

1.0 Title Page

Statistical Analysis Plan

Study M13-694

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

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Version 3.0

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3.0 Introduction

This statistical analysis plan (SAP) is created based on Study Protocol M13-694, incorporating Amendments 1, 2, 3, 4, 5, 6 and 7. Study M13-694 examines the safety and efficacy of veliparib (ABT-888) in combination with standard platinum-based chemotherapy (carboplatin/paclitaxel) and then as monotherapy in maintenance for high grade serous epithelial, ovarian, fallopian tube, or primary peritoneal cancer.

This SAP provides details to guide the analyses for baseline, efficacy, and safety variables and describes the populations and variables that will be analyzed and the statistical methods that will be used for primary and follow-up analyses for Study M13-694 (Analysis timing is defined in Section 4.5).

Version 3.0 of the SAP was created after finalization of the interim CSR to add an additional interim analysis of Overall Survival per the request of the FDA and allow provision for additional interim analyses if warranted. No changes to any analysis previously conducted will be made.

Analyses will be performed using SAS[®] Version 9.4 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective of the study is to evaluate whether PFS is prolonged with the addition of veliparib to standard platinum-based chemotherapy (carboplatin/paclitaxel) and then continued as maintenance therapy when compared to chemotherapy alone (Arm 3 versus Arm 1). This will be evaluated in three nested cohorts defined in Section 5.1: subjects with *BRCA*-deficient tumors, subjects with homologous recombination deficient (HRD) tumors, and the whole patient population.

Secondary objectives include evaluations of OS (Arm 3 versus Arm 1 and Arm 2 versus Arm 1), PFS (Arm 2 versus Arm 1), Disease Related Symptom (DRS) scores (Arm 3

versus Arm 1 and Arm 2 versus Arm 1), and safety of the 3 study arms. These will be evaluated within the three patient populations.

The tertiary objectives include progression free survival 2 (PFS2), time to first subsequent therapy (TTFST), time to second subsequent therapy (TSSST), and other PRO endpoints (which will be specified in a separate analysis plan). These will also be evaluated by comparing Arms 3 and 2 with Arm 1, within the three patient populations.

4.2 Design Diagram

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

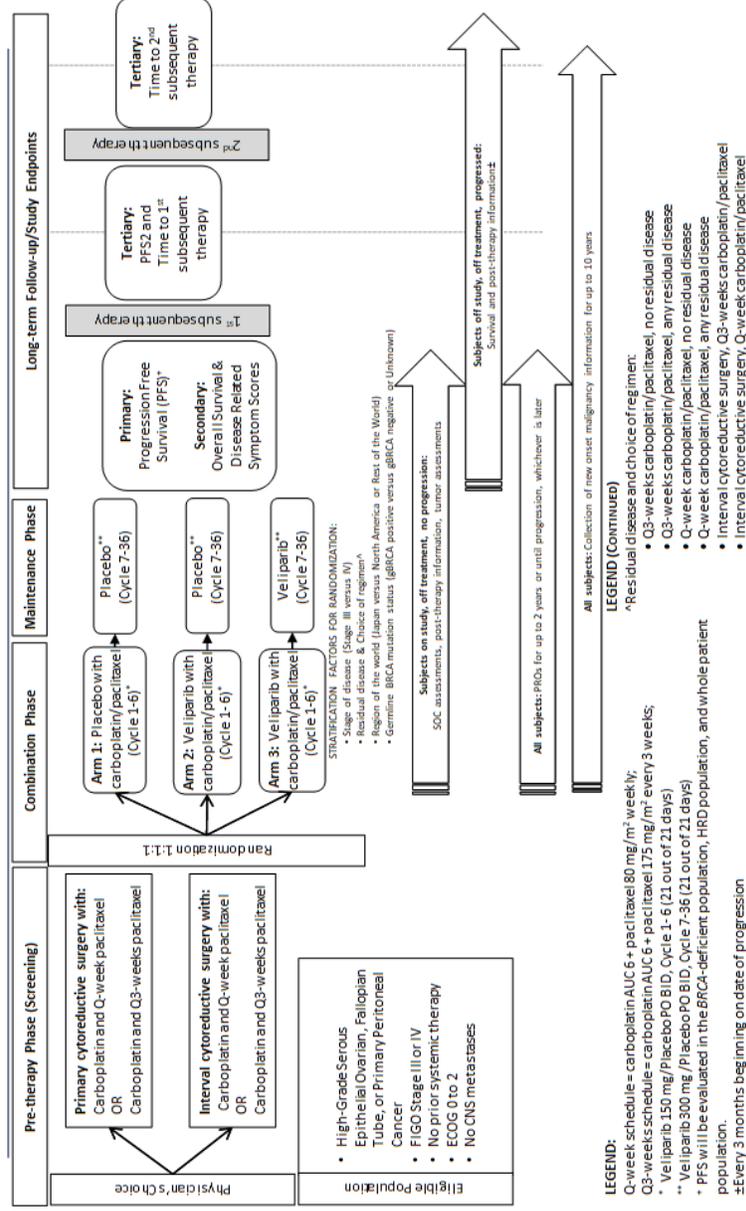
Subject randomization was stratified by stage of disease, residual disease and choice of regimen, region of the world, and *gBRCA* mutation status (*gBRCA* was added during the course of the study). Approximately 1100 subjects were planned for enrollment, and 1140 subjects were randomized in a 1:1:1 ratio to one of the following three treatment Arms:

- Arm 1: Carboplatin/paclitaxel plus placebo for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;
- Arm 2: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by placebo maintenance therapy for 30 additional 21-day cycles;
- Arm 3: Carboplatin/paclitaxel plus veliparib for six 21-day cycles followed by veliparib BID maintenance therapy for 30 additional 21-day cycles.

Subjects that were found not to tolerate paclitaxel, could instead receive docetaxel but had to temporarily discontinue veliparib due to lack of safety data for this combination. Subjects were allowed to restart veliparib in the maintenance phase once treatment with docetaxel had ended.

The study consists of five phases: a Pre-Therapy Phase (Screening), a Combination Therapy Phase, a Maintenance Therapy Phase, a Long-Term Follow-Up Phase, and a Survival Phase. An overview of the study design is shown in [Figure 1](#).

Figure 1. Overall Study Design



4.3 Sample Size

The trial was planned to enroll approximately 1100 subjects (with 1:1:1 randomization ratio for Arm 1:Arm 2:Arm 3) in the whole population, including approximately 264 subjects with *BRCA*-deficient status (assuming 24% of the subjects in the whole population are *BRCA*-deficient) to power the hypotheses specified in the *BRCA*-deficient and whole populations (Table 1). Detailed sample size calculations for the PFS and OS endpoints of the *BRCA*-deficient, HRD and whole populations are described in Section 4.3.1 – Section 4.3.2.

In order to calculate the needed number of subjects in each of the 3 arms, the same statistical assumptions were used to power both the comparisons of PFS and OS between Arm 3 versus Arm 1 [3vs1], and between Arm 2 versus Arm 1 [2vs1], within each population.

The associated power for the alpha level and population can be found in Table 1.

Throughout the SAP, 'Month 36' is used as the surrogate for the time of primary analysis of PFS for all three populations; 'Month 48' is used as the surrogate for the time of the additional interim analysis of OS for all three populations, conducted approximately one year after the primary analysis of PFS; 'Month 58' is used as the surrogate for the time of final analysis of OS in Whole population; and 'Month 77' is used as the surrogate for the time of final analysis of OS in both *BRCA*-deficient and HRD populations.

Table 1. Power and Sample Size Calculation

Type I Error	Population	No. of Subjects per Arm (N)	PFS				OS					
			Power	Median PFS in Arm 1	Hazard Ratio	No. of Events for 2 Arm Comparison	Projected Endpoint Mature Time (Months)	Power	Median OS in Arm 1	Hazard Ratio	No. of Events for 2 Arm Comparison	Projected Endpoint Mature Time (Months)
alpha = 0.025	BRC4-deficient	88	87%	21	0.50	79	36	87% ^a	53	0.50	79	77
	HRD	160	91.5%	18	0.60	170	36	90% ^a	47	0.60	166	77
	Whole	367	96.5%	15.5	0.70	446	36	91.5% ^b	41.5	0.70	350	58
			94.1%	15.5	0.7	391	36					

PFS = progression-free survival; OS = overall survival

- a. Assumes 3 efficacy interim analyses (at Month 36, Month 48, and Month 58, respectively) with alpha spending of 0.000001 at each of the 3 interim analyses. The multiplicity adjusted alpha for the final analysis at Month 77 is 0.025, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.
- b. Assumes 2 efficacy interim analyses at Month 36 and Month 48 with alpha spending of 0.000001. The alpha for the final analysis at Month 58 is 0.025. The multiplicity adjusted alpha for the analysis at Month 77 is 0.025, provided all preceding null hypotheses in the hierarchical testing sequence are rejected.

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

4.3.1 Hypotheses related to PFS

PFS (Arm 3 versus Arm 1, and Arm 2 versus Arm 1):

Testing of PFS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the population of interest.

Testing of PFS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the PFS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the population of interest.

***BRCA*-deficient Population:** A total of 79 events would provide 87% power for a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in PFS assuming a true hazard ratio of 0.5 (between Arm 3 and Arm 1, or between Arm 2 and Arm 1).

Assuming a median PFS of 21 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 3:Arm 1 and Arm 2:Arm 1) were needed to have a matured PFS endpoint at around 36 months taking into account a dropout rate of 10%.

