1.0 Title Page

Statistical Analysis Plan

Study M12-895

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

Date: 07 Apr 2019

Version 5.0

1.1 SAP Update: Summary of Changes

The purpose of this update is to:

- Remove statistical comparisons for demographic and baseline characteristics among treatment groups in Section 7.0 and Section 11.0.
- Refine summary of study drug exposure and remove statistical comparisons on study drug exposure among treatment groups and summary of compliance in Section 9.0.
- Remove cutoff date for OS analysis and include all deaths in the OS analysis in Section 10.0.
- Add efficacy analysis of duration of response in Section 10.0.
- Specify the number of days in censoring rules for modified PFS analysis in Section 10.0.
- Remove censoring 30 days post last dose for PFS and OS analyses in Section 10.0.
- Clarify definition of treatment-emergent AE and remove statistical comparisons of AE among treatment groups in Section 11.0.
- Clarify and simply AE listings and remove subgroup analyses of AE in Section 11.0.
- Clarify summary of number of deaths in Section 11.0.
- Present only descriptive statistics for the mean change and mean difference of change from baseline to scheduled visits and final observation for laboratory and vital sign data in Section 11.0.
- Remove statistical comparisons of shifts from baseline NCI CICTAE version 4.0 grades to maximum and final post-baseline grades in Section 11.0.
- Remove analyses of vital signs using criteria for potentially clinically significant vital sign values in Section 11.0.

2.0 Table of Contents

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3.0 Introduction

Veliparib is a potent PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutic agents. Veliparib increases sensitivity of tumor cells to DNA-damaging agents in vitro and in vivo and inhibits PARP in murine tumors in vivo and human peripheral blood mononuclear cells (PBMCs) and human tumors ex vivo.

This study is to evaluate the efficacy and tolerability of veliparib in combination with temozolomide (TMZ) or veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with BRCA1 or BRCA2 mutated locally recurrent (and not amenable to therapy with curative intent) or metastatic breast cancer, who have received no more than two prior lines of cytotoxic therapy for metastatic disease.

This statistical analysis plan will provide details to further elaborate statistical methods as outlined in the protocol Study M12-895 and will describe analysis conventions to guide the statistical programming work. The SAP will be signed off before the study database is locked.

Analysis will be performed using SAS Version 9.2 or upper (SAS Institute, Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

This study is to evaluate the efficacy and tolerability of veliparib in combination with temozolomide (TMZ) or veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel.

The primary objective of the study is to assess the progression-free survival (PFS) of oral veliparib in combination with temozolomide (TMZ) or in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with

BRCA1 or BRCA2 mutated locally recurrent (and not amenable to therapy with curative intent) or metastatic breast cancer.

The secondary objectives of the study are to assess overall survival (OS), clinical benefit rate (CBR) through the end of Week 18 and objective response rate (ORR) in those subjects treated with veliparib in combination with TMZ or treated with veliparib plus carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel. In addition, CIPN as assessed by the change from baseline in sensory scale at Week 18 from EORTC QLQ-CIPN20 will be assessed in those subjects treated with veliparib in combination with carboplatin and paclitaxel versus placebo in combination with carboplatin and paclitaxel.

The tertiary objectives are to assess Eastern Cooperative Oncology Group (ECOG) performance status, quality of life (QoL), CIPN assessed by the other EORTC QLQ-CIPN 20 scales and NCI-CTCAE 4.0 grading for peripheral neuropathy, and exploratory correlative endpoints.

4.2 Design Diagram

This is a Phase 2, randomized, partially blinded, multinational, multicenter study to evaluate the efficacy and tolerability of veliparib in combination with TMZ or veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in approximately 290 subjects with BRCA1 or BRCA2 germline mutation (as documented by the Sponsor core laboratory) and with locally recurrent or metastatic breast cancer who have received no more than two prior lines of cytotoxic therapy for metastatic disease. Approximately 120 research sites will participate.

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

Under the original protocol, 4 subjects were randomized in a 1:1:1 ratio (Group 1) to one of the three treatment arms (veliparib 40 mg BID + TMZ; veliparib 80 mg BID + carboplatin + paclitaxel; or placebo BID + carboplatin + paclitaxel).

Following protocol Amendment 1, approximately 290 subjects will be randomized in a 1:1:1 ratio (Group 2) to one of the three treatment arms (veliparib 40 mg BID + TMZ; veliparib 120 mg BID + carboplatin + paclitaxel; or placebo BID + carboplatin + paclitaxel) at all study centers.

The dose schedules for all three groups of the study are detailed below.

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

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

Note: A maximum of 24 cycles of veliparib + TMZ (additional cycles may be given, if both the investigator and the AbbVie Medical Monitor confirm that the subject would benefit from continued treatment).

