Statistical Analysis Plan

213356

A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

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MODELING AND SIMULATION ANALYSIS PLAN

Population PK, Exposure-Response, and PK/PD Modeling of Niraparib

Certara Reference Number	TES-PKER-NIRAPARIB-648, TES-PKER-NIRAPARIB-649
Investigational Product	Niraparib
PK Analyte	Plasma niraparib
PD Analytes/Endpoints	Efficacy: Progression-free survival Safety: thrombocytopenia, anemia, neutropenia, nausea, insomnia, anxiety PD: Platelet count
Sponsor	TESARO
Version	Final Version 1.0 9 July 2018

MODELING AND SIMULATION ANALYSIS PLAN APPROVAL

Sponsor: TESARO

Analysis Title: Population Pharmacokinetic, Exposure-Response, and Pharmacokinetic/Pharmacodynamic Analysis of Niraparib

Investigational Product: Niraparib

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AIC	Akaike information criterion
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	two times daily
BSV	between-subject variability
C_{avg}	average concentration up to time of disease progression
CI	confidence interval(s)
C_{max}	maximum concentration
C_{min}	minimum concentration
CR	complete response
CWRES	conditional weighted residual
DLT	dose-limiting toxicity
DV	observed values
ECOG	Eastern Cooperative Oncology Group
ER	estrogen receptor
ER+	estrogen receptor-positive
FE	food effect
FOCE INTER	first order conditional estimation method of NONMEM with interaction

Abbreviation	Definition
gBRCA	germline breast cancer gene
HER2	human epidermal growth factor receptor 2
HRDpos	homologous recombination deficient-positive
IPRED	individual predicted concentration
MTD	maximum tolerated dose
MTT	mean transit time
NONMEM	nonlinear mixed-effects modeling software
PARP	poly adenosine diphosphate-ribose polymerase
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRED	population predicted values concentrations
PTEN	phosphatase and tensin homolog
QC	quality control
QD	once daily
RP2D	recommended Phase 2 dose
SAS	Statistical Analysis System
US	United States
VPC	visual predictive check(s)

1 INTRODUCTION

Niraparib (formerly MK-4827, trade name Zejula), is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) -1 and -2 inhibitor being developed by TESARO and approved in the United States (US) for treatment of ovarian cancer.

Niraparib has been administered as a single agent and in combination in Phase 1, 2, and 3 studies. Completed single-agent studies of niraparib include PN001, a Phase 1 dose-escalation and confirmation study in patients with advanced solid tumors or hematologic malignancies, and PR-30-5011-C (NOVA), a Phase 3 study trial of maintenance with 300 mg once daily (QD) niraparib versus placebo in patients with platinum sensitive ovarian cancer. Niraparib efficacy was independently evaluated in patients with and without germline breast cancer gene (gBRCA) mutation. Progression-free survival (PFS) was the primary efficacy endpoint. Thrombocytopenia is one of the major adverse events (AEs) in patients treated with niraparib. Grade 3 and 4 thrombocytopenia occurred in 29% of patients in the niraparib arm in NOVA and necessitated dose reductions and interruptions. A new dosing paradigm has been proposed to allow patients to reach their optimal dose more rapidly and with fewer Grade 3 or 4 AEs without compromising efficacy.

This analysis plan describes the methodology used to evaluate the pharmacokinetics (PK) of niraparib, including sources of PK variability in patients with advanced solid tumors, to assess the safety and efficacy exposure-response relationships of niraparib in patients with ovarian cancer, and to quantify the pharmacokinetic/pharmacodynamic (PK/PD) relationship between niraparib PK and thrombocytopenia in patients with ovarian cancer. PK/PD simulations will then be used to support optimal dosing strategies to minimize the probability of thrombocytopenia while maintaining efficacy.

2 ANALYSIS OBJECTIVES

The overall goal of this analysis is to support optimal dosing strategies to minimize the probability of thrombocytopenia while maintaining efficacy. Specific objectives are as follows:

1. Develop a population PK model for niraparib to assess the sources of PK variability.

2. Explore the relationship between niraparib exposure and PFS in patients with ovarian cancer.

3. Explore the relationship between niraparib exposure and safety in patients with ovarian cancer.

4. Develop a population PK/PD model of niraparib-induced thrombocytopenia and investigate sources of variability in the PK/PD relationship.

5. Perform PK/PD simulations to evaluate the proposed new niraparib dosing paradigm and, potentially, alternative dosing paradigms.

3 ANALYSIS STRATEGY

A population PK model for niraparib will be developed to assess sources of variability in niraparib PK. This model will be used to derive model-predicted plasma exposures measures of niraparib, e.g., area under the concentration-time curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}). Details are provided in Section 4.3.4. The exposure measures will then be used to perform exposure-response analysis for efficacy (PFS) and safety (non-hematological toxicity and hematological toxicity including thrombocytopenia).

A population PK/PD model will be developed to relate niraparib PK to niraparib-induced thrombocytopenia. Post hoc PK parameter estimates from the final niraparib population PK model will be used to obtain the concentrations to drive the pharmacodynamic (PD) effect of reduction in platelet count. A covariate analysis will be conducted to assess sources of variability in the PK/PD relationship. The final population PK/PD model will be used to perform simulations to assess the risk of thrombocytopenia under the new niraparib dosing paradigms as well as under alternative dosing paradigms.

Population PK and population PK/PD models developed in a previous project (TESA-PCS-100) will be used as starting points for model development.

4 MATERIALS AND METHODS

4.1 OVERVIEW OF STUDY DATA INCLUDED IN THE ANALYSIS

The population PK model will be developed using data from Phase 1 study PN001 and Phase 3 study PR-30-5011-C (NOVA). Study designs are summarized in Table 1, and details are provided in Sections 4.1.1.1 and 4.1.1.2.

PN001 was a Phase 1 dose-escalation and confirmation study in patients with advanced solid tumors or hematologic malignancies (TESARO 2016). The study consisted of three parts – Part A, Part B, and Part D Intensive PK sampling was done in Parts A and B and sparse sampling was done in Part D.

PR-30-5011-C (NOVA) was a Phase 3 study trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer (TESARO 2015). Niraparib efficacy was independently evaluated in patients with and without gBRCA mutation.

Progression-free survival (PFS) was the primary efficacy endpoint. Intensive PK sampling was done in patients enrolled in the food effect and QTc substudies, and sparse sampling was done in all other patients.

Table 1 Clinical Studies Included in the Analysis

Study Number, Type	Study Design, N	Drug Dose and Regimen	Sampling
PN001 Phase 1 dose escalation and confirmation in patients with advanced solid tumors or hematologic malignancies	Phase 1, multicenter, open-label, nonrandomized, cohort-based, dose-escalation and confirmation study N = 104	Part A: Continuous QD dosing for the first 21 days in Cycle 1, followed by a 7 day treatment holiday prior to starting Cycle 2 for the dose escalation component. QD continuously in 21-day cycles from Cycle 2 onward. Dose levels (mg): 30, 40, 60, 80, 110, 150, 210, 290, 300, and 400 Part B: 300 mg QD continuously for 21-day cycles with no treatment holidays. Part C: Not enrolled Part D: 300 mg QD continuously for 28-day cycles with no treatment holidays.	**PK** Part B at Screening: Cycle 1 Day 1 pre-dose, 1, 1.5, 2, 3, 4, 6, 8, and 12 h; Cycle 1 Days 2, 3, 5, 8, 12, and 21: pre-dose; Cycle 2 Day 1 (Day 22) at pre-dose and 1, 1.5, 2, 3, 4, 6, 8, and 12 h post-dose.
PR-30-5011-C (NOVA) Phase 3 maintenance trial of niraparib vs. placebo trial of maintenance with niraparib in patients with platinum sensitive ovarian cancer	Main study: randomized double-blind placebo-controlled N = 553 Food effect substudy: open-label crossover single-dose study N = 17 QTc substudy: open-label N=26	Main study: 300 mg or matching placebo (2:1) Food Effect: 300 mg single dose QTc: 300 mg	**PK** Main: Cycle 1/Day 1 and on Cycle 2/ Day 1 pre-dose and 2 h. Cycle 4/Day 1 and Cycle 8/Day 1: pre-dose only. US subset: pre-dose and at 1, 1.5, 2, 3, 4, 6, and 8 h. Food effect substudy: Days 1 and 8, pre-dose and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h Days 1 and 8. Cycle 1 Day 1 and Cycle 2 Day 1: pre-dose and 2h. Cycle 4 Day 1 and Cycle 8 Day 1: pre-dose.

Study Number, Type	Study Design, N	Drug Dose and Regimen	Sampling
			QTc substudy: Day 1 pre-dose and at 1, 1.5, 2, 3, 4, 6, and 8 h. Cycle 2 Day 1: pre-dose and 2 h. Cycle 4 Day 1 and Cycle 8 Day 1: pre-dose. **PD (platelets)** Screening; Cycle 1 Days 1, 8, 15, 21; Cycle 2 Day 1; subsequent cycles Day 1; and at discontinuation.

PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily.

4.1.1 Clinical Study Summaries

4.1.1.1 PN001

Title: A Phase 1 Study of MK-4827 in Patients with Advanced Solid Tumors or Hematologic Malignancies

Objectives:

Primary

- To establish a recommended Phase 2 dose (RP2D) for niraparib based on safety and tolerability, PK, and PD in patients with advanced and treatment-refractory cancer.

Secondary

- To explore the clinical activity of niraparib in patients with advanced refractory tumors and sporadic platinum-resistant epithelial ovarian cancer.

- To assess the tolerability, AE profile, and clinical activity of niraparib in the following groups: patients with relapsed or refractory T-cell prolymphocytic leukemia or ataxia teleangiectasia mutated-deficient chronic lymphocytic leukemia (not enrolled); patients with phosphatase and tensin homolog-(phosphatase and tensin homolog [PTEN])-deficient colorectal cancer; patients with partially platinum sensitive epithelial ovarian cancer; patients with

relapsed or refractory endometrial carcinoma; and patients with relapsed triple-negative or high grade estrogen receptor-positive (ER+) breast cancer.

Details:

The study was a Phase 1, multicenter, open-label, nonrandomized, cohort-based, dose-escalation and confirmation study of the PARP inhibitor niraparib (previously known as MK-4827) in patients with advanced solid tumors. Dosing schedules and PK sample collection times are given in Table 1.

Part A represented the initial dose escalation and RP2D confirmation stage. During the dose escalation portion, an accelerated titration Phase 1 clinical trial design was used with 100% dose increments in single patient cohorts, beginning with the starting dose of 30 mg QD and escalating up to the maximum tolerated dose (MTD). Episodes of dose-limiting toxicity (DLT) within the first 21 days of Cycle 1 were used to decide whether to escalate the dose, where DLT was defined by occurrence of specific treatment-related hematologic or non-hematologic AE. MTD was defined as the dose at which the estimated mean DLT rate was closest to the target toxicity rate of 20%. The determination of MTD, along with PK and PD data and acute and chronic toxicity, was to inform the choice of RP2D. 300 mg QD was selected as the RP2D.

Part B examined the RP2D in patients with locally advanced or metastatic prostate cancer or sporadic platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients began treatment at the RP2D of 300 mg QD as determined from Part A. Patients took niraparib continuously in 21-day cycles with no treatment holiday.

Part D examined the RP2D in patients with PTEN-deficient colorectal cancer, persistent or recurrent endometrial carcinoma, sporadic partially platinum-sensitive recurrent epithelial ovarian cancer, or breast cancer that either lacks expression of the estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) or is high grade ER+ and HER2 negative (HER2-). Patients began treatment at the RP2D of 300 mg QD, as determined from Parts A and B. Patients took niraparib continuously in 28-day cycles with no treatment holiday.

A total of 104 patients enrolled in the study and received at least 1 dose of niraparib: 60 patients in Part A, 40 patients in Part B, and 4 patients in Part D. Patients were allowed to have dose adjustments (interruptions or reductions or both) to manage AEs after the RP2D was reached. In addition, patients whose doses had been escalated from their starting doses could have dose adjustments.

4.1.1.2 PR-30-5011-C (NOVA)

Title: A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

Objectives:

Primary

- To assess the efficacy of niraparib as maintenance therapy in patients who have platinum sensitive ovarian cancer as assessed by the prolongation of PFS.
- Food effect substudy: To assess the effect of a high fat meal on the PK of a single 300 mg dose of niraparib in patients with ovarian cancer.
- QTc substudy: To evaluate QTc; to evaluate the antitumor activity and durability of response; and to explore potential biomarkers such as those related to DNA repair deficiency following treatment with niraparib in patients who have ovarian cancer (regardless of platinum sensitivity and burden of disease as long as no standard therapy exists or the patient has refused standard therapy).

Secondary

- To evaluate additional measures of clinical benefit.
- To evaluate the safety and tolerability of niraparib compared to placebo in the indicated target population.

Details:

The main study of PR-30-5011-C was a double-blind, 2:1 randomized, placebo-controlled study in platinum-sensitive ovarian cancer patients who had either gBRCA mutation (gBRCAmut) or a tumor with high-grade serous histology, but without a gBRCA mutation (non-gBRCAmut) who were in response to their last platinum-based therapy. Enrollment into the cohorts was determined prospectively by the results of Myriad's Integrated BRACAnalysis® testing. The patients must have received at least 2 platinum-based regimens, had a response to their last platinum regimen, and have no measurable disease > 2cm and normal CA-125 (or > 90% decrease) following their last treatment. The primary objective was to assess the efficacy of niraparib as maintenance therapy in patients with platinum sensitive recurrent high-grade serous ovarian cancer; PFS was the primary efficacy measure. The statistical analysis of the primary endpoint of PFS for the non-gBRCAmut cohort was performed in a hierarchical manner, with a test for the group of patients with homologous recombination deficient-positive (HRDpos) tumors performed first, followed by a test of the overall non-gBRCAmut cohort, if the results of the first test was statistically significant. Stratification factors for

randomization included: time to progression after the penultimate (next to last) platinum therapy before study enrollment (6 to < 12 months and ≥ 12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the last platinum regimen (CR and PR). Dosing schedule and PK sample collection times are given in Table 1.

There were 2 independent patient cohorts in this study: gBRCAmut and non-gBRCAmut patients. A total of 203 patients were enrolled in the gBRCAmut cohort and 350 patients were enrolled in the non-gBRCAmut cohort. Overall, 553 patients were randomized, 372 patients to niraparib and 181 patients to placebo.

Study PR-30-5011-C1 (NOVA QTc substudy) was an open-label evaluation of the effects of niraparib on QTc measurements in patients with histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Twenty patients were planned for this study, and 26 were enrolled.

PR-30-5011-C2 (NOVA FE substudy) was a 14-day, open-label, crossover substudy conducted at 6 US sites to evaluate the effect of a high fat meal on niraparib (single dose) exposure. In Sequence AB, patients fasted (nothing to eat or drink except water) for at least 10 hours before receiving a single dose of 300 mg niraparib; patients continued to fast for at least 2 hours following the dose. In Sequence BA, patients fasted for at least 10 hours before consuming a high fat meal. Within 5 minutes of finishing the meal, a single dose of 300 mg niraparib was administered orally and patients resumed fasting for at least 4 hours. Patients also underwent intensive (triplicate) electrocardiogram monitoring on food effect (FE) Days 1 and 8 to coincide with PK blood sampling. After a 7-day PK assessment and wash-out period, all patients received their second single dose of niraparib on Day 8 under the opposite (fasting versus high fat meal) circumstance. After the completion of the 14-day FE substudy, patients began daily dosing at 300 mg QD niraparib on Cycle 1/Day 1.

4.2 DATASET PREPARATION

4.2.1 Data Programming and Quality Control

Assembly of the population PK and exposure-response datasets will be performed using R (version 3.3.2 or higher) or Statistical Analysis System (SAS®) (version 9.3 or higher). Once assembled, the analysis datasets will undergo a formal quality control (QC) review by an analyst other than the data programmer. The QC review will include exploratory plots of the constructed data to identify potential errors. In addition, individual predicted concentration-time profiles from a preliminary model run will be compared to observed profiles in order to identify potential errors in dosing history.

If datasets are modified over the course of the analysis, the file name of each version of the dataset will be unique.

4.2.2 Evaluable Subjects

For the population PK analysis, an individual will be defined as evaluable if the individual has at least one measurable niraparib concentration observation after the first dose of niraparib with associated sampling and dosing time.

For the safety and efficacy exposure-response analyses for NOVA, an individual will be defined as evaluable if the following criteria are satisfied:

- Patients randomized to niraparib:
    - The patient is evaluable for the population PK analysis and therefore has PK parameter estimates to enable estimation of niraparib exposure.
    - The patient was evaluated for the endpoint in question.
- Patients randomized to placebo: the patient has data for the endpoint in question.

For the efficacy exposure-response analysis, patients in the placebo arm will be included in the exploratory plots but not in the stratified Cox regression analysis.

For the PK/PD analysis, an individual will be defined as evaluable if the following criteria are satisfied:

- Patients randomized to niraparib must meet both of the following criteria:
    - The patient is evaluable for the population PK analysis and therefore has PK parameter estimates.
    - The patient has at least one platelet count measurement at baseline or a later time point.
- Patients randomized to placebo: the patient has at least one platelet count measurement at baseline or a later time point.

4.2.3 Covariate Variables

The evaluation of the impact of covariates on the niraparib population PK, exposure-response, and PK/PD models will focus on the most clinically relevant covariates. Covariates to be tested are listed in Table 2 for the population PK model.

