1.0 Title Page

Statistical Analysis Plan

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

Date: 30 May 2019

Version 3.0

1.1 SAP Update: Summary of Changes

The purpose of this update is to:

- Specify that RECIST overall responses are modified following local therapy on target lesions. The progression free survival and objective response endpoints are impacted.
- Indicate that the primary analysis cutoff date was chosen by the project team to be April 05th, 2019.
- Change the description of the PFS2 endpoint to reflect accurately the way that the endpoint will be analyzed.
- Add a set of efficacy summaries for subjects treated with crossover veliparib.
- Expand the descriptions of the use of Cox modeling in PFS and OS, for the ITT population and in subgroups.
- Describe two additional progression free survival analyses with additional censoring mechanisms.
- Remove a proposed additional PFS summary stratified by ECOG and region, as the number of subjects with one of the ECOG categories was found to be low.
- The list of adverse events of special interest has been expanded to include secondary malignancies and teratogenicity.
- A summary of time to adverse events resulting in study drug interruption or dose reduction has been added.
- Update the details for the presentation of veliparib plasma concentration data.

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the AbbVie Global Statistics Department for veliparib (ABT-888) study Protocol M12-914 dated 17 Jun 2016. It provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work.

This is the third version of the SAP for Protocol M12-914.

Unless noted otherwise, all analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective of this study is to assess the progression-free survival (PFS) of veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with BRCA-associated metastatic or locally advanced unresectable breast cancer.

The secondary objectives of the study are to assess overall survival (OS), clinical benefit rate (CBR) through the end of Week 24, objective response rate (ORR), and progression-free survival on subsequent therapy (PFS2).

The tertiary objectives are to assess Eastern Cooperative Oncology Group (ECOG) performance status, quality of life (QoL), and duration of overall response.

4.2 Design

This is a Phase 3 randomized, double-blind, multinational, multicenter study to evaluate the efficacy and tolerability of veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with BRCA1 or BRCA2 mutation as documented by the Sponsor core laboratory with HER2-negative metastatic or

locally advanced unresectable breast cancer who have received no more than two prior lines of DNA-damaging cytotoxic therapy for metastatic disease.

Subjects will be randomized in a 2:1 ratio to veliparib in combination with carboplatin and paclitaxel (veliparib/C/P) or placebo for veliparib in combination with carboplatin and paclitaxel (placebo/C/P). Subject randomization will be stratified by receptor status (estrogen receptor [ER]-positive and/or progesterone receptor [PgR]-positive versus ER-negative and PgR-negative status), prior platinum therapy (yes versus no), and the presence or absence of central nervous system metastases.

In the main study period, subjects will receive veliparib/placebo in combination with carboplatin/paclitaxel until unacceptable toxicity or radiographic progression occurs or until subjects experience a robust and durable response for which the investigator considers the potential risks of continued cytotoxic chemotherapy to outweigh the benefits. The dose schedules for the combination therapy are detailed below.

Table 1. Veliparib/Placebo and Carboplatin Dose Schema

Days	**–2**	**–1**	**1**	**2**	**3**	**4**	**5**	**6 – 19**
Veliparib or Placebo	Twice a day	Twice a day	Twice a day*	Twice a day	Twice a day	Twice a day	Twice a day	No drug dosing
Carboplatin			IV					No drug dosing

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

Table 2. Paclitaxel Dose Schema

Days	**–2**	**–1**	**1**	**2 – 7**	**8**	**9 – 14**	**15**	**16 – 19**
Weekly Paclitaxel			IV		IV		IV	

Dosing of study drug will begin 2 days prior to the start of the carboplatin/paclitaxel infusion (on Cycle Day –2) and will continue twice a day for 7 consecutive days. Subjects will receive carboplatin and paclitaxel via intravenous infusion on Cycle Day 1. Subjects will also receive paclitaxel on Cycle Days 8 and 15.

Carboplatin and paclitaxel are to be given only after study drug dosing on Cycle Days –2 and –1 have been confirmed. If study drug has not been taken for 2 days then a new supply of study drug is to be dispensed and Cycle Days –2 and –1 are to be repeated for the cycle.

The subject's Cycle Day 1 ANC and platelet counts must meet protocol-specified minimum values or else treatment should be delayed. In such cases veliparib will be re-administered after the delay for 2 days prior to infusion with paclitaxel and carboplatin. For subjects receiving paclitaxel on the second and third weeks of a cycle, ANC and platelet counts must meet protocol-specified minimums or else treatment should be withheld. When an investigator has determined that a subject should discontinue the blinded portion of the study, a Final Visit will be conducted. All subjects will have one Follow-Up Visit approximately 30 days after the last dose of veliparib or placebo. This Follow-Up Visit does not need to be conducted if the Final Visit is ≥ 30 days after the last dose of veliparib or placebo.

Post-treatment therapy and survival information will be collected every 2 months (or as requested by Sponsor to support data analysis) beginning on the date the subject is registered off study until the endpoint of death, the subject has become lost-to follow-up, or until study termination by the AbbVie.

Subjects who discontinue the blinded study because of disease progression may be eligible to receive veliparib monotherapy starting at 300 mg BID in the crossover study period upon unblinding and confirmation that they were receiving placebo. If the subject tolerates veliparib at 300 mg BID for 2 weeks, veliparib may be increased to 400 mg BID at the investigator's discretion. Treatment with veliparib monotherapy should continue until a second disease progression event or unacceptable toxicity occurs.