Table 2. Treatment Schema for Subjects Randomized to Veliparib + Carboplatin + Paclitaxel or Placebo + Carboplatin + Paclitaxel Treatment Arm

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

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

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

Subjects randomized to veliparib/placebo + carboplatin + paclitaxel with controlled disease and with tolerable side effects may continue to receive treatment until reaching a protocol-defined event of disease progression or experiencing unmanageable toxicity. If both carboplatin and paclitaxel have been discontinued due to toxicity, veliparib will also be discontinued.

When an investigator has determined that a subject should discontinue the study, a Final Visit will be conducted. All subjects will have one Follow-Up Visit approximately 30 days after the last dose of veliparib + TMZ or veliparib/placebo + carboplatin + paclitaxel. This Follow-Up Visit does not need to be conducted if the Final Visit is ≥ 30 days after the last dose of veliparib + TMZ or Veliparib + carboplatin + paclitaxel or placebo + carboplatin + paclitaxel.

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

4.3 Sample Size

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

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

A total of approximately 290 subjects with BRCA mutation as documented by the Sponsor core laboratory will be enrolled into Group 2 of the study to accrue the required PFS events in a reasonable study duration.

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 36 subjects in Group 2 of the study have met at least one of the following criteria:

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

Subsequent reviews will be based on recommendations from the IDMC.

In addition, an interim futility analysis will be conducted and will be reviewed by the IDMC after the first 30 subjects with deleterious mutations (as determined by the sponsor core lab) with at least one measurable lesion at baseline are randomized to the veliparib + TMZ treatment group (across both Group 1 and Group 2) and complete the Week 27 tumor assessment or discontinue the study prior to the Week 27 tumor assessment.

The pre-specified futility criteria are as follows: If there are less than 5 responders (CR + PR) in the 30 subjects, then futility will be declared for the veliparib + TMZ treatment group. This futility criterion corresponds to Bayesian posterior probability of at least 90% that the true objective response is $\leq 25\%$.

If futility is declared at the time of the futility analysis, any remaining subjects on veliparib + TMZ will be given the option either to receive veliparib 120 mg BID + carboplatin + paclitaxel or discontinue therapy. These subjects will not be included in the efficacy analysis comparing veliparib 120 mg BID + carboplatin + paclitaxel treatment group to placebo + carboplatin + paclitaxel treatment group in order to avoid the crossover effects.

The planned unblinded safety interim was performed in August 2013. The IDMC recommended having another safety interim when approximately 80 subjects in Group 2 of study have met at least one of the above safety interim analysis criteria.

The interim futility analysis and the second safety interim analysis (as recommended by the IDMC) were conducted by the IDMC in July 2014. The IDMC recommended that TMZ treatment group could continue and there were no safety concerns. The detailed IDMC recommendation can be found in the study document file.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Two study populations will be analyzed as defined below.

Intent-To-Treat (ITT) population – consists of all subjects randomized by IVRS/IWRS. The data from the ITT population will be analyzed by the treatment group assignment given at the time of randomization, even if the subject does not receive the correct treatment, or does not follow the protocol until completion.

As Treated (AST) population – consists of all subjects randomized by IVRS/IWRS and took at least 1 dose of study drug (veliparib/placebo). The data from AST population will be analyzed by the actual treatment that subject received.

5.2 Variables Used for Stratification of Randomization

The randomization will be stratified by ER/PgR (ER and/or PgR positive versus ER and PgR negative), prior cytotoxic therapy use (yes versus no), and ECOG 0 – 1 versus 2.

Randomization schedules will be generated using a stratified permuted block with mixed block size of 3 and 6. The mixed block size of 2 and 4 will be used if the veliparib 40 mg BID + TMZ treatment group is terminated at the interim futility analysis.

6.0 Analysis Conventions

General Considerations

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05. The date of randomization is defined as the date that the IVRS/IWRS issues a randomization number.

All analyses (except for efficacy endpoints) will be summarized by each treatment group for Group 1 and Group 2 of the study separately.

The analyses of all efficacy endpoints will include only randomized subjects in Group 2 of the study who have been documented to have deleterious mutations by the sponsor core lab. Sensitivity analyses will be conducted using all randomized subjects' data in Group 2 of the study to evaluate the impact of any discrepancies between results from the local laboratory and from the Sponsor core laboratory.

All subjects who receive at least one dose of the study drug veliparib or placebo (AST population) will be included in the safety analysis.

Comparisons will be performed between veliparib 40 mg BID + TMZ and placebo BID + carboplatin + paclitaxel as well as between veliparib 120 mg BID + carboplatin + paclitaxel and placebo BID + carboplatin + paclitaxel in Group 2 of the study.

Definition of Study Drug

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

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 representing the worse outcome will be selected as the grade/value for that day for the shift analysis of lab parameters, EORTC QLQ-CIPN20 scores, QoL, and performance status (ECOG); the arithmetic average will

be calculated and used as the value for that day for mean changes in laboratory and vital signs parameters.

Definition of Baseline

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

Definition of Final Observation

For EORTC QLQ-CIPN20, EORTC QLQ-C15/BR23, ECOG, lab, and vital signs variables, the Final Observation is defined as the last non-missing observation collected after first dose study drug but up to 30 days of last dose of study drug (veliparib/placebo).