For the thrombocytopenia exposure-response and longitudinal PK/PD models, the following covariates will be tested:

- Age
- Race
- Baseline body weight
- Baseline body mass index (BMI)
- Baseline platelet count
- Baseline neutrophil count
- Baseline hemoglobin count
- Baseline lactate dehydrogenase
- Baseline albumin
- Baseline bilirubin
- Baseline aspartate aminotransferase (AST)
- Baseline alanine aminotransferase (ALT)
- Baseline alkaline phosphatase (ALP)
- Prior thrombocytopenia
- Prior myelosuppression
- Duration of last platinum therapy
- Cumulative duration of prior platinum therapies in all prior lines of treatment
- Lines of platinum therapy
- Time from last platinum therapy

If PFS exposure-response modeling is performed, the following covariates will be tested:

- Age
- Race

- Duration of prior chemotherapy
- Duration of last platinum therapy
- Cumulative duration of prior platinum therapies in all prior lines of treatment
- Lines of chemotherapy
- Time from last chemotherapy
- Lines of platinum therapy
- Time from last platinum therapy

In the stratified Cox regression analysis for PFS, the following stratification variables will be applied: time to progression after the penultimate (next to last) platinum therapy before study enrollment (6 to < 12 months and ≥ 12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the last platinum regimen (complete response [CR] and partial response [PR]).

Table 2 Covariates to be Evaluated in the Population PK Model

	PK Parameter Groups		
Covariate	**Volume of Distribution**	**Clearance**	**Absorption/Bioavailability**
baseline body weight	X	X	X
baseline BMI	X	X	X
sex	X	X	X
race	X	X	
prandial state			X
gBRCA mutation status		X	
HRDpos status		X	
cancer diagnosis		X	
creatinine clearance capped at 150 mL/min		X	
age	X	X	
liver function tests (AST, ALT, ALP, BILI)		X	
albumin	X	X	
baseline platelet count		X	

	PK Parameter Groups		
Covariate	**Volume of Distribution**	**Clearance**	**Absorption/Bioavailability**
ECOG performance status		X	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; BMI: body mass index; ECOG = Eastern Cooperative Oncology Group; gBRCA = germline breast cancer gene; HRDpos = homologous recombination deficient-positive; PK = pharmacokinetic.

Derivation methods of computed covariates are provided in Table 3.

Table 3 Description of Covariates and Associate Derivation Methods

Covariate	Description and/or Derivation
CLCR	Cockcroft-Gault equation: $$CLCR = \frac{(140 - age) \times bodyweight\ (kg)}{serum\ creatinine\ (mg/dL) \times 72} \times 0.85(if\ female)$$

CLCR = creatinine clearance

Covariates other than those listed in this section may also be included in the covariate search. For categorical covariates if a particular category has less than 10% of the data, a new categorical covariate combining categories may be created.

4.2.4 Handling of Missing and Erroneous Data

Concentration samples with missing or uncertain corresponding dosing data and all subsequent concentration samples for the patient will be excluded from the analysis. For samples with missing time information, time will be imputed based on dosing time and nominal time where possible; otherwise those samples will be excluded from the analysis. Samples with missing date information will be excluded. In the PK analysis, concentration samples that are below the assay quantitation limit will be treated as missing and excluded from the analysis. If more than 10% of the data following the first dose of study drug are below the lower limit of quantitation, then likelihood-based methods of imputation may be considered (e.g., M3 likelihood imputation).

For the safety and efficacy exposure-response analyses, missing safety and efficacy endpoint data will not be imputed. For the population PK/PD analysis, platelet count data with missing dates will be excluded.

When all values of a continuous covariate are missing for an analysis patient, the mean or median value adjusted for other demographic factors (e.g., sex or age) may be used as an imputed value. Missing categorical covariates will be flagged with an appropriate missing value code in the analysis data set (e.g., -99) but grouped together with the most common covariate category during covariate model building. If more than 10% of patients have missing values for a covariate, that covariate will be excluded from the

analysis. As a sensitivity analysis, the analysis may be done on the subset of patients with non-missing values for the covariate.

Outliers can have disproportionate effects on model parameters and should be excluded from model-building, particularly during the covariate testing phase. Prior to model-building, exploratory graphical analysis will be used to identify unusual patterns and/or data points, whether there be one or more points within a given patient or all points for a patient.

Initial runs of the base population PK model will also be used to flag potential outlier values. Data observations for which the absolute value of the associated conditional weighted residual is greater than 4 (|CWRES| > 4) will be flagged and may be excluded (by use of a flag variable) from the analysis during the covariate model building. In accordance with the accepted population PK reporting guidelines (Food and Drug Administration 1999, Food and Drug Administration 2003, European Medicines Agency 2007), the final population PK model will be rerun using the entire data set (i.e., data set with the outliers and data observations where |CWRES| > 4).

4.3 SOFTWARE AND COMPUTATIONAL APPROACH

The analyses will be carried out according to the US Guidance for Industry: Population Pharmacokinetics (Food and Drug Administration 1999), US Guidance for Industry: Exposure Response (Food and Drug Administration 2003), and the European Union Guidance on Reporting the Results of Population Pharmacokinetic Analyses (European Medicines Agency 2007).

4.3.1 Software

Nonlinear mixed-effects modeling software (NONMEM®) (version 7.3 or higher), a software package for nonlinear mixed-effects analysis (ICON, Hanover, MD, US), will be used for population PK and PK/PD modeling. Either first order conditional estimation method of NONMEM with interaction (FOCE INTER) or stochastic estimation methods may be used for model development. NONMEM and/or R (version 3.3.0 or higher) will be used for simulations, e.g., to derive exposure measures for subsequent exposure-response analyses and to explore different dosing regimens. R will be used for exposure-response analyses and modeling.

SAS or R will be used for data preparation, graphical analysis, model diagnostics, and statistical summaries. Xpose® and Pearl Speaks NONMEM (PsN®) (Department of Pharmacy, Uppsala University, Uppsala, Sweden) may also be used for model diagnostics and facilitation of NONMEM tasks such as covariate testing.

4.3.2 Population PK Analysis

4.3.2.1 Nonlinear Mixed Effects Modeling Algorithms

Plasma concentration-time data will be analyzed using a nonlinear mixed effects modeling approach using NONMEM. FOCE INTER will be the primary method used for model parameter estimation. If the FOCE INTER method should prove infeasible due to instability, non-convergence, and/or excessive run times, alternative estimation methods may be employed. Such methods may include importance sampling, stochastic approximation expectation-maximization, or a sequential application of two or more of these methods. The iterative two-stage method may also be applied as a means for refining initial parameter estimates as inputs for the more robust estimation methods. In addition, supplemental runs of the final population model may optionally be performed using these alternative estimation methods, as a stability check on the final model parameters.

4.3.2.2 Development of the Base Structural Population PK Model

The structural base model previously developed using data from Study PN001 will be used as a starting point for model development to describe the time course of plasma concentrations. This was a two-compartment model with first-order absorption and linear elimination. Three-compartment models may be evaluated depending on the shape of the observed concentration-time profiles of the NOVA data. Other structural models for the distribution and absorption components may be tested as needed. The effect of dose on absorption rate and bioavailability will be explored as part of the structural population PK model.

The inter-individual random effects on the parameters will be modeled assuming a log-normal distribution as given by the following expression:

$$\theta_{ki} = \theta_k \times e^{\eta_{ki}}$$

where where θ_{ki} denotes the parameter value for the i^{th} patient, θ_k denotes the typical parameter value, and η_{ki} denotes the inter-individual random effect, also called ETA, for the i^{th} patient – assumed to have mean of 0 (zero) and variance ω_k^2. Collectively, the vector of random effects (across the parameters indexed by k) has covariance matrix (Ω). Covariance matrix structures including diagonal and blocked diagonal structures will be evaluated after the completion of covariate model building. Inter-occasion variability, if modeled, will also be assumed to follow a log-normal distribution.

The residual error structure will be assumed to follow an additive, proportional, or combined additive and proportional error model described by the following:

$$Y_{ij} = C_{ij} \times \left(1 + \varepsilon 1_{ij}\right) + \varepsilon 2_{ij}$$

where Y_{ij} is the j^{th} observed concentration for the i^{th} patient, C_{ij} is the corresponding predicted concentration, and $\varepsilon 1_{ij}$ (proportional) and $\varepsilon 2_{ij}$ (additive) are the residual errors under the assumption that $\varepsilon \sim N(0,\sigma^2)$. The best residual error structure will be selected.

4.3.2.3 Covariate Selection for the Population PK Model

Covariates of interest (see Section 4.2.3) will be tested in a stepwise process. The covariate selection will be performed using a forward addition process followed by backward deletion. Before beginning the stepwise search, a screening process may be used to select parameter-covariate relationships that will be tested in the stepwise covariate search. For example, each parameter-covariate relationship could be added one at a time to the structural model, and only parameter-covariate relationships significant at the 0.01 level in this univariate testing will be taken forward into the full stepwise covariate search process. Alternatively, ETA versus covariate plots (scatter plots for continuous covariates and box plots for categorical covariates) may be examined for PK parameters with low shrinkage (< 30%) and only those revealing an ETA-covariate relationship (e.g., based on correlation and/or p-values) will be included in the stepwise search.

The likelihood ratio test will be used to evaluate the significance of incorporating or removing fixed effects into the population model based on significance levels that are set *a priori*. For forward selection and backward deletion, significance levels of 0.01 and 0.001 will be employed, respectively (Joerger 2012). Highly correlated covariates (e.g., correlation coefficient R > 0.3) will not be included together on the same parameter.

When all of the statistically significant covariates have been included in the model from the stepwise process, the model will be reduced by removing clinically irrelevant covariates. The effect of a continuous covariate will be deemed clinically irrelevant if the PK parameter estimate of a typical (median) person differs by less than 20% from a person with an extreme covariate value (10^{th} and 90^{th} percentiles). For discrete covariates, a covariate will be deemed clinically irrelevant if the PK parameter estimate differs by less than 20% between categories of a covariate.

All continuous covariates will be initially incorporated into the population model using a scaled structure based on the median or other reference value of the covariate in the population. This approach ensures that covariate effects are relative to an individual in the middle of the population distribution for that covariate. All categorical covariates will be initially incorporated into the population model using a proportional structure with the most common level of the covariate being the reference. This approach ensures that categorical covariate effects are relative to a reference group or category. The mathematical structures of the covariate models are shown below:

Continuous **Categorical**

$$P_{ki} = \theta_k \times \left(\frac{X_{ij}}{M(X_j)}\right)^{\theta_j} \qquad P_{ki} = \theta_k \times (1+\theta_j)^{X_{ij}}$$

Note: P_{ki} is the population estimate of the parameter P_k for patient i, X_{ij} is the value of continuous covariate X_j for patient i or an indicator variable for patient i for categorical covariate X_j with value 1 for the non-reference category and 0 for the reference category, $M(X_j)$ is the median of covariate X_j in the analysis dataset, θ_k is the typical value of the parameter P_k, and θ_j is a coefficient that reflects the effect of covariate X_j on the parameter.

If these parameterizations prove inadequate to capture the observed relationship, other parameterizations may be evaluated. Such alternatives may include dichotomization/discretization or truncation/censoring of continuous covariates and/or piecewise linear functions. Other continuous functions may also be considered if deemed appropriate based on plots of random effects versus the covariate of interest. In order to ensure that the model that emerges from the covariate testing process does not neglect any important covariate effects, random effects from the tentative final model will be plotted versus covariates and evaluated for residual trends in parameter-covariate relationships.

4.3.2.4 Evaluation of the Variance-Covariance Matrix in the Population PK Model

At the end of covariate testing, alternative variance-covariance structures for Ω will be evaluated, including partial and full block structures. Such a structure will be deemed suitable if it provides a statistically significant ($p< 0.01$) improvement in the model objective function and if it improves model stability as measured by the condition number and/or a successful covariance step. The model that results from this step of the model building process will be considered the final model.

4.3.2.5 Evaluation of the Final Population PK Model

A number of standard diagnostic plots will be used throughout model development to assess the ability of each model to describe the observed data (Nguyen et al 2017). These diagnostic plots will include observed (DV) versus individual (IPRED) and population (PRED) predicted concentrations, CWRES/Individual Weighted Residuals versus PRED and time, and quantile-quantile plots or histogram of residuals. The utility of the diagnostic plots will be dependent on a reasonable level of eta- and epsilon-shrinkage. As a general rule, if estimates of shrinkage are less than 30%, plots based upon random effects or residuals will be regarded as being useful for diagnostic purposes.

Bootstrap resampling techniques will be used to evaluate the stability of the final model and to estimate confidence intervals (CIs) for the model parameters. This analysis will be conducted by repeatedly fitting the final model to bootstrap replicates of the dataset.

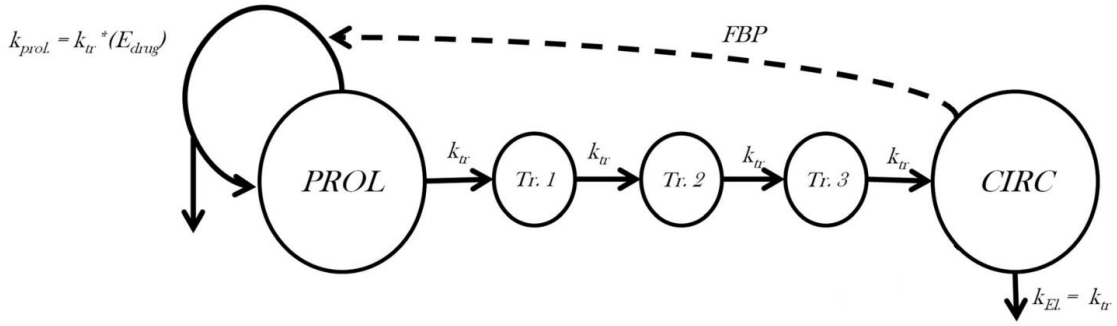
Confidence intervals will be calculated based on the distribution of the parameter estimates from the bootstrap runs. Visual predictive checks (VPCs) will be used to evaluate the predictive ability of the final model. VPCs will be performed with prediction correction and will include a minimum of 200 simulations.

4.3.3 Population PK/PD Analysis

4.3.3.1 Development of the Base Structural Population PK/PD Model

The time course of platelet counts will be analyzed using NONMEM. The selection of estimation method will follow the same approach described in Section 4.3.2.1 for the population PK model. PK/PD modeling will be performed using a sequential approach. First, the population PK model will be developed, and post hoc PK parameters from the final PK model will be used, together with niraparib dosing history, to derive the concentration-time profiles that will serve as input to drive the drug effect in the PK/PD model.

Figure 1 Semi-mechanistic PK/PD Model of Thrombocytopenia



$$\frac{dPROL}{dt} = k_{prol} \cdot (E_{drug}) \cdot FBP \cdot PROL - k_{tr} \cdot PROL$$

$$\frac{dTr\ 1}{dt} = k_{tr} \cdot PROL - k_{tr} \cdot Tr\ 1$$

$$\frac{dTr\ 2}{dt} = k_{tr} \cdot Tr\ 1 - k_{tr} \cdot Tr\ 2$$

$$\frac{dTr\ 3}{dt} = k_{tr} \cdot Tr\ 2 - k_{tr} \cdot Tr\ 3$$

$$\frac{dCIRC}{dt} = k_{tr} \cdot Tr\ 3 - k_{El} \cdot CIRC$$

$$FBP = \left(\frac{BASE}{CIRC}\right)^{\gamma}$$

PROL, TrN (where N = 1, 2, or 3), and CIRC represent the proliferation, transit and circulation compartments, respectively. BASE is the baseline platelet value. FBP represent the feedback on proliferation. The drug effect (E_{drug}) affects the proliferation rate constant (k_{prol}). k_{tr} and k_{El} are the rate constants of transit and elimination respectively. t denotes the time in days. Adapted from du Rieu et al 2014.

The PK/PD model for niraparib-induced thrombocytopenia will be based on published semi-mechanistic thrombocytopenia PK/PD models, e.g., Bender et al 2012, Fouilard et

al 2013, and du Rieu et al 2014. The general model structure and equations are presented in Figure 1. The model consists of a proliferative platelet pool compartment PROL (representative of bone marrow); three transit compartments Tr1, Tr2, and Tr3, (representative of blood cell maturation), and a final circulating platelet compartment from which platelet measurements are sampled. A feedback mechanism (represented by FBP in Figure 1) increases the proliferation rate when circulating platelet levels drop below the baseline value. The action of the drug is to inhibit proliferation.

Initially, E_{max} and sigmoid E_{max} models will be used to describe the drug effect E_{drug} as follows:

$$Edrug = 1 - \frac{Imax \cdot C^{\gamma}}{IC_{50}{}^{\gamma} + C^{\gamma}}$$

Where I_{max} is the maximum fractional inhibition of the proliferation rate, C is plasma niraparib concentration, IC_{50} is the plasma concentration of niraparib resulting in half-maximal inhibition, and γ is the sigmoidicity factor. γ may be fixed to 1 or estimated.

Other parameterizations of the drug effect will also be explored such as follows:

Linear model: $E_{drug} = 1 - Slope \cdot C$

Power model: $1 - Coefficient \cdot C^{\delta}$

The mean transit time (MTT) can be calculated from the transit rate constants ktr as:

$$MTT = \frac{n+1}{ktr}$$

where n is the number of transit compartments (in this case, 3).

Before PK/PD modeling begins, exploratory plots of the time course of platelet counts will be generated. If the plots reveal stable platelet counts over time for the placebo patients, placebo patients may be excluded from PK/PD modeling.