HRD Population: This population was not in the original protocol design consideration. Assuming a HR = 0.6 between Arm 3 and Arm 1, or Arm 2 and Arm 1, we can expect at least a total of 170 PFS events in Arm 3 and Arm 1 combined, and Arm 2 and Arm 1 combined at the time of primary analyses of PFS in *BRCA*-deficient and Whole populations. A total of 170 events would provide 91.5% power with a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in PFS assuming a true hazard ratio of 0.6 (between Arm 3 and Arm 1, and Arm 2 and Arm 1). Assuming a median PFS of 18 months in Arm 1 and an enrollment period of 18 months, approximately 160 subjects per arm in a 1:1 randomization ratio (Arm 3:Arm 1, and

Arm 2:Arm 1) are needed to have a matured PFS endpoint at around 36 months taking into account of a dropout rate of 10%.

Whole Population: A total of events between 391 and 446 would provide power between 94.1% and 96.5%, with a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in PFS assuming a true hazard ratio of 0.7 (between Arm 3 and Arm 1, or between Arm 2 and Arm 1).

Assuming a median PFS of 15.5 months in Arm 1 and an enrollment period of 18 months, and taking into account a dropout rate of 10%, approximately 367 subjects were needed per arm in a 1:1 randomization ratio (Arm 3:Arm 1, and Arm 2:Arm 1) in order to have a matured PFS endpoint at around 36 months.

4.3.2 Hypotheses related to OS

OS (Arm 3 versus Arm 1, and Arm 2 versus Arm 1):

Testing of OS (Arm 3 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 3 (C/P + veliparib → veliparib) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the population of interest.

Testing of OS (Arm 2 versus Arm 1) evaluates whether the veliparib-containing regimen in Arm 2 (C/P + veliparib → placebo) decreases the OS event rate relative to reference regimen in Arm 1 (C/P + placebo → placebo) in the population of interest.

BRCA-deficient Population: A total of 79 events would provide 87% power with a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in OS, assuming a true hazard ratio of 0.5 (between Arm 3 and Arm 1, or between Arm 2 and Arm 1).

Assuming a median OS of 53 months in Arm 1 and an enrollment period of 18 months, approximately 88 subjects per arm in a 1:1 randomization ratio (Arm 3:Arm 1, and Arm 2:Arm 1) were needed to have a matured OS endpoint at around 77 months, taking

into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the primary analyses of PFS and final analysis of OS analysis for the whole population.

HRD Population: A total of 166 events would provide 90% power with a 1-sided log-rank test at a 0.025 significance level to detect a statistically significant improvement in OS, assuming a true hazard ratio of 0.6 (between Arm 3 and Arm 1, and Arm 2 and Arm 1).

Assuming a median OS of 47 months in Arm 1 and an enrollment period of 18 months, approximately 160 subjects per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) are needed to have a matured OS endpoint at around 77 months, taking into account of a dropout rate of 10% and 2 efficacy interim analyses that occur at the time of the primary PFS and final analysis of OS for the whole population.

Whole Population: Under the design considerations in the original protocol, a total of 350 events would provide 91.5% power for a 1-sided log-rank test at a 0.025 significance level, respectively, to detect a statistically significant improvement in OS assuming a true hazard ratio of 0.7 (between Arm 3 and Arm 1, or between Arm 2 and Arm 1).

Assuming a median OS of 41.5 months in Arm 1 and an enrollment period of 18 months, and taking into account of a dropout rate of 10% and an efficacy interim analysis that occurs at the time of the PFS analysis, approximately 367 subjects were needed per arm in a 1:1 randomization ratio (Arm 3 versus Arm 1) to have a mature OS endpoint at around 58 months.

4.4 Interim Analysis

Interim Efficacy Analyses for Overall Survival

Overall survival is expected to mature at Month 58 in the whole population and at Month 77 for the *BRCA*-deficient and HRD populations.

The Overall Survival hypotheses (Arm 3 versus Arm 1, or Arm 2 versus Arm 1) in the *BRCA*-deficient, HRD, and Whole populations will be tested at the following time points. The order of the testing sequence will follow that in Section 10.7.

The first interim analysis for all three populations will occur at the time of the primary analyses of PFS (~Month 36) with an alpha of 0.000001.

The second interim OS analysis for all three populations will occur approximately one year after the first interim with an alpha of 0.000001.

The third interim OS analysis in the *BRCA*-deficient and HRD populations will occur at the time when the Whole population matures (~Month 58) with an alpha of 0.000001.

The final analyses of OS in each population will occur when the *BRCA*-deficient population matures (~Month 77) and will have an alpha of 0.025 if all null hypotheses tested previously according to the testing sequence are rejected. The final analysis for Whole Population, planned to be performed along with the analyses of mature OS data in *BRCA*-deficient and HRD populations, will still be based on the data from the time when the targeted number of OS data was achieved in the Whole Population (~Month 58).

If future analyses need to be performed as requested by regulatory agencies, an alpha of 0.000001 will be spent for each of those additional analyses without amending the SAP.

Interim Safety Analyses

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

The first IDMC meeting reviewed safety data on July 29, 2016. The IDMC saw no concerning safety signals and recommended continuing the study. They also recommended an additional IDMC meeting in 6 months due to the fast enrollment rate. In

addition, the IDMC noted a significant imbalance of *gBRCA* status across treatment groups, and recommended adding *gBRCA* status as a randomization stratification factor to potentially correct this imbalance. This recommendation was based on the expectation that *BRCA* status is a strong prognostic and predictive factor for patients' responses to the study regimen. AbbVie followed the IDMC's recommendation and added the *gBRCA* stratification factor in September 2016.

The study proceeded to have three subsequent IDMC meetings to review safety data, on January 17, 2017, July 31, 2017, and May 04, 2018. No further IDMC meetings are scheduled at the time of finalization of this SAP.

4.5 Analysis Timing

The 'data cutoff date' for the primary analyses of PFS will be determined when the total number of PFS events in Arms 1 and 3 combined have reached 79 in the *BRCA*-deficient population, 170 in the HRD population, and 391 in the whole population. Since this is a blinded study involving 3 arms, an independent statistical data analysis center will be used to confirm that the above stated criteria for the total number of PFS events between Arms 1 and 3 have been reached.

The first interim analysis of OS will occur in the *BRCA*-deficient, HRD and whole populations at the time of the primary analyses for PFS.

Per FDA request, a second interim analysis of OS for the three populations will be conducted, approximately one year after the primary analysis.

For the whole population, the final analysis of OS will occur after the total number of deaths between Arms 1 and 3 have reached 350. At the time of the final analysis of OS for the whole population, interim analysis of OS will be performed for *BRCA*-deficient and HRD populations.

For the *BRCA*-deficient and HRD populations, final analyses of OS will occur after the total number of deaths in Arms 1 and 3 reaches 79 in the *BRCA*-deficient population and 166 in the HRD population.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

The study populations are defined as follows:

- Whole population (ITT population) – all subjects randomized by IRT.
- *BRCA*-deficient population – all subjects in the ITT population with either a germline (*gBRCA*) and/or tissue (*tBRCA*) deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2* as determined using centralized testing.
- HRD population – all subjects in the *BRCA*-deficient population as well as those determined as having homologous repair deficiency tumors based on HRD score as determined using centralized testing.
- As Treated (AST) population – all subjects who were randomized by IRT and took at least one dose of veliparib/placebo. The data from the AST population will be analyzed by the actual treatment that subject received.

For all efficacy analyses, subjects in the Whole population, *BRCA*-deficient population, and HRD population will be analyzed by the treatment group assignment given at the time of randomization, regardless of actual treatment received, or failure to follow the protocol until completion.

5.2 Variables Used for Stratification of Randomization

Subject randomization was stratified into 48 groups as defined by combining categories of the four randomization stratification factors (*gBRCA* was added per the IDMC's recommendation during the course of the study) that follow:

1. Stage of the disease
 - a. III

- b. IV
2. Residual disease and choice of regimen
 - a. Q3-weeks carboplatin/paclitaxel, no residual disease
 - b. Q3-weeks carboplatin/paclitaxel, any residual disease
 - c. Q-week carboplatin/paclitaxel, no residual disease
 - d. Q-week carboplatin/paclitaxel, any residual disease
 - e. Interval cytoreductive surgery, Q3-weeks carboplatin/paclitaxel
 - f. Interval cytoreductive surgery, Q-week carboplatin/paclitaxel
 3. Region
 - a. Japan
 - b. North America or Rest of World
 4. Germline *BRCA* mutation status
 - a. *gBRCA* positive (germline deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2*)
 - b. *gBRCA* negative (wildtype or unknown)

Stratification factors to be used in stratified efficacy analyses are described below in Section 6.0.

6.0 Analysis Conventions

General Considerations

The date of randomization is defined as the date that the IRT issues a randomization number.

All randomized subjects will be included in the efficacy analyses. All subjects who receive at least one dose of veliparib/placebo will be included in the safety analysis.

Data Cutoff Date

Only data occurring on or before the 'data cutoff date' will be used in all analyses and summaries of safety and efficacy data. Unless otherwise specified, the same 'data cutoff date' will be used for all three populations. Data occurring after the cutoff date may be used in determining end dates for calculation of exposure (e.g., exposure or adverse event duration) or last known alive dates.

Definition of Study Drug

Unless otherwise specified, the study drug in this document refers to veliparib/placebo.