4.3 Sample Size

Assuming the true hazard ratio in favor of the veliparib + carboplatin + paclitaxel treatment group is 0.69 for PFS, a total of 344 PFS events will be needed for the study to

have at least 90% power at two-sided α level of 0.05 to detect a statistically significant treatment effect for the veliparib + carboplatin + paclitaxel treatment group using the log-rank test for PFS.

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

A total of approximately 500 subjects will be enrolled into the study to observe 344 PFS and 357 death events.

4.4 Interim Analysis

To ensure subject safety, an independent data monitoring committee (IDMC) will review unblinded safety data (which will include all subjects enrolled in the study) when approximately 60 subjects have met at least one of the following criteria:

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

Subsequent reviews will be based on recommendations from the IDMC.

An alpha of 0.0001 will be allocated for PFS at the interim analysis although there is no intention to stop the study early for efficacy.

A total of five interim analyses on safety information have been conducted during the trial. The final PFS analysis will be tested at one sided alpha of 0.025.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

ITT population: Includes randomized subjects who have been documented to have suspected deleterious or deleterious mutations by the sponsor core lab. In this population subjects will be grouped according to the treatment assigned at randomization.

As-Treated (AST) population: Includes subjects who receive at least one dose of study drug (veliparib or placebo). In this population subjects will be grouped by the actual treatment received on the first dosing day.

Crossover population: Includes subjects who receive at least one dose of veliparib in the crossover study period.

5.2 Variables Used for Stratification of Randomization

Subjects will be randomized in a 2:1 ratio to veliparib/C/P or placebo/C/P and stratified by receptor status (ER and/or PgR-positive versus ER/PgR negative), prior platinum therapy (yes versus no), and presence of CNS metastases (yes versus no).

6.0 Analysis Conventions

General Considerations

Except where otherwise noted, statistical significance will be determined by a one-sided significance level of 0.025 for all efficacy analyses and by two-sided significance level of 0.05 for all safety statistical analyses.

The following conventions are applicable to analyses of blinded study period data.

Definition of Study Drug

Study drug in this document refers to veliparib or placebo for veliparib.

Usage of Multiple Values Reported on the Same Day

In cases where multiple values are collected on the same day (including baseline visit and post-baseline visits), the worst (e.g., maximum grade) value will be selected as the value for that day for the shift analysis of laboratory parameters; the arithmetic average will be calculated and used as the value for that day for mean changes in quality of life and performance status parameters.

Definition of Baseline

Unless otherwise specified, the baseline for the main study period is defined as the last non-missing observation collected on or prior to the first dose of study drug, or to the date of randomization for non-treated subjects.

Definition of Final Observation

For QoL, laboratory, and vital signs variables, the final observation is defined as the last non missing observation collected within 30 days following the last dose of study drug.

Definition of Study Rx Days (Days Relative to the First Dose of Study Drug)

Study Rx Days are calculated for each time point relative to the first dose date of study drug (veliparib/placebo).

When the date of a study event is on, or later than, the date of first dosing with study drug, then the study day for the event is defined to be the event date – the first dosing date + 1. When the date of an event is prior to the date of first dosing with study drug then study day is defined to be the event date – the first dosing date.

Definition of Within – Cycle Rx Days

Cycle Rx Days for each cycle are calculated for each time point relative to first dose of veliparib/placebo/carboplatin/paclitaxel in each cycle.

Definition of Analysis Windows

During the treatment period, all time points and corresponding time windows are based on Cycle Rx Days, the first dose date of study drug in each cycle.

For longitudinal analyses such as the analysis of mean changes in QoL and ECOG, values, the time windows specified in Table 3 describe how the data will be assigned to the protocol specified visits. Analysis time windows are constructed using the following algorithm:

- Determine the nominal Cycle Rx Day for each scheduled visit.
- Determine the window around a specific nominal Cycle Rx Day according to Table 3.
- If more than one observation is included in a time window, the observation closest to the nominal day should be used. If there are two observations equally distant to the nominal day, the later one will be used in analyses.

Table 3. Time Windows for Longitudinal Analysis of ECOG and QoL

Scheduled Visit	Nominal Cycle Rx Day	Time Window (Cycle Rx Day Range)
Cycle 1 Day 1	BASELINE	As baseline definition
Cycle 2 Day 1	1	(–7, 7)
Cycle X Day 1	1	(–7, 7)

* For quality of life measures X is every other cycle starting with C4.

For longitudinal analyses, the data will be analyzed as long as there are observations for at least 5 subjects in each treatment group.

Total Daily Doses

Study drug administration may be documented with multiple records for overlapping treatment periods. In such cases the overall total daily dose for a day will be calculated as the sum of the reported total daily doses for the day rounded to the nearest 10 milligrams.

Determination of Times-to-Event

The event time for a subject meeting one of the criteria for clinical benefit rate, progression-free survival, overall survival, or PFS2 will be calculated as the difference between the date that the event occurs and the randomization date plus 1 day. Response durations will be calculated as the difference between the date at which the response was first observed and the date at which disease progression is reported plus 1 day.

Censoring conventions for additional PFS analyses

In the primary analysis of progression-free survival, all evaluable data obtained in the blinded study period through the primary analysis cutoff date will be analyzed. In additional analyses of PFS, other censoring rules will be applied, as described next.

Impact of Local Therapy: procedures during study treatment such as surgery or radiative therapy may result in the RECIST overall response becoming unevaluable. When the local therapy is on one or more target lesions then the overall response will be considered to be Non-CR/Non-PD in such instances until criteria for progressive disease are met, except when anti-cancer therapy initiation is grounds for censoring.

Anti-cancer Therapies: Local therapies reported in the radiographic assessment data and post-treatment therapies initiated prior to a PFS event will be considered together as anti-cancer therapies. The earliest local therapy date or post-treatment therapy start date will be the overall anti-cancer therapy start date.