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

Definition of Cycle Rx Days in Each Cycle

Cycle Rx Days for each cycle are calculated for each time point relative to the first dose of treatment combination (veliparib/placebo + carboplatin/paclitaxel or veliparib + TMZ) in each cycle.

Definition of Analysis Windows

During the treatment period, all time points and corresponding time windows are based on Cycle Rx Days.

For visit-wise longitudinal analyses such as mean change in EORTC QLQ-CIPN20, QoL, ECOG, laboratory, and vital signs values, the time windows specified in Table 3, Table 4, and Table 5 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, Table 4, and Table 5.
- 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 Visit-Wise Analysis (QoL, ECOG, Lab, and Vital Signs) – Veliparib + TMZ Treatment Arm

Scheduled Visit	Nominal Cycle Rx Day	Time Window (Cycle Rx Day Range)
Cycle 1 Day 1	Baseline	As Baseline definition
Cycle 1 Day 15	15	(> 1, 18)
Cycle 1 Day 22	22	(19, 25)
Cycle 2 Day 1	1	(–3, 4)
Cycle 2 Day 15	15	(12, 18)
Cycle 2 Day 22	22	(19, 25)
Cycle X Day 1	1	(–3, 4)

Note: Hematology, ECOG and Vital Signs will be assessed on C1D1, C1D15, C1D22, C2D1, C2D15, C2D22, on Day 1 of each subsequent cycle and the Final Visit. Chemistry will be assessed on C1D1, C1D15, C2D1, C2D15, on Day 1 of each subsequent cycle and the Final Visit. Urinalysis sample will be collected on Day 1 of each cycle, and the Final Visit. QoL will be assessed at C1D1 and C2D1, on Day 1 of every other cycle starting with Cycle 4, and the Final Visit.

Table 4. Time Windows for Visit-Wise Analysis for Vital Signs – Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arm

Scheduled Visit	Nominal Cycle Rx Day	Time Window (Cycle Rx Day Range)
Cycle 1 Day 1	Baseline	As Baseline definition
Cycle 1 Day 3	3	(2, 6)
Cycle 1 Day 17	17	(14, 18)
Cycle X Day 1	1	(–3, 1)
Cycle X Day 3	3	(2, 6)

Note: Vital Signs will be assessed on C1D1, C1D3, C1D17, on Day 1 and Day 3 of each subsequent cycle and at the Final Visit.

Table 5. Time Windows for Visit-Wise Analysis (EORTC QLQ-CIPN20, QoL, ECOG, and Lab) – Veliparib/Placebo + Carboplatin + Paclitaxel Treatment Arm

Scheduled Visit	Nominal Cycle Rx Day	Time Window (Cycle Rx Day Range)
Cycle 1 Day 1	Baseline	As Baseline definition
Cycle 1 Day 17	17	(14, 18)
Cycle X Day 1	1	(–3, 4)

Note: Hematology, chemistry and ECOG will be assessed on C1D1, C1D17, on Day 1 of each subsequent cycle and the Final Visit. Urinalysis sample will be collected on Day 1 of each cycle, and the Final Visit. EORTC QLQ-CIPN20 and QoL will be assessed at C1D1, on Day 1 of every other cycle starting with Cycle 2, and the Final Visit.

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

ITT population will be used in the demographic, baseline characteristics, medical history, and previous/concomitant medication and prior oncology therapies.

There will be no statistical comparison for the demographic and baseline characteristics between the treatment groups.

7.1 Demographic and Baseline Characteristics

Continuous demographic data (e.g., age, height, and weight) will be summarized with mean, standard deviation, and range. Frequencies and percentages will be computed for the following parameters (but not limited to): gender, race, BRCA1 status, BRCA2 status, ER/PgR status, HER2 status, triple negative breast cancer, disease status (measurable versus non-measurable disease), number and sites of metastases including visceral (lung or liver), prior oncology therapy regimens including cytotoxic therapy use, hormonal therapy use, and other agents, and ECOG performance status.

In addition, demographic and baseline characteristics will also be summarized by stratification variables (ER/PgR, prior cytotoxic therapy use, and ECOG) under which subjects are randomized in IVRS/IWRS and by stratification variables entered on the electronic Case Report Forms (eCRF).

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. There will be no statistical comparison for the medical history between treatment groups.

7.3 Prior/Concomitant Medications and Prior Oncology Therapies

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.

The frequency and percentage of subjects who have 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.

There will be no statistical comparison for the prior and concomitant medications and prior oncology therapies between treatment groups.

8.0 Patient Disposition

All ITT subjects will be included in the analyses. The treatment groups assigned by IVRS/IWRS will be used in the summaries of patient disposition and there will be no statistical comparison for the patient disposition between treatment groups. The screen failure reasons will be summarized for the screen failure subjects.

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

In addition, the study drug discontinuation reasons and study discontinuation will be summarized by treatment group.