Definition of Study Treatment

Unless otherwise specified, the study treatment in this document refers to veliparib/placebo, carboplatin, paclitaxel, and as applicable, docetaxel.

Stratification Variables to be Adjusted for in Stratified Efficacy Analyses

Due to suspected sparseness of data in some strata observed through blinded summaries, a subset of the randomization stratification factors will be used for all stratified efficacy analyses. The subset was chosen based on the differences observed between the stratification levels in the efficacy data (pooled across three treatment groups).

Additionally, based on the pooled data, Residual Disease was further collapsed as the Interval Surgery and Any Residual Disease after Primary Surgery showed similar efficacy.

Whole population: Primary Plan: Residual Disease (2 levels: No Residual Disease after Primary Surgery versus Any Residual Disease after Primary Surgery or Interval Surgery), Stage of Disease (Stage III versus Stage IV), Choice of Paclitaxel Dosing Regimen (Q-weekly versus Q3-weekly) and *BRCA*-deficient status (*BRCA*-deficient versus *BRCA* wildtype or unknown) will be used in all stratified analyses of the efficacy endpoints for the whole population. However, if any of the 16 stratum cells due to the above strategy

result in 0 PFS events for Arms 1 and 3 combined, then Choice of Paclitaxel Dosing Regimen will be dropped from the set of factors. The set of factors will be consistent among all stratified efficacy analyses based on the whole population (unless specified otherwise).

BRCA-deficient and HRD populations: Residual Disease (2 levels: No Residual Disease after Primary Surgery versus Any Residual Disease after Primary Surgery or Interval Surgery) and Stage of Disease (Stage III versus Stage IV) will be used in all stratified analyses of the efficacy endpoints for the *BRCA*-deficient and HRD populations.

The stratification factor value under which the subject is randomized by the IRT will be used in the efficacy analyses for all factors except *BRCA*-deficient status. Since tissue *BRCA* status was not a randomization factor, and not all subjects were randomized by germline *BRCA* status, the actual results from the central testing will be used for the analyses (i.e., not the *gBRCA* status used for stratification at randomization).

Dealing with Multiple Values on the Same Day

In cases where multiple values are collected on the same day (including baseline visit and post-baseline visits), the maximum grade value will be selected as the value for that day for the shift analysis of lab parameters; the worst score calculated for that day will be used for analysis of quality of life (QoL), and performance status (ECOG).

Definition of Baseline

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

Definition of Final Visit

For laboratory and vital signs variables, Final Visit is defined as the last non-missing observation collected within 30 days following the last dose of study treatment. All post-

baseline assessments collected more than 30 days after the last dose of study treatment will not be included in the analyses of laboratory and vital signs variables.

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

Study Rx Days are calculated for each time point relative to the first dose date of any component of study treatment. They are defined as the number of days between the day of the first dose of study treatment and the specific time point. Rx days are negative values when the time point of interest is prior to the first study treatment dose day. Rx days are positive values when the time point of interest is after the first study treatment dose day. The day of the first dose of study treatment is defined as Study Rx Day 1, while the day prior to the first study treatment dose is defined as Study Rx Day –1 (there is no Study Rx Day 0).

Definition of Cycle Rx Days in Each Cycle

During the combination phase (Cycles 1 through 6), Cycle Rx Days for each cycle are calculated for each time point relative to the first dose of veliparib/placebo/carboplatin/paclitaxel/docetaxel in each cycle.

During the maintenance phase (Cycles 7 through 36), Cycle Rx Days are calculated for each time point relative to the first dose of veliparib/placebo in each cycle.

Subjects that have discontinued study therapy and are in the Long Term Follow Up without Disease Progression Phase will still have QoL data summarized as treatment cycles. Cycle Rx Days will be calculated by taking the last available Cycle start date while on treatment, and iteratively adding 21 days to define the nominal day of each Cycle Rx Day up until Cycle 36.

Definition of Analysis Windows for DRS

All time points and corresponding time windows are based on Cycle Rx Days.

For visit wise longitudinal analyses such as mean change from baseline to all post-baseline assessments in DRS, the time windows specified in describe how the data will be assigned to the protocol specified visits. Analysis time windows are constructed using the following algorithm:

- Determine the nominal Cycle Rx Day for each scheduled visit.
- Determine the window around a specific nominal Cycle Rx Day as in [Table 2](#).
- If more than one assessment is included in a time window, the assessment closest to the nominal day should be used. If there are two observations equally distant to the nominal day, the later one will be used in analyses.

The data will only be analyzed for visits that have at least 5 subjects' observations for each treatment group.

Table 2. Time Windows for Visit-Wise Analysis of DRS

Scheduled Visit	Nominal Cycle Rx Day	Time Window while On Study Therapy (Study Rx Day Range)	Time Window when Off Study Therapy (Study Rx Day Range)
Combination Phase:			
Cycle 1	Baseline	As Baseline Definition	As Baseline Definition
Cycle 3	1	(-3, 4)	(-21, 21)
Cycle 5	1	(-3, 4)	(-21, 21)
Maintenance Phase			
Cycle 7	1	(-3, 4)	(-21, 21)
Cycle 9	1	(-3, 4)	(-21, 21)
Cycle XX ^a	1	(-3, 4)	(-21, 21)

a. Every other cycle until Cycle 35.

Determination of Censoring Dates for OS, TTFST, and TTSST

The censoring date for overall survival, time to first subsequent therapy and time to second subsequent therapy for a subject will be the last assessment date from the following list of data record types:

- Vital signs

- Physical exam
- Lab variables, including SAE lab reports
- ECOG performance status
- Quality of life measures
- Study drug administration
- Tumor assessments scan date
- Transfusions
- Electrocardiogram
- Adverse event
- PK blood draws
- Date of Cytoreductive Surgery
- Concomitant Medications
- Post treatment therapy
- Survival follow-up (last-known-alive date)
- Randomization Date

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

Partial Dates

The following rules will apply for partial start dates:

- Missing day will be imputed as the first day of the month
- Missing month and day will be imputed as January 1st
- For partial adverse event start dates: if the first dose date is available, and the adverse event end date is missing or after the first dose date, then the imputed start date would be the maximum of the first dose date and the imputed value under the above two criteria.

The following rules will apply for partial end dates:

- Missing day will be imputed as the last day of the month
- Missing month and day will be imputed as December 31st
- For partial adverse event end dates: the imputed value can never be set later than the subject death date, when the death date is available.
- For partial exposure end dates:
 - For veliparib records, missing day will be imputed as the maximum of the first day of the month and the exposure record start date
 - For veliparib records, missing month and day will be imputed as the maximum of January 1st of the provided year and the exposure record start date
 - For chemotherapy, if any part of the date is missing, the end date will be imputed as the record start date
 - For all study treatment, if the end date is completely missing, then the end date will be imputed as the exposure record start date

Definition of Treatment-Emergent Adverse Events

Adverse Events will be considered "treatment-emergent" when their onset is on or after the day of the first dose of study treatment and also are at most 30 days after the last dose of any study treatment (including docetaxel if applicable).

If the onset date for an adverse event is reported with a month and year but without the day of the month, and the reported month matches that of the start of study treatment, then the adverse event will be treatment-emergent. If the reported month matches the month in which the 30 day follow-up period ends then the adverse event will be treatment-emergent. If an onset or end date for an adverse event is reported with a year only in such a way that it cannot be determined definitively if the adverse event is treatment-emergent by comparing with dosing data, the adverse event will be considered treatment-emergent.

NCI Grades for Laboratory Variables

Laboratory variable values will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 Published:

May 28, 2009 (v4.03: June 14, 2010)¹ for some analyses. Criteria are specified for the assignment of grades with values between 1 and 4. The criteria are unidirectional: any one set of criteria constitute a screening either for low or high values of potential clinical significance.

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

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

Definition of Safety Subgroups for Adverse Event and Laboratory Summaries

Adverse Events and Laboratory values may be summarized according to the following clinically important safety subgroups.

- Combination Period: defined as the first dose date of veliparib/carboplatin/paclitaxel to the day before the first dose date veliparib during Cycle 7. For subjects not dosed after Cycle 6, the Combination Period is defined as the first dose date of veliparib/carboplatin/paclitaxel to the last dose date of any component of the study treatment + 30 days.
- Maintenance Period: defined as the first dose date of veliparib that occurs after the end of Cycle 6 to the last dose date of veliparib + 30 days. Only subjects that were dosed with veliparib after the end of Cycle 6 will be included in safety summaries regarding Maintenance Period.
- Q-weekly Dosing: for AE and Lab summaries by choice of dosing schedule, the actual dosing schedule the subject was under will be used (not necessarily what the subject was randomized as).
- Q3-weekly Dosing: for AE and Lab summaries by choice of dosing schedule, the actual dosing schedule the subject was under will be used (not necessarily what the subject was randomized as).

- Subjects Dosed With Docetaxel: All subjects that received at least one dose of docetaxel.

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications and Prior Oncology Therapies

The ITT population will be used in the analyses of demographic, baseline characteristics, medical history, and previous/concomitant medication. Prior oncology therapies will only be summarized for subjects with a history of another cancer.

All summaries and analyses will be presented by each treatment arm, and may also be summarized separately for the *BRCA*-deficient and HRD populations.