Missed radiographic assessments: In instances where two missed radiographic assessments have occurred a subject's data will be censored at the last assessment before the gap. Assessments are scheduled to occur at nine-week intervals with a window of five days around the target date: gaps of more than 18 weeks and five days (131 days) will be considered as two missed assessments.

Interval censoring: Analysis with interval censoring will be performed using the EM-ICM (Expectation Maximization-Iterative Convex Minorent) method for finding the

maximum likelihood estimate of the probability function for the event (PD) to occur at a point within an interval (between tumor assessment visits and also in the case of longer intervals due to missed tumor assessment visits). SAS code that will be used for the analysis is described in the reference *Analyzing Interval-Censored Survival Data with SAS® Software, Ying So and Gordon Johnston, SAS Institute Inc., Cary, NC, Se Hee Kim, University of North Carolina, Chapel Hill, NC. SAS Global Forum 2010.* A Kaplan-Meier curve will be produced from non-parametric maximum likelihood estimates (NPMLE) obtained from macro EMICM, specifying the EM-ICM algorithm. Generalized log-rank tests from Zhao & Sun and Sun, Zhao & Sun will be obtained from SAS macro ICSTEST.

Determination of Censoring Dates for Overall Survival

The overall survival censoring date for a subject will be the latest assessment date from the following list of data record types:

- Vital signs
- Physical exam
- Lab variables, including SAE lab reports
- ECOG performance status
- Quality of life measures
- Study drug administration
- Tumor assessments
- Transfusions
- Electrocardiogram
- Adverse event (event start date)
- Survival follow-up (last-known-alive date)

Records that indicate that the assessment was not done will not be used in determining the censoring date.

Censoring conventions for Objective Responses

Impact of Local Therapy: procedures during study treatment such as surgery or radiative therapy may result in the RECIST overall response becoming unevaluable. When the local therapy is on one or more target lesions then the overall response will be considered to be Non-CR/Non-PD in such instances until criteria for progressive disease are met. The response duration will be censored at the date of the latest assessment through the date of local therapy.

PFS2 Events

The following study outcomes will be counted as a PFS2 event;

- Radiographic progression on a post-treatment anti-cancer therapy
- Radiographic progression reported during crossover treatment with veliparib
- Subject deaths.

Progressions on post-treatment anti-cancer therapy and deaths may have been reported either in the blinded study period or in post-treatment follow-up.

Determination of Censoring Dates for PFS2

If a subject has not had a PFS2 event and has not yet entered survival follow-up then the subject's data will be censored at the date of the last available radiographic assessment. If a subject does not have a post-baseline radiographic assessment then the randomization date will be used for censoring. Once in survival follow-up, the last known alive date from follow-up will be the censoring date.

Definition of Treatment-Emergent Adverse Events

Adverse Events will be considered "treatment-emergent" when their onset is on or after the day of the first dose of study drug and also are at most 30 days after the last dose of

study drug. Events must also occur prior to the initiation of crossover treatment with veliparib.

If the onset date for an adverse event is reported with a month and year but without the day of the month, and the reported month matches that of the start of treatment with study drug, then the adverse event will be treatment-emergent. Similarly, if the reported month matches the month in which the post-treatment follow-up period ends then the adverse event will be treatment-emergent.

Laboratory Test Data

Central lab serum chemistry test results for this study are available from the Roche and Abbott Architect analysis platforms. When a sample was analyzed initially using the Roche platform, a projected Architect value for each test has been supplied by the lab vendor along with the Roche platform test value. Projected Roche values are similarly available along with Architect test results when the sample was analyzed initially with the Abbott system. The Architect values, actual or projected, will be used in analyses of lab test data.

NCI Grades for Laboratory Variables

Laboratory test values will be graded using CTCAE version 4.03 criteria prior to analysis. Criteria are specified for the assignment of grades with values between 1 and 4. The criteria are unidirectional: any one set of criteria constitute a screening either for low or high values of potential clinical significance.

For laboratory tests for which a normal range limit is one end of the grade 1 range then values that are either within the normal range or outside it in the direction opposite the test will be classified as grade 0 values. For other tests, values outside the grade 1 range in the direction opposite that of the test will be classified as grade 0.

There can be instances in which the criteria for more than one grade apply to a lab test value. In those instances the highest applicable grade will be assigned to the value.

7.0 Demographics, Baseline Characteristics, Medical History, Previous and Concomitant Medications

These summaries will be prepared by treatment group for the ITT population. A separate demographics summary will be produced for the crossover population.

7.1 Demographic and Baseline Characteristics

Continuous demographic data (e.g., age, height, and weight) will be summarized with mean, standard deviation, minimum, maximum, and range. Frequencies and percentages will be computed for the following categorical parameters:

- sex
- race and ethnicity
- geographic region
- core lab and historical BRCA1 and BRCA2 status
- ER/PgR status (ER/PgR+, triple-negative)
- sites of metastases (per investigator), including
  - bone disease only
  - any bone disease
  - liver, metastases
  - lung metastases
  - central nervous system metastases
  - all sites other than bone, liver, lung and CNS
- prior platinum therapy use
- prior cytotoxic therapy
  - for metastatic breast cancer
  - in the neoadjuvant and adjuvant settings
- history of central nervous system metastases
- presence of measurable disease (per investigator)
- number of target and non-target lesions (per investigator)

- ECOG performance status.

Prior platinum therapy use and estrogen and progesterone status will be summarized both as recorded in the process of randomization and in the subject's oncology history. Prior cytotoxic therapies will be identified by the project team from the oncology history data and then summarized.

