapy Phase (Screening) ^a	Combination Phase (Cycles 1 – 6)				Maintenance Phase (Cycles 7 – 36)			Therapy Completion Visit	Follow-Up Visit ^c
		C1D1	Day 8 and Day 15 ^b	Cycle 2 – Cycle 6	Every 9 Weeks from C1D1 then End of the Combination Phase ^c	Every Other Cycle (C7, C9, C11, etc.)	Study Drug Evaluation ^d	Every 12 Weeks for 2 Years, then Every 6 Months for 3 Years, Then Annually ^c		
Informed Consent	X									
Medical and Cancer History	X									
Physical Exam ^f	X ^f	X ^g		X		X	X ^h		X	X
ECG	X									
Vital Signs	X	X	X	X		X	X ^h		X	X
ECOG PS	X	X		X		X			X	X
Serum Pregnancy Test	X ⁱ	X ⁱ		X ⁱ					X	X
Hematology ^{j,k,l}	X	X ^{j,k}	X ^{j,k}	X ^{j,k}		X ^{j,k}			X	X
Chemistry ^{j,k}	X	X ^{j,k}	X ^{j,k}	X ^{j,k}		X ^{j,k}			X	X
Urinalysis ^j	X									
PT/INR, PTT ^m	X ^m	X ^m		X ^m		X ^m				
CA-125 Blood Draw ⁿ	X	X		X				X	X	X
Randomization ^o		X								
Tumor Assessment ^p	X ^q				X ^r			X	X ^s	
Chest X-Ray	X ^t									
NFOSI-18 ^{u,v}	X	X		X		X			X	X
EQ-5D-5L ^{u,v}	X	X		X		X			X	X

Table 1. Study Procedures for Pre-Therapy, Combination and Maintenance Phases (Continued)

Procedure	Pre-Therapy Phase (Screening) ^a	Combination Phase (Cycles 1 – 6)				Maintenance Phase (Cycles 7 – 36)			Therapy Completion Visit	Follow-Up Visit ^e
		C1D1	Day 8 and Day 15 ^b	Cycle 2 – Cycle 6	Every 9 Weeks from C1D1 then End of the Combination Phase ^c	Every Other Cycle (C7, C9, C11, etc.)	Study Drug Evaluation ^d	Every 12 Weeks for 2 Years, then Every 6 Months for 3 Years, Then Annually ^c		
Review Subject Calendar				X		X	X			
Veliparib/Placebo Dispensing		X ^w		X ^w		X ^w	X ^w			
Monitor AEs	X	X	X ^x	X		X	X ^x		X	X
Prior and Concomitant Medication Assessment	X	X	X	X		X			X	X

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 \geq 1,500 and PLT \geq 100,000. Hematological parameters will be assessed as determined by the investigator.
Interval Surgery: Subject may restart veliparib/placebo when ANC \geq 1,500 and PLT \geq 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 $> 1.5 \times$ 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. Subsequent to the primary analysis and implementation of Protocol Amendment 8, imaging scans are not required to be sent to the independent 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.

Table 1. Study Procedures for Pre-Therapy, Combination and Maintenance Phases (Continued)

- 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.
- 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

Procedure	Completion or Discontinuation of Therapy Without Disease Progression (Long Term Follow-Up Phase)			Discontinuation of Therapy due to Disease Progression (Survival Phase)	
	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 ^c	At Least Every 3 Months Until Disease Progression	Every 6 Months Until Disease Progression	Every 3 Months Beginning on Date of Progression	Every 6 Months Beginning on Date of Progression
Physical Exam		X ^a			
Vital Signs		X ^a			
ECOG PS		X ^a			
CA-125 Blood Draw	X				
Tumor Assessment ^h	X				
NFOSI-18 ^b		X ^b		X ^b	
EQ-5D-5L ^b		X ^b		X ^b	
Monitor AEs		X ^d			
Survival Information ^{e,f}		X		X	
Post-Therapy Information ^{e,f}		X		X	
Review for New Onset Malignancy ^g			X		X

- a. Assessments (except for PROs) may be performed according to standard of care or every 3 months for up to 3 years (from C1D1). As of Amendment 8, all patients are beyond 3 years post C1D1, therefore these assessments are no longer required.
- 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. Subsequent to the primary analysis and implementation of Protocol Amendment 8, these PRO assessments are no longer required.