7.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Country
- Region (as randomized) [North America vs. Japan vs. Rest of World].
- Region (confirmed post randomization) [North America vs. Japan vs. Rest of World]
- Race
- Age (continuous and categorical [< 65 years vs. ≥ 65 years])
- Height
- Weight
- Type of Ovarian Cancer [High-grade serous epithelial ovarian vs. High-grade serous epithelial fallopian tube vs. High-grade serous epithelial primary peritoneal]
- History of Other Cancer [History vs. No History]
- CA-125 level [\leq ULN vs. $>$ ULN]
- Germline *BRCA* status (as randomized) [*gBRCA* Positive vs. *gBRCA* Negative vs. Unknown vs. Not randomized by *gBRCA*]

- Germline *BRCA* status (central testing) [*BRCA1/2* mutation vs. *BRCA1/2* wildtype]
- Tissue *BRCA* status [*BRCA1/2* mutation vs. *BRCA1/2* wildtype]
- *BRCA*-deficient status [germline or tissue *BRCA1/2* mutation vs. *BRCA1/2* wildtype]
- Type of *BRCA*-deficiency [germline *BRCA1/2* mutation vs. tissue *BRCA1/2* mutation and germline *BRCA1/2* wildtype vs. *BRCA1/2* wildtype]
- Type of *BRCA1/2* mutation [*BRCA1* vs. *BRCA2* vs. *BRCA1* and *BRCA2* vs. *BRCA1/2* wildtype]
- HRD status [HRD vs. non-HRD]
- HRD and *BRCA*-deficient status [HRD and *BRCA1/2* mutation vs. HRD and *BRCA1/2* wildtype vs. non-HRD]
- Stage of Disease at randomization [III vs. IV]
- Stage of Disease as confirmed by investigator after randomization [III vs. IV]
- Residual Disease and Choice of Regimen at randomization
 - Q3-weekly paclitaxel, no residual disease
 - Q3-weekly paclitaxel, any residual disease
 - Q-weekly paclitaxel, no residual disease
 - Q-weekly paclitaxel, any residual disease
 - Interval cytoreductive surgery, Q3-weekly paclitaxel
 - Interval cytoreductive surgery, Q-weekly paclitaxel
- Residual Disease and Choice of Regimen as confirmed by investigator after randomization (categories as above; where microscopic or any macroscopic residual disease is classified as any residual disease and no residual disease is classified as no residual disease)
- Choice of Surgery at randomization [primary vs. interval]
- Choice of Surgery as confirmed by investigator after randomization [primary vs. interval vs. no surgery received]
- Residual Disease at randomization [no residual disease vs. any residual disease vs. interval surgery]

- Residual Disease after primary surgery, as confirmed by investigator after randomization [no residual disease vs. microscopic residual disease only vs. any macroscopic residual disease]
- Residual Disease after interval surgery [no residual disease vs. microscopic residual disease only vs. any macroscopic residual disease]
- Choice of Dosing Regimen at randomization [Q-weekly vs. Q3-weekly]
- Choice of Dosing Regimen as confirmed by investigator after randomization [Q-weekly vs. Q3-weekly]
- Smoking history [current smoker vs. past smoker vs. never smoked vs. unknown]
- Alcohol history [current user vs. past user vs. never vs. unknown]
- ECOG performance status [0, 1, vs. 2]

The number of subjects with missing information will also be summarized.

Categorical data will be summarized by numbers and percentages in each category.

Continuous data will be summarized by mean, standard deviation, median, IQR, minimum and maximum values.

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The frequency and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment group. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system. There will be no statistical comparison for the medical history among the treatment groups.

7.3 Prior and Concomitant Medications and Prior Oncology Therapies

The frequency and percentage of subjects who took at least one dose of medication other than study treatment will be summarized by the generic name coded by WHO dictionary. This analysis will be performed for prior and concomitant medications separately. Any medication initiated before the first day of treatment with study therapy is a prior treatment. Medications initiated during the study from the first day of study treatment, or else initiated before study treatment and continued into the study treatment period, are concomitant medications. Prior Oncology Therapies will be presented in a separate summary for subjects treated for another type of cancer prior to entering the study.

There will be no statistical comparison for the prior and concomitant medications among the treatment groups.

8.0 Subject Disposition

Analyses for the subject disposition will be performed on the ITT population at the time of the primary analysis and final analysis as appropriate. The treatment groups assigned by IRT will be used in the summaries of subject disposition and there will be no statistical comparison for the subject disposition.

The screen failure reasons will be summarized for the screen failure subjects.

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

The frequency and percentage of subjects who discontinued study, veliparib/placebo, carboplatin, or paclitaxel will be summarized for each treatment group. All reasons for discontinuation and the primary reason for discontinuation of each drug (including docetaxel) will be summarized by treatment group.

The frequency and percentage of subjects who underwent primary or interval surgery will be summarized by randomized surgery type. For subjects that did not undergo surgery,

the reasons may be summarized and a subject listing may be provided containing additional details.

9.0 Study Drug Exposure and Compliance

9.1 Study Treatment Exposure

Analyses for the exposure to study treatment will be performed on the AST population.

The number of cycles that subjects are exposed to veliparib/placebo, carboplatin, paclitaxel, and docetaxel (for subjects dosed with docetaxel) will be summarized by treatment group. Frequencies and percentages of the maximum cycle dosed will be displayed for each component of study treatment by treatment group.

In addition, the following will be summarized for veliparib/placebo only:

Days exposed to study drug (days) is defined as the total number of individual days a subject received study drug.

Days exposed to study drug (intervals): the frequency and percentage of subjects exposed to veliparib/placebo will be summarized for each of the following duration intervals.

- 1 to 63 days [≤ 3 cycles]
- 64 to 126 days [$3 < \text{cycles} \leq 6$]
- 127 to 252 days [$6 < \text{cycles} \leq 12$]
- 253 to 378 days [$12 < \text{cycles} \leq 18$]
- 379 to 504 days [$18 < \text{cycles} \leq 24$]
- 505 to 630 days [$24 < \text{cycles} \leq 30$]
- ≥ 631 days [> 30 cycles]

Average dosed days per cycle of study drug is defined as the total number of days a subject received study drug divided by the number of cycles that the subject is exposed to study drug.

For all summaries of all components of the study treatment, descriptive statistics (mean, standard deviation, median, and range) will be used to summarize duration of exposure and number of cycles exposed by treatment group.

9.1.1 Dose Reductions, Interruptions, Delays and Intensity

The frequencies and percentages of subjects having dose reduction (all treatments), interruption (veliparib/placebo only), or delay (carboplatin, paclitaxel, docetaxel) will be summarized for each treatment group. Summaries of veliparib will be done for the entire treatment period, and will also be separated by combination period (Cycle 1 through Cycle 6) and maintenance (Cycle 7 through Cycle 36).

Dose Reductions

Carboplatin/paclitaxel/docetaxel: If a subject has any dose reduction from the previous dose of carboplatin/paclitaxel/docetaxel, this subject will be considered as having experienced dose reduction of carboplatin/paclitaxel/docetaxel, respectively. For carboplatin, this is calculated using the AUC. For paclitaxel and docetaxel, this calculation is done using the investigator-selected dose level (mg/m²).

Veliparib: The data entry guidelines for BID dosing for veliparib instructs that each skipped dose is recorded into EDC. To only summarize true dose reductions and not days when only a single dose was taken, the following convention will be used: Dose reductions for veliparib will be calculated by first finding the maximum total daily dose per cycle. If a subject has a reduction from the previous cycle's maximum total daily dose, then this subject will be considered as having experienced a dose reduction of veliparib.

Dose Interruptions

Dose interruptions are defined for veliparib/placebo only. If a subject skips 1 or more consecutive days, this subject will be considered as having experienced a dose interruption of veliparib/placebo.

By definition, all interval surgery subjects that undergo surgery will have a dose interruption of veliparib. Therefore, the summary of dose interruptions will also be divided into primary versus interval surgery subjects, according to the surgery type the subject actually received.

Dose Delays

Dose delays are defined for carboplatin, paclitaxel and docetaxel.

For carboplatin, Q3-weekly dosing of paclitaxel, and docetaxel, a dose delay is defined as more than 27 days between consecutive dose dates of the respective therapy. For Q-weekly dosing of paclitaxel, a dose delay is more than 13 days between consecutive dose dates.

Dose Intensity for Chemotherapy

Dose intensity will be calculated for carboplatin and paclitaxel per [Table 3](#). For paclitaxel, intensities will be summarized by actual dosing schedule (weekly versus Q3 weekly). There is no planned dose level of docetaxel, and so will not be summarized for subjects that switched to docetaxel.

Table 3. Dose Intensity for Carboplatin and Paclitaxel

	Actual Total Dose (ATD)	Planned Total Dose (PTD)	Actual Dosing Days (ADD)^a	Ideal Dosing Days (IDD)^a	Dose Intensity (%)
Carboplatin	Actual total dose AUC (mg/mL/min)	AUC 6 (mg/mL/min) * total number of administrations of carboplatin	Last dose date + 21 – first dose date	Number of administrations * 21	100* (ATD/PTD) * (IDD/ADD)
Paclitaxel (weekly)	Actual total dose (mg/m2)	80 mg/m2 * total number of administrations of paclitaxel	Last dose date + 7 – first dose date	Number of administrations * 7	100* (ATD/PTD) * (IDD/ADD)
Paclitaxel (Q3 weekly)	Actual total dose (mg/m2)	175 mg/m2 * total number of administrations of paclitaxel	Last dose date + 21 – first dose date	Number of administrations * 21	100* (ATD/PTD) * (IDD/ADD)

a. For interval surgery subjects, ADD and IDD will be calculated for Cycles 1 - 3 and 4 - 6 separately, and summed together to get a final total value of dosing days.