Random effects and residual variability will be modeled similar to the approach used in the population PK model (Section 4.3.2.2), except that between-subject variability (BSV) may be modeled additively for some PK/PD parameters, such as I_{max}:

$$\theta_{ki} = \theta_k + \eta_{ki}$$

4.3.3.2 Covariate Selection for the Population PK/PD Model

Covariates of interest for the PK/PD model (Section 4.2.3) will be tested in a stepwise process using the methodology described for the population PK model in Section 4.3.2.3.

4.3.3.3 Evaluation of the Variance-Covariance Matrix in the Population PK/PD Model

This will be done using the same methodology used for the population PK model as described in Section 4.3.2.4.

4.3.3.4 Evaluation of the Final Population PK/PD Model

This will be done using the same methodology used for the population PK model as described in Section 4.3.2.5. Standard diagnostic plots will be generated, and a prediction-corrected VPC will be performed. However, because of potentially long run times for the population PK/PD model, a bootstrap may not be feasible.

In addition, the ability of the model to predict the incidence of thrombocytopenia (e.g., Grade 3 or higher) will be assessed. The incidence of thrombocytopenia in simulated patients with the same covariates, dosing history, and platelet count sampling as those in the analysis dataset will be summarized by simulation replicate, and the median and 95% prediction intervals (2.5^{th} and 97.5^{th} percentiles of simulated incidence of thrombocytopenia) will be compared to the observed incidence. Comparisons may also be stratified by covariates of interest.

4.3.4 Exposure-Response Analysis

4.3.4.1 Exploratory Exposure-Response Analyses

For the exposure-response analyses, the safety endpoints will be treated as binary variables and the efficacy endpoint of PFS will be treated as a time-to-event variable. These analyses will include only data from the NOVA study. The exposure measures to be investigated are average niraparib exposure (i.e., AUC, C_{max}, C_{min}) up to the time of the first event (i.e., adverse event or disease progression). For patients who do not experience a given event during the study, the average exposure up to the end of treatment (for safety endpoints) or time of censoring (for PFS) will be used for that endpoint. A different average exposure value will be calculated for each endpoint.

The average exposure (e.g., AUC, C_{max}, C_{min}) will be approximated by multiplying the individual model-predicted steady-state exposure at the nominal dose of 300 mg QD by the relative dose intensity up to the time of event (RDI). RDI will be calculated as:

$$RDI = \frac{total\ dose\ up\ to\ time\ of\ event}{300\ mg\ \times study\ day\ at\ occurrence\ of\ event}$$

This assumes that niraparib dosing begins on study Day 1

For PFS, the average concentration (C_{avg}) up to the time of disease progression or censoring may be analyzed in place of AUC as a predictor of PFS. C_{avg} will be

calculated as the average daily AUC up to the time of event or end of treatment/censoring time divided by 24 hours.

Steady-state exposures at 300 mg QD may also be explored as exposure measures. Note that C_{max} may not be included in any of the exposure-response analyses if the shrinkage in volume of distribution is deemed too high (e.g., > 30%) to permit reliable estimation of patient-level C_{max} values.

Exploratory Exposure-Response Analyses for Safety

The safety endpoints that will be investigated in this analysis are Grade 1 or higher and Grade 3 or higher thrombocytopenia, anemia, neutropenia, nausea, insomnia, and anxiety occurring at any point during the study. For these binary safety endpoints, a tabular or graphical summary of AEs by niraparib exposure quantiles (e.g., quartiles) will be provided. Results from the placebo arm will be included in the summaries. The relationship between niraparib exposure (AUC, C_{max}, and C_{min} – presented separately) and the probability of experiencing AEs of a given grade or higher will be evaluated using univariate logistic regression analysis (example shown in Figure 2; plot in report may differ). P-values where given will be descriptive only (not adjusted for multiplicity).

In the univariate logistic regression, the probability that a patient will experience an AE will be assumed to be independent within each patient:

$$g\{P(Y=1)\} = Baseline + f(Exposure)$$

where g{P(Y=1)} denotes the logit transformation of the probability of occurrence of a specific AE for a particular patient, Baseline is the logit transformation of the probability of occurrence of the AE without exposure to niraparib, f(Exposure) is a function describing the drug effect given a particular exposure measure of niraparib. The function for f(Exposure) will be evaluated as a linear relationship, given by the equation below:

$$f(Exposure) = Slope \times Exposure$$

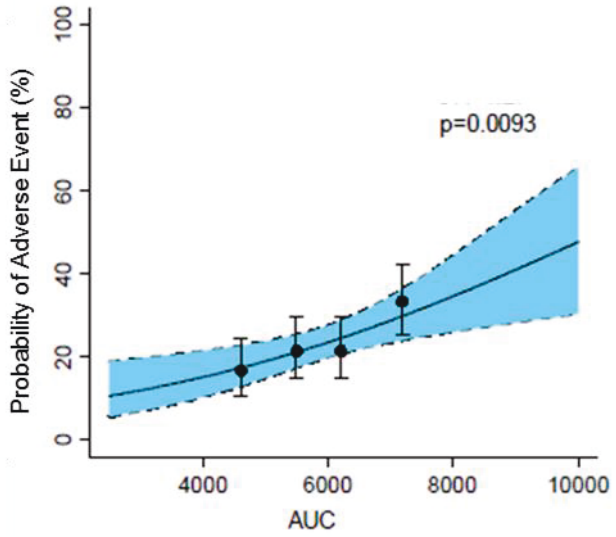
In addition, the following plots will be provided:

- For patients randomized to niraparib, the distribution of exposures (niraparib AUC, C_{max}, and C_{min}) in patients who experienced the AE and those who did not will be compared using boxplots

- Scatter plots of niraparib exposure in quartiles versus Cycle 1 thrombocytopenia

Separate analyses may be done separately for gBRCA versus non-gBRCA groups. Plots may also be stratified by gBRCA mutation status.

Figure 2 Example of Logisitic Regression Plot for a Binary Variable



Exploratory Exposure-Response Analyses for Efficacy

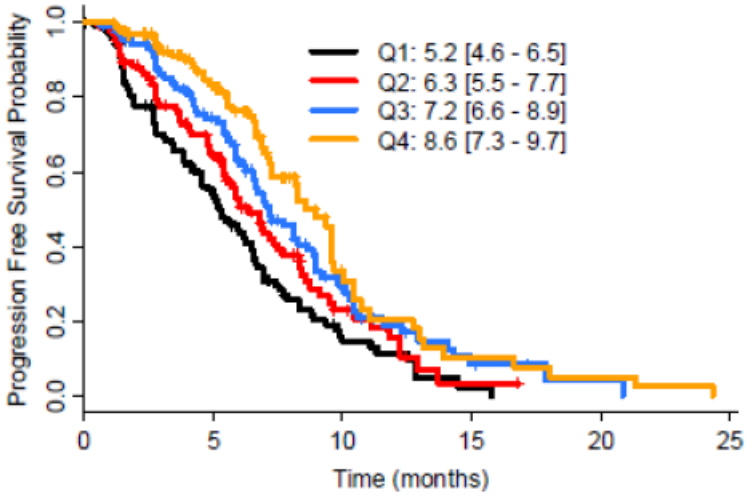
Niraparib C_{max}, C_{min}, and AUC or C_{avg} up to the time of event will be presented separately as predictors of PFS.

Separate plots and analyses will be done for the following groups of patients:

1. gBRCA cohort
2. Overall non-gBRCA cohort
3. HRDpos subset of non-gBRCA cohort.

Kaplan-Meier plots will be derived for exposure-response evaluation according to niraparib exposure quantiles (e.g., quartiles) in the NOVA study (example shown in Figure 3). A survival curve for the placebo group will also be included in the plot. P-values assessed by stratified Cox regression versus exposure as a continuous variable (likelihood ratio test using coxph in R) will also be provided. (Placebo data will not be included in the Cox regression.) The following stratification variables will be applied: time to progression after the penultimate (next to last) platinum therapy before study enrollment (6 to < 12 months and ≥ 12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the last platinum regimen (CR and PR).

Figure 3 Example of Kaplan-Meier Plot for PFS



4.3.4.2 Development of the Base Exposure-Response Model

An exposure-response model will be developed for the probability of Grade 3 or higher thrombocytopenia.

If a statistically significant relationship is detected between at least one niraparib exposure measure (AUC, C_{max}, C_{min}, or C_{avg}) and PFS based on the exploratory analysis described in Section 4.3.4.1, an exposure-response model may be developed for PFS. For each of the patient subsets, a separate exposure-response model will be developed for PFS.

For both models (thrombocytopenia and PFS), the base model will be selected as the univariate logistic regression model (for thrombocytopenia) or stratified Cox regression model (for PFS) with the niraparib exposure measure that resulted in the lowest Akaike Information Criterion (AIC) value or the most clinically relevant exposure measure. Note that different exposure measures may be selected for the thrombocytopenia and PFS models.

4.3.4.3 Covariate Selection for the Exposure-Response Model

Thrombocytopenia Exposure-Response Model

Multiple logistic regression using selected covariates (Section 4.2.3) will be performed.

To avoid model instability due to correlations between explanatory variables, only one of a set of highly correlated covariates will be included in the model. Co-linearity of categorical covariates will be assessed qualitatively through contingency tables. Within each group of correlated variables, the explanatory variable that will be carried forward

into the main model building phase will be the one whose univariate regression yields the best objective function value. However, in instances in which two or more covariates yield approximately equivalent univariate fits, the variable which is most meaningful from a biological/clinical perspective may instead be selected for progression to the main model building phase.

The initial model for the probability of Grade 3 or higher thrombocytopenia will include terms for the full set of (non-redundant) explanatory variables, i.e., the selected niraparib exposure measure and other covariates. This initial model will only consider main effect parameters for each covariate (i.e., no interaction terms). Should the full model fail to converge at this stage or following addition of bivariate interaction terms, an alternative process of model development may be used, e.g., forward addition followed by backward elimination or alternatively, adjusting covariate groups to improve stability.

Following identification of the full model, a stepwise backward elimination procedure will then be applied using the stepAIC function from the MASS library in R. This function will iteratively drop model terms in order to minimize the AIC, a criterion which favors parsimonious models. Bivariate interaction terms between the exposure measure and each of the remaining explanatory variables will then be added to the model, provided such interactions have a plausible clinical/biological interpretation. A second backward elimination procedure using stepAIC will then be applied to the model with interaction terms. Following the final backward elimination step, covariate terms that are not significant at $\alpha = 0.05$ will be dropped from the model. The resultant model will be further assessed with respect to biological plausibility. In this step, model terms that were retained throughout the statistical evaluation but do not have a plausible biological interpretation may be optionally deleted from the model. Similarly, terms that did not survive the backward elimination procedures, but are of clinical interest may be optionally re-included.

Odds ratios and associated 95% CIs will be reported for the covariates included in the final model.

PFS Exposure-Response Model

PFS will be analyzed as a time-to-event variable using a survival model. Placebo data will not be included in the model. A stratified Cox proportional hazard model in which covariates are multiplicatively related to hazard (proportional hazard) will initially be used to characterize the impacts of exposure and other covariates on survival time. An advantage of using this model is that it is possible to estimate the covariate effect parameters without explicitly considering the hazard function. The following stratification variables will be applied: time to progression after the penultimate (next to last) platinum therapy before study enrollment (6 to < 12 months and ≥ 12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the last platinum regimen (CR and PR).

Separate models will be developed for the following groups of patients:

1. gBRCA cohort
2. overall non-gBRCA cohort
3. HRDpos subset of non-gBRCA cohort.

The hazard rate at time t for patient i with covariate vector X_i in a given stratum is given by:

$$\lambda(t|X_i) = \lambda_0(t) \exp(\beta_1 X_{i1} + \cdots + \beta_p X_{ip}) = \lambda_0(t) \exp(X_i \beta)$$

where $\lambda_0(t)$ is the underlying hazard, X_i is the vector of explanatory variables for patient i, and β is the vector of parameters for covariate effects.

The Cox proportional hazard model predicts survival time (T) such that:

$$\log T = \log T_0 \beta^T \boldsymbol{X}$$

where T is the time to event, T_0 is the baseline survival time, **X** is the vector of explanatory variables, and β is the vector of parameters for covariate effects.

Covariate modeling for PFS will start with a full model that includes all non-redundant covariates of interest and using the stepAIC function in R to drop terms. The rest of the covariate modeling procedure will follow the methodology used for the thrombocytopenia exposure-response model. Following model development the validity of the Cox proportional hazard assumption will be tested by assessing proportionality of hazards using graphical and/or statistical methods such as those available in the *cox.zph* tool in R.

Hazard ratios and associated 95% CIs will be reported for the covariates included in the final PFS model.

4.3.4.4 Evaluation of the Final Exposure-Response Model

For the thrombocytopenia logistic regression exposure-response model, VPCs will be used for model evaluation. The VPCs will compare the observed and simulated proportions of patients (simulated median and 95% prediction interval) experiencing Grade 3 or higher thrombocytopenia. VPCs will be based on 1000 replications of the available data and may be stratified by covariates of interest.

The appropriateness of the Cox proportional hazard models for PFS will be primarily assessed through goodness of fit plots, as this semi-parametric approach does not lend itself to simulation based diagnostics such as VPCs. Model diagnostics will include plots

of Martingale residuals versus covariates of interest to screen for any misspecification or omissions with respect to covariate effects (Venables, Ripley 2002).

4.3.5 Simulations

4.3.5.1 Purpose of Simulations

The purpose of the PK/PD simulations is to simulate platelet counts under various niraparib dosing regimens, including the body weight- and baseline platelet-based dose regimen proposed by TESARO to reduce the incidence of thrombocytopenia, and thus the need for dose adjustments or interruptions, while maintaining efficacy. The simulations will provide justification for the proposed dose regimen or suggest alternative regimens.

4.3.5.2 Simulation Methods

A minimum of 3000 virtual patients will be generated for the simulations, with enough patients (at least 500) receiving each simulated dose regimen. Baseline characteristics for virtual patients will be generated by sampling with replacement from all NOVA study patients included in the population PK or population PK/PD analyses (including patients randomized to placebo), with patient as the sampling unit.

Fixed effect parameter estimates (including covariate effects) and BSV from the final population PK and PK/PD models will be used to simulate niraparib concentration profiles and platelet count time courses following each simulated dosing regimen. Alternatively estimated ETA values may be sampled from the analysis datasets for the simulation of BSV. Residual variability and parameter estimate uncertainty will not be included in the simulations.

The percent of patients predicted to experience thrombocytopenia of a given severity (e.g., Grade 3 or higher) will be summarized by dosing regimen and by relevant covariate values, if applicable. The time course of platelet counts (median and 95% prediction intervals) will also be presented graphically for selected regimens and scenarios.

5 ANALYSIS REPORT

Separate stand-alone reports will be generated for (1) the population PK and exposure-response analyses and (2) the population PK model. The reports will include the following sections:

1. TITLE PAGE

   SIGNATURE PAGE

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS
4. SUMMARY
5. INTRODUCTION
6. ANALYSIS OBJECTIVE(S)
7. MATERIALS AND METHODS
8. RESULTS
9. DISCUSSION
10. APPLICATION OF RESULTS
11. REFERENCES
12. APPENDICES
    - 12.1 Base Model Results
    - 12.3 Final Model Results
    - 12.4 Additional Figures Not Included in the Text

In addition, datasets, model files, and outputs for the analysis as electronic files (as CDISC datasets, Excel, or SAS transport files) will be provided for the final analyses.

6 REFERENCES

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7 TABLES, FIGURES, AND LISTINGS TO BE INCLUDED IN THE REPORT

7.1 IN-TEXT SUMMARY TABLES AND FIGURES

Table 1 Clinical studies included in the analyses

Table 2 Baseline characteristics of patients included in the analysis

Table 3 Parameter estimates for the final population model

Table 4 Parameter estimates for each exposure-response model (thrombocytopenia, PFS)

Table 5 Summary of simulated incidence of thrombocytopenia

Figure 1 Selected goodness-of-fit plots for base and final population model

Figure 2 Exposure-response diagnostics for thrombocytopenia model

Figure 3 Exposure-response diagnostics for PFS model (if applicable)

Figure 4 Simulation of PK and PD profiles (platelet counts) for selected regimens

7.2 TABLES, FIGURES, AND LISTINGS IN APPENDIX

Figure 1 Diagram of final population model

Figure 2 Complete goodness-of-fit plots for base and final population model

Figure 3 Pairwise scatterplots or boxplots for continuous and categorical covariates

Figure 4 Visual predictive check stratified by covariates of interest

Additional tables and/or figures may be generated if deemed appropriate.

TITLE PAGE

TESARO, INC.