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the CRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment group. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Previous Treatment and Concomitant Medications

The frequency and percentage of subjects who took at least one dose of medication other than study drug will be summarized by the generic name coded by the WHO dictionary. This analysis will be performed for prior and concomitant medications separately. Any medication initiated before the first day of treatment with study drug is a prior treatment. Medications initiated during the study from the first day of treatment with study drug, or else initiated before treatment with study drug and continued into the study treatment period, are concomitant medications.

The frequency and percentage of subjects who have had prior oncology therapies will be summarized by regimen names. In addition, the best response to any therapies prior to study drug (or randomization for non-treated subjects) will be summarized.

8.0 Subject Disposition

The number of randomized subjects and the number of treated subjects will be summarized by treatment group and by investigator site/country.

The numbers and percentages of discontinuations of study drug, carboplatin, paclitaxel and the study will be summarized by treatment group and reason for discontinuation.

9.0 Study Drug Exposure

Analyses of study drug exposure listed below will be performed on the AST population.

Exposure to study drug, carboplatin, and paclitaxel in the main study period will be summarized using the following measures:

- Total days of exposure
- Cycles of exposure
- Dose reductions
- Dose delays

When subjects discontinue carboplatin and paclitaxel but continue to receive study drug as a single-agent, the study drug regimen changes from seven days per cycle at 120 mg BID to daily dosing, initially at 300 mg BID. Days of exposure to study drug in the main study period will be summarized over the following sub-periods:

- Combination therapy
- Single-agent therapy
- Total study drug exposure.

Days of exposure to veliparib in the crossover period will be summarized separately.

Total days of exposure to study drug will be calculated using the start and end dates in the study drug administration records. Exposure to study drug is presumed for each day from

the start date through the end date in a study drug administration record. Days of exposure to carboplatin and paclitaxel will be determined from the number of records reported for each subject, as each record covers one day of treatment with those therapies.

The number of cycles received is to be determined from the visit schedule information associated with the study drug administration records.

For total days of exposure and cycles of exposure, descriptive statistics (mean, standard deviation, median, and range) will be presented by treatment group for study drug, carboplatin, and paclitaxel.

Cycles of exposure to study drug, paclitaxel, and carboplatin, will be summarized further with subject frequency counts and percentages by treatment group. In these summaries, cycles of exposure will be grouped in multiples of six (1 to 6 cycles, 7 to 12 cycles, and so on) prior to tabulation until the total number of subjects remaining is at most 25. The number and percentage of subjects treated with three days of paclitaxel in each of the first 12 cycles will be tabulated.

If the difference between starting dose dates of two consecutive cycles of paclitaxel or carboplatin exceeds 35 days then a subject will be considered as having had a delay in dosing with those agents. The percentages of subjects with treatment delays will be summarized for each treatment group.

A permanent decrease in the total daily dose of veliparib will be counted as a dose reduction. Carboplatin dose reductions will be identified based on the reported AUC dose levels. The body surface area based dose level (mg/m^2) will be used to identify dose reductions of paclitaxel. Dose level changes in study drug following discontinuations of paclitaxel and carboplatin will be summarized separately. The percentages of subjects with dose reductions will be summarized for each treatment. The number and percentage of subjects treated at the initial dose level or with one or two dose reductions at the end of each of the first 12 cycles will be tabulated. The counts and percentages of dose reductions at the final dosing level will also be tabulated.

10.0 Efficacy Analysis

10.1 General Considerations

The analysis set for efficacy endpoints will be the ITT population. Except where noted, comparisons of efficacy endpoints will be performed between the two treatments as assigned by the IVRS/IWR (veliparib + carboplatin + paclitaxel versus placebo + carboplatin + paclitaxel).

The primary and secondary efficacy endpoints that include radiographic assessments will be based on investigators' assessments, per RECIST 1.1.

The primary analysis cutoff date is April 05th, 2019, by which time at least the requisite number of PFS needed for performing the primary analysis at 90% power is expected to have occurred. The corresponding database will be termed the Primary PFS database.

Overall Survival will be analyzed with data from the Primary PFS database, with a second OS analysis planned at a later date at which 357 deaths have occurred in the event that the first analysis is not statistically positive. The Lan DeMets alpha-spending function with an O'Brien-Fleming boundary will be used to ensure that the one-sided false positive rate will be 0.025 or less for overall survival.

10.2 Primary Efficacy Analysis

The primary efficacy analysis will be a comparison of progression-free survival between the veliparib + carboplatin + paclitaxel and the placebo + carboplatin + paclitaxel treatment groups.

For a given subject, time to PFS will be defined as the number of days from the date the subject was randomized to the date the subject experiences radiographic disease progression (as determined by the investigators), or to the date of death (all causes of mortality) if disease progression is not reached. All events of disease progression occurring on or before the Primary Analysis Cutoff date will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously

discontinued study drug. Events of death will be included for subjects who had not experienced disease progression, provided the death occurred on or prior to the primary analysis data and within 9 weeks (63 days) of the last available disease progression assessment. If the subject does not have an event of disease progression and the subject has not died on or before the Primary Analysis Cutoff date the subject's data will be censored at the date of the subject's last available disease progression assessment. If the randomized subject did not have any post-baseline disease progression assessments, the subject's data will be censored on the date of randomization.

The distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology and compared between treatment groups using the log-rank test, stratified by prior platinum therapy (Yes versus No) and receptor status (ER and/or PgR positive versus ER/PgR negative).

A Cox proportional hazard model, stratified by prior platinum therapy and ER/PgR receptor status, will be used to estimate the hazard ratio and 95% confidence interval comparing the two treatment arms.