10.0 Efficacy Analysis

10.1 General Considerations

Efficacy analyses will be performed on all randomized subjects within the whole population, *BRCA*-deficient population and HRD populations. The date of randomization is defined as the date when the randomization number is issued by IRT.

All data occurring on or before the 'data cutoff date' (defined in Section 6.0) will be included in all efficacy analyses. Data occurring after the 'data cutoff date' will be excluded for PFS, PFS2 and DRS. For OS, TTFST and TTSST, it will be used in determining the censoring date (as described in Section 10.3.1, Section 10.4.2, and Section 10.4.3).

For the final analyses of OS, the 'data cutoff date' will correspond to when data mature (~58 months for whole population, ~77 months for *BRCA*-deficient and HRD populations).

For all time to event analyses (PFS, PFS2, OS, TTFST, TTSST), the following conventions will be used:

- The distribution of the endpoint will be estimated for each treatment arm using Kaplan-Meier methodology.
- For both the *BRCA*-deficient population and the HRD population, the endpoint will be compared between each of the treatment arms (Arm 3 or Arm 2) and the control arm (Arm 1) using the log-rank test, stratified by the factors described in Section 6.0.
- For the whole population, the endpoint will be compared between each of the treatment arms (Arm 3 or Arm 2) and the control arm (Arm 1) using the log-rank test, stratified by the factors described in Section 6.0.
- The Cox Proportional Hazard Model will be used to estimate the hazard ratio and 95% confidence interval comparing each of the treatment arms (Arm 3 or Arm 2) and the control arm (Arm 1) within each population, stratified by the factors described in Section 6.0.
- For all endpoints, the median time and its 95% confidence interval will be estimated for each treatment arm within each population.

10.2 Primary Efficacy Analysis

The primary efficacy endpoint is progression-free survival (PFS). PFS will be defined as the number of days from the date that the subject was randomized to the date the subject experiences an event of disease progression, according to RECIST criteria version 1.1 (as determined by the investigator) or to the date of death (all causes of mortality) if disease progression is not reached. If the subject does not have an event of disease progression according to RECIST criteria versions 1.1 (as determined by the investigator) nor has the subject died, the subject's data will be censored at the date of the subject's last evaluable disease assessment. Data for subjects without any post-baseline radiographic assessments

and that did not die within 89 days (12 weeks + 5 days) of randomization, will be censored at the date of random assignment.

Handling of Intercurrent Events

- The following events of PD/death will be included:
 - Events that occur after a subject discontinues or completes study treatment
 - Events that occur after a subject starts a new therapy (so long as the subject has not withdrawn consent from protocol tumor assessments)
- The following events of PD/death will be censored
 - Events that occur after too much time has passed since the last valid radiologic assessment according to the below table

Disease Progression or Death after too much time between scans

Per the protocol, the scan schedule is as follows: (every 9 weeks, then at the end of the Combination Phase, then every 12 weeks for 2 years, then every 6 months for 3 years, and then annually). Due to the complexity of this scan schedule and to prevent the gap between valid assessments prior to PD from getting too wide for the later time periods, the following programming conventions are implemented:

	Randomization \leq last evaluable scan prior to PD/Death Date $<$ 2.5 years*	2.5 \leq last evaluable scan prior to PD/Death Date $<$ 5.5 years*	5.5 \leq last evaluable scan prior to PD/Death Date
Definition of Interval	12 weeks	6 months	1 year
Number of Intervals allowed missing prior to PD before event is censored	2	1.5	1.5
Skipped intervals prior to PD	24 weeks (168 days + 5 days)	9 months (270 days + 5 days)	18 months (548 days + 5 days)
Number of Intervals allowed missing prior to death before event is censored	1	1	1
Skipped interval Prior to death	12 weeks + 5 days	6 months (182 days + 5 days)	12 months (365 days + 5 days)

* 2.5 years = 913.125 days; 5.5 years = 2,008.875 days.

The three primary efficacy analyses are defined by:

- comparing PFS in Arm 3 versus Arm 1 in the *BRCA*-deficient population using the log-rank test, stratified by factors defined in Section 6.0, at the 1-sided 0.025 α level;
- comparing PFS in Arm 3 versus Arm 1 in the HRD population using the log-rank test, stratified by factors defined in Section 6.0, at the 1-sided α level as specified in Section 10.7;
- comparing PFS in Arm 3 versus Arm 1 in the whole population using the log-rank test, stratified by factors defined in Section 6.0, at the 1-sided α level as specified in Section 10.7.

The distribution of PFS will be summarized per considerations in Section 10.1.

The study will be successful if the first analysis in the multiplicity testing procedure described in Section 10.7 (comparison of PFS [Arm 3 v Arm 1] in the *BRCA*-deficient

population) is statistically significant. If this comparison is statistically significant, the other two primary endpoints will be analyzed for statistical significance in the specified order.

10.3 Secondary Efficacy Analyses

10.3.1 Overall Survival

OS will be defined as the number of days from the day the subject is randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurs while the subject is still taking study drug, or after the subject discontinues study drug. If a subject has not died, then the data will be censored at the date when the subject is last known to be alive, using the data as specified in Section 6.0. However, if a subject is known to either be alive or have had died after the 'data cutoff date,' then the subject's data will be censored at the 'data cutoff date.'

The six secondary efficacy analyses for OS include comparing OS in Arm 3 versus Arm 1 and Arm 2 versus Arm 1 in the *BRCA*-deficient population, the HRD population, and the whole population. Each comparison will be tested using the log-rank test, stratified by factors defined in Section 6.0, at the α level as specified in Section 10.7;

The distribution of OS will be summarized per considerations in Section 10.1.

10.3.2 Progression-Free Survival

The three secondary efficacy analyses of PFS include comparing PFS in Arm 2 versus Arm 1 in the *BRCA*-deficient population, the HRD population, and the whole population. Each comparison will be tested using the log-rank test, stratified by factors defined in Section 6.0, at the α level based on the pre-specified α allocation rule in Section 10.7.

The analyses of PFS will be performed per Section 10.1.

10.3.3 Patient Reported Outcomes

Disease Related Symptoms

The overall mean change from baseline for the disease related symptom physical (DRS) scores measured at each assessment point up to disease progression or 2 years if progression has not been reached will be a secondary endpoint of the study. No alpha will be spent on these endpoints.

DRS scores are collected at odd numbered cycles, and will be summarized through Cycle 35, which is approximately 2 years of study therapy assuming no interruptions. The visits windows are detailed in Section 6.0.

The secondary efficacy analyses for DRS are defined by the following comparisons, which will be performed in the *BRCA*-deficient population, HRD population and the whole population:

- The comparison of mean changes from baseline in total DRS score to each scheduled assessment until disease progression or death, for up to 2 years, between Arm 3 and Arm 1, and Arm 2 and Arm 1 using a mixed-model for repeated measures (MMRM) model with observed DRS score.

A separate MMRM model will be used for each of the three populations. Only subjects with a baseline and at least one post-baseline assessment will be included in the model. Each model will include the fixed categorical effects of treatment group, stratification factors (as specified per population in Section 6.0), time point (each scheduled assessment up to 2 years), and treatment group-by-time point interaction, and the continuous fixed covariate of baseline DRS score. The REPEATED statement will be used for time point in PROC MIXED with blocks in the covariance matrix identified by subject nested within treatment group. Restricted maximum likelihood estimation will be utilized and an unstructured covariance structure will be used to model the within-subject error. In the event that the model does not converge with unstructured covariance, AR(1) will be used.

If AR(1) does not converge, compound symmetry structure will be used. If convergence has still not been met, then a simple summary of ANCOVA by visit will be produced.

Calculation of DRS at each timepoint

The score range of the FOSI-DRS Score is 0 – 36, where a high score is considered good and a score of 0 would be a severely symptomatic subject.

Individual Item Scores:

Item Codes GP1, GP4, GP6, 03, HI7, Cx6 and O1 are considered "reverse" items and the subject's item response will be subtracted from 4 to correct for the direction as follows

$$\text{Individual Item Score} = (4 - \text{Item Response})$$

For Item Codes C3 and GF5, no correction to the subject's item response is necessary:

$$\text{Individual Item Score} = \text{Item Response}$$

DRS Score

FOSI-DRS score = (Sum of Individual Item Scores × 9)/(number of items answered).

10.4 Tertiary Efficacy Analyses

10.4.1 Progression-Free Survival 2 (PFS2)

Progression-Free Survival 2 (PFS2) is defined as the number of days from the day the subject is randomized to the earliest date of disease progression reported on any line of subsequent therapy or death by any cause. This is regardless of the subject having a documented PD for the primary PFS analysis prior to starting a subsequent therapy. Therefore, the same event of progression may be used for both the primary PFS analysis and the analysis of PFS2, provided the subject has not withdrawn consent from the protocol tumor assessments. Additionally, an event of PFS2 may be either radiographic or clinical progression, such as increase in CA-125, and will be documented by the

investigator. Any death that occurs prior to either a documented first progression, or a documented second progression, will be considered as an event of PFS2.

In summary, the following will be considered PFS2 events:

- The earliest event of progression (of any type), as determined by the investigator, that occurs after the initiation of a subsequent therapy
- Any death that occurs prior to the subject achieving the above described event of progressive disease, regardless if the subject started a subsequent therapy

If the subject does not have an event of PFS2, the following censoring rules will apply:

- If the subject is still being followed per protocol scan schedule for a primary PFS event, PFS2 will be censored at the same date as for the primary PFS analysis.
- If the subject is no longer being followed for primary PFS (for any reason), PFS2 will be censored at the subject's most recent post-treatment therapy start date or end date as applicable

The tertiary efficacy analyses for PFS2 are defined by comparing PFS2 in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the *BRCA*-deficient population, HRD population and the whole population. PFS2 may also be compared between Arm 2 and Arm 3 as an exploratory analysis.