PR-30-5011-C

A PHASE 3 RANDOMIZED DOUBLE-BLIND TRIAL OF MAINTENANCE WITH NIRAPARIB VERSUS PLACEBO IN PATIENTS WITH PLATINUM SENSITIVE OVARIAN CANCER

STATISTICAL ANALYSIS PLAN

Version 3.0 [Final]

Date: 17 June 2016

SIGNATURE PAGE

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1. ABBREVIATIONS

Term	Definition/Usage
AE	adverse event
ANCOVA	Analysis of Covariance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
$BRCA^{wt}$	BRCA wild type
CA-125	cancer antigen 125
CDx	companion diagnostic
CFI	chemotherapy-free interval
CI	confidence interval
CIPN	Chemotherapy Induced Peripheral Neuropathy
CMH	Cochran-Mantel Haenszel
CR	complete response
CT	computed tomography
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D-5L	European Quality of Life (EuroQOL) 5-Dimensions 5-Levels
FDA	Food and Drug Administration
FE	Food effect
FOSI	Functional Assessment of Cancer Therapy – Ovarian Symptom Index
FUACT	follow-up anti-cancer treatment
$gBRCA^{mut}$	germline BRCA mutation
GCIG	Gynecologic Cancer Intergroup
HR	hazard ratio
HRD	homologous recombination deficiency
HUI	health utility index

Term	Definition/Usage
IDMC	independent data monitoring committee
IRC	independent review committee
ITT	intent-to-treat
KM	Kaplan-Meier
LLN	lower limit of normal
LS	least squares
LSM	least-squares means
LSSE	least-squares standard errors
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
CCI [redacted]	
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival 2
PK	pharmacokinetic(s)
PP	per-protocol
PR	partial response
PRO	patient-reported outcome
PT	preferred term
Q1	lower quartile
Q3	upper quartile
QOL	quality of life
QTc	corrected QT
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
Rel Day	relative study day
SAE	serious adverse event
SAF	safety population

Term	Definition/Usage
SAP	statistical analysis plan
sBRCA^{mut}	somatic BRCA mutation
SD	stable disease
StdDev	standard deviation
SI	international system of units
SOC	system organ class
tBRCA^{mut}	tumor BRCA mutation
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
TFST	time to first subsequent therapy
TSST	time to second subsequent therapy
ULN	upper limit of normal
US / USA	United States / United States of America
VAS	visual analog scale
WHO-DD	World Health Organization Drug Dictionary

2. DEFINITIONS

Germline BRCA mutation (gBRCA^{mut}) – A germline BRCA mutation is an inherited deleterious or suspected deleterious mutation in either a BRCA1 or BRCA2 tumor suppressor gene. Harmful mutations in either of these genes may produce a hereditary breast-ovarian cancer syndrome in affected persons. Cells with deleterious or suspected deleterious germline BRCA1 or BRCA2 mutations have a defect in the repair of double-strand deoxyribonucleic acid (DNA) breaks (DSB) by the error-free mechanism of homologous recombination (HR). This defect results in the repair of such lesions by error-prone mutagenic pathways, such as single-strand annealing (SSA) and nonhomologous end joining leading to genomic instability. Women with harmful germline mutations in either BRCA1 or gBRCA2 have a risk of breast cancer that is about 5 times the normal risk, and a risk of ovarian cancer that is about 10 to 30 times normal.

Somatic BRCA mutation (sBRCA^{mut}) – A somatic BRCA mutation is a deleterious or suspected deleterious alteration in the BRCA1 or BRCA2 genes that is acquired after conception (not hereditary). Somatic mutations can occur in any cell of the body except the germ cells (sperm and egg) and therefore are not passed on to children. A somatic BRCA mutation may also confer increased risk of cancer in affected cells. These mutations are not present in the germline.

Tumor BRCA mutation (tBRCA^{mut}) – A deleterious or suspected deleterious BRCA1 or BRCA2 mutation found in a tumor. It can be either a germline or a somatic mutation.

BRCA wild type (BRCA^{wt}) – A tumor which does not possess either a deleterious or suspected deleterious germline or a somatic BRCA mutation.

Homologous recombination deficiency (HRD) – Dysregulation in the homologous recombination pathway (due to genetic mutations or alterations) leading to cellular genomic instability and an inability to efficiently repair damaged DNA. HRD positive cells are more susceptible to the effects of DNA damaging agents such as platinum agents or PARP inhibitors.

HRD positive – HRD positive status may be determined by the myChoice HRD test. Any tumor that scores ≥ 42 or has a deleterious or suspected deleterious BRCA1/2 mutation (germline or somatic) would be considered HRD positive via this test.

HRD negative – HRD negative status may be determined by the myChoice HRD test. Any tumor that scores < 42 and does not possess a deleterious or suspected deleterious BRCA1/2 mutation would be considered HRD negative via this test.

3. INTRODUCTION

This statistical analysis plan (SAP) describes the analytical methods to be used for the data from TESARO, Inc. Protocol PR-30-5011-C and includes a detailed description of data handling rules, hypotheses to be tested, analysis populations, and statistical methods.

The SAP is based upon the following study documents:

- Study Protocol Version 6.0 dated 9 March 2016
- Electronic Case Report Form (eCRF) Version 2.0 dated 23 October 2014

Separate analysis plans describe the analyses of specific variables and sub-studies of PR-30-5011-C, as follows:

- Safety data analysis for the Food Effect (FE) sub-study
- Corrected QT (QTc) sub-study (efficacy and safety)
- ECG and PK data analysis for a subset of 24 patients from the main PR-30-5011-C study and patients in the FE sub-study
- Patient-reported outcomes (PROs).

This study is double-blind, randomized, and placebo-controlled, in platinum sensitive ovarian cancer patients who have either a germline BRCA mutation (gBRCA^{mut}) or a tumor with high grade serous or high grade predominantly serous histology but without the gBRCA^{mut} (non-gBRCA^{mut}). The treatment allocation is 2:1 for niraparib:placebo. Additional requirements for patients include, but are not limited to:

- Received at least 2 platinum-based regimens, with the last regimen being platinum-based therapy.
- Had a response (Response Evaluation Criteria in Solid Tumors [RECIST] complete response [CR] or partial response [PR]) to their last regimen.
- Have no measurable lesion > 2 cm.
- Normal cancer antigen 125 (CA-125) (or > 90% decrease during the last platinum regimen which is stable for at least 7 days).

The study is intended to assess whether maintenance treatment (post response on chemotherapy) with niraparib will extend progression-free survival (PFS) in this population vs. no treatment. This objective will be independently evaluated in gBRCA^{mut} and non-gBRCA^{mut} patient cohorts. In the non-gBRCA^{mut} cohort the primary end point statistical analysis will be performed in a hierarchical manner, with a test for the HRD positive subset (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) performed first, followed by a test of the overall non-gBRCA^{mut} cohort if the first test is statistically significant at a one-sided α level of 0.025. Both HRD and gBRCA mutation analyses are performed by a centralized test at a central reference laboratory. Cohort assignment is determined prior to randomization based on reference laboratory results for gBRCA mutation analysis. Patients assigned to the non-gBRCA^{mut} cohort whose HRD status cannot be determined (e.g., due to insufficient tissue) will be included in the test of the overall

non-gBRCA^{mut} cohort but excluded from the test for the HRD positive subset. These patients will also be analyzed as a separate subset.

Patients with Integrated BRACAnalysis® result will be assigned within a gBRCAmut cohort or a non-gBRCAmut cohort as per Table 1.

Table 1: Cohort Assignment Based on Myriad Report

MYRIAD Report Results	Cohort for Randomization
Positive for a Deleterious Mutation	gBRCA^{mut} cohort
Genetic Variant, Suspected Deleterious	gBRCA^{mut} cohort
Genetic Variant, Favor Polymorphism	Non-gBRCA^{mut} cohort
Genetic Variant of Uncertain Significance	Non-gBRCA^{mut} cohort
No Mutation Detected	Non-gBRCA^{mut} cohort

A separate randomization list was created for each cohort. Within each cohort randomization was stratified by the following stratification factors:

- Time to progression after the penultimate (next-to-last) platinum therapy before study enrollment:
  - 6 to < 12 months.
  - ≥ 12 months.
- Use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes or no).
- Best response during the last platinum regimen (CR or PR).

Clinic visits are scheduled for the beginning of every cycle (4 weeks ±3 days). A RECIST (version 1.1) tumor assessment via computed tomography (CT) or magnetic resonance imaging (MRI) scan of abdomen/pelvis and clinically indicated areas is required at the end of every 2 cycles (8 weeks with a window of ±7 days from date of visit) through Cycle 14, then at the end of every 3 cycles (12 weeks with a window of ±7 days) until progression. If a patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up, scans should continue at the specified intervals. The PROs (Functional Assessment of Cancer Therapy – Ovarian Symptom Index [FOSI], European Quality of Life scale, 5-Dimensions [EQ-5D-5L], and a neuropathy questionnaire) are collected in a coordinated fashion with RECIST tumor imaging while on study treatment and following discontinuation of treatment, regardless of progression status (at the nearest study visit to the imaging exam after every 2 cycles through Cycle 14, then after every 3 cycles). If the patient discontinues study treatment, assessment of PROs is performed at that time and then 8 weeks (±2 weeks) later, regardless of subsequent treatment. After treatment discontinuation, PROs, response, tolerability with subsequent anti-cancer treatment, and survival will continue to be collected.

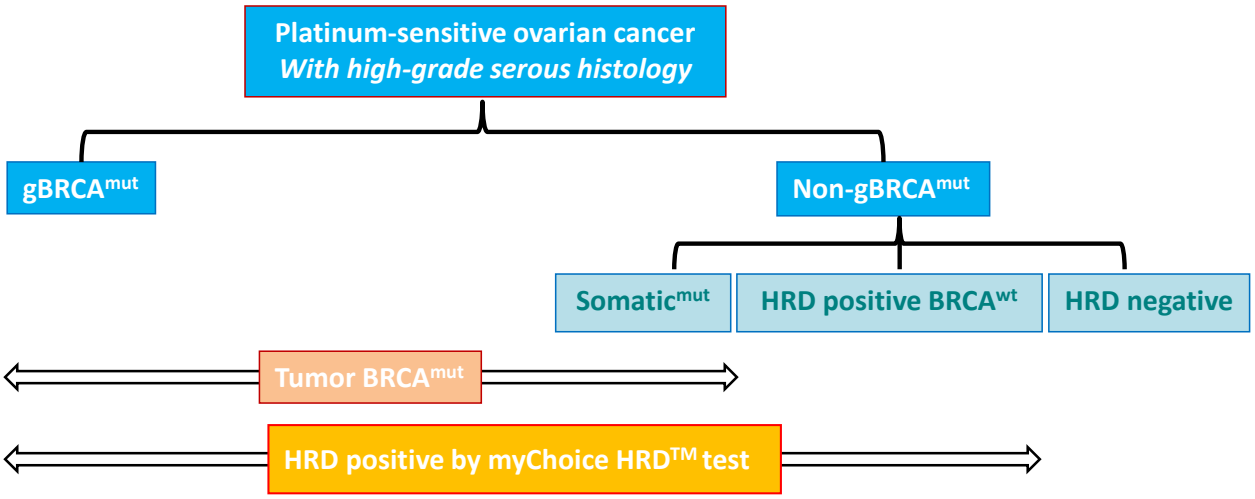
An independent data monitoring committee (IDMC) was established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the patients participating in the study. The IDMC was tasked with making a recommendation to the Sponsor to continue or stop the trial based on their regular

review of safety information and one interim analysis of efficacy data from the gBRCA^{mut} cohort. Based on the feedback from the United States (US) Food and Drug Administration (FDA), and to maintain the robustness of the study, the interim analysis for efficacy was not conducted.

4. STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of niraparib as maintenance therapy in patients who have platinum sensitive ovarian cancer, as assessed by the prolongation of PFS. This objective will be independently evaluated in a cohort of patients with deleterious germline BRCA mutation (gBRCA^{mut}) and in a cohort of patients who have high grade serous or high grade predominantly serous histology but without such gBRCA mutations (non-gBRCA^{mut}).



The statistical analysis of the primary endpoint of PFS for the gBRCA^{mut} cohort will be performed for the overall gBRCA^{mut} cohort. Originally, the gBRCA^{mut} cohort sample size was determined based on the assumption that niraparib will result in an improvement in median PFS of 4.8 to 9.6 months (corresponding to a hazard ratio [HR] of 0.50 for niraparib relative to placebo). For a true HR of 0.50, 140 PFS events will provide > 95% power assuming a 2:1 randomization (1-sided alpha = 0.025).

During the course of the study and in a face-to-face Type C meeting with the FDA, the following feedback was obtained:

- The gBRCA cohort may be overpowered to detect a small PFS difference that may not be clinically relevant.
- The Sponsor must provide evidence to determine whether there may be a differential response to niraparib in the patient population with gBRCA mutation vs somatic^{mut} vs HRD positive^{wt}.

In order to address this feedback, the Sponsor plans to reduce the power of the gBRCA^{mut} cohort from > 95% to 90%, as well as for the hierarchically primary analysis of the HRD-positive subset of the non- gBRCA^{mut} cohort, and conduct analyses for both the cohorts at the same time. In addition, analyses of efficacy will be performed to determine if there is a different responsiveness to niraparib in the various mutational subgroups, as requested by the FDA; some of these analyses may be descriptive only since they were not pre-specified in the protocol and sample sizes may be small.

The revised sample size for this test is approximately 100 PFS events in the gBRCA cohort, and in the HRD+ subset of the non- gBRCA^{mut} cohort, to maintain 90% power.

At the time the study protocol was developed, it was unclear which of several candidate biomarkers may have been appropriate for assessment as a companion diagnostic (CDx) to the use of niraparib as maintenance treatment in patients who had received multiple platinum therapies. The non-gBRCA^{mut} cohort was designed such that the effect of a biomarker classifier of DNA repair status may be evaluated.

Subsequently, a DNA-based assay that is capable of detecting HRD regardless of its etiology or mechanism has been developed by Myriad Genetics, Inc. (Salt Lake City, UT) and is called myChoice HRD^{TM}. As a result, the initial study objective that was to have used study data to choose a biomarker and determine an appropriate cut-off for positivity is no longer required.

This assay has applicability in the evaluation of ovarian and breast cancer therapies. Myriad has shown that an elevated HRD score is highly associated with defects in homologous recombination pathway genes in both breast and ovarian cancer, and is therefore likely to predict response to niraparib. Based on work by Myriad, a threshold value has been independently determined to classify patients into HRD positive versus HRD negative (Timms et al, 2014).

Niraparib has been evaluated in a number of patient-derived xenograft models of breast and ovarian cancer. All models exhibiting sensitivity to niraparib have shown a high degree of genomic instability, characterized by an HRD score of 42 or greater (Wang et al, SABCS 2014 and Haluska et al, EORTC-NCI-AACR poster 2014).

The myChoice HRD™ test is a next generation sequencing (NGS) test using DNA extracted from formalin fixed paraffin-embedded tumor tissue that identifies homologous recombination deficient breast and ovarian cancer by detecting variants in the *BRCA1* and *BRCA2* genes of the tumor and quantitating genomic instability of the tumor. Patients with a positive HRD result include patients with tumors having a BRCA^{mut} (gBRCA^{mut} and/or somatic BRCA^{mut}) or a score of ≥ 42. These individuals are considered to have a homologous recombination deficient tumor. Tumors with a score below 42 and no identified deleterious or suspected deleterious BRCA1/2 mutation are considered HRD negative.

Tumor tissue from all patients within the 2 cohorts will be tested with the myChoice HRD™ test.

The statistical analysis of the primary endpoint of PFS for the non-gBRCA^{mut} cohort in the NOVA study will be performed in a hierarchical manner, with a test for the HRD positive subset (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) performed first, followed by a test of the overall non-gBRCA^{mut} cohort if the first test is statistically significant. Details of these primary objectives and the statistical methods used for evaluation are presented in Section 6.6.1.

An exploratory, descriptive analysis of PFS, overall survival (OS) and all other secondary endpoints will be performed for patients within all the subgroups (somatic BRCA^{mut}, HRD positive/BRCA^{wt}, and HRD negative). Per the FDA's request, the analyses of the overall non-gBRCA^{mut} cohort and for somatic BRCA^{mut} and HRD positive/BRCA^{wt} and HRD negative subsets within the non-gBRCA^{mut} cohort will be conducted at the same time.

An exploratory analysis will assess the efficacy of niraparib in patients in the non-gBRCA^{mut} cohort who exhibit HRD pooled with the gBRCA^{mut} cohort, and for tumor BRCA^{mut} an

additional secondary analysis for submission to the European Medicines Agency (EMA) will be performed by pooling somatic $BRCA^{mut}$ with the $gBRCA^{mut}$ cohort.

4.2 Secondary Objectives

Main secondary objectives include the following:

- To evaluate additional measures of clinical benefit, including PROs, progression-free survival 2 (PFS2), time to first subsequent therapy (TFST), time to second subsequent therapy (TSST) (as defined in Section 5.1.2), chemotherapy-free interval (CFI), and OS in the different subgroups for the study.
- To evaluate the safety and tolerability of niraparib compared to placebo in the different subsets for the study.
- To evaluate concordance of a candidate companion BRACanalysis diagnostic test compared to the centralized myChoice HRD mutation test used in this study, if needed.

Two additional objectives of the NOVA study, to evaluate QTc in a subset of niraparib-treated ovarian cancer patients, and to assess the effect of a high fat meal on the PK of a single 300 mg dose of niraparib in patients with ovarian cancer, will be addressed in separate statistical analysis plans.

5. EFFICACY AND SAFETY VARIABLES

5.1 Efficacy

5.1.1 Primary Efficacy Variable

Progression-free survival is the primary efficacy variable and defined as the date of randomization to the earlier of either date of progressive disease (PD) or death by any cause. Progression-free survival (months) will be calculated as:

(PD/Death date - randomization date + 1) / 30.4375.

Determination of the date of PD for the primary efficacy endpoint will be determined by central blinded review. This review will be based first, but not exclusively, on imaging assessment according to RECIST v.1.1 (Appendix A) criteria. Because of the pelvic location of the primary tumor and the frequent occurrence of peritoneal disease, imaging may not always be reliable for documentation of PD.