10.3 Secondary Efficacy Analyses

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

10.3.1 Overall Survival

Time to death (overall survival) for a given subject will be defined as the number of days from the date the subject was randomized to the date of the subject's death. All events of death which occur up to the analysis cutoff date will be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject

discontinued study drug. If a subject has not died, the data for the subject will be censored at the date last known to be alive or at the analysis cutoff date if that is earlier.

The distribution of overall survival will be estimated for each treatment group using Kaplan-Meier methodology and compared between two treatment groups using the log rank test, stratified by prior platinum therapy (Yes versus No) and receptor status (ER and/or PgR positive versus ER/PgR negative).

10.3.2 Clinical Benefit Rate

The clinical benefit rate for each treatment group will be obtained from a time-to-event analysis of radiographic disease progression per the investigator. The endpoint will be defined to be the progression-free rate at 24 weeks (168 days).

Progression-free rates at 24 weeks will be estimated for each treatment arm using Kaplan-Meier methodology. 95%-confidence intervals for the rates will be obtained using a log-log transformation. Standard errors for the rates will also be obtained from the time-to-progression model. A chi-square test statistic constructed as the ratio of the squared difference of the Kaplan-Meier estimates of the progression-free rates and the estimate of the associated variance of the difference will be used to test the null hypothesis that the clinical benefit rate at Week 24 for the two treatment groups are the same.

All events of disease progression in the primary PFS analysis database will be included, regardless of whether the event occurred while the subject was still taking, or had previously discontinued, study drug. If the subject has not yet progressed then the subject's data will be censored at the date of the last evaluable disease progression assessment. Subjects without post-baseline assessments will be censored at the date of randomization.

10.3.3 Objective Response Rate

The objective response rate (ORR) will be calculated as the proportion of subjects who have a confirmed PR or CR based on assessment by the investigators per RECIST

(version 1.1). Subjects in the ITT population with at least one measurable lesion at baseline will be included in the analysis, as will be the case for the analysis of any response data.

ORR will be estimated for each treatment group and compared between two treatment groups using a CMH test stratified by prior platinum therapy (Yes versus No) and estrogen/progesterone receptor status (ER and/or PgR positive versus ER/PgR negative). In addition, 95% confidence interval will be constructed for ORR.

10.3.4 Progression-Free Survival on Subsequent Therapy (PFS2)

PFS2 will be defined as the number of days from the date of randomization to the time of disease progression on subsequent therapy or death from any cause.

The distribution of PFS2 will be estimated for each treatment group using Kaplan-Meier methodology and compared between two treatment groups using the log-rank test, stratified by prior platinum therapy (Yes versus No) and receptor status (ER and/or PgR positive versus ER/PgR negative).

10.4 Tertiary Efficacy Analyses

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses will be performed to compare the effects of veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel on quality of life, performance status, and duration of radiographic response.

Subjects must have both a baseline and post-baseline assessment to be included in these analyses.

10.4.1 Quality of Life

Quality of life assessments will be performed through the use of the EORTC QLQ-C30, EORTC BR23, and EQ-5D-5L questionnaires. Pain assessments will be analyzed via the

Brief Pain Inventory Short Form (BPI-SF). Performance status over time will be analyzed using the ECOG scale.

EORTC QLQ-C30

The overall and domain specific scores will be calculated from the 30 items in the EORTC QLQ-C30 for each subject based on the QLQ-C30 scoring instruction. The items and scales of the QLQ-C30 are as follows:

Table 4. EORTC QLQ-C30 Scales

	Scale	Number of Items	Item Range	Item Numbers
Global Health Status/Quality of Life				
Global Health Status/Quality of Life	QL2	2	6	29, 30
Functional Scales				
Physical Functioning*	PF2	5	3	1 – 5
Role Function*	RF2	2	3	6 – 7
Emotional Functioning*	EF	4	3	21 – 24
Cognitive Functioning*	CF	2	3	20, 25
Social Functioning*	SF	2	3	26 – 27
Symptom Scales				
Fatigue	FA	3	3	10, 12, 18
Nausea and Vomiting	NV	2	3	14 – 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite Loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial Difficulties	FI	1	3	28

* Function scales.

Note: Item range is the difference between the possible maximum and the minimum response to individual items.

Scoring algorithms for scales are as follows:

For all Scales, the Raw Score (RS) is the Mean of the Component Items:

If items I_1, I_2,…, In are included in a scale, the procedures are as follows:

Raw Score (RS) = (I_1 + I_2 +… + In)/(number of non-missing items),

Then the Functional Scales:

Score = (1 - (RS-1)/range)*100, where range is provided by the table above.

For example:

Emotional Functioning: RS = (Q21 + Q22 + Q23 + Q24)/4

EF Score = (1 - (RS-1)/3)*100

For the Symptoms Scales/Items and Global Health Status/QOL:

Score = ((RS – 1)/range)*100

For example:

Fatigue: RS = (Q10 + Q12 + Q18)/3

FA Score = ((RS-1)/3)*100

Descriptive statistics will be presented for baseline, each scheduled post-baseline visit, and the final visit, of domain specific scores by each treatment group. Mean change (95% CI) from baseline to each scheduled post-baseline visit within each treatment group and the mean difference of change (95% CI) from baseline to each scheduled post-baseline visit and the final visit between the two treatment groups will be obtained from the ANCOVA model with treatment group as the factor and baseline value as a covariate.

EORTC QLQ-BR23

The EORTC QLQ-BR23 is a 23-item breast cancer-specific questionnaire about the common side effects of therapy, body image, sexuality, and outlook for the future. Domain specific scores will be calculated from the 23 items for each subject based on the QLQ-BR23 scoring instructions. The items and scales of the QLQ-BR23 are as follows.