The efficacy analyses of PFS2 will be summarized per guidelines in Section 10.1.

10.4.2 Time to the First Subsequent Therapy

Time to the First Subsequent Therapy (TTFST) will be defined as the number of days from the day the subject is randomized to the start of the first subsequent therapy (after discontinuation of protocol study treatment) or death of any cause. If the subject does not have an event of TTFST, the subject's data will be censored at the date the subject was last known to be alive and not have received subsequent therapy, i.e., the subject's last visit (including on therapy study visit, long-term follow-up without disease progression visit)

or survival follow-up. If the subject is known to have an event of TTFST after the 'data cutoff date,' or the subject is known to be alive and without an event of TTFST after the cutoff, then the subject's data will be censored at the 'data cutoff date.' See Section 6.0 for more censoring details.

The tertiary efficacy analyses for TTFST are defined by comparing TTFST in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the *BRCA*-deficient population, the HRD population, and the whole population. TTFST may also be compared between Arm 2 and Arm 3 as an exploratory analysis.

The efficacy analyses of TTFST will be summarized and analyzed per guidelines in Section 10.1.

10.4.3 Time to the Second Subsequent Therapy

Time to the Second Subsequent Therapy (TTSST) will be defined as the number of days from the day the subject is randomized to the start of the second subsequent therapy or death of any cause. If the subject does not have an event of TTSST, the subject's data will be censored at the date the subject was last known to be alive and not have received a second subsequent therapy, i.e., the subject's last visit (including on therapy study visit, long-term follow-up without disease progression visit) or survival follow-up. If the subject is known to have an event of TTSST after the 'data cutoff date,' or the subject is known to be alive and without an event of TTSST after the cutoff, then the subject's data will be censored at the 'data cutoff date'. See Section 6.0 for more censoring details.

The tertiary efficacy analyses for TTSST are defined by comparing TTSST in Arm 3 versus Arm 1 and Arm 2 versus Arm 1, in the *BRCA*-deficient population, the HRD population, and the whole population. TTSST may also be compared between Arm 2 and Arm 3 as an exploratory analysis.

The efficacy analyses of TTSST will be summarized and analyzed per guidelines in Section 10.1.

10.4.4 Additional PRO Endpoints

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

10.5 Additional Efficacy Analyses

In addition to the stratified log-rank test for the primary and secondary efficacy endpoints, the following analyses may be performed for the comparison of PFS, and OS, between the two treatment groups, and within the three analysis populations.

- Un-stratified log-rank test and the Cox proportional hazards model for PFS, OS.
- Modified PFS endpoint to examine sensitivity to different censoring methods, described in detail below under Supplemental Analyses for PFS Endpoint.
- Modified efficacy endpoint OS to censor at the date of subject's initiation of other post anti-cancer therapies.
- Landmark analyses of PFS at end of Combination Phase (at 4.5 months), at 10 months (~6 months after the end of chemotherapy), and at 24 months.
- Landmark analyses of OS at 24, 30 and 36 months.
- Median Follow-Up Time on Study, calculated via reverse K-M method.
- PFS per central review based on central review of tumor assessments for all subjects, and analyzed following the same methodology as for the primary endpoint of PFS.
- Concordance of the investigator and central review evaluation of progression may also be summarized.

Supplemental Analyses for PFS Endpoint

In addition to the Primary PFS analysis, modified PFS analyses will be performed to examine the sensitivity to various censoring methods. A summary of these are in the following table.

Type of Censoring	Name for Analysis					
	Primary	Mod 1	Mod 2	Mod 3	Mod 4	Mod 5
First Post-Treatment Anti-Cancer Therapy	No	Censor	No	No	No	No
Death window implementation	Censor	Censor	Censor	No	Censor	No
Blind Break	No	No	Censor	No	No	No
Missing Scans prior to PD	Censor	Censor	Censor	Censor	No	No

No means do not censor for the event.

First Post-Treatment Anti-Cancer Therapy: PFS will be censored at the last evaluable tumor assessment prior to the date of subject's initiation of other anti-cancer therapies.

Blind Break: PFS will be censored at the last evaluable tumor assessment prior to the date of investigator blind break.

Tumor Marker CA-125

CA-125 values will be presented as cross-tabulations of baseline versus maximum on treatment value within each of the cycle windows as follow: Cycles 1 – 3 (not including value used as baseline), Cycles 4 – 6, Cycles 7 – 12, Cycles 13 – 18, Cycles 19 – 24, Cycles 25 – 30, Cycles 31 – 36. The first dose date of the cycle defines the start of the window, and 1 day prior to the start date of the next cycle window defines the end of the cycle window. Within each cycle window, the maximum CA-125 value will be categorized into 1 of 3 categories: \leq ULN, $>$ ULN & $<$ $2 \times$ ULN, or $\geq 2 \times$ ULN. Summaries will be presented within the *BRCA*-deficient, HRD, and whole populations.

10.6 Efficacy Subgroup Analyses

Subgroup analyses will be performed for the endpoints of PFS and OS within each efficacy analysis population (*BRCA*-deficient, HRD, and whole, as appropriate) to evaluate the impact of the baseline characteristics on treatment effect. Analyses performed in the whole population will be stratified by *BRCA*-deficient status. Analyses performed within *BRCA*-deficient and HRD populations will be unstratified.

The subgroups will be (but not limited) as follows:

- *BRCA*-deficient status [*BRCA1/2* mutation vs. *BRCA1/2* wildtype] (central testing)

- Type of *BRCA*-deficiency [germline *BRCA1/2* mutation vs. tissue *BRCA1/2* mutation and germline *BRCA1/2* wildtype vs. *BRCA1/2* wildtype].
- Type of *BRCA1/2* mutation [*BRCA1* vs. *BRCA2* vs. *BRCA1* and *BRCA2* vs. *BRCA* wildtype].
- HRD status [HRD vs. non-HRD]
- HRD and *BRCA*-deficient status [HRD and *BRCA1/2* mutation vs. *BRCA1/2* wildtype vs. non-HRD vs. HRD].
- Race [White, Black, Other]
- Region [North America vs. Japan vs. Rest of World].
- Stage of Disease [III vs. IV] (as randomized)
- Residual Disease and Choice of Regimen (as randomized)
- Residual Disease post Interval Surgery [No Disease (post interval surgery) vs. Any Disease (post interval surgery)]
 - Note: this only includes interval surgery subjects
- Residual Disease (Efficacy Stratification Factor) [No Residual Disease After Primary Surgery vs. Any Residual Disease After Primary Surgery or Interval Surgery].
- Age group [< 65 years vs. ≥ 65 years]
- Smoking history [current smoker vs. past smoker vs. never smoked]
- ECOG [0 vs. ≥ 1]

10.7 Multiplicity Adjustment

The multiplicity considerations of this study include three treatment arms, (two pairwise comparisons), three populations, and multiple endpoints.

Three treatment arms are annotated in [Table 4](#).

Table 4. 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: *BRCA*-deficient population, HRD population, and whole population.

The hypotheses of interest are listed below:

Table 5. 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)

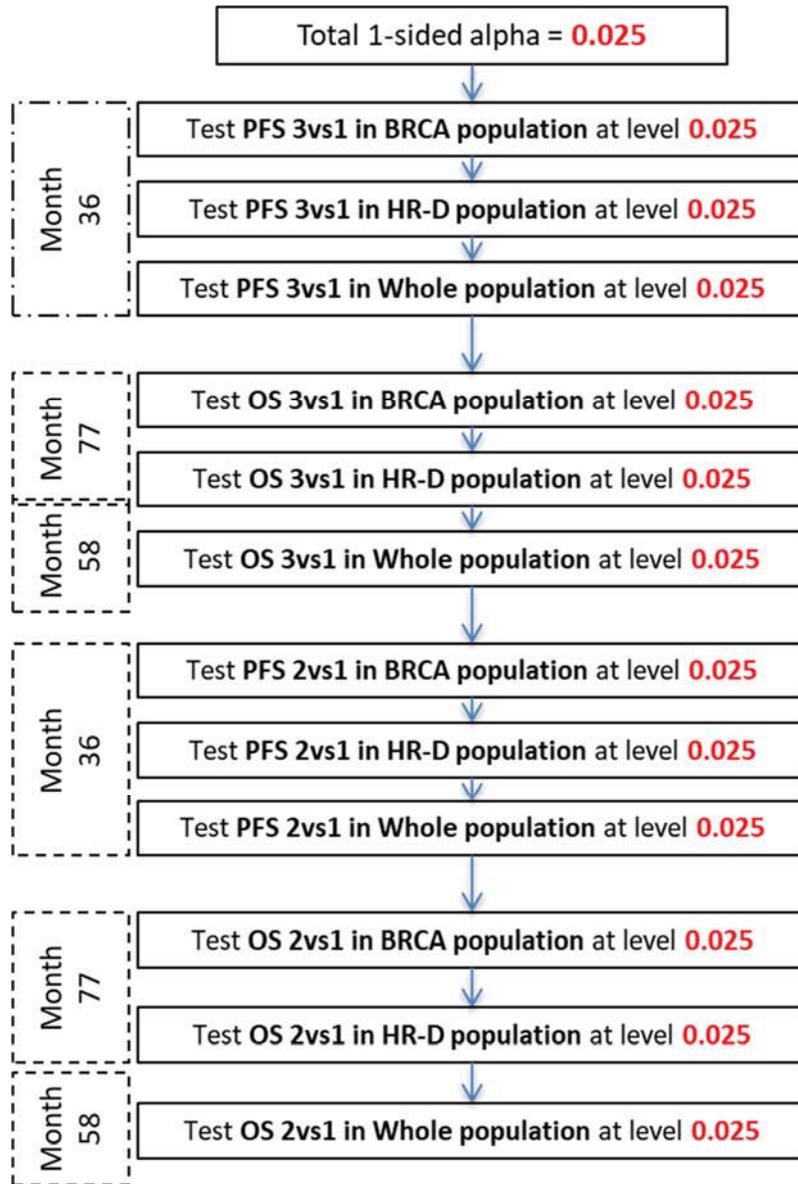
PFS = Progression Free Survival; OS = Overall Survival; DRS = Disease Related Symptom