Criteria other than RECIST may be applied to define PD; thus, PD will be determined if at least 1 of the following criteria is met:

1. Tumor assessment by CT/MRI unequivocally shows PD according to RECIST v.1.1 criteria (Appendix A, Table 6) as confirmed by the central independent radiologists.
    a) If a patient had a CT/MRI of the abdomen/pelvis and clinically indicated areas within the 28-day screening window before Cycle 1/Day 1 but prior to signing the main ICF, the patient is not required to complete an additional CT/MRI scan for study screening. CT/MRI scans completed during screening prior to signing the main ICF must have been performed and be able to be submitted per the image acquisition guidelines.
2. Additional diagnostic tests (e.g., histology/cytology, ultrasound techniques, endoscopy, positron emission tomography [PET]) identify new lesions or determine existing lesions qualify for unequivocal PD AND CA-125 progression according to Gynecologic Cancer Intergroup (GCIG) criteria (Table 2).
3. Definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes ([a] intractable cancer-related pain; [b] malignant bowel obstruction/worsening dysfunction; or [c] unequivocal symptomatic worsening of ascites or pleural effusion) AND CA-125 progression according to GCIG criteria (Table 2).

Progressive disease will not be diagnosed in case of CA-125 progression in the absence of at least 1 of the criteria defined above. In order to declare PD using the criteria 2 and 3 above, both investigator and central independent clinician must agree on the progression of disease.

When required to determine progression, CA-125 levels should be evaluated ±2 weeks from the primary PD assessments (i.e., diagnostic test or clinical parameters) and must be confirmed by a second determination at least 7 days later. In case assessments of CA-125 levels occur greater than 2 weeks from the primary PD assessments, the date of the primary assessment of PD will be used to define the date of PD. GCIG criteria for CA-125 progression are shown in Table 2.

Table 2: CA-125 Progression[1]

Baseline	Post-Baseline Results *(Requires 2 CA-125 results ≥ 7 days apart,* within ± *14 days of clinical documentation)*		
	Last value prior to < 14 days to PD	**Initial and if applicable confirmation (± 14 days to PD)**	**Confirmation (≥14 Days to PD)**
> ULN	Within normal range	≥ 2 x ULN	≥ 2 x ULN
> ULN	Missing or > ULN	≥ 2 x nadir	≥ 2 x nadir
≤ ULN	Any (missing or not)	≥ 2 x ULN	≥ 2 x ULN

[1] According to Gynecologic Cancer Intergroup (GCIG) criteria

The central blinded clinician will review clinical and radiographic data supporting clinical progression and will determine if the patient had protocol-defined clinical progression, and at which time point. The central blinded clinician will not provide an opinion on the presence or timing of radiographic progression. The central blinded clinician may not modify lesion selection performed by the independent radiologists. They may not select target lesions from clinical sources, even if no radiographic target lesions are present as determined by the independent radiologists. If lesions assessed by physical exam are documented by the investigator sites and the assessments provided to the central blinded clinician, they will be assessed qualitatively and incorporated into the central blinded clinician's assessment.

For the purpose of the primary endpoint, the date of progression will be determined using information from radiology review, the central blinded clinician, and the investigator at the site. For radiology progression date, the central review will be used. For clinical progression, both the central blinded clinician review and the investigator review will be used. If the investigator does not determine clinical PD, this cannot be overturned by the central blinded clinician determination of PD. Alternatively, an investigator assessment of PD will be invalidated if it is not substantiated by central blinded clinician. The actual date of progression will be designated by either the radiology review or the investigator; the central blinded clinician cannot specify the date of progression, he/she can only verify whether or not PD occurred at specified dates (±7 days). For the purpose of determining the date of progression, Table 3 will be used.

Table 3: Progressive Disease

Central Reviewers		Investigator	Date of PD
Radiologist	**Blinded Clinician**		
PD	PD	Clinical PD	Earliest of Radiology and Investigator
PD	No PD	Clinical PD	Radiology
PD	PD	Non-PD	Radiology
PD	No PD	Non-PD	Radiology
Non-PD	PD	Non-PD	No PD
Non-PD	No PD	Clinical PD	No PD
Non-PD	PD	Clinical PD	Investigator

Censoring for PFS will occur for the following reasons at the following time points:

1. No adequate post-baseline radiological assessments; therefore PFS is censored at the date of randomization unless death occurred within 17 weeks of randomization (in which case the death is an event) or clinical PD is determined.
2. Patients known to be alive and known not to have started new (non-protocol) anti-cancer treatment, who are progression-free, and who have a baseline and at least 1 post-dosing radiological assessment, are censored at the date of the last radiological assessment that verified lack of PD.
3. Patients starting new anti-cancer treatment prior to progression or death are censored at the date of last radiological assessment documenting no progression prior to the new treatment.
4. Documentation of progression or death after an unacceptably long interval (> 17 weeks, i.e., 2 consecutive missed or indeterminate overall response assessments) since the last radiological assessment will be censored at the date of last radiological assessment documenting no progression.
5. Discontinuation of study treatment due to disease progression according to the investigator that was later overturned during central blinded review will be censored on the date of last radiological assessment.

Inter-rater agreement between central and investigator determination of overall response will be assessed. Summaries will include a contingency table of investigator versus central overall response, and a table presenting the simple kappa coefficient (calculated by treatment arm) and 95% CI, and p-value from the test of kappa = 0.

5.1.2 Secondary Efficacy Endpoints

5.1.2.1 Progression-free Survival 2

PFS2 is defined as the date of randomization in the current study to the earlier date of assessment of progression on the next anti-cancer therapy following study treatment or death by any cause.

1. Patients who do not receive a next anti-cancer therapy due to death on the current study will have PFS2 set equal to the date of death.
2. Progression will be determined by the investigator via clinical and radiographic assessment using the same criteria as used in the current study (clinic and radiology notes may serve as source documentation).
3. If progression cannot be determined, the start date of the second line of subsequent anti-cancer therapy will be used as a surrogate for PD.
4. If date of progression, date of death, and start date of the second line of subsequent anti-cancer therapy are unknown, then PFS2 will be censored at the stop date of the first line of subsequent anti-cancer therapy. If the stop date is unknown, PFS2 will be censored on the last contact date.

Progression-free survival 2 (months) will be calculated as:

(PD/Death date on next anti-cancer therapy - randomization date + 1) / 30.4375.

5.1.2.2 Chemotherapy-free Interval

The CFI is defined as the time from last platinum dose until initiation of next anticancer therapy (excluding maintenance therapy). If no anticancer therapy (excluding maintenance therapy) is initiated, CFI will be censored on the last date of treatment on the current study. In addition, CFI relative to CFI from penultimate platinum regimen will be evaluated (clinic notes may serve as source documentation).

The CFI (months) will be calculated as:

(Next Anti-cancer start date – Last Prior Platinum end date + 1) / 30.4375.

5.1.2.3 Overall Survival

Overall survival is defined as the date of randomization to the date of death by any cause. Patients known to be alive will be censored at the last known survival follow-up date. The OS (months) will be calculated as:

(Death date - randomization date + 1) / 30.4375.

5.1.2.4 Time to CA-125 Progression

Time to CA-125 progression is defined as the date of randomization to the date of progression as defined by CA-125 (see Table 2). Time to CA-125 progression will be calculated as:

(Laboratory collection date for CA-125 progression - randomization date + 1) / 30.4375.

Patients known to be alive but who have not progressed by CA-125 criteria will be censored at the last known assessment date. Patients who die will be censored at the date of death.

5.1.2.5 Time to First Subsequent Therapy

TFST is defined as the date of randomization to the earlier of the start date of first follow-up anti-cancer treatment (FUACT) or death. Patients alive and not starting a first FUACT will be censored at the date last known to be alive. TFST (months) will be calculated as:

(Start date of first FUACT – randomization date + 1)/30.4375.

5.1.2.6 Time to Second Subsequent Therapy

TSST is defined as the date of randomization to the earlier of the start date of second FUACT or death. Patients alive and not starting a second FUACT will be censored at the date last known to be alive. TSST (months) will be calculated as:

(Start date of second FUACT – randomization date + 1)/30.4375.

5.1.2.7 BRCA and HRD Concordance

Concordance of myChoice HRD testing with centralized BRACAnalysis testing, with respect to identifying gBRCA^{mut} patients, will be evaluated.

5.1.2.8 Functional Assessment of Cancer Therapy - Ovarian Symptom Index

The FOSI is a validated 8-item measure of symptom response to treatment for ovarian cancer (Beaumont et al, 2007) based on a subset of questions from the FACT-O questionnaire. Patients respond to their symptom experience over the past 7 days using a 5-point Likert scale of CCI CCI to CCI For items 1 through 6 and item 8, the score used for calculating the

total score is the difference between the patient's response and 4. For item 7, the score used for calculating the total score is the patient's response. The total score is calculated by multiplying the sum of all items scored by 8 and dividing the result by the number of responses. If 5 or more responses are recorded, the FOSI can be scored; otherwise, the FOSI score is recorded as missing. The FOSI score range is CCI to CCI

In addition to analyzing the overall FOSI score, analyses of the following specific questions will be performed: CCI CCI ” as these questions are of particular interest when determining the impact of maintenance therapy on quality of life (QOL).

5.1.2.9 EQ-5D-5L

The EQ-5D-5L (EuroQol, 1990) measures the patient’s perceived health state today in the following 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain has 5 possible levels: CCI (level 1), CCI (level 2), CCI (level 3), CCI (level 4), and (level 5) CCI problems. Each domain is assigned a level, which are combined to create a 5-digit number describing the patient’s health state (e.g., 11111, 12345). For each patient, an index value is determined from the health states using the US value set (Szende et al, 2014). In addition, a visual analog scale (VAS) score is included in the scale, which measures current health status from 0 to 100 where 0 is given the verbal label CCI and 100 is given the label CCI

5.1.2.10 Neuropathy Questionnaire

A neuropathy questionnaire measures the patient's symptom experience over the past 7 days using a 5-point Likert scale of CCI (0) to CCI (4). There are 2 items, which ask if CCI

5.1.3 Exploratory Endpoints

The following endpoints were not specified in the protocol but are included because they may be helpful in the interpretation of study results or in the design of future studies.

CCI

CCI

[redacted]

5.2 Safety

5.2.1 Exposure to Study Drug

Exposure to study drug will be captured by a variety of endpoints characterizing the number, duration, and amount of study drug taken during the study:

- Number of cycles started.
- Total Duration (calculated as Last dose date - First dose date minus any skipped or interrupted + 1).
- Dose Intensity (mg/day) will be calculated as the sum of total daily doses ingested divided by Total Duration.
- Relative Dose Intensity (%) will be calculated as (Dose Intensity / 300) × 100.
- Dose reductions, defined as:
    - Dose consumed is less than prescribed for any reason;
    - Dose consumed is less than prescribed due to adverse event (AE).
- Dose interruptions, defined as:
    - Dose consumed is 0 mg for any reason (includes missed doses);
    - Dose consumed is 0 mg due to AE (planned interruptions include dose interruption after a Grade 3 or 4 [defined in the next section] non-hematologic AE, which the investigator considers to be related to administration of study drug, or dose interruption due to hematologic toxicity as defined in Table 3 of the protocol [amendment 6]).

5.2.2 Adverse Events

Adverse events, including abnormal hematologic and chemistry laboratory results, will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) classification system Version 18.0. The severity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02. Adverse events leading to death or discontinuation of study treatment, events classified as CTCAE Grade 3 or higher, study treatment-related events, adverse events of special interest (AESI) (see Table 5), serious AEs (SAEs), and AEs leading to dose interruption, dose reduction and discontinuation of treatment will be presented.

Treatment-emergent AEs (TEAEs) are AEs that meet 1 of the following criteria:

- Occurred for the first time after the start of study treatment and within 30 days following the final dose of study treatment and were not seen prior to the start of treatment.
- Were seen prior to the start of treatment but increased in CTCAE severity or were deemed by the investigator as related to study treatment during study treatment.

Note: If the start date of an AE is partially missing and treatment emergence cannot be determined (i.e., the partial date is uninformative), the AE will be considered a TEAE.

Adverse events will be collected from the time of signing the main ICF through the end of treatment (EOT) visit. New SAEs (including deaths) will be collected for 30 days after the EOT visit. Any AEs recorded in the database that occur from the time of main study informed consent to first dose will be listed only; they will not be included in safety analyses. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

Drug related TEAEs are defined as TEAEs considered at least possibly related to treatment as judged by the investigator or relationship was missing. Events that are a continuation of laboratory abnormalities are not considered drug-related unless there is an increase in severity and the increase is judged by the investigator to be caused by the treatment.

Exposure adjusted incidence rate will be analyzed as the number of patients experiencing the AE divided by the person-time at risk expressed as person exposure years, which is defined as follows: for patients experiencing an AE, time from first dose of study medication to first onset of the AE (converted to years); for patients completing the study, time from first to last dose of study medication (converted to years); for patients still on study, time from first dose of study medication to the visit immediately following the last visit that study drug was dispensed (converted to years).

5.2.3 Laboratory Assessments

Laboratory assessments will be performed locally at each center's laboratory by means of their established methods. All laboratory values will be converted to international system or units (SI units) and classified as normal, low, or high based on normal ranges supplied by the local laboratories and upon employing standardization. Laboratory assessments will be assigned to a Cycle based on the collection date of the sample relative to the start dates of the Cycle based on study drug dispensation.

When local laboratories report different reference ranges for a particular test, these results will be normalized prior to calculating changes from baseline (Chuang-Stein, 2001). The reference range used by the majority of laboratories will be used as the "standard reference range" for a particular test. If 2 or more reference ranges are used by an equal number of laboratories, or no majority exists, the widest reference range will be used as the "standard reference range." Results from laboratories which use a reference range different from the "standard reference range" will be converted using the following formula:

$$x' = \max\left(0,\ \frac{x - \mathrm{lLLN}}{\mathrm{lULN} - \mathrm{lLLN}} \times (\mathrm{sULN} - \mathrm{sLLN}) + \mathrm{sLLN}\right),$$

where x is the result reported by the local laboratory; x' is the normalized result; lLLN and lULN are the lower and upper limits of normal from the local laboratory, respectively; and sLLN and

sULN are the lower and upper limits of normal from the "standard reference range." Normalized laboratory values will be used to calculate summary statistics; however, shift analyses and patient listings of laboratory data will be based on the values and normal ranges reported by the local laboratories, expressed in SI units.

The following laboratory values will be collected and analyzed: complete blood cell count (hemoglobin, platelets, mean platelet volume, mean corpuscular volume, white blood cells, and differential white cell counts), coagulation factors (activated partial thromboplastin time and international normalized ratio), serum chemistry (sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyl transferase, alkaline phosphatase, aspartate aminotransferase [AST], alanine aminotransferase [ALT], urea or blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase), and urinalysis (specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen, and bilirubin).

5.2.4 Electrocardiogram Measurements

The ECG measurements, including PR interval, QT interval, RR interval, and QRS complex, will be calculated by the local clinical site. QTc will be used for the data analysis and interpretation. Commonly used techniques including Bazett's (QTcB) and Fridericia's (QTcF) methods will be calculated within the electronic data capture system. QTcF will be used for the primary QT evaluation.

5.2.5 Pharmacokinetics

The PK analyses are specified in a separate analysis plan.

6. STATISTICAL METHODS

Summaries of demographic, disposition, baseline, efficacy, and safety data will be provided for both the gBRCA^{mut} and non-gBRCA^{mut} cohorts. In the non-gBRCA^{mut} cohort, patient data will be summarized for the somatic BRCA^{mut} and HRD positive/BRCA^{wt} and HRD negative subsets and overall. Efficacy and safety data will be analyzed separately for the all the subsets within the non-gBRCA^{mut} cohort; but may be also be combined across cohorts. The Food Effect Substudy, QTc Safety Substudy, PK, pharmacodynamic, and biomarkers data analyses will be conducted under separate analysis plans. Efficacy data will be analyzed for the intent-to-treat (ITT) and per-protocol (PP) populations, and safety data analysis will be performed on the Safety population (SAF). The analyses of the overall non-gBRCA^{mut} cohort and for all the subsets within the non-gBRCA^{mut} cohort will be conducted at the same time.

6.1 Study Populations

Patients not randomized will not be included in any analysis population. Ingesting study drug (i.e., niraparib or placebo) will be defined as ingesting any portion of the study drug regardless of subsequent vomiting.

6.1.1 Intent-to-Treat Population

The ITT population will be defined as all randomized patients, and patients will be analyzed according to the study drug assigned via randomization even if no study drug was ingested. Patients who were incorrectly stratified during randomization will be analyzed and presented under the stratum assigned during randomization.

6.1.2 Per-Protocol Population

The PP population will be defined as all patients randomized in the main study who did not have major protocol deviations that may significantly impact the interpretation of efficacy results, as defined in Section 6.3.2.

Patients excluded from the PP population will be identified prior to database lock and treatment unblinding and release for analysis. Protocol deviation listings and analysis population classifications will be produced. A blinded review of these data will be performed to decide if any patient data will be excluded from the PP population. The review process (including reviewers) and exclusion decisions will be documented. PP analyses will be used as supportive to the primary ITT analyses.

Patients who were incorrectly stratified during randomization will be analyzed and presented under the correct stratum.

6.1.3 Safety Population

The SAF population will be defined as all patients who ingested any amount of study drug. The SAF population will be the primary analysis population for the safety and drug exposure analyses. Patients will be analyzed according to the study drug consumed (i.e., as treated) and the stratum to which they were randomized, even if the stratum was incorrect. Patients randomized to placebo who ingested any amount of niraparib will be analyzed and presented with the niraparib group.

6.2 General Considerations

Separate displays will be presented for gBRCA^{mut} and non-gBRCA^{mut} cohorts; within the non-gBRCA^{mut} cohort, patient data will be presented for patients who are HRD positive (as well as the breakdown of HRD+ into somatic BRCA^{mut} and HRD positive/BRCA^{wt}) and HRD negative as well as overall for the cohort. Each display will be presented in the following order: niraparib, placebo, and overall for all proposed efficacy and safety analyses in the plan.