Table 5. EORTC QLQ-BR23 Scales

Functional Scales	Scale Name	Number of Items	Item Range	Item Numbers
Body Image	BRBI	4	3	9 – 12
Sexual Functioning	BRSEF	2	3	14, 15
Sexual Enjoyment	BRSEE	1	3	16
Future Perspective	BRFU	1	3	13
Symptom Scales/Items				
Systemic Therapy Side Effects	BRST	7	3	1 – 4, 6, 7, 8
Breast Symptoms	BRBS	4	3	20 – 23
Arm Symptoms	BRAS	3	3	17 – 19
Upset by Hair Loss	BRHL	1	3	5

Descriptive statistics will be presented for baseline, each scheduled post-baseline visit, and the Final Visit of domain specific scores by each treatment group. Mean change (95% CI) from baseline to each scheduled post-baseline visit and the Final Visit within each treatment group and the mean difference of change (95% CI) from baseline to each scheduled post-baseline visit and the Final Visit between treatment groups will be obtained from the ANCOVA model with treatment group as the factor and baseline value as a covariate.

EQ-5D-5L

EQ-5D-5L consists of 5 items: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and a self-rated health visual analogue scale (EQ VAS). An EQ-5D-5L utility score will be calculated based on US preference-weighted index score method. If any of the 5 items are missing, the utility score is set to missing. Mean change

in utility score (and 95% CI) from baseline to each scheduled post-baseline visit within each treatment group and the mean difference of change (95% CI) from baseline to each scheduled post-baseline visit and the final visit between the two treatment groups will be obtained from the ANCOVA model with treatment group as the factor and baseline value as a covariate.

Item 6 of EQ-5D-5L, a visual analog scale (VAS) will be analyzed using the same methodology as detailed for the utility score.

Brief Pain Inventory

The Short Form of the Brief Pain Inventory includes four questions pertaining to pain severity reported by the subject on a scale of 0 (no pain) – 10 (pain as bad as is imaginable). Summary statistics for each question on severity will be reported by treatment group. Summary statistics on pain severity overall will be reported by treatment group. Pain severity overall is scored as the average of the 4 pain severity items (i.e., average, worst, least, current) and will be provided if at least 2 items are completed.

There are seven questions in the inventory used to gauge the degree of interference in subject activity due to pain, scored from 0 – 10. Pain interference is scored as the mean of the seven pain interference items, if at least four of the seven total items are completed. Positive change scores denote improved QoL except for the symptom scale which is reversed. The subject's responses will be included in an evaluation of the average degree of interference in subject activity at each assessment.

Mean change (95% CI) from baseline to each scheduled post-baseline visit and the Final Visit within each treatment group and the mean difference of change (95% CI) from baseline to each scheduled post-baseline visit and the Final Visit between treatment groups will be obtained from the ANCOVA model with treatment group as the factor and the baseline value as a covariate. Analyses will be done for each item as well as sub-domain scales.

10.4.2 Performance Status

Descriptive statistics on the ECOG score will be presented for baseline, each scheduled post-baseline visit, and the Final Visit for each treatment group. Mean change (95% CI) from baseline to each scheduled post-baseline visit and the Final Visit within each treatment group and the mean difference of change (95% CI) from baseline to each scheduled post-baseline visit and the Final Visit between treatment groups will be obtained from an ANCOVA model with treatment group as the factor and baseline ECOG score as a covariate.

10.4.3 Duration of Overall Response

The distribution of the duration of overall response will be estimated for each treatment group using Kaplan-Meier methodology.

The duration of overall response for a given subject will be defined as the number of days from the day the criteria are met for CR or PR (whichever is recorded first) to the date that PD is documented. If a subject's response is ongoing at the analysis cutoff date then the subject's data will be censored at date of the last disease progression assessment performed on or prior to the cutoff.

Subjects in the ITT population with at least one measurable lesion at baseline will be eligible for inclusion in the analysis. Subjects who never experience a confirmed PR or CR will not be included in the analysis.

10.4.4 Crossover Period Efficacy

For subjects receiving crossover veliparib therapy, progression-free survival, objective response, best response, clinical benefit rate at 6 months, and duration of response will be summarized. The start date for the time-to-event analyses will be the first day of treatment with crossover veliparib. The analyses will otherwise be carried out as described for the ITT population.

10.5 Additional Efficacy Analyses

The primary endpoint may also be analyzed for all randomized subjects, regardless of whether or not the subject has a deleterious mutation confirmed by the Sponsor core lab, or for the AST population restricted to subjects with confirmed or suspected mutations.

In addition to the stratified log-rank test for the primary endpoint, the unstratified log-rank test. Stratified and unstratified Cox proportional hazards models may be used for the comparison of PFS between two treatment groups.

PFS and ORR based on data from the central reader will be analyzed using the same methodology as detailed in previous sections.

Cox proportional hazard modeling will be performed to compare PFS and OS by treatment group in subgroups. Subgroup analyses within the ER/PgR status levels will be performed with treatment alone in the Cox model. Cox modeling with ER/PgR status as stratification factor along with the treatment in the model will be used to examine PFS and OS in subgroups including but not limited to the following: BRCA1/2 status (BRCA1 positive or suspected mutation versus negative; BRCA2 positive or suspected mutation versus negative), prior platinum therapy use, ECOG performance status (0 versus 1 versus 2), geographic region (US versus non-US), race (white or any other race), age group (< 45 versus ≥ 45), and history of CNS (Yes versus No). A hazard ratio, 95% confidence interval, and p-value will be obtained for each subgroup and tabulated. The hazard ratios and confidence intervals will also be displayed visually in forest plots.