Table 2. Study Procedures for Long Term Follow-Up and Survival Phase (Continued)

- 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.
- 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. Subsequent to the primary analysis and implementation of Protocol Amendment 8, imaging scans are not required to be sent to the independent central imaging vendor.

Table 3. Schedule of Pharmacogenetic and Pharmacodynamic Procedures

Procedure	Visit Schedule	Timing of Sample Collection	Sampling Plan
			Specimen Matrix
Optional Pharmacogenomic Sample	C1D1, C3D1	Prior to Dosing	Blood Frozen –20°C or colder
<i>BRCA</i> Sequencing: Bridging Sample	C1D1	Prior to Dosing	Blood Frozen –20°C or colder
Germline <i>BRCA</i> Sample	Screening	Prior to Dosing	Blood Ambient
Plasma Markers ^a	C1D1, C3D1, C5D1	Prior to Dosing	Blood → Plasma ^b Frozen –20°C or colder
	Therapy Completion Visit	Anytime during the clinic visit	
Serum Markers	C1D1, C3D1, C5D1	Prior to Dosing	Blood → Serum ^b Frozen –20°C or colder
	Therapy Completion Visit	Anytime during the clinic visit	
Pre-therapy tumor biopsy sample (Required): Archival Tissue or Newly Collected Biopsy	Pre-therapy Phase ^c		Pre-Study Treatment FFPE tissue blocks (Room Temperature or Refrigerated-FFPE)
Optional tissue sample	C1D1 – Therapy Completion Visit ^d	Anytime over the course of the study, including the Therapy Completion Visit	Archived FFPE tissue blocks (Room Temperature or Refrigerated-FFPE)

- 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

Procedure	Visit Schedule	Before Drug Administration	After Veliparib AM Dose ^a	Sampling Plan
				Specimen Matrix
Veliparib PK Sampling	C1D1	0-hour ^b	1, 2, 3 hours	Blood → Plasma Frozen –20°C or colder
Veliparib PK Sampling	C2D1, C3D1, C4D1	0-hour ^b		Blood → Plasma Frozen –20°C or colder

a. The Veliparib PK sampling draws may be completed within a window of $\pm 10\%$.

b. 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:

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

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

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if indicated) Lymphocytes Monocytes Basophils (if indicated) Eosinophils (if indicated) Platelet count (estimate not acceptable) Mean corpuscular volume Mean corpuscular hemoglobin concentration RBC distribution width	Blood urea nitrogen (BUN) Serum creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Chloride Calcium Inorganic phosphorus ² Total protein Glucose Albumin Magnesium ² Bicarbonate (if available, Japan only)	Specific gravity Ketones pH Protein Blood Glucose
		Serum Pregnancy Tests
		<i>Human Chorionic Gonadotropin (hCG)⁴</i>
Coagulation	Special Chemistry	Tumor Markers
Activated Partial Thromboplastin Time (aPTT) ¹ International Normalized Ratio (INR) ¹	<i>BRCA1</i> and <i>BRCA2</i> germline mutation ³	CA-125

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.³³ 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. Subsequent to the primary analysis and implementation of Protocol Amendment 8, imaging scans are not required to be sent to the independent central imaging vendor.

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.^{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.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. 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. Following the primary analysis and implementation of Protocol Amendment 8, PRO collection will no longer be required.

- 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. As of Amendment 8, all patients are beyond 3 years post C1D1, therefore these assessments are no longer required.
- 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](#). Following the primary analysis and implementation of Protocol Amendment 8, PRO collection will no longer be required.