- P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places. However, if a p-value is presented to 4 decimal places in the analysis output, it will not be rounded again. Instead, it will be presented to 4 decimal places. P-values less than 0.001 will be presented as "< 0.001."
- Confidence intervals (CIs) will be presented to 1 more decimal place than the raw data.
- All safety data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. Post-treatment study days are numbered relative to the last dose and are designated as Day +1, Day +2, etc.
- Weeks will be calculated as number of days divided by 7.
- Months will be calculated as number of days divided by 30.4375.
- Years will be calculated as number of days divided by 365.25.
- Treatment cycles are 28 days long. While dose interruptions are permitted, the start of each cycle cannot be delayed and is fixed relative to Cycle 1/Day 1.
- All report outputs will be produced using SAS® Version 9.3 or a later version in a secure and validated environment.
- Baseline measurement is defined as the last available observation prior to randomization. For ECG, the average of each of the triplicate ECG measures will be used for analysis.
- End of Study is defined as the last available post-treatment assessment.
- Unscheduled assessments will be included in listings only, unless the visit is considered part of the baseline definition, CA-125 calculations, or an AE.
- All tables, figures, and listings (TFL) will include footers at the bottom of the page reflecting the path and date of the datasets, datasets used to generate the TFL, date and time of the generation of the output.

6.2.1 Continuous Data

Continuous data will be summarized as: n, mean, standard deviation (StdDev), lower quartile (Q1), median, upper quartile (Q3), minimum, and maximum, unless otherwise stated. Mean and quartiles will be reported to 1 more decimal place than the raw data, while the StdDev will reported to 2. Minimum and maximum values will be reported to the same number of significant digits as the raw data. The maximum number of decimal places reported shall be 4 for any summary statistic. All continuous parameters will have the number of patients reporting that particular parameter (i.e., n).

For continuous variables, change from baseline may be analyzed at a single timepoint and/or over time. Analysis of continuous variables and change from baseline at a single timepoint will be performed using an analysis of covariance (ANCOVA) model including treatment as a fixed effect and baseline as a covariate, unless stated otherwise. Analysis of continuous variables over time will be analyzed using a repeated measures model including treatment, visit, and treatment-by-visit interaction as fixed effects and baseline as a random effect, unless stated otherwise. In both instances the baseline stratification factors will be included as fixed effects in the model.

An unstructured variance-covariance structure will be used to account for the relationship between repeated assessments where estimation will be carried out using restricted maximum-likelihood estimation. If the model does not converge with the unstructured covariance structure, a spatial covariance structure will be considered and, if that does not converge, an autoregressive heterogeneous, autoregressive, or compound symmetry variance/covariance matrix will be applied (in that order). The Kenward-Roger approximation for the denominator degrees of freedom will be used.

Adjusted means (least-squares means [LSM]), least-squares standard errors (LSSE), least-squares mean difference and standard error, along with 95% CIs will be reported by treatment group overall and by treatment group and visit, where applicable. The LSMEAN treatment*visit / slice = visit will be used to test for differences between treatment groups at each visit. LSMEANS and 95% CIs will be displayed using line graphs for scheduled visits only, where EOT is mapped to the next planned visit. Number of observations at each scheduled timeline will be displayed at the bottom of each graph. Unscheduled visits will not be displayed. Percent change from baseline may be summarized using descriptive statistics but will not have formal analysis applied.

6.2.2 Categorical Data

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Percentages will be based on the patients with a non-missing parameter. Percentages will be reported to 1 decimal place. Percentages will not be presented for zero counts.

Binary data will be analyzed and compared between the treatment groups using the normal approximation to the difference in binomial proportions.

6.2.3 Time-to-Event Data

Time-to-event data will be compared using a stratified log-rank test where stratification factors are those used for randomization, unless otherwise specified. In addition, time-to-event endpoints may also be compared between the 2 treatment arms using an unstratified log-rank test where appropriate. Cox proportional hazard models may be used to explore the potential influences of baseline stratification factors on time-to-event endpoints. When applicable, the estimated hazard ratio (HR) and 2-sided 95% CI will be provided. Graphical displays using the Kaplan-Meier (KM) methods, median event times, number of events and censored observations, and 2-sided median 95% CIs, based on the Brookmeyer-Crowley method, will be provided unless specified otherwise.

Estimates of the 1-year, 2-year, 3-year, 4-year, and 5-year (as data is available) survivor function may be estimated using the KM method and a 2-sided 95% CI for the log [-log(survival

probability)] calculated using a normal approximation and then back transformed to give a CI for specified survival time.

6.2.4 Missing and Partial Dates

Missing and partial dates will be queried. Imputed dates will be characterized as another numeric variable. Imputed date values will be performed according to the most conservative approach. If any date is imputed and requested on a listing the original non-imputed date will be provided on the same listing as reference. In general imputed dates will only be *used for analysis purposes*.

Missing dates will be imputed based on the following algorithm.

- If the day of the month is missing for any date used in a calculation, the first day of the month will be used to replace the missing day unless the calculation results in a negative time duration (e.g., date of resolution cannot be prior to day of onset). If the day of the month and the month is missing for any date used in a calculation, January 1 will be used to replace the missing date.

An imputed start date for FUACT will be compared to the EOT date. If the imputed FUACT start date is before the EOT date, the FUACT start date will be imputed as EOT date plus 1. This imputation will be used only to determine whether or not a PFS event should be censored.

6.2.5 Visit Windows

Visit windows will be applied to clinical laboratory, vital signs, ECG, and PRO endpoints. If multiple scheduled measurements are observed for a single visit the measurement closest to the scheduled date will be used. If dates are equally close the visit preceding the date will be used. Table 4 details the visit windows.

Table 4: Visit Windows (Inclusive)

	Screening (-28 to -1)	
-	**Randomization (-3 Days to 1st dose day)**	
Cycle	**Day 1**	**Day 15**
1	Day of First Dose (1)	13 to 17
2	27 to 31	41 to 45
3	55 to 59	69 to 73
4	83 to 87	97 to 101
5	111 to 115	125 to 129
6	139 to 143	153 to 157
7	167 to 171	181 to 185
8	195 to 199	209 to 213
9	223 to 227	237 to 241
10	251 to 255	265 to 269
n	28 day interval	28 day interval

6.3 Population and Disposition

Summaries of patient enrollment and disposition will be provided for both the gBRCA^{mut} and non-gBRCA^{mut} cohorts. In the non-gBRCA^{mut} cohort, patient data will be summarized for the somatic BRCA^{mut} and HRD positive/BRCA^{wt} and HRD negative subsets and overall for the cohort.

6.3.1 Patient Disposition

Patient disposition will be summarized for each cohort. The following summaries will be provided:

- Number screened and the number and percentage of patients in the ITT, SAF, and PP populations.
- Number and percentage of patients randomized but not treated.
- Number and percentage of patients discontinuing study and treatment, including the reason for early discontinuation.
- All deaths will be summarized (on-treatment, in follow-up, overall).
- Time to treatment discontinuation from randomization will be graphed using a KM plot, where patients not discontinuing treatment at time of analysis will be censored on the date of the last treatment received.
- Time to study discontinuation from randomization will be graphed using a KM plot, where patients not discontinuing study at time of analysis will be censored on the date of the last non-missing survival follow-up.

6.3.2 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as "minor" or "major." Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments, and therefore would result in a patient being excluded from the PP population. Major deviations will be identified and finalized prior to database lock and documented. Examples of major protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses are outlined below. Complete details will be included in a separate Protocol Deviation Plan, which will be appended to the final version of this SAP.

Major Protocol Deviation	**Population Exclusions**
Randomized but did not take any study medication	Exclude from SAF and PP
Consumed the incorrect study medication per randomization scheme	Exclude from PP
Major Protocol Violations	Exclude from PP
Non-compliant (< 80% compliant with intended study medication) other than as allowed by protocol	Exclude from PP
Took prohibited medication that impacts efficacy	Exclude from PP

The following protocol deviation summaries will be provided:

- Number and percentage of patients with a major protocol deviation by treatment group and type of deviation.

6.4 Statistical Analysis Considerations

6.4.1 Statistical Hypotheses

The primary statistical hypothesis for this study is to test for differences in PFS within each cohort using a stratified log-rank test.

- H_0: HR (niraparib/placebo) ≥ 1.
- H_a: HR (niraparib/placebo) < 1.

Stratification factors include:

- Time to progression after the penultimate platinum therapy before study enrollment at:
  - 6 to < 12 months.
  - ≥ 12 months.
- Use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes or no).
- Best response during the last platinum regimen (CR or PR).

6.4.2 Determination of Sample Size

The gBRCA^{mut} and non-gBRCA^{mut} cohorts are treated as 2 independent cohorts/studies where each cohort is allocated 1-sided alpha = 0.025. Each cohort will have a separate randomization and the primary PFS analysis will be performed separately for each cohort. For these sample size calculations, the assumptions used were based on published data provided for a placebo-controlled trial of olaparib against placebo in a similar maintenance setting (Ledermann et al, 2012).

The cohorts are sized to address the PFS endpoint and to ensure adequate data to monitor safety and OS. The gBRCA^{mut} cohort sample size is determined based on the assumption that niraparib will result in an improvement in median PFS of 4.8 to 9.6 months (corresponding to an HR of 0.50 for niraparib relative to placebo). For a true HR = 0.50, 140 PFS events will provide > 95% power assuming a 2:1 randomization (1-sided alpha = 0.025). The assumptions used when the study was initiated are as follows:

Approximately 180 gBRCA^{mut} patients will be enrolled over approximately 24 months with 140 PFS events expected to occur 33 months after the initial patient enrollment in the main study.

Subsequent to that, the FDA commented during a face-to-face Type C meeting that the gBRCA cohort may be overpowered to detect a small PFS difference that may not be clinically relevant.

In order to address this feedback, the Sponsor plans to reduce the power from > 95% to 90% and conduct analyses for both the cohorts at the same time. The new sample size for this test would be approximately 100 PFS events in the gBRCA cohort, to maintain 90% power.

The non-gBCRA^{mut} sample size was determined to maintain the intended hierarchical testing procedure under the assumption that approximately 40% of the non-gBRCA^{mut} cohort is expected to be classified as HRD positive subset (somatic BRCA^{mut} and HRD positive/BRCA^{wt}). PFS sample size for the HRD positive subgroup is determined based on the same PFS assumption used for the gBRCA^{mut} cohort. For a true HR = 0.50, based on a median PFS of 9.6 months for the niraparib-treated patients and 4.8 months for placebo patients, in the non-gBRCA cohort who are HRD positive, 98 PFS events will provide 90% power assuming a 2:1 randomization (1-sided alpha = 0.025). The overall non-gBRCA cohort analysis would require 140 PFS events for > 95% power, again at a 1-sided $\alpha = 0.025$, under the assumption that the overall cohort median PFS for niraparib is 9.6 months. A total enrollment of 180 non-gBRCA^{mut} patients would be required. An additional 130 patients will be enrolled into the non-gBRCA cohort in order to obtain a sufficient number of events in the HRD positive subset. These patients will be enrolled over approximately 20 months with the required PFS events expected to occur 26 and 31 months after the initial enrollment for the overall non-gBRCA cohort and for the HRD positive subset (somatic BRCA^{mut} and HRD positive/BRCA^{wt}), respectively.

It is hypothesized that the HRD positive subset (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) of the non-gBRCA cohort may have a similar superiority in PFS for Niraparib against placebo; therefore, this number of events would be appropriate for the statistical comparison of Niraparib versus placebo in this subgroup as well.

6.4.3 Data Monitoring and Interim Analysis

An IDMC will monitor the safety of the patients on a periodic basis. The IDMC will determine whether the trial should be terminated based on ongoing reviews of safety data. If the results at the interim analysis or at any time during the study indicate serious safety concerns, the Sponsor may elect to stop the clinical trial.

An interim analysis was originally planned when approximately 60% of the total 140 PFS events (85 PFS events) had occurred. However, based on advice from the US FDA and given the enrollment in the entire study, a decision was reached to not conduct an interim analysis for the gBRCA cohort. Patients will be followed for OS after the PFS analysis. The final analysis of OS for the clinical study report will be done after the maturity of the primary endpoint (PFS) and after all patient data have been submitted and cleaned, unless other arrangements are agreed upon by the Sponsor. The analysis will be performed at the time of official data base release.

6.4.4 Handling of Dropouts or Missing Data

Handling of missing or partial dates is discussed in Section 6.2.4.

If baseline tumor assessment is inadequate, the patient cannot be assessed for response, where an inadequate baseline assessment includes:

- Not all required baseline assessments were done.
- Assessments were done outside the required window.
- Measurements were not provided for 1 or more target lesions.
- One or more lesions designated as target were not measurable.

6.4.5 Multicenter Studies

For the purpose of the summaries and analyses, the term 'Center' will be used to define each investigator site. All sites will be pooled together in the efficacy analyses. Consistency of treatment effects across geographic regions and assessment of site to site variability may be explored. Geographical region will be defined according to the following table:

Region	**Country**
Region 1: USA and Canada	Canada, USA
Region 2: Western Europe, Australasia and Israel	Austria, Belgium, Denmark, France, Germany, Israel, Italy, Norway, Spain, Sweden, and United Kingdom
Region 3: Eastern Europe, Latin America and Asia	Hungary, Poland

6.4.6 Adjustments for Covariates

All Cox Proportional Hazards Models will include randomization stratification factors as "strata" in SAS PROC PHREG. Unless otherwise noted, the randomization stratification factors will be included as covariates in the analyses of all primary, secondary, and exploratory efficacy endpoints.

Potential influences of other baseline patient characteristics in addition to the pre-specified stratification factors, such as age, ethnic origin, ECOG performance status, geographical region, selected biomarkers, and other potential factors on the primary PFS and OS endpoints, may be evaluated in an exploratory manner by including them in Cox Proportional Hazards Models as covariates.

For each potential covariate, a statistical test for the presence of a treatment-by-covariate interaction will be performed, by including the interaction term in the primary analysis model. If any of the treatment-by-covariate interactions are found to be statistically significant at the 10% level ($p<0.10$), it will be retained in the final model; otherwise it will be excluded.

6.4.7 Multiple Comparisons/Multiplicity

Within each cohort (gBRCA^{mut} and non-gBRCA^{mut}) the overall family-wise Type 1 error rate will be controlled at 1-sided 0.025 significance level. For the non-gBRCA^{mut} cohort, a hierarchical testing method will be used to control Type 1 error, where the first statistical test will be performed on the HRD positive (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) subset, followed by a test on the entire non-gBRCA^{mut} cohort. Other endpoints will be statistically analyzed and used in support of the primary analysis. The analysis of tumor BRCA and the PRO outcomes will be considered as important secondary endpoints for a submission to the EMA.

6.4.8 Examination of Subgroups

Exploratory analyses using PFS and OS will be examined for each of the following subgroups: age (<65 years of age, ≥65 years of age), race (white, non-white), geographic region (as defined in Section 6.4.5), time to progression after the penultimate platinum therapy before study enrollment (6 to <12 months, ≥12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), best response during the last platinum regimen

(CR and PR), concomitant chemotherapy with platinum in the last and penultimate regimens (yes, no), the number of prior platinum regimens (2 and > 2) and duration of penultimate platinum therapy (< 6 months, ≥ 6 to <12 months, ≥ 12 months).

A test for a treatment by subgroup interaction will be provided for each subgroup separately. For each subgroup separately, the Cox proportional hazards model will be fitted and a table showing the HR and 95% CIs within each subgroup category will be provided. A statistical test for the presence of a treatment-by-subgroup interaction will be performed, by including the interaction term in the primary analysis model using Cox regression. If the treatment-by-subgroup interaction is found to be statistically significant at the 10% level ($p<0.10$), this may be taken as evidence of heterogeneity of the treatment effect across the subgroup categories, and conclusions based on the model with no interaction will be interpreted with caution. Kaplan Meier curves for each subgroup category will be provided.

The homogeneity of the treatment effect across the multiple subgroups analyzed will be investigated using graphical methods. A Forest plot will be produced that shows the results of all the subgroup analyses on the same graph for visual interpretation and descriptive comparison of subgroup results.

Within the non-gBRCA^{mut} cohort, an exploratory, descriptive analysis of PFS, OS and all other secondary endpoints will be performed for patients in the HRD positive subset (somatic BRCA^{mut} and HRD positive/BRCA^{wt}), and for HRD negative patients. Patients assigned to the non-gBRCA^{mut} cohort whose HRD status cannot be determined (e.g., due to insufficient tissue) will be summarized separately. Formal hypothesis testing will not be performed. The purpose of this analysis is to provide evidence of a consistent response to niraparib. A figure of the HR and 95% CI for all subgroup analyses will be produced.

An additional secondary analysis will be performed to assess the treatment effect on the primary endpoint of PFS in patients whose cancer expresses tumor BRCA. This analysis will be performed on data obtained from both study cohorts, from the two types of tumor BRCA, germline and somatic. The patients in the gBRCA cohort express germline BRCA, and patients in the non-gBRCA cohort who are HRD-positive and have deleterious (or suspected deleterious) tumor BRCA (i.e., somatic BRCA) will be used in this analysis. Since the data from the 2 separate cohorts should be regarded as being from two separate "studies," based on the overall study design, a meta-analysis approach will be used. The Fisher combination test will be performed, calculated as follows (with k=2):

$$X = -2\sum_{i=1}^{k} \ln(P_i)$$

with X following a χ^2_{2k} distribution, from which a p-value for the global hypothesis of efficacy of niraparib for tumor BRCA can be obtained. An estimate of the tumor BRCA treatment effect will be based on the simple pool of the gBRCA and somatic BRCA data.