Progression free survival and OS will be compared by treatment group in the above subgroups by performing log-rank tests. The log-rank tests within ER/PgR strata will be unstratified. The logrank test performed on all other subgroups will be stratified by ER/PgR status.

In two additional PFS analyses data will be censored prior to the date of the final radiographic assessment if some or all of the following study events occur before then: 1) at the date of initiation of other anti-cancer therapies after randomization, 2) at the date of

local therapy on at least one of the target or non-target lesions, 3) at the date of the last radiographic assessment prior to a gap when two or more assessments are missed, and 4) at the date of a site blind break. In one analysis data will be censored if an anti-cancer therapy is initiated or local therapy is received. In the second analysis data will be censored if any of the above-identified events have occurred. This modified data will be analyzed using the same methodology as detailed for the primary PFS analysis.

Additional analyses may also be performed for PFS, such as 1) including only data and events occurring on treatment or within 30 days of the last dose of study drug; and 2) analysis using interval censoring methods.

10.6 Handling of Multiplicity

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

An additional multiplicity issue is introduced through the multiple testing of the OS endpoint. It is anticipated that, at the analysis time of the primary efficacy endpoint PFS, there will be too few deaths to support an adequately powered OS analysis. Therefore, two OS analyses are planned, the first one based on the "Primary PFS Analysis" database, and the second one based on the "OS Analysis" database (with a total of 357 deaths). Statistical significance for OS will be declared if a significant result is obtained for either analysis, consistent with group-sequential testing methods specified in Section 10.1.

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will be performed on the as-treated (AST) and crossover populations.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent 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. Analyses will not include those events that have an onset greater than 30 days after the last dose of study drug.

Treatment-emergent adverse events will be coded and summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding dictionary. The percentages of subjects experiencing an adverse event at a given NCI CTCAE version 4.03 terminology grade and relationship to study drug will be provided.

Comparisons of the percentages of subjects in the AST population experiencing an adverse event between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel will be performed using Fisher's exact test. *P* values > 0.100 when rounded to three decimal places will not be presented.

The numbers and percentages of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event categories:

- All adverse events
- Events with a reasonable possibility of being related to study drug according to the investigator.
- Events with a reasonable possibility of being related to carboplatin according to the investigator
- Events with a reasonable possibility of being related to paclitaxel according to the investigator
- NCI grade 3 or higher adverse events
- NCI grade 3 or higher Events with a reasonable possibility of being related to study drug according to the investigator

- NCI grade 3 or higher Events with a reasonable possibility of being related to carboplatin according to the investigator
- NCI grade 3 or higher Events with a reasonable possibility of being related to paclitaxel according to the investigator
- All adverse events broken down by maximum NCI terminology grade
- Serious adverse events
- Serious adverse events with a reasonable possibility of being related to study drug
- Serious adverse events with a reasonable possibility of being related to carboplatin
- Serious adverse events with a reasonable possibility of being related to paclitaxel
- Events leading to discontinuation of study participation
- Events leading to discontinuation of study drug
- Events leading to discontinuation of carboplatin
- Events leading to discontinuation of paclitaxel
- Events leading to discontinuation of study participation with a reasonable possibility of being related to study drug
- Events leading to discontinuation of study drug with a reasonable possibility of being related to study drug
- Events leading to discontinuation of carboplatin with a reasonable possibility of being related to carboplatin
- Events leading to discontinuation of paclitaxel with a reasonable possibility of being related to paclitaxel
- Events leading to discontinuation of study participation due to disease progression
- Events leading to discontinuation of study drug due to disease progression
- Events leading to discontinuation of carboplatin due to disease progression
- Events leading to discontinuation of paclitaxel due to disease progression
- Events leading to discontinuation of study not due to disease progression
- Events leading to discontinuation of study drug not due to disease progression

- Events leading to discontinuation of carboplatin not due to disease progression
- Events leading to discontinuation of paclitaxel not due to disease progression
- Events leading to study drug interruption
- Events leading to study drug dose reduction
- Events leading to carboplatin interruption
- Events leading to carboplatin dose reduction
- Events leading to paclitaxel dose interruption
- Events leading to paclitaxel dose reduction
- Any treatment emergent adverse event leading to death
- Any treatment-emergent adverse event leading to death with a reasonable possibility of being related to study drug

The above-listed summaries that apply to treatment with single-agent veliparib therapy will be prepared for the crossover population and for adverse events with onset during blinded single-agent therapy.

A summary of times to first adverse events leading to study drug interruption or dose reduction will be produced. The number of subjects having such an event, the median and range of the times will be tabulated by treatment group.

11.2.2 Adverse Events of Special Interest

Treatment-emergent adverse events and serious adverse events of special interest based on Standard or Custom MedDRA Queries (SMQ-s or CMQ-s) will also be summarized. The adverse event types and MedDRA queries used are described in the following table:

Table 6. Adverse Events of Special Interest

Adverse Event of Special Interest	Search Criteria	Event Definition/Medical Concept
Nausea and vomiting	Nausea and vomiting MedDRA preferred terms (PT code 10028813, 10047700)	Treatment-emergent adverse events coded to MedDRA preferred terms
Seizures	Convulsions SMQ 20000079 (query for convulsions)	Treatment-emergent adverse events coded to MedDRA terms on the broad search list.
Anemia	Haematopoietic erythropenia SMQ 20000029	Treatment-emergent adverse events coded to MedDRA terms on the broad search list.
Thrombocytopenia	Haematopoietic thrombocytopenia SMQ 20000031	Treatment-emergent adverse events coded to MedDRA terms on the broad search list.
Neutropenia	Hematological Toxicity-Neutropenia CMQ 80000154	Treatment-emergent adverse events coded to MedDRA terms on the broad search list.
Infection events within 14 days after neutropenia events	Infections CMQ 80000018 and hematological toxicity-neutropenia CMQ 80000154	Treatment-emergent adverse events from the MedDRA terms on the broad search list.
Haemorrhages events within 14 days after thrombocytopenia	Haemorrhage terms (excl laboratory terms) SMQ 20000039 and hematopoietic thrombocytopenia SMQ 20000031	Treatment-emergent adverse events from the MedDRA terms on the broad search list.
Second/Secondary Malignancies	Malignant Tumors SMQ 20000194 and Tumors of Unspecified Malignancy SMQ 20000195	Treatment-emergent adverse events from the MedDRA terms on the narrow search list for malignancies are used as a starting point for medical review to search for secondary malignancies.
Myelodysplastic Syndromes (MDS)	Myelodysplastic syndrome SMQ (Narrow) 20000217	Treatment-emergent adverse events from the MedDRA terms on the search list.
Acute Myeloid Leukemia (AML)	Acute myeloid leukaemia PT (10000880)	Treatment-emergent adverse events from the MedDRA preferred terms on the search list.
Changes in reproductive organ function	SMQ 20000210 (fertility disorders)	Treatment-emergent adverse events from the MedDRA terms on the search list.
Teratogenicity		Pregnancies and outcomes will be analyzed individually as they occur.

For the infection after neutropenia AESI, subjects who have an infection at most 14 days after a report of neutropenia will be identified. Subjects with a hemorrhage (bleeding) adverse event within 14 days following a report of thrombocytopenia will be counted in the hemorrhages/thrombocytopenia AESI. In each case the 14 day comparisons will be based on the start dates of the adverse events.

With the exception of secondary malignancies and teratogenicity, adverse events identified through the searches will be tabulated. An overview summary of adverse event types for each AESI will be produced. Tabulations of all treatment-emergent events, events with grade > three, and serious adverse events will be provided for each AESI by system organ class and primary MedDRA preferred term.

11.3 Deaths

The number of subject deaths will be summarized 1) for deaths occurring while the subject was still receiving study drug in this study; 2) for deaths occurring off treatment within 30 days after the last dose of study drug; and 3) for all deaths in this study regardless of the number of days after the last dose of study drug. There will be no statistical comparison for above analyses.

11.4 Analysis of Laboratory and Vital Signs Data

11.4.1 General Considerations

Laboratory test variables for which NCI 4.03 common terminology criteria exist will be classified per those criteria and then analyzed in shift summaries. The AST population will be subject to analysis.

The vital signs variables to be analyzed are systolic and diastolic blood pressure, heart rate and body temperature.

11.4.2 Analyses of Laboratory Test Data Using NCI CTCAE Criteria

For hematology and chemistry variables for which NCI CTCAE 4.03 criteria exist, baseline and post-baseline hematology and chemistry variable observations will be categorized as grade 0 to grade 4. For each graded variable, cross tabulations will be made of the number of subjects with each baseline grade versus post-baseline observations at both the maximum and final observation grade. Additionally, for each variable, the number and percentage of subjects that have a baseline observation categorized as grade 0 to grade 2 and also have a grade 3 or 4 post-baseline observation at maximum grade or final observation will be presented. Subjects for whom the baseline grade is 3 or higher for a laboratory test will not be included in the shift summary for that variable. Shift rates for the two treatment groups in the AST population will be compared using Fisher's exact tests.

A listing of all observations collected during the study will be generated for subjects that had at least one post-baseline observation classified as a grade 3 or 4 value per NCI CTCAE 4.03 criteria. A corresponding listing will be produced for lab test results reported for subjects receiving veliparib in the crossover period.

11.5 Analyses of Vital Signs Using Criteria for Potential Clinical Significance

Vital signs values will be assessed for potential clinical significance through the application of criteria developed at AbbVie as detailed in the following table:

Table 7. Criteria for Potential Clinical Significance in Vital Signs Variables

Systolic Blood Pressure	> 150 mmHg and > 20 mmHg higher than baseline < 70 mmHg and a decrease of ≥ 30 mmHg from baseline
Diastolic Blood Pressure	> 100 mmHg and higher than baseline < 50 mmHg and a decrease of ≥ 20 mmHg from baseline
Pulse Rate	> 120 bpm and an increase of ≥ 30 bpm from baseline < 50 bpm and a decrease of ≥ 30 bpm from baseline
Temperature	≥ 38.9°C ≤ 35.6°C

The frequency and percentage of subjects with post-baseline values meeting Criteria for Potentially Clinically Significant Vital Signs values will be summarized. Subjects must have at least one post-baseline measurement to be included in the summary. If a subject does not have a vital signs measurement at baseline but has post-baseline measurement which meets the above absolute criteria for blood pressure and pulse rate, this subject will be considered as meeting the potentially clinically significant vital signs values for the measurement. A listing will be provided that presents all reports of a vital signs variable for subjects with a value meeting the criteria for potential clinical significance. Comparisons of the rates of subjects in the AST population meeting the above criteria between veliparib 120 mg BID + carboplatin + paclitaxel and placebo for veliparib 120 mg BID + carboplatin + paclitaxel will be performed using Fisher's exact test.

12.0 Pharmacokinetic Analyses

12.1 Tabulations and Summary Statistics

Plasma concentrations of veliparib and possible metabolites(s) will be listed for each subject by scheduled visit. Summary statistics will also be computed for each subject randomized to the veliparib treatment by scheduled visit and nominal time.