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 \geq 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 ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Malignant Lymph Nodes	Pathological lymph nodes with ≥ 10 to < 15 mm short axis.

**Special Considerations
Regarding Lesion
Measurability**

Bone lesions

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 ≥ 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.³⁷ 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 ≥ 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 \times 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 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

New Lesion	Overall Response
No (Absent)	nonPD (No disease)
Yes (Present)	PD (Progressive Disease)
Not Evaluated	NE*

* 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:

Overall Response for Subjects with Measurable Disease at Baseline			
Target Lesion	Non-Target Lesion	Unequivocal New Lesion*	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Calculating Final Response for Non-Measurable Disease:

Overall Response for Subjects with Non-Measurable Disease at Baseline		
Non-Target Lesion	New Lesion	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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).⁴³

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-HT₃ 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-HT₃ 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

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Veliparib (ABT-888)	Capsule	50 mg or 100 mg	Oral	AbbVie
Placebo	Capsule	Placebo to match 50 mg and 100 mg	Oral	AbbVie

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

Standard of Care Products	Dosage Form	Route of Administration
Carboplatin (commercially available)*	Solution in a vial	Intravenously
Paclitaxel (commercially available)*	Solution in a vial	Intravenously
Docetaxel (commercially available)*	Solution in a vial	Intravenously

* 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

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

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/SD.

Prior to unblinding, a separate document **requesting unblinding with rationale** must be submitted and processed. The AbbVie TA MD/SD 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.³⁹ 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 cancer³⁹ 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 $\geq 1,000$ cells/mm³ and the platelet count recovers to $\geq 75,000$ /mm³ (Grade 1).

For dose-limiting neutropenia, veliparib/placebo should be held until the ANC recovers to $\geq 1,000$ cells/mm³. 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 reinstated, the dose will remain the same.

Unless required per the Investigator, there should be no modifications for uncomplicated Grade 4 neutropenia lasting ≤ 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 ≥ 1000 cells/ mm^3 and the platelet count is $\geq 75,000/\text{mm}^3$. While subjects with an ANC 1000 – 1499/ mm^3 or platelet count 75,000 – 99,000/ 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/ mm^3 and the platelet count $\geq 50,000$ cells/ mm^3 . For subjects with an ANC < 500 cells/ mm^3 or platelets $< 50,000$ cells/ mm^3 , 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	Brief Table Title	Summary of Guidance	Note:
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: <ol style="list-style-type: none"> Dose limiting hematological toxicities (Table 10) Reduced ANC or Platelets on Day 1 <ul style="list-style-type: none"> 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). Delayed hematological recovery for > 7 days. 	If ANC recovers to ≥ 1500/mm ³ and Platelets recover to ≥ 100,000/mm ³ 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/mm ³ and Platelets ≥ 75,000/mm ³
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: <ol style="list-style-type: none"> Dose limiting hematological toxicities (Table 10) Reduced ANC or Platelets on Day 1 <ul style="list-style-type: none"> 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/mm ³ and Platelets recover to ≥ 100,000/mm ³ 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/mm ³ and Platelets ≥ 75,000/mm ³
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/mm³) or Reduced Platelets (75,000 – 99,000/mm³) on Day 1, or Cycle Delay > 7 Days due to Hematologic Toxicity

ANC	PLT	First Occurrence*	Second Occurrence	Third Occurrence**
Yes	No	Reduce carboplatin one AUC unit (AUC 5) and add G-CSF	Reduce carboplatin one AUC unit (AUC 4)	Discontinue veliparib/placebo and notify AbbVie TA MD
Yes	Yes	Reduce carboplatin one AUC unit (AUC 5) and add G-CSF	Reduce carboplatin one AUC unit (AUC 4)	Discontinue veliparib/placebo and notify AbbVie TA MD
No	Yes	Reduce carboplatin one AUC unit (AUC 5)	Reduce carboplatin one AUC unit (AUC 4)	Discontinue veliparib/placebo and notify AbbVie TA MD