6.5 Demographic, Baseline, and Physical Examination

6.5.1 Demographic and Baseline Characteristics

The demographic and baseline summary will include the following variables:

- Age (years) calculated as date of birth minus the date of informed consent / 365.25.

- Age categories (18 to 64, 65 to < 75, ≥ 75; and ≥ 65).
- Ethnicity (White, Black/African American, Asian, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander and Other).
- Weight (in kilograms, at screening).
- Height (in centimeters, at screening).
- Body mass index (BMI) (kg/m^2), calculated using the patient's height and weight (without patient wearing shoes) in the formula. BMI (kg/m^2) = weight (kg) / height $(m)^2$.
- BRCA1 and BRCA2 gBRCA gene type (for $gBRCA^{mut}$ cohort only).
- Time to progression after the penultimate (next to last) platinum therapy before study enrollment (6 - < 12 months and ≥ 12 months).
- Use of bevacizumab in conjunction with the penultimate or last platinum regimen.
- Best response during the last platinum regimen.
- Number of prior platinum courses.
- Time from last platinum therapy to start of study drug
- ECOG status at screening.
- Primary diagnosis (serous epithelial ovarian, fallopian tube, or primary peritoneal cancer).
- Duration since initial diagnosis of primary cancer (Ovarian) to randomization.
- Cancer stage (FIGO) at time of initial diagnosis.
- Sites of metastatic disease.
- Histology.
- Prior radiotherapy (yes/no).
- Prior cancer surgery for study indication (yes/no).
- Number of surgery procedures (1, 2, ≥ 3).
- Prior history of myelosuppression (Yes/No)
- Prior myelosuppression (thrombocytopenia, leukopenia, anemia, neutropenia) by grade.
- Duration of prior myelosuppression events.
- Baseline platelet count.
- Baseline hemoglobin level.
- Baseline mean platelet volume.
- Baseline mean corpuscular volume.

6.5.2 Medical History

Medical history will be coded using the latest version of the MedDRA. The number and percentage of patients experiencing at least 1 such diagnosis per MedDRA System Organ Class (SOC) and preferred term (PT) will be summarized.

6.5.3 Physical Examination

Number and percentage of patients experiencing at least 1 abnormal result will be summarized by body system.

6.5.4 Prior and Concomitant Medication

All medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD) version Sept2015. Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the treatment withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior only. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication. Concomitant medication will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 and PT in frequency tables by treatment for each cohort. Patients with more than 1 medication in a given ATC level and PT will be counted only once in that category.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

- Number and percentage with at least 1 concomitant medication by ATC level 3.
- Number and percentage with at least 1 prior medication by ATC level 3.
- Number and percentage with at least 1 prior and concomitant medication by ATC level 3.
- Number and percentage with at least 1/2/3/4/5 prior platinum treatment.
- Months on prior platinum – Each platinum treatment will be summed then totaled within each patient.
- Total Months (First to Last) Platinum – Difference between the start of the first platinum and the end date of the last platinum.
- Months since last platinum – Difference between the last platinum and date of randomization.

- Number and percentage with at least 1/2/3/4/5 prior chemotherapy regimen.
- Months on prior chemotherapy regimens summed for each treatment and by type, over the patient's lifetime.

6.6 Efficacy Analysis

6.6.1 Progression-free Survival - Primary Efficacy Evaluation

The determination of PFS in the primary efficacy analyses will be based upon the determinations made by the Independent Review Committee (IRC) for this study.

The stratified log-rank test on PFS (time to event analysis using progression or death due to any cause as the event, also termed PFS event) will be performed using SAS PROC LIFETEST with method = PL option. The STRATA statement will include the following 3 stratification factors: time to progression after the penultimate platinum therapy before study enrollment (6 - < 12 months and ≥ 12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the last platinum regimen (CR or PR). The hazard ratio with two-sided 95% confidence interval will be derived from the stratified Cox proportional hazards model using SAS PHREG procedure with ties=EXACT option in the model. In this analysis the baseline hazard function will be allowed to vary across strata; i.e. the MODEL statement will include treatment group variable as the only covariate and the STRATA statement will include the 3 stratification variables used in randomization.

The Kaplan-Meier estimate of the PFS survival distribution will be computed for comparison of the two treatment groups using SAS PROC LIFETEST with method=KM option, and will include the number of patients at risk plotted over time by treatment group. A hierarchical testing method will be used in the non-gBRCA^{mut} cohort using the same methodology mentioned above. First, the subset of patients who are determined to be non-gBRCA and HRD positive (somatic BRCA^{mut} and HRD positive/BRCA^{wt}) by the Myriad HRD test (denoted as HRD positive) will be analyzed for a statistically significant treatment group difference in PFS by the stratified log-rank test at α-level 0.025 1-sided. If that test is statistically significant, then the overall non-gBRCA^{mut} cohort will be evaluated by the same method, also at α-level 0.025 1-sided.

The primary analysis of PFS will be performed on the ITT population, with a supportive analysis performed on the PP population.

Several sensitivity analyses (accompanied by a Forest plot that shows the results of all the sensitivity analyses together) will be performed on PFS, using the ITT population:

- Unstratified log-rank testing along with Cox regression modeling using treatment only.
- Investigator assessment of PFS using a stratified log-rank and associated Cox regression model.
- An IRC analysis using only RECISTv1.1 as progressions.
- An IRC analysis treating censors due to subsequent anti-cancer treatment, discontinuation due to any reason, missed tumor assessments as events. For this analysis, the date of progression would be imputed as the date of initiation of subsequent anti-cancer

treatment, the date of discontinuation, or the date of the last non-missing tumor assessment (in cases where the patient has no further assessments).

- Use of the scheduled assessment date to show progression if the off-scheduled assessment was after the previous scheduled date. This would be done only for progression, not for censored observations, i.e., if the last available observation is after a scheduled assessment and indicates progression has not occurred, then that observation would be used in this sensitivity analysis.

Within the non-gBRCA^{mut} cohort, an exploratory, descriptive analysis of PFS, OS and all other secondary endpoints will be performed for patients in the HRD positive subset (somatic BRCA^{mut} and HRD positive/BRCA^{wt}), and for HRD negative patients. Patients assigned to the non-gBRCA^{mut} cohort whose HRD status cannot be determined (e.g., due to insufficient tissue) will be summarized separately. Formal hypothesis testing will not be performed. The purpose of this analysis is to provide evidence of a consistent response to niraparib. A figure of the HR and 95% CI for all subgroup analyses will be produced.

6.6.2 Overall Survival

Overall survival will be analyzed in the same manner as for the primary efficacy PFS. In addition, as sensitivity analyses, an unstratified log-rank test and associated Cox regression model will be performed.

6.6.3 Progression-free Survival 2

Progression-free survival 2, as defined in Section 5.1.2.1, will be analyzed in the same manner as for the primary efficacy PFS. An additional sensitivity analysis will be performed; for this analysis, if date of progression, date of death, and start date of the second line of subsequent anti-cancer therapy are unknown, then PFS2 will be counted as an event at the end date of the first line of subsequent anti-cancer therapy.

6.6.3.1 Time to First Subsequent Therapy

The TFST, defined as the time from randomization to first subsequent therapy or death, will be analyzed in the same manner as for the primary efficacy PFS.

6.6.3.2 Time to Second Subsequent Therapy

The TSST is defined as the time from randomization to second subsequent therapy or death in order to provide re-assurance that Nirapirab maintenance therapy did not adversely affect sensitivity to subsequent chemotherapy. The TSST will be analyzed in the same manner as for the primary efficacy PFS.

6.6.4 Concordance of the Diagnostic Test for gBRCA^{mut} and for HRD

Concordance of the myChoice® HRD test (Myriad Genetics) with the centralized BRACAnalysis® test (Myriad Genetics) for gBRCA mutation test (BRACAnalysis® test from Myriad Genetics) with respect to identifying gBRCAmut patients will be evaluated. The sensitivity of the HRD test to the centralized test with respect to gBRCAmut status will be determined along with the corresponding 95% confidence bounds. In this analysis, sensitivity will be defined as the proportion of patients in the gBRCAmut cohort that also have a positive HRD test result. Since somatic BRCA can also be obtained from the myChoice® HRD test, an additional analysis of sensitivity may be performed by using a positive result for either germline

or somatic BRCA mutation as the truth standard. However, since it is very likely that the HRD test may show positive results due to genetic scarring that are not related to BRCA, specificity may not be possible to assess, therefore analysis of specificity will not be performed.

6.6.5 Patient-reported Outcomes Evaluations

The FOSI, the EuroQoL 5 Dimension 5 Level (EQ-5D-5L), and a neuropathy questionnaire will be utilized in this study. For continuous variables, changes from baseline in overall score will be analyzed descriptively by treatment group for all sub groups.

When applicable missing items will be handled based on the specific PRO instrument. For missing overall scores a sensitivity analysis will be performed where missing values will be imputed with the worst possible score. Patients missing baseline evaluations would not be included in the PRO analyses.

For each treatment group and at each time point, the number and percentage of patients who complete the questionnaires will be summarized in a table, as well as the reasons for non-completion of these measures. An instrument is considered complete if at least 1 item was answered by the patient.

Number and percentages of missing data for the PRO endpoints will be compared between the treatment groups. Differences in the proportion of dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) between the treatment groups will be tested using a Fisher's exact test.

These analyses will be repeated for the questions of particular interest on the FOSI.

Longitudinal Growth Curve Model

The primary analysis set for the PRO endpoints will be the ITT population.

The FOSI score will be derived per the FACT manual. Changes from baseline in overall score will be analyzed descriptively by treatment group. A mixed-effects growth-curve model adjusting for fixed and random covariates (individual, change trajectory, baseline demographic values, and the 3 stratification factors) will be conducted. Given the number and variance of assessments per patient, a polynomial linear model will be the pre-specified model tested for each outcome.

Assessments for each patient in subsequent cycles are assumed to be correlated over time. Two random-effects are considered in this model: individual patient effect and rate of change over time. The unstructured covariance will be used to evaluate the relationship between these 2 random variables. Estimation will be carried out using restricted maximum-likelihood estimation.

In case convergence problems occur, suitable covariance structures will be tested and the most parsimonious and adequate covariance structure will be selected before the database lock. Kenward-Roger approximation for the denominator degrees of freedom will be used. No adjustments for multiple comparisons will be made.

The EQ-5D index will be derived per the manual. Analysis of the EQ-5D index and EQ-VAS will follow the same methodology as for the FOSI. In addition, an EQ-5D health status profile, which consists of a display of the numbers and percentages of patients in each of the 5 response levels for each of the 5 dimensions, will be provided.

The individual neuropathy questionnaire items will be analyzed using the Pearson chi-square test for association between treatment and ordinal response (0-[redacted], 4-[redacted]). The number and percentage of patients reporting each response will be displayed along with the p-value from the chi-square test.

Time to Symptom Worsening

Time to symptom worsening as reported by the patient requires derivation of meaningful change thresholds followed by the calculation and statistical evaluation of time to this meaningful change (e.g., decline).

Derivation of Meaningful Change Threshold

Time to symptom worsening on the overall FOSI score is defined as the time from randomization to the first FOSI assessment with a worsening score comparing to its baseline score using minimally important difference (MID) thresholds. The MID thresholds are computed as the smallest difference in scores between groups in the domain of interest (e.g., FOSI) which patients perceive as beneficial and will be computed using published MID thresholds of change between 2-3 points (Beaumont et al, 2007).

Categorization of MIDs at post-baseline assessments are as follows:

- if their change score from baseline was greater than 1 MID, categorization at this assessment as "Improved";
- if their change score from baseline was within 1 MID, categorization at this assessment as "Stable";
- if their change score from baseline was less than 1 MID, categorization at this assessment as "Worsened."

Based on the MID statistics, the patients will be classified and presented by treatment group by MID status at each post-baseline assessment and by study period (maintenance and progression). The proportion of patients categorized as "worsened" by 1 MID will be determined at each assessment time point. The cumulative percent of patients categorized as "worsened" by 1 MID will be determined at each time point.

Tests of proportions will then be calculated by each post-baseline assessment for each domain assessed using the Chi-square test. All p-values from these tests will be reported.

In addition to the above analysis, the number and percentages of patients with Chemotherapy Induced Peripheral Neuropathy (CIPN) will be reported by MID category (Improved, Stable, and Worsened) by treatment group and by cohort.

Assessment of Time to Symptom Worsening by an MID

Modeling of Patients with a worsening FOSI score post-baseline will be censored at the date of the last FOSI assessment or death/discontinuation. Patients without baseline and/or post-baseline FOSI assessments will be censored at the date of randomization.

Time-to-event endpoints will be summarized using the KM method and displayed graphically when appropriate. Median event times and 2-sided 95% CI for each median will be provided.

Health State Utility Analysis

The relationship between health state and patient reported health utility is evaluated through a cross-sectional analysis of adjusted EQ-5D health utility index (HUI) scores by health state. More specifically, this analysis seeks to evaluate the mean health utility of patients in the period following their baseline QOL assessment prior to disease progression. To achieve this, EQ-5D HUI scores will be averaged for all post-baseline visits prior to disease progression with and without CIPN. These means will then be adjusted via a mixed model on the following covariates: histology, region, prior treatment, age, duration on prior treatment, and baseline FOSI score. Least squares (LS) mean estimates of the adjusted HUI scores will be presented cross-sectionally by treatment arm and compared with mean adjusted HUI scores at Baseline and disease progression (defined as the first post-progression QOL assessment) along with the standard error of each estimate.

The final mixed model is described below, where Y indicates mean HUI scores, i denotes patient while j denotes treatment. All covariates are represented in the model as X. This model will be replicated by cohort and HRD positive subset (somatic $BRCA^{mut}$ and HRD positive/$BRCA^{wt}$) within the non-gBRCAmut cohort.

$$Y_{ij} = \beta_0 + \beta_1 X_{ij} + \beta_{2ij} + \ldots \beta_n (X)_{ij} + \varepsilon_{ij}$$

The final mixed model is included below, where Y indicates mean HUI scores, i denotes patient while j denotes time point. All covariates are represented in the model as X.

$$Y_{ij} = \beta_0 + \beta_1 X_i + \beta_2 \text{Treatment}_j + \ldots \beta_n (X^*\text{Treatment})_{ij} + \varepsilon_{ij}$$

Disutility Analysis of Adverse Events

The relationship between AEs and overall health utility is of particular importance in evaluating the relative benefit/risk of different treatment options. To better understand the relationship between safety and response on the FOSI as well as EQ-5D utility scores, a disutility analysis of certain AEs (Fatigue, etc.) will be conducted to identify which AE signs and symptoms are associated with statistically significant differences in overall health utility and FOSI symptoms during the stable treatment period (defined as all post-baseline assessments prior to disease progression including 2-way interaction with the fixed treatment factor).

These impacts will be assessed through the development of adjusted EQ-5D HUI and FOSI scores (independent models) derived from mixed models using the following covariates: histology, region, prior treatment, age (continuous), treatment, baseline FOSI performance score and baseline EQ-5D score. Separate nested models will be developed in order to assess the unique contribution of each AE type. Relative differences in the severity of different AEs will be taken into account by developing separate disutility estimates for severe/life threatening (CTCAE Grades 3 and 4) AEs in addition to the overall AE analysis (CTCAE Grades 1-4). As such, separate statistics are reported for each of the 2 AE severity categories (CTCAE All Grades and CTCAE Grade 3/4). Statistical models will mimic the same format as previously stated, ($Y_{ij} = \beta_0 + \beta_1 X_i + \beta_2 \text{Timepoint}_j + \ldots \beta_n (X^*\text{Timepoint})_{ij} + \varepsilon_{ij}$) where the outcome variable is HUI and FOSI scores and covariates and fixed effects are those previously stated. Nested models will include individual AEs as categorical covariates in the final model.

The impact of each AE event on the individual FOSI and HUI scores will be presented using LS mean estimates of the AE as a fixed effect relative to a reference point. For the overall analysis, the LS mean HUI and FOSI score estimates of patients who did not present with said AE event during the stable treatment period is used as a reference. The statistical significance of the resulting estimate was determined via the ANCOVA procedure, with a pre-specified alpha of 0.05. Treatment related differences in disutility impact will also be presented and assessed for statistical significance using the ANCOVA procedure at alpha 0.05.

Treatment related differences will be further evaluated using a simple descriptive analysis of statistically significant (for the overall population) AE events. The frequency of each AE event during the stable treatment period is presented by AE severity type (CTCAE Grades 3 and 4 vs Grades 1-4) and then stratified by treatment arm.

The statistical model for the ANCOVA will be $Y_{ij} = \mu + \alpha_i + \beta AE_{jj} + \varepsilon_{ij}$ where the outcome variable is FOSI and HUI scores and treatment and AEs are the fixed effects. All 2-way interactions between treatment will be included in the model.

6.6.6 Chemotherapy-free Interval

The analysis methods for PFS will be used to analyze CFI.

6.6.7 Time to CA-125 Progression

The analysis methods used for PFS will be used to analyze time to CA–125 progression.

CCI

CCI

6.7 Safety Analysis

6.7.1 Study Treatment Exposure

Extent of treatment will be summarized as follows:

- Number and percent of patients beginning 1, 2, 3 … 12 and > 12 cycles.
- Number of cycles started (mean, median, minimum, maximum) will be reported.
- Overall treatment exposure defined as date of last dose – date of first dose +1 will be summarized.
- Time on study will be based on last visit date or date of death relative to randomization date + 1.