Note: PFS (Arm 3 versus Arm 1) denotes the null hypothesis: Arm 3 (C/P + veliparib → veliparib) does not increase PFS compared to Arm 1 (C/P + placebo → placebo). Other PFS and OS notations in this table are defined similarly. DRS (Arm 3 versus Arm 1) denotes the null hypothesis of no difference in DRS scores between Arm 3 and Arm 1. DRS (Arm 2 versus Arm 1) is defined similarly. Note that no alpha will be spent on DRS analyses.

Criteria to Determine Testing Sequence

Since subject randomization was not prospectively stratified by HRD status, two testing scenarios were available and depended only on the balance of treatment arms within the HRD population. Since upon unblinding at the time of the primary analysis, the treatment ratio between Arm 3 and Arm 1 was not greater than the previously defined ratio of 2.53:1, the following Testing Sequence applies.

Figure 2. Testing Procedure



Testing Scenario:

- A fixed-sequence testing procedure will be used to control the Type I error rate at 0.05 from the primary efficacy endpoint sequentially through the secondary efficacy endpoints. Each of the comparisons in this sequence will be tested at a 1-sided 0.025 level. There will be no multiplicity adjustment on the DRS scores or the tertiary efficacy endpoints.

At Month 36 ($\alpha = 0.025$),

1. Test PFS (Arm 3 versus Arm 1) in *BRCA*-deficient population,
2. Test PFS (Arm 3 versus Arm 1) in HRD population,
3. Test PFS (Arm 3 versus Arm 1) in whole population
 - In parallel, $\alpha = 0.000001$ will be spent on interim OS analyses

At Month 48 per request of FDA, $\alpha = 0.000001$ will be spent on the second interim OS analyses for *BRCA*-deficient, HRD and whole populations.

At Month 58 when OS matures in the whole population, $\alpha = 0.000001$ will be spent on second interim OS analyses for *BRCA*-deficient and HRD populations.

At Month 77 ($\alpha = 0.025$, provided all preceding null hypotheses in the hierarchical testing sequence at Month 36 are rejected)

4. Test OS (Arm 3 versus Arm 1) in *BRCA*-deficient population,
5. Test OS (Arm 3 versus Arm 1) in HRD population,
6. Test OS (Arm 3 versus Arm 1) in whole population (based on data from Month 58)
7. Test PFS (Arm 2 versus Arm 1) in *BRCA*-deficient population (based on data from Month 36),
8. Test PFS (Arm 2 versus Arm 1) in HRD population (based on data from Month 36),

9. Test PFS (Arm 2 versus Arm 1) in whole population (based on data from Month 36)
10. Test OS (Arm 2 versus Arm 1) in *BRC*A-deficient population (based on data from Month 77),
11. Test OS (Arm 2 versus Arm 1) in HRD population (based on data from Month 77),
12. Test OS (Arm 2 versus Arm 1) in whole population (based on data from Month 58)

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will be performed on the AST population. All subjects who took at least one dose of veliparib/placebo will be included. Treatment groups in the safety summaries will be based on the actual treatment the subject receives.

Summaries involving docetaxel will only be performed on subjects who were dosed with docetaxel.

Where applicable, only *P* values ≤ 0.100 when rounded to three digits will be presented.

11.2 Analysis of Adverse Events

Analyses of adverse events will include only "treatment-emergent" events and are defined in Section 6.0. Treatment-emergent adverse events will be summarized by preferred terms within a System and Organ Class according to the MedDRA adverse event coding dictionary. Grading of treatment-emergent adverse events will be according to NCI CTCAE Version 4.0 terminology grade provided by the investigator.

11.2.1 Adverse Event Overview

An overview of treatment emergent adverse events will be presented for each treatment arm consisting of the number and percentage of subjects experiencing at least one event for the following adverse event categories:

- Any adverse event
- Any adverse event that is rated by the investigator as a reasonable possibility of being related to each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel*
- Any NCI terminology grade 3 or grade 4 adverse event
- Any NCI terminology grade 3, grade 4, or grade 5 adverse event**
- Any serious adverse event.
- Any adverse event leading to discontinuation of each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel.
- Any adverse event leading to discontinuation of each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel due to disease progression.
- Any adverse event leading to discontinuation of each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel not due to disease progression.
- Any adverse event leading to interruption or reduction of veliparib/placebo
- Any adverse event leading to dose interruption of veliparib/placebo
- Any adverse event leading to dose reduction of each of: veliparib/placebo, carboplatin, paclitaxel, and docetaxel
- Any adverse event leading to dose reduction or delay of each of: carboplatin, paclitaxel, and docetaxel
- Any adverse event leading to dose delay of each of: carboplatin, paclitaxel, and docetaxel
- Any adverse event of special interest (as listed in [Table 6](#))
- Any adverse event leading to death
- Any adverse event leading to death with a reasonable possibility of being related to veliparib by the investigator
- All deaths.

* Only summaries for veliparib/placebo will be presented in the SOC/PT tables.

** No summary will be presented in the SOC/PT tables.

11.2.2 Adverse Event by SOC and PT

In addition to the AE categories listed under Adverse Event Overview (unless noted otherwise), the numbers and percentages of subjects experiencing treatment-emergent adverse events will be summarized by treatment group for the following adverse event categories:

- Any adverse event with number broken down by maximum NCI terminology grade.
- Any adverse event that is rated by the investigator as a reasonable possibility of being related to veliparib/placebo with NCI terminology grade 3 or grade 4 adverse event
- Any adverse event leading to discontinuation of veliparib/placebo with a reasonable possibility of being related to veliparib (as rated by investigator)
- Any serious adverse event leading to discontinuation of veliparib/placebo with a reasonable possibility of being related to veliparib (as rated by investigator)
- Any serious adverse event with number broken down by maximum NCI terminology grade.
- Any NCI terminology grade 3 or grade 4 serious adverse event
- Any serious adverse event that is rated by the investigator as a reasonable possibility of being related to veliparib/placebo
- Any serious adverse event that is rated by the investigator as a reasonable possibility of being related to veliparib/placebo with NCI terminology grade 3 or grade 4 serious adverse event

For all adverse event summaries, the number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to SOC and PT for each treatment arm. Subjects reporting more than one AE for a given PT will only be counted once for that term. Subjects reporting more than one adverse event within an SOC will only be counted once for that SOC. Subjects reporting more than one AE will only be counted once in the overall total. The SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC.

11.2.3 Adverse Event by Frequency

The number and percentage of subjects experiencing treatment-emergent adverse events and treatment-emergent serious adverse events will be tabulated according to preferred term and sorted by overall frequency. For adverse events with a frequency greater than 10% in any treatment group, comparisons of the rates of subjects experiencing an adverse event will be done between Arm 3 versus Arm 1 and Arm 2 versus Arm 1 using Fisher's exact test. For testing the rates of AEs experienced in the maintenance phase, a 5% cutoff will be applied.

11.2.4 Adverse Events of Special Interest

Treatment-emergent adverse events and serious adverse events of special interest based on Standardized (SMQ-s) or Company (CMQ-s) MedDRA Queries, will be summarized. The search criteria for each event is located in [Table 6](#). The rates of these events will be summarized by MedDRA system organ class and preferred term. The same overview summary as for TEAE, and listing of subjects' data, will be provided for each AESI.

Table 6. Adverse Events of Special Interest

Adverse Event of Special Interest	Search Criteria	Event Definition/Medical Concept
Nausea and vomiting	Nausea and vomiting preferred terms MedDRA preferred terms (PT code 10028813, 10047700)	Treatment-emergent adverse events coded to either of those two MedDRA preferred terms
Seizures	Convulsions SMQ 20000079 (query for convulsions)	Treatment-emergent adverse events coded to MedDRA preferred terms on the broad search list.
Anemia	Haematopoietic erythropenia SMQ 20000029	Treatment-emergent adverse events coded to MedDRA preferred terms on the broad search list.
Thrombocytopenia	Haematopoietic thrombocytopenia SMQ 20000031	Treatment-emergent adverse events coded to MedDRA preferred terms on the broad search list.
Neutropenia	Hematological Toxicity-Neutropenia CMQ 80000154	Treatment-emergent adverse events coded to MedDRA preferred 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 preferred terms on the broad search list.
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 terms on the 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	Secondary Malignancies SMQs, 20000194 and 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.
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.