* G-CSF 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/mm³) or Reduced Platelets (75,000 – 99,000/mm³) on Day 1, or Cycle Delay > 7 Days due to Hematologic Toxicity

ANC	PLT	First Occurrence*	Second Occurrence	Third Occurrence**
Yes	No	Reduce carboplatin one AUC unit (AUC 5) and add G-CSF	Discontinue Day 15 paclitaxel dose	Discontinue veliparib/placebo and notify AbbVie TA MD
Yes	Yes	Reduce carboplatin one AUC unit (AUC 5) and add G-CSF	Reduce carboplatin one AUC unit (AUC 4) and discontinue Day 15 paclitaxel dose	Discontinue veliparib/placebo and notify AbbVie TA MD
No	Yes	Reduce carboplatin one AUC unit (AUC 5)	Reduce carboplatin one AUC unit (AUC 4)	Discontinue veliparib/placebo and notify AbbVie TA MD

* G-CSF 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/mm³) or Reduced Platelets (75,000 – 99,000/mm³) 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

ANC < 500	PLT < 50	First Occurrence*	Second Occurrence	Third Occurrence
Yes	No	Reduce carboplatin one AUC unit (AUC 5) and add G-CSF with the next cycle	Discontinue Day 15 paclitaxel dose with the next cycle	Discontinue veliparib/placebo and notify AbbVie TA MD
Yes	Yes	Reduce carboplatin one AUC unit (AUC 5) and add G-CSF with the next cycle	Reduce carboplatin one AUC unit (AUC 4) and discontinue Day 15 paclitaxel dose with the next cycle	Discontinue veliparib/placebo and notify AbbVie TA MD
No	Yes	Reduce carboplatin one AUC unit (AUC 5) with the next cycle	Reduce carboplatin one AUC unit (AUC 4) with the next cycle	Discontinue veliparib/placebo and notify AbbVie TA MD

* 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/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 $< 75,000$ /mm³ 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

Drug	Regimen –2 Level	Regimen –1 Level	Regimen Starting Dose
Paclitaxel (Q3-week)	110 mg/m ² Day 1	135 mg/m ² Day 1	175 mg/m ² Day 1
Paclitaxel (Q-week)	60 mg/m ² Days 1, 8	80 mg/m ² Days 1, 8	80 mg/m ² Days 1, 8, 15
Carboplatin (Q-week and Q3-week)	4	5	6
Veliparib/Placebo	50 mg BID	100 mg BID	150 mg BID

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 $> 1.5 \times \text{ULN}$, 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 \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/mm³ 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/mm³ 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 \leq 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 \leq Grade 1 or baseline.

Subjects should have an ANC \geq 1,000/mm³ and a platelet count \geq 75,000/mm³ 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 < $1.0 \times 10^9/L$, fever $\geq 38.5^\circ C$)
- Grade 3 thrombocytopenia with active bleeding
- Grade 4 thrombocytopenia

Non-Hematological Toxicities

- Any CTCAE \geq 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

Dose Level	Veliparib/Placebo
Starting Dose Level	300 mg BID (if unable to escalate dose due to toxicity then continue current dose)
Dose Level +1	400 mg BID
Dose Level -1	300 mg BID
Dose Level -2	250 mg BID*

* 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.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility hospitalization for respite care, or hospitalization due solely to progression of the underlying cancer.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). 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 Published: May 28, 2009 (v4.03: June 14, 2010).⁴³

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

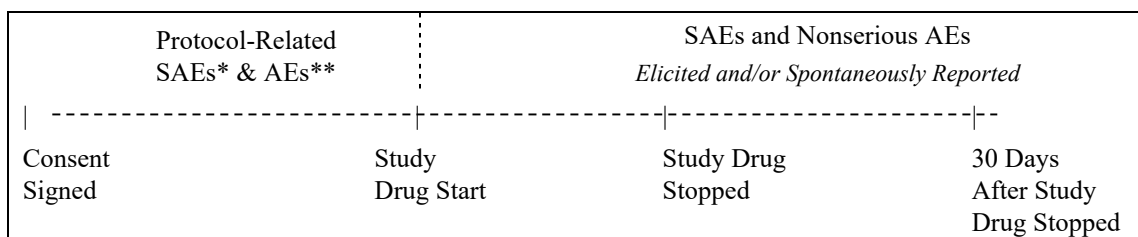
All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study-specific informed consent until therapy administration.