Duration and Intensity of Study Treatment

- Duration of treatment (months), dose intensity (mg/days), and relative dose intensity summarized as a continuous variable (see Section 5.2.1 for definitions).

Dose Reduction, Dose Interruptions, and Missed Doses

- Number and percentage of dose reduction regardless of causality and due to AEs.
- Number and percentage of dose interruptions regardless of causality and due to AEs.
- Number and percentage of discontinuations regardless of causality and due to AEs.

In addition, dose reduction, interruptions, and discontinuations will be summarized by cycle.

Time from last dose to subsequent therapy, defined as the last dose date of study treatment to the first subsequent cancer therapy, will be summarized. Additionally the number and percentage of subsequent treatments, duration of subsequent treatment, and response will be summarized.

6.7.2 Study Treatment Compliance

Patient compliance with the study drug will be assessed via pill counts. Study drug compliance will be defined by the dosing compliance ratio: the number of capsules prescribed (per dose prescribed) less number of capsules returned by the patient divided by the number of capsules prescribed during the same period multiplied by 100. Unused capsules not returned and not reported as missed doses will be assumed to have been consumed.

A patient is evaluated as compliant if the patient has taken 80% to 120% of the expected capsules during participation in the study. Overall compliance rate and proportion of patients considered as compliant and compliance rate by cycle will be summarized.

6.7.3 Adverse Events

6.7.3.1 Overview

The number and percentage of patients reporting a TEAE will be summarized by SOC, PT, toxicity grade, and relationship to study drug.

The toxicity grade of AEs as assessed by the investigator will be graded using NCI CTCAE v4.02. Within the same MedDRA PT, only the most severe AE for each patient will be counted in tabulations by severity. Within a MedDRA SOC, patients with more than 1 MedDRA PT will be counted only once for the most severe AE reported.

The relationship of each AE to the study drug will be summarized as assessed by the investigator. All AEs for which the relationship to study drug is missing will be considered as Related. Within the same MedDRA PT, only the AE with the highest ranked relationship to treatment for each patient will be counted in tabulations by relationship to treatment. Within a MedDRA SOC, patients with more than 1 MedDRA PT will be counted only once for the AE that is most related to treatment. The imputation for a missing relationship will take place prior to determining the most related AE within a SOC or PT for a given patient.

A high-level overview of TEAEs will be presented in a summary table. This table will include the number and percentage of patients for the following categories: any TEAE, any related TEAE, any AE leading to treatment discontinuation/study termination, treatment interruption, or dose reduction, any treatment-emergent SAEs, pregnancies and deaths.

Subgroup analyses of TEAEs will be conducted based on age (< 65 vs ≥ 65 years), race (white vs non-white), number of prior platinum therapies (2 vs > 2), duration of penultimate platinum therapy (< 6 months vs ≥ 6 to < 12 months, vs ≥ 12 months), and cancer subtype (serous epithelial ovarian, fallopian tube, or primary peritoneal cancer).

The following lists the AE tables to be displayed; those designated with an '*' will be produced for the subgroups described above.

- Overview of AEs.*
- TEAE by SOC and PT.*
- TEAE by PT ($\geq$ 5% incidence rate).*
- TEAE by PT $\geq$ 10% incidence rate difference from placebo).
- TEAE by PT ($>$ 10% incidence rate).
- Related TEAE by SOC and PT.
- Treatment-emergent SAEs by SOC and PT.*
- Related treatment-emergent SAEs by SOC and PT.
- TEAE by SOC and PT and maximum grade.
- Related TEAE by SOC and PT and maximum grade.
- Grade $\geq$ 3 TEAEs by SOC and PT.*
- Related Grade $\geq$ 3 TEAEs by SOC and PT.

- TEAEs resulting in death by SOC and PT.
- TEAEs resulting in study drug interruption by SOC and PT.
- TEAEs resulting in study drug dose reduction by SOC and PT
- TEAEs resulting in study drug withdrawal by SOC and PT.*
- TEAEs of specific interest (see Section 6.7.3.2) by AESI category and PT:
    - All AESIs*
    - Grade ≥ 3*
    - SAEs
    - AESI resulting in drug interruption
    - AESI resulting in dose reduction
    - AESI resulting in study drug withdrawal

Tables structured as listings will be provided for the following:

- Deaths.
- Serious AEs.
- AEs resulting in study drug interruption.
- AEs resulting in study drug dose reduction.
- AEs resulting in study drug withdrawn.
- AESI
- Patients developing myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML); this listing will include the following:
    - Age and weight of patients with documented AML/MDS,
    - Number of previous chemotherapy regimens,
    - Types of previous chemotherapies,
    - Time from last platinum to start of study drug
    - Prior history of myelosuppression
    - Myelosuppression AESIs on study

The most common TEAEs will be summarized. 'Most common' will be defined as those events occurring in ≥ 5% and in > 10% of patients in either treatment group. Adverse event summaries will be ordered in terms of decreasing frequency for SOC (as applicable), and PT within SOC, in the treatment group (niraparib then placebo).

6.7.3.2 Adverse Events of Special Interest

The frequency and percentage of AESI as outlined in Table 5 will be presented for each AESI category overall and by MedDRA PT within the category for the niraparib and placebo arms. Table 5 provides the AESI categories and the criteria for selection of MedDRA PTs for each

AESI category, including use of Standardized MedDRA Queries (SMQs), High Level Terms (HLTs), and PTs; a complete list of PTs for each AESI is provided in Appendix B, Section 8.2.

Tabulations of all treatment-emergent AESIs, Grade ≥ 3 AESIs, AESI reported as serious events, AESI leading to dose interruption, dose reduction and withdrawal of study drug, and Grade ≥ 3 AESI leading to discontinuation will be produced. A summary of all myelosuppression AESI and myelosuppression AESI ≥ Grade 3 in severity as outlined in Table 5 will be produced to display the incidence of these events amongst patients with and without a prior history of myelosuppression. The rates of the reported AESI category of thrombocytopenia will be summarized by baseline platelet level and of the AESI category of anemia by baseline hemoglobin level. Grade of laboratory parameters is based on CTCAE v4.03 categories. Tabulations will be also produced for AESI categories of thrombocytopenia, anemia, leukopenia, and neutropenia based on prior history of thrombocytopenia, anemia, leukopenia, and neutropenia, respectively. Tabulations of all AESI and ≥ Grade 3 AESI will be produced for the patient subgroups described above for all TEAEs.

A summary tabulation will be provided for frequency and percent of patients who experienced AESI of thrombocytopenia and who did and did not receive platelet transfusion (WHO drug PTs of platelets or platelets concentrated); who experienced AESI of anemia and who did and did not receive red blood cell transfusion (WHO drug PTs of blood cells, packed human; red blood cells; red blood cells concentration; blood transfusion, auxiliary products) or who did and did not receive erythropoietin; and who experienced AESI of neutropenia and who did and did not receive colony stimulating factors (WHO drug PTs of filgrastim or granulocyte colony stimulating factor).

For each AESI category, a table summarizing time to first onset will be produced by event type for all events regardless of severity and for ≥ Grade 3 events; these data will also be displayed graphically.

Table 5: Adverse Events of Special Interest

AESI Term	MedDRA V18.1 Criteria for Selection of Preferred Terms[1]
Thrombocytopenia events[2]	Haematopoietic thrombocytopenia SMQ (Broad)
Anemia events[2]	Haematopoietic erythropenia SMQ (Broad)
Leukopenia events[2]	Haematopoietic leukopenia SMQ (Broad)
Neutropenia events[2]	Selected PTs related to neutropenia in the Haematopoietic leukopenia SMQ (Broad)
Pancytopenia events[2]	Haematopoietic cytopenias SMQ (Broad)
MDS/AML events[2]	MedDRA PTs associated with MDS/AML
Fatigue events	Asthenic conditions HLT
Pneumonitis events	Pneumonitis and Acute interstitial pneumonitis PTs
Overdose events	Overdose and Accidental overdose PTs

AESI = adverse event of special interest; AML = acute myelogenous leukemia; HLT = high-level term; MDS = myelodysplastic syndrome; MedDRA = medical dictionary for regulatory activities; PT = preferred term; SMQ = Standardized MedDRA Query.

[1] The list of preferred terms for each of the AESIs is provided in Appendix B, Section 8.2.

[2] Myelosuppression AESIs.

6.7.3.3 Examination of Adverse Events Controlling for Duration of Drug Exposure

Since patients' duration of exposure to study drug will vary, AEs will also be presented as rates normalized for cumulative exposure. Total duration of exposure will be calculated as the last treatment date – first treatment date +1.

In these tables, incidence rates per patient-exposure year (PEY) will be calculated as the number of patients experiencing an event in the numerator, and the total exposure time in PEY in the denominator. PEY is defined as follows: for each patient with the AE, the exposure-years will be the time of exposure to the drug in years at the time of first occurrence of the AE; for patients without the AE, the exposure-years will be defined as their total exposure in years on the study. For recurring events, the first occurrence of an AE (by MedDRA PT) will be reported. This tabulation will be conducted for all TEAEs by MedDRA SOC and PT.

The US FDA guidance recommends examining AE incidence by cumulative exposure time (as discussed above), but notes that it is necessary to assume a constant risk of AEs across time for such analyses. If there is not a constant risk for a given AE, the incidence per PEY analysis would be biased. Therefore, a second method will be used to summarize AEs occurring by duration of exposure to study treatment within specific reporting intervals as defined by cycles of therapy. The number of patients on study, that is patients who have not withdrawn from the study, at the start of the reporting interval (number at risk)will be used as the denominator for incidence and prevalence calculations.

Reporting of Incidence by Cycle: For incidence rates by cycle (ie, Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, >Cycle 6), specific AEs will be assigned to the relevant time period if the start date of the AE occurs within the period. For recurrent events during a reporting interval, the first event occurrence is reported. For events that recur in more than one reporting interval (event start

date is in different reporting intervals), the event will be reported in the first applicable reporting interval. In addition, incidence adjusted for exposure on a per-interval basis will be performed. This analysis will calculate the cumulative exposure in patient-months up to the beginning of each interval, and divide the total number of patients with first incidence of the specific event in the interval by this cumulative exposure. Incidence of AESIs and the potentially bothersome gastrointestinal events of nausea and vomiting will be analyzed using these methods, for any severity event as well as for ≥ Grade 3 events.

Reporting of Prevalence by Cycle: For prevalence rates by cycle, specific AEs will be assigned to the relevant time period if the AE occurs within the period, regardless of the interval in which the event started. For events that recur in more than one reporting interval (event occurs in different reporting intervals), the event will be reported in each applicable reporting interval. In addition, prevalence adjusted for exposure on a per-interval basis will be performed. This analysis will calculate the cumulative exposure in patient-months up to the beginning of each interval, and divide the total number of patients with any occurrence of the specific event in the interval by this cumulative exposure. Prevalence of AESIs and the gastrointestinal events of nausea and vomiting will be analyzed using these methods, for any severity event as well as for ≥ Grade 3 events.

6.7.3.4 Examination of Duration of Adverse Events

The duration of AESIs by category and the gastrointestinal events of nausea and vomiting will be calculated on a per-patient basis as the sum of the durations of each discrete episode of occurrence. The duration in days of overlapping occurrences will be calculated as the first start date to the last stop date +1. The average duration over patients for these events of any severity and of ≥ Grade 3 severity will be summarized with descriptive statistics. AEs that are recorded as ongoing at the time of the patient's last assessment prior to the date of data cutoff will contribute a duration for that specific event based on the duration from the event start date to the date of the data cut-off.

As individual events of long duration may be clinically relevant, the incidence of AESI of anemia events and fatigue events of ≥ 28 days in duration for events of any severity and for events of ≥ Grade 3 severity will be tabulated. In addition, events of ≥ Grade 2 hematologic toxicities (defined as AESI of thrombocytopenia, leukopenia, neutropenia, or pancytopenia events) ≥ 28 days with any grade anemia ≥ 28 days will be summarized. Note that these durations are for specific instances of the event, and not based on cumulative time with the event. Incidence categories of 0, 1, 2, 3, and 4 or more will be summarized.

6.7.4 Clinical Laboratory Evaluation

Hematologic and chemistry laboratory results will be graded according to the cut points defined in the NCI CTCAE v4.02 severity grade. All laboratory values will be converted to and reported in SI units. Laboratory analyte results will be summarized by maximum CTCAE grade as available. Continuous results will be analyzed using change from baseline and shift values.

Change from baseline will be summarized and analyzed according to the largest increase, decrease, and at EOT, irrespective of scheduled or unscheduled visit. Graphical line mean changes over time may be provided, but due to the varying visits no repeated measures analysis will be performed.

Shift from baseline to the smallest, largest, and end of therapy will be reported using number and percentage of patients. Baseline and post-baseline results will be categorized as Low, Normal, or High relative to the normal range, or by CTCAE grade as applicable. For platelet count decrease, an additional category for CTCAE v4.03 will be included for values that are < 10,000/µL.

A listing of potential Hy's Law cases (i.e., patients with AST or ALT > 3×ULN in combination with bilirubin > 2×ULN and ALP within the normal range or ≤ 1.5 ULN) will be also presented. Additionally a Hy's Law (DILI) plot will be produced which plots peak ALT and peak total bilirubin in 1 panel and peak AST and peak total bilirubin in a second panel. Data from placebo and niraparib patients will be distinguished using different symbols.

A distribution boxplot of liver function test (albumin, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin and GGT) and selected hematology and other chemistry laboratory test values over time will be presented by treatment group. A side panel will be added to the plot to show the distribution of maximum values.

A by-patient listing of all laboratory data will be provided by treatment group, with abnormal values highlighted, and including center, patient identifier, age, race, weight and visit. Laboratory reference ranges will also be listed.

6.7.5 Vital Signs

Summaries of vital signs parameters (blood pressure, pulse rate, temperature and respiration rate) will be presented by visit and treatment group. Summary statistics will be produced for both observed and change values from baseline for each parameter.

Change from baseline will be summarized and analyzed according to the largest increase, decrease, and at the EOT, irrespective of scheduled or unscheduled visit. Graphical line mean changes over time may be provided.

All vital signs and physical examination findings will be presented in data listings.

6.7.6 Electrocardiogram Measurements

Summary displays for ECG parameters [heart rate, RR interval, PR interval, QRS interval, QT (uncorrected) interval, QTcB interval and QTcF interval] will be produced. Baseline will be defined as the average of the triplicate (if triplicates were collected) closest readings prior to dosing on the first day that study medication is administered.

A summary of the number and percentage of patients with QTcF interval exceeding predefined upper limits (> 450 ms, > 480 ms, > 500 ms) will be provided. A summary of the number and percentage of patients with change from baseline in QTcF interval exceeding predefined upper limits (> 30 ms, > 60 ms) will be provided.

Change from baseline will be summarized and analyzed according to the largest increase, decrease, and at the EOT, irrespective of scheduled or unscheduled visit. Graphical line mean changes over time may be provided.

Only derived QTcF will be reported along with QT machine corrected (QTc). Unplanned ECGs are captured when there are AEs suggestive of arrhythmia, and such unplanned records will not be included as part of the summaries.

No values will be imputed for missing data except for averaging of triplicate measurements. If 1 or 2 of the triplicate measurements for an ECG parameter are missing, the average of the remaining 2 measurements or the single measurement will be used in analyses. If all triplicate measurements are missing at a time point for an ECG parameter, no values will be imputed for this time point and no analyses related to this time point will be performed. Patients who have data on other days or unscheduled ECGs but not at the times of the formal statistical analysis will be included in the categorical tables but not the descriptive summaries.

6.8 Pharmacokinetic Analysis

Details of the PK analysis will be contained in a separate analysis plan.

6.9 Additional Biomarker Analysis

The proportion of patients belonging to different categories of genomic markers of HRD in both germline and tumor DNA will be summarized descriptively. Association between biomarkers and clinical outcomes will be explored. Association between biomarkers (e.g., somatic BRCA 1 and 2 mutations and other biomarkers) and clinical outcomes (e.g., PFS, OS, CFI, PFS2) may be performed.

6.10 Changes in the Conduct of the Study or Planned Analysis

The protocol originally planned to implement an adaptive signature design (Freidlin and Simon, 2005) within the non-gBRCA^{mut} cohort, as follows. Based on this design, if the overall treatment effect was not statistically significant in the non-gBRCA^{mut} cohort, then a biomarker classifier would be tested on tumor from the first half of the study and replicated on tumors from the second half. The overall 1-sided alpha level for the non-gBRCA^{mut} cohort would be prospectively allocated as follows: 0.02 for the full cohort and 0.005 for patients in the validation set with a classifier result predicting Niraparib sensitivity. The biomarker classifier may have also been investigated in tumors even if the overall population showed a significant treatment effect. This approach will no longer be used, since the decision was reached to utilize the HRD test as the biomarker. However, this approach may be used to assess the utility of other biomarkers.

Based on feedback received from the FDA, the consistency of the PFS response to niraparib within additional subsets of the non-gBRCA^{mut} cohort was added. QoL analyses of specific FOSI questions were also added.

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8. APPENDICES

8.1 Appendix A: RECIST Version 1.1

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least 1 dimension:

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm)
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease**:** Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions**:** Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes**:** Nodes with short axis < 10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

- All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.
- If 2 target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to < 10 mm (normal), the actual measurement should still be recorded.

Non-target disease

- All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in 1 organ may be recorded as a single item on the eCRF (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate. Progression has not been documented, and
    - one or more target measurable lesions have not been assessed,
    - or assessment methods used were inconsistent with those used at baseline,
    - or 1 or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure),
    - or 1 