9.0 Study Drug Exposure and Compliance

9.1 Study Drug Exposure

Analyses for the study drug exposure will be performed on the AST population. Subjects who were randomized but did not receive study drug (veliparib or placebo) will not be included in the analyses.

Duration of exposure is defined as total number of days a subject received study drugs. Average dose days per cycle is defined as total number of days a subject received study drugs dividing by the total number of cycles a subject actually received. Duration of exposure is summarized for study drugs, TMZ, carboplatin, and paclitaxel separately. Average dose days per cycle will be summarized for study drugs and TMZ.

Descriptive statistics (mean, standard deviation, median, and range) will be presented for the duration of exposure, average dose days per cycle for study drugs (veliparib or placebo) as well as TMZ, and the number of cycles for study drugs (veliparib or placebo) as well as TMZ, carboplatin, and paclitaxel.

In addition, the frequencies and percentages of subjects having dose reduction, interruption will be summarized for each treatment group.

If a subject has any dose reduction from the previous dose of study drugs, TMZ, carboplatin, and paclitaxel, this subject will be considered as having dose reduction of study drug, TMZ, carboplatin and paclitaxel, respectively. Carboplatin dose reduction will be based on AUC dose. The body surface area dose (mg/m^2) will be used to determine dose reduction of TMZ or paclitaxel. If a subject receives only one dose in the study, this subject will not be included in the summary of dose reduction.

If a subject skips 2 or more consecutive days of dosing within a cycle, or number of days on study drug is less than 7 days in a cycle, or number of days on TMZ is less than 5 days in a cycle, this subject will be considered as having a dose interruption of study drug or TMZ. If a subject receives only one dose in the study, this subject will not be included in the summary of dose interruption. The summary of dose interruption will be summarized for study drugs (veliparib or placebo) as well as TMZ.

There will be no statistical comparison for summary of exposure.

10.0 Efficacy Analysis

10.1 General Considerations

Unless otherwise specified, all ITT subjects with deleterious mutations documented by the sponsor core lab for Group 2 of the study will be included in the efficacy analysis.

Comparisons will be performed between veliparib 40 mg BID + TMZ and placebo BID + carboplatin + paclitaxel as well as between veliparib 120 mg BID + carboplatin + paclitaxel and placebo BID + carboplatin + paclitaxel for Group 2 of study.

The required number of PFS events for the study was expected to occur in February 2016. To operationalize the data retrieval and data cleaning efforts, the 'PFS Cutoff' date for the analysis of primary PFS endpoint is set as 04 March 2016.

The 'PFS Cutoff' date will be used for the analysis of all imaging related efficacy endpoints (PFS, CBR, ORR, and Duration of Response) and overall survival.

For PFS, ORR, Duration of Response and CBR analyses, if the subject has prematurely blind broken before 'PFS Cutoff' date, disease progression assessment data after prematurely blind broken will not be included.

10.2 Primary Efficacy Analysis

The primary efficacy analysis will be a comparison of progression-free survival (PFS) between veliparib + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel. Comparisons between treatments groups will be performed using a Hochberg testing procedure for multiplicity adjustment (see Section 10.6 for details).

For a given subject, time to PFS will be defined as the number of days from the date the subject was randomized to the date the subject experiences an event of disease progression (as determined by the central imaging center), or to the date of death (all causes of mortality), if disease progression is not reached. All events of disease progression (as determined by the central imaging center) occurring on or before the 'PFS 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 an event of disease progression (by central imaging center), provided the death occurred within 9 weeks (63 days) of the last evaluable disease progression assessment (by central imaging center). If the subject does not have an event of disease progression (by central imaging center) and the subject has not died as defined above on or before the 'PFS Cutoff' date, the subject's data will be

censored at the date of the subject's last evaluable disease progression assessment (by central imaging center) on or before the 'PFS Cutoff' date.

If the randomized subject did not have any post-baseline disease progression assessment, the subject's data will be censored on the date of randomization. If the subject has prematurely blind broken before 'PFS Cutoff' date, disease progression assessment data after prematurely blind broken will not be included.

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

10.3 Secondary Efficacy Analyses

Secondary efficacy analyses comparing the effects of veliparib + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel on the following set of endpoints will be performed: overall survival (OS), clinical benefit rate through the end of Week 18 (CBR), objective response rate (ORR), and Chemotherapy-Induced Peripheral Neuropathy (CIPN).

If only one veliparib treatment group is statistically significantly better than the placebo group for the primary endpoint of PFS, then statistical significance will not be declared for any secondary endpoints, regardless of the observed *P* values. *P* values for secondary efficacy analyses will be subject to multiple comparison adjustments using the fixed sequence testing method, with analyses performed in the following order: OS, ORR, CBR, and CIPN. For each secondary endpoint, Hochberg testing procedure will be used to preserve the family-wise error rate for multiple comparisons.

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 will be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject discontinued study drug. If a subject has not died, the data will be censored at the date last known to be alive.