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



* 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.

FAX to: +1 (847) 938-0660

Email to: PPDINDPharmacovigilance@abbvie.com

For safety concerns, contact the Therapeutic Area Safety Team at:

Oncology Safety Team

[REDACTED]
1 North Waukegan Road
North Chicago, IL 60064

Office: (847) 935-2609

Email: SafetyManagement_Oncology@abbvie.com

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

Medical Monitor:

[REDACTED] MD
US Oncology Research
The Woodlands, TX

Mobile: [REDACTED]

Email: M13-694-MedMonitors@abbvie.com

Primary Therapeutic Area Medical Director:

[REDACTED] MD, PhD., FACP
[REDACTED]
1 North Waukegan Road
North Chicago, IL 60064

Office: [REDACTED]

Mobile: [REDACTED]

Email: M13-694-MedMonitors@abbvie.com

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

Phone: +1 (973) 784-6402

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:

Primary Contact:

[REDACTED]
AbbVie
Wegalaan 9
2132 JD Hoofddorp, Netherlands

Office:

Mobile:

Email:

[REDACTED]

Alternate Contact (Primary):

[REDACTED] MD
US Oncology Research
The Woodlands, TX

Mobile:

Email:

M13-694-MedMonitors@abbvie.com

Alternate Contact (Secondary):

[Redacted] Ph.D.
AbbVie
[Redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [Redacted]
Fax: [Redacted]
Cell: [Redacted]
Email: [Redacted]

Alternate Contact (Secondary):

[Redacted] MD, PhD Group
AbbVie
[Redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [Redacted]
Cell: [Redacted]
Email: M13-694-MedMonitors@abbvie.com

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 ≤ 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 Efficacy Endpoints

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, the HRD population, and the whole population, at least one efficacy interim analyses will be performed.

The first interim analysis will occur at the time of the final PFS analysis.

The alpha of the final OS analyses will depend on prior interim analyses as described in the SAP. Additional details regarding the secondary analyses, including any interim efficacy analyses (e.g., at the request of a regulatory agency), will be specified in the SAP.

8.1.4 Multiplicity Adjustment

This is a three-arm, randomized, placebo-controlled Phase 3 clinical trial. All 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

Arm	Description
Arm 1: C/P + placebo → placebo	Reference regimen
Arm 2: C/P + veliparib → placebo	Veliparib administered in the combination therapy phase only
Arm 3: C/P + veliparib → veliparib	Veliparib administered in both combination therapy and maintenance therapy phases

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

PFS (Arm 3 versus Arm 1)	PFS (Arm 2 versus Arm 1)
OS (Arm 3 versus Arm 1)	OS (Arm 2 versus Arm 1)
DRS (Arm 3 versus Arm 1)*	DRS (Arm 2 versus Arm 1)*

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.¹⁵⁻¹⁷ 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 were proposed dependent on the level of the balance of treatment arms within the HRD population. Further details on these testing scenarios are detailed in SAP v2.0.

The multiple testing procedure governing the analysis of data when the primary endpoint (PFS) matures are specified in the SAP v2.0, finalized before the database was unblinded. The appropriate control of overall type I error in the context of subsequent analyses, including interim analyses conducted at the behest of regulatory agencies, will be specified in subsequent SAP amendments, as warranted.

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)⁴³ 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),⁴³ 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 (K_a), 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](#).