11.2.4.1 Time to Onset of AESI

Summary statistics (N, mean, standard deviation, median, minimum, and maximum) will be generated for the time from first dose to onset (in days) using the first AESI event for each subject.

11.2.4.2 Prevalence and Incidence Rates of AESI

Prevalence and incidence of AESI for each PT, each SOC, and overall will be provided for time periods in groups of 3 cycles, relative to the first dose of any study treatment: Cycles 1 - 3, 4 - 6, 7 - 9, 10 - 12, 13 - 15, 16 - 18, 19 - 21, 22 - 24, 25 - 27, 28 - 30, 31 - 33, and 34 - 36. The 30 day safety window will be applied and grouped into the last cycle for each subject. For each time period, the incidence for any given PT will be calculated as follows:

- The numerator for each time period will be the number of subjects who had the first occurrence of an adverse event in that time period and are included in the denominator.
- The denominator for each time period will be the number of subjects who took at least one dose of study treatment in the time period and did not experience an event within any previous period.
- Incidence for each time period = numerator/denominator.

The numerator and the corresponding incidence for each PT will be presented for each of the time periods.

For each time period, the prevalence for any given PT will be calculated as follows:

- The numerator for each time period will be the number of subjects who had an occurrence of an adverse event in that time period or in a previous time period and that was ongoing in the current time period and are included in the denominator.
- The denominator for each time period will be the number of subjects who took at least one dose of study treatment in the time period.

- Prevalence for each time period = numerator/denominator.

The numerator and the corresponding prevalence for the PT will be presented for each of the time periods.

11.2.5 Adverse Event Subgroup Assessments

The incidence of treatment emergent adverse events overview, TEAE by SOC and by PT of all treatment-emergent adverse events, grade 3 and 4 events, serious adverse events, leading to veliparib discontinuation, AEs leading to death, and AEs of special interest will be assessed for the subgroups defined below:

- Age categories [< 65 years, ≥ 65 years]
- Region [US, Japan, Rest of World]
- Combination Period (Cycles 1 through 6),
- Maintenance Period (Cycles 7 through 36),
- Q-weekly Dosing,
- Q3-weekly Dosing
- Subjects Dosed with Docetaxel.

Refer to Section 6.0 for more details on defining the latter 5 groups.

11.3 Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of the last dose of study drug, (2) for deaths occurring more than 30 days of the last dose of study drug and (3) for all deaths in this study regardless of the number of days relative to the last dose of study drug. There will be no statistical test for above analyses.

11.4 Analysis of Laboratory and Vital Signs Data

All of the below summaries will be summarized by for the entire AST population, as well as the following subgroups described in detail in Section 6.0: Combination Period

(Cycles 1 through 6), Maintenance Period (Cycles 7 through 36), Q-weekly Dosing, Q3-weekly Dosing, and Subjects Dosed with Docetaxel.

See Section 6.0 for additional information regarding laboratory data conventions.

Analyses of Laboratory Data Using NCI CTCAE

For hematology and chemistry variables for which NCI CTCAE Version 4 (v4.03) criteria exist, baseline and post-baseline hematology and chemistry variable observations will be categorized as grade 0 to grade 4.

The percentage of subjects experiencing a shift from baseline to the maximum value post-baseline, and from baseline to the final value, according to the categories below will be presented:

- Grade 0 or unknown at baseline, to Grade 1 to Grade 4 post-baseline, or worsened from an abnormal baseline value by at least one grade post-baseline
- Grade 0 or unknown to Grade 2 at baseline, to Grade 3 or Grade 4 post-baseline and from Grade 3 at baseline to Grade 4 post-baseline

Cross-tabulation of the frequency of categorized baseline grades versus maximum post-baseline grades and baseline grades versus final value will be presented. All treated subjects will be included in the cross tabulation regardless whether baseline or post-baseline measurements are collected.

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

Drug-Induced Liver Injury

Elevations relative to the upper limit of normal (ULN) in alanine transaminase (ALT), AST, total bilirubin, and alkaline phosphatase as outlined in the FDA Guidance for

Industry pertaining to premarketing clinical evaluations for drug-induced liver injury (DILI) will be summarized using the maximum post-baseline values:

- ALT: $> 3 \times -$, $> 5 \times -$, $> 10 \times -$, or $> 20 \times \text{ULN}$
- AST: $> 3 \times -$, $> 5 \times -$, $> 10 \times -$, or $> 20 \times \text{ULN}$
- Total bilirubin $> 2 \times \text{ULN}$
- Alkaline phosphatase $> 1.5 \times \text{ULN}$
- ALT or AST ($> 3 \times \text{ULN}$) accompanied by total bilirubin ($> 2 \times \text{ULN}$) at the same visit (potential Hy's Law criteria 3)

Plots will be generated for total bilirubin vs. ALT values and total bilirubin vs. AST values in the eDISH format. For each subject, the visit with the maximum total bilirubin value relative to the ULN, then the maximum ALT (or AST) value relative to the ULN will be used in the plot. A listing of lab data for subjects meeting potential Hy's law criteria will be provided.

Table 7. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ALT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN	Death
AST	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN	Death
Alkaline Phosphatase	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN	Death
Total Bilirubin	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN	Death
Hemoglobin (low)	< LLN – 100 g/L	< 100 – 80 g/L	< 80 g/L	--	Death
Hemoglobin (high)	CH > 0.0 – 20.0 g/L	CH > 20.0 – 40.0 g/L	CH > 40.0 g/L	--	Death
White blood cells	< LLN – 3.0 × 10 ⁹ /L	< 3.0 – 2.0 × 10 ⁹ /L	< 2.0 – 1.0 × 10 ⁹ /L	< 1.0 × 10 ⁹ /L	Death
Absolute Neutrophil Count	< LLN – 1.5 × 10 ⁹ /L	< 1.5 – 1.0 × 10 ⁹ /L	< 1.0 – 0.5 × 10 ⁹ /L	< 0.5 × 10 ⁹ /L	Death
Platelet count	< LLN – 75.0 × 10 ⁹ /L	< 75.0 – 50.0 × 10 ⁹ /L	< 50.0 – 25.0 × 10 ⁹ /L	< 25.0 × 10 ⁹ /L	Death
Glucose (high)	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L	> 27.8 mmol/L	Death
Glucose (low)	< LLN – 3.0 mmol/L	< 3.0 – 2.2 mmol/L	< 2.2 – 1.7 mmol/L	< 1.7 mmol/L	Death
Creatinine	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 6 × ULN	> 6 × ULN	Death
Uric acid	> ULN – 590 mcmmol/L	--	--	> 590 mcmmol/L	Death
Inorganic phosphate	< LLN – 0.8 mmol/L	< 0.8 – 0.6 mmol/L	< 0.6 – 0.3 mmol/L	< 0.3 mmol/L	Death
Calcium (low)	< LLN – 2.0 mmol/L	< 2.0 – 1.75 mmol/L	< 1.75 – 1.5 mmol/L	< 1.5 mmol/L	Death
Calcium (high)	> ULN – 2.9 mmol/L	> 2.9 – 3.1 mmol/L	> 3.1 – 3.4 mmol/L	> 3.4 mmol/L	Death
Albumin	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	--	Death
Lymphocyte	< LLN – 0.8 × 10 ⁹ /L	< 0.8 – 0.5 × 10 ⁹ /L	< 0.5 – 0.2 × 10 ⁹ /L	< 0.2 × 10 ⁹ /L	Death

Table 7. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values (Continued)

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Sodium (low)	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L	Death
Sodium (high)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L	> 160 mmol/L	Death
Potassium (low)	< LLN – 3.0 mmol/L	--	< 3.0 – 2.5 mmol/L	< 2.5 mmol/L	Death
Potassium (high)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L	> 7.0 mmol/L	Death
Magnesium (low)	< LLN – 0.5 mmol/L	< 0.5 – 0.4 mmol/L	< 0.4 – 0.3 mmol/L	< 0.3 mmol/L	Death
Magnesium (high)	> ULN – 1.23 mmol/L	--	> 1.23 – 3.30 mmol/L	> 3.30 mmol/L	Death
Bicarbonate	< LLN – 16 mmol/L	< 16 – 11 mmol/L	< 11 – 8 mmol/L	< 8 mmol/L	Death

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

Vital signs values will be assessed for potential clinical significance through the application of criteria developed at AbbVie as detailed in [Table 8](#) below.

Table 8. Potential Clinical Significance Criteria for Vital Signs

Systolic Blood Pressure	> 150 mmHg and > 20 mmHg higher than baseline < 70 mmHg and a decrease of \geq 30 mmHg from baseline
Diastolic Blood Pressure	> 100 mmHg and higher than baseline < 50 mmHg and a decrease of \geq 20 mmHg from baseline
Pulse Rate	> 120 bpm and an increase of \geq 30 bpm from baseline < 50 bpm and a decrease of \geq 30 bpm from baseline
Temperature	\geq 38.9°C \leq 35.6°C
Weight	> 10% decrease from baseline

The frequency and percentage of subjects with post-baseline values meeting Criteria for Potentially Clinically Significant Vital Signs values will be summarized. All subjects who have at least one post-baseline measurement will be included in the summary. If a subject does not have vital signs recorded at baseline, but has a post-baseline value which met the above criteria for blood pressure and pulse rate, this subject is considered as meeting the potentially clinically significant vital signs values for the measurement. A separate listing will be provided that presents all of the subjects and values that meet the criteria.

12.0 References

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
Published: May 28, 2009 (v4.03: June 14, 2010). Available from:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.