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

All deaths collected in the extracted clinical database will be included in the final OS analysis.

10.3.2 Clinical Benefit Rate

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

For a given subject, time to progression-free will be defined as the number of days from the date the subject was randomized to the date the subject experiences a confirmed event of disease progression (as determined by the central imaging center). All confirmed

events of disease progression occurring on or before the 'PFS 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. If the subject does not have an event of disease progression on or before the 'PFS Cutoff' date, the subject's data will be censored at the date of the subject's last evaluable disease progression assessment (by central imaging center) on or before the 'PFS Cutoff' date. If the randomized subject did not have any post-baseline disease progression assessment, the subject's data will be censored on the date of randomization.

If the subject has prematurely blind broken before 'PFS Cutoff' date, disease progression assessment data after prematurely blind broken will not be included.

10.3.3 Objective Response Rate

Objective response rate is calculated as the proportion of subjects who have confirmed PR or CR based on assessment by the central imaging center per RECIST (version 1.1). All ITT subjects with deleterious mutations documented by the sponsor core lab who had at least one measurable lesion at baseline will be included in the analysis. If the subject has prematurely blind broken before 'PFS Cutoff' date, disease progression assessment data after prematurely blind broken will not be included.

The proportion of subjects with a confirmed complete or partial objective response based on RECIST (version 1.1) will be estimated for each treatment group and compared between the treatment groups (veliparib + TMZ and placebo + carboplatin + paclitaxel as well as veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel) using CMH test stratified by ER/PgR (ER and/or PgR positive versus ER and PgR negative) and prior cytotoxic therapy use (yes versus no). In addition, 95% confidence interval will be constructed for ORR.

10.3.4 Duration of Overall Response (DoR)

DoR for a given subject will be defined as the number of days from the day the criteria are met for confirmed CR or PR (whichever is recorded first) based on assessment by the

central imaging center per RECIST (version 1.1) to the date that PD or death, whichever is early. If a subject is still responding on or before the "PFS Cutoff" date then the subject's data will be censored at date of the last available disease progression assessment on or before the "PFS Cutoff." All events of death occurring on or before "PFS Cutoff" date will be included for subjects who had not experienced disease progression provided the death occurred within provided the death occurred within 9 weeks (63 days) of the last evaluable disease progression assessment. If the subject does not have an event of disease progression (by central imaging center) and the subject has not died as defined above on or before the 'PFS Cutoff' date, the subject's data will be censored at the date of the subject's last evaluable disease progression assessment on or before the 'PFS Cutoff' date.

The distribution of DoR as well as the median DoR with corresponding 95% CI will be estimated for each group using the Kaplan-Meier methodolody.

10.3.5 Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Chemotherapy-Induced Peripheral Neuropathy (CIPN) as assessed by the change from baseline in sensory scale at Week 18 in EORTC QLQ-CIPN20 will be assessed in those subjects treated with veliparib in combination with carboplatin and paclitaxel versus placebo in combination with carboplatin and paclitaxel. The definition of sensory scale is described in Section 10.6.

Change from baseline in sensory scale at Week 18 will be summarized and compared between two treatment groups, using an analysis of covariance (ANCOVA) model with treatment group as the factor and the corresponding baseline value as a covariate.

10.4 Tertiary Efficacy Analyses

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses will be performed comparing the effects of veliparib + TMZ and placebo + carboplatin + paclitaxel as well as veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel on chemotherapy-induced peripheral neuropathy assessed by NCI CTC AE 4.0

Grading, QoL, and performance status. For analyses of QoL and performance status, the data will be analyzed at visits with at least 5 subjects overall for each treatment group.

10.4.1 Analysis of Chemotherapy-Induced Peripheral Neuropathy by NCI CTCAE 4.0 Grading

Chemotherapy-Induced Peripheral Neuropathy (CIPN) as assessed by AE 4.0 grading for peripheral neuropathy will be analyzed in those subjects treated with veliparib/placebo in combination with carboplatin + paclitaxel.

The frequencies and percentages of subjects experiencing a treatment emergent grade 3 or 4 peripheral neuropathy (SMQ 20000034 broad) will be summarized. Comparisons of the percentages of subjects experiencing grade 3 or 4 peripheral neuropathy between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel will be performed using Fisher's exact test.

10.4.2 Quality of Life

All subjects who do not have baseline measurement or any post-baseline measurements on ITT population will not be included in QoL analyses. Post-baseline measurements will be obtained according to the visit window as in Table 3 and Table 5. Post-baseline measurements more than 30 days after the last study visit will not be included.

EORTC-QLQ-CIPN20 Questionnaire

At the scheduled post-baseline visits, the EORTC QLQ-CIPN20, a 20-item questionnaire module developed to evaluate various aspects of CIPN, will be obtained according to the visit window as Table 5. This questionnaire provides 3 different scores for 3 domain scales – sensory scale (Item 31 – 36, 39, 40, and 48), motor scale (Item 37 – 38, 41 – 45, and 49), and autonomous scale (Item 46 – 47, 50). The individual items and the multi-item scale should be scored such that the higher scores represent more symptoms/problems (i.e., higher score = worse).

	Scale	Number of Items	Item Range	Item Numbers (According CRF)
Sensory Scale	SS	9	3	31 – 36, 39, 40, 48
Motor Scale	MS	8	3	37, 38, 41 – 45, 49
Autonomic Scale	AS	3	3	46, 47, 50
Overall Scale	Overall	20	3	31 – 50

Scoring algorithms for scales are as follows:

If items I1, I2,…, In are included in a scale, the procedure are as follows:

Raw Score (RS) = (I1+I2+…+In)/(number of non-missing items)

Score = (RS-1)/range*100, where range is 3.

For each of the 4 scales, note that, if a subject completed more than 50% of the items in a scale, then the raw score of that subject will contribute to the summary statistics of that scale. If a subject completed less than 50% of the items in a scale, then the raw score of that subject will be dropped from the calculation of the summary statistics of that scale.

Descriptive statistics will be presented for baseline, each scheduled post-baseline visit and the Final Observation. Changes from baseline to each visit in each of the 3 scores will be summarized and compared between two treatment groups, using an analysis of covariance (ANCOVA) model with treatment group as the factor and the corresponding baseline value as a covariate.

Addition exploratory analyses may be performed, such as 1) including treatment duration as a covariate in the ANCOVA model to adjust for the confounding factor of treatment duration; 2) performing a repeated measures mixed model to evaluate the overall mean change from baseline in EORTC QLQ-CIPN20.

EORTC QLQ-C15-PAL

The overall and domain specific scores will be calculated from the 15 items in EORTC QLQ-C15-PAL for each subject based on the QLQ-C15-PAL instruction. The items and scales of the QLQ-C15-PAL are as follows.

	Scale	Number of Items	Item Range	Item Numbers
Global Health Status/Quality of Life				
Global Health Status/Quality of Life	QL	1	6	15
Functional Scales				
Physical Functioning	PF2	3	3	1 – 3
Emotional Functioning	EF	2	3	13, 14
Symptom Scales				
Fatigue	FA	2	3	7, 11
Nausea and Vomiting	NV	1	3	9
Pain	PA	2	3	5, 12
Dyspnoea	DY	1	3	4
Insomnia	SL	1	3	6
Appetite Loss	AP	1	3	8
Constipation	CO	1	3	10

Scoring algorithms for the scales are as follows:

For QL, PA, DY, SL, AP, and CO:

If items I1, I2,…,In are included in a scale, the procedure are as follows: Raw Score (RS) = (I1 + I2+…+In)/n, Score = (RS-1)/range*100, where range is provided by the table above.

For PF2, EF, FA, and NV:

Physical Functioning		Emotional Functioning			Fatigue			Nausea and Vomiting	
Sum of Items 1 – 3[a]	PF2 Score	Item 13	Item 14	EF Score	Item 7	Item 11	FA Score	Item 9	NV Score
3	0.0	'Not at all'	'Not at all'	100.0	'Not at all'	'Not at all'	0.0	'Not at all'	0.0
4	6.7	'Not at all'	'A little'	83.3	'Not at all'	'A little'	22.2	'A little'	16.7
5	13.3	'Not at all'	'Quite a bit'	66.7	'Not at all'	'Quite a bit'	33.3	'Quite a bit'	50.0
6	20.0	'Not at all'	'Very much'	50.0	'Not at all'	'Very much'	55.6	'Very much'	100.0
7	26.7	'A little'	'Not at all'	83.3	'A little'	'Not at all'	22.2		
8	33.3	'A little'	'A little'	66.7	'A little'	'A little'	33.3		
9	46.7	'A little'	'Quite a bit'	50.0	'A little'	'Quite a bit'	55.6		
10	60.0	'A little'	'Very much'	41.7	'A little'	'Very much'	66.7		
11	73.3	'Quite a bit'	'Not at all'	66.7	'Quite a bit'	'Not at all'	33.3		
12	93.3	'Quite a bit'	'A little'	50.0	'Quite a bit'	'A little'	44.4		
		'Quite a bit'	'Quite a bit'	41.7	'Quite a bit'	'Quite a bit'	66.7		
		'Quite a bit'	'Very much'	16.7	'Quite a bit'	'Very much'	88.9		
		'Very much'	'Not at all'	50.0	'Very much'	'Not at all'	44.4		
		'Very much'	'A little'	41.7	'Very much'	'A little'	66.7		
		'Very much'	'Quite a bit'	16.7	'Very much'	'Quite a bit'	88.9		
		'Very much'	'Very much'	0.0	'Very much'	'Very much'	100.0		

a. Items 1 – 3 are scored: 0 = 'Very much,' 1 = 'Quite a bit,' 2 = 'A little,' 3 = 'Not at all.'

If a subject completed more than 50% of the items in a scale, then the raw score of that subject will contribute to the summary statistics of that scale. If a subject completed less than 50% of the items in a scale, then the raw score of that subject will be dropped from the calculation of the summary statistics of that scale.

Descriptive statistics will be presented for the baseline, each scheduled post-baseline visit, and the Final Observation of both overall and domain specific scores by each treatment group. Mean change (95% CI) from baseline to each scheduled post-baseline visit and the Final Observation within each treatment group and the mean difference of change (95% CI) from baseline to each scheduled post-baseline visit and the Final Observation between 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 instruction. The items and scales of the QLQ-BR23 are as follows.

	Scale Name	Number of Items	Item Range	Item Numbers in Study M12-895 CRF
Function scales				
Body Image	BRBI	4	3	39 – 42
Sexual* Function	BRSEF	2	3	44, 45
Sexual* Enjoyment	BRSEE	1	3	46
Future Perspective	BRFU	1	3	43
Symptom Scales/Items				
Systemic Therapy Side Effects	BRST	7	3	31 – 34, 36, 37, 38
Breast Symptoms	BRBS	4	3	50 – 53
Arm Symptoms	BRAS	3	3	47, 48, 49
Upset by Hair Loss	BRHL	1	3	35

Items for scales marked as* are scored positively (i.e., "very much" is best) and therefor use the same algebraic equation as for symptom scales.

BRSEE, sexual enjoyment, is not applicable if item 45 is 'not all all.'

BRHL, upset by hair loos, is not applicable if item 34 is 'not all all.' The 'not applicable' item is considered as missing item.

For all scales, the Raw Score, RS, is the mean of component items:

Raw Score (RS) = (I1 + I2 +…+ In)/n

For Function Scales (BRBI, BRFU):

Score = (1-(RS-1)/range) × 100

For all Symptom Scales and Function Scales (BRSEF, BRSEE):

Score = (RS-1)/range) × 100

A high score for a function scale represents a high/health level of functioning. A high score for a symptom scale/item represents a high level of symptomatology/problems.

If a subject completed more than 50% of the items in a scale, then the raw score of that subject will contribute to the summary statistics of that scale. If a subject completed less than 50% of the items in a scale, then the raw score of that subject will be dropped from the calculation of the summary statistics of that scale.

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

treatment group as the factor and baseline value as a covariate. Male subjects may be excluded from the analyses for some questionnaires specifically for women.

10.4.3 Performance Status

All subjects who do not have baseline measurement or any post-baseline measurements on ITT population will not be included in ECOG analyses. ECOG at the scheduled post-baseline visits will be obtained according to the visit window. Post-baseline measurements more than 30 days after the last study visit will not be included.

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

10.5 Additional Efficacy Analyses

The primary and secondary efficacy endpoints may also be analyzed using all ITT subjects' data, regardless whether or not the subject has deleterious mutation confirmed by the Sponsor core lab.

In addition to the stratified log-rank test for the primary and secondary efficacy endpoints, the unstratified log-rank test, Wilcoxon test, and the Cox proportional hazards model may be used for the comparison of PFS and overall survival between veliparib + TMZ and placebo + carboplatin + paclitaxel as well as between veliparib + carboplatin + paclitaxel and placebo + carboplatin + paclitaxel.

PFS, ORR, and CBR at Week 18 based on radiological and clinical assessment by Investigator will also be analyzed using the same statistical methodology as that for the corresponding primary and secondary efficacy endpoints.

For those subjects who take other anti-cancer therapies after discontinuation of the study drug, the PFS will be censored at the date of subject's initiation of other anti-cancer therapies. In addition, the following modified PFS endpoints may be performed, such as 1) including all PFS events regardless of early blind break; 2) PFS events will be censored at last tumor assessments prior to the PFS events if the PFS events occurred immediately after more than one missed tumor assessments (e.g., the disease progression event occurred more than 140 days (126 days + 14 days)). The modified primary and secondary efficacy endpoints will be analyzed using the same methodology as detailed in previous sections.

For PFS and OS, additional analyses may also be performed, such as 1) using a Cox proportional hazard model to explore the effect of baseline factors including (but not limited to) the following: ER/PgR status, prior cytotoxic therapy use and line of therapy, ECOG performance status, and stage of the disease; 2) subgroup analysis by ER/PgR status, by prior cytotoxic therapy use and line of therapy, by ECOG performance status, by stage of the disease, by region, by subsequent therapy type (including other PARP inhibitor use); and 3) using interval censoring methods to analyze PFS.

In addition, time to the first subsequent therapy (TTFST) and time to the second subsequent therapy (TTSST) defined in below may be analyzed. The same methodology as used in the analysis of PFS will be used in the analysis of TTFST and TTSST.

Time to the first subsequent therapy (TTFST) is defined as the number of days from when the subject is randomized to the start of the first subsequent therapy or death of any cause whichever occurs first. If the subject does not have an event of TTFST, the subject's data will be censored at the date of subject's last known alive date.

Time to the second subsequent therapy (TTSST) is defined as the number of days from when the subject is randomized to the start of the second subsequent therapy or death of any cause whichever occurs first. If the subject does not have an event of TTSST, the subject's data will be censored at the date of subject's last known alive date.

In addition, grade 3 or 4 peripheral neuropathy leading to study drug dose reduction/interruption may be performed. Time to the first G3/G4 peripheral neuropathy and time to grade 3 or 4 peripheral neuropathy leading to study drug dose reduction/interruption may be performed if the event rate is high enough to allow such an analysis. Number and percent of subjects with CNS progression may be summarized.

10.6 Handling of Multiplicity

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

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 "PFS Final Analysis" database, and the second one based on the "OS Final Analysis" database. Statistical significance for OS will be declared if a significant result is obtained for either analysis, consistent with group-sequential testing methods. The Lan DeMets alpha spending function with an O'Brien-Fleming boundary will be used to ensure that the two-sided false positive rate will be 0.05 or less for overall survival.

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will be performed on AST population. Subjects who were randomized but did not receive study drug (veliparib or placebo) will not be included in the analyses of safety.

Safety summaries will be presented by treatment group (veliparib 40 mg BID + TMZ, veliparib BID + carboplatin + paclitaxel or placebo BID + carboplatin + paclitaxel).

In addition, the safety data from the veliparib 40 mg BID + TMZ group in both Group 1 and Group 2 of the study may be combined.

Statistical comparisons will only be made for Group 2 of the study. There will be no statistical comparison for the demographic and baseline characteristics between the treatment groups.

11.2 Analysis of Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug (veliparib or placebo) and within 30 days after the last dose of study drug.

11.2.1 Analysis of Treatment-Emergent Adverse Events

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 percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE version 4.0 toxicity grade, and relationship to study drug will be provided. There will be no statistical comparison for above analyses.

The frequencies and percentages of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event categories (but not limited to):

- Any treatment-emergent adverse event
- Any treatment-emergent adverse event that is rated at least possibly related to study drug/TMZ/Carboplatin/paclitaxel by the investigator (Probably Related or Possibly Related)
- Any treatment-emergent NCI toxicity grade ≥ 3
- Any treatment-emergent NCI toxicity grade ≥ 3 and with probably related or possibility related to study drug/TMZ/Carboplatin/paclitaxel
- Any treatment-emergent NCI toxicity grades 3 or 4
- Any treatment-emergent NCI toxicity grade 3 or 4 and with probably related or possibility related to study drug/TMZ/Carboplatin/paclitaxel
- Any treatment-emergent serious adverse event
- Any treatment-emergent serious adverse events with and with probably related or possibility related to study drug/TMZ/Carboplatin/paclitaxel
- Any treatment-emergent adverse event leading to discontinuation of study either due to disease progression or not due to disease progression
- Any treatment-emergent adverse event leading to discontinuation of study drug/TMZ/Carboplatin/paclitaxel either due to disease progression or not due to disease progression
- Any treatment-emergent adverse event leading to study drug/TMZ/Carboplatin/paclitaxel interruption or dose reduction
- Any treatment-emergent adverse event leading to death
- Any treatment-emergent adverse event leading to death rated at least possibly related to study drug by the investigator (Probably Related or Possibly Related)

In addition, the treatment-emergent adverse events and serious adverse events of special interest based on SMQ (broad) or CMQ (broad) may be summarized. There will be no statistical comparison for above analyses.

11.3 Death

The number of subject deaths will be summarized 1) for deaths occurring within 30 days after the last dose of study drug 2) for deaths occurring more than 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 Longitudinal Analysis of Laboratory and Vital Signs Data

Changes from baseline are analyzed for each scheduled post-baseline visit and the Final Observation for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters including diastolic/systolic blood pressure, heart rate, and body temperature. If more than one measurement exists for a subject on a particular day, an arithmetic average will be calculated. The average will be considered to be that subject's measurement of that day. Post-baseline measurement more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline visit or do not have any post-baseline visits will not be included. The data will be analyzed at visits with at least 5 subjects overall for each treatment group.

Descriptive statistics will be presented for baseline, each scheduled post-baseline, and the Final Observation by each treatment group. Mean change from baseline to each scheduled post-baseline visit and the Final Observation within each treatment group and the mean difference of change from baseline to each scheduled post baseline visit and the Final Observation between treatment groups will be obtained by the descriptive statistics.

11.5 Analysis of Laboratory Data Using NCI CTCAE Criteria

Blood chemistry and hematology determinations will be categorized according to NCI CTCAE version 4.0 grades, and shifts from baseline NCI CTCAE version 4.0 grades to maximum and final post-baseline grades will be assessed. The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the grade of the last post-baseline measurement collected

no more than 30 days after the last dose of study drug. If multiple values are available for a post-baseline measurement, then the value with the highest NCI CTCAE grade will be used in the assessment of shift.

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