Throughout the Protocol, the timing of maturity of each endpoint within each population is an estimate based on the original design assumptions and do not necessarily reflect the exact month on study the analysis will occur. Therefore the "Month 36," "Month 48," etc... should be considered as surrogates only for the timing of each particular analysis.

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, 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, 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, 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, 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, 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, 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 *BRC A*-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, 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, 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 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 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 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 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 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 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 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

Type I Error	Population	No. of Subjects per Arm (N)	PFS				OS			Projected Endpoint Mature Time (Months)
			Power	Expected Hazard Ratio	No. of Events for 2 Arm Comparison	Projected Endpoint Mature Time (Months)	Power	Expected Hazard Ratio	No. of Events for 2 Arm Comparison	
alpha = 0.025	<i>BRCA-deficient</i>	88	87%	0.50	79	36	87% ^a	0.50	79	77
	HRD	160	91.5%	0.60	170	36	90% ^a	0.60	166	77
	Whole	367	94.1%	0.70	391	36	91.5% ^b	0.70	350	58

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

Type I Error	Population	No. of Subjects per Arm (N)	Power	PFS			OS			Projected Endpoint Mature Time (Months)
				Expected Hazard Ratio	No. of Events for 2 Arm Comparison	Projected Endpoint Mature Time (Months)	Power	Expected Hazard Ratio	No. of Events for 2 Arm Comparison	
alpha = 0.025	BRCA-deficient	88	87%	0.50	79	36	87% ^a	0.50	79	77
	HRD	160	91.5%	0.60	170	36	90% ^a	0.60	166	77
	Whole	367	94.1%	0.70	391	36	91.5% ^b	0.70	350	58
alpha = 0.0224	HRD	160	90.8%	0.60	170	36	-	-	-	-
	Whole	367	93.6%	0.70	391	36	-	-	-	-
alpha = 0.0125	HRD	160	86.2%	0.60	170	36	-	-	-	-
	Whole	367	90.1%	0.70	391	36	-	-	-	-
alpha = 0.0024	HRD	160	70%	0.60	170	36	68.6%	0.60	166	77
	Whole	367	76%	0.70	391	36	70%	0.70	350	58

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 final OS analyses will occur when the required numbers of OS endpoints have accrued in all populations, and will be based on required events. 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:

-
- 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:
- 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](#).

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

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed 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.

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

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 (EMA) 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: 08 March 2021

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator


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

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

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9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
 10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.



Appendix B. List of Protocol Signatories

Name	Title	Functional Area
		Clinical
		Clinical Program Development
		Statistics
		Pharmacokinetics

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 $\pm 5\%$ 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 $>1.5 \times$ 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:

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

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.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) = (((Height (cm)/2.54) – 60) × 2.3) + 45.5

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- **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.

STAGE I: Tumor confined to ovaries	
IA	Tumor limited to one ovary, capsule intact, no tumor on surface, negative washings
IB	Tumor involves both ovaries, otherwise like 1A
<i>IC Tumor limited to 1 or both ovaries</i>	
IC1	Surgical spill
IC2	Capsule rupture before surgery or tumor on ovarian surface
IC3	Malignant cells in the ascites or peritoneal washings
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	
<i>IIIA (positive retroperitoneal lymph nodes and/or microscopic metastases beyond the pelvis)</i>	
IIIA1	Positive retroperitoneal lymph nodes only
	IIIA1 (i) Metastases \leq 10 mm
	IIIA1 (ii) Metastases $>$ 10 mm
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement \pm positive retroperitoneal nodes
IIIB	Macroscopic, extrapelvic, peritoneal metastases \leq 2 cm \pm retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen

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 ($> 5\times$).
- 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

Adverse Events Expected Due to Ovarian Cancer or Progression of Ovarian Cancer*

Abdominal pain
Abdominal distension
Ascites
Intestinal obstruction
Colonic obstruction
Small intestinal obstruction
Pleural effusion
Constipation

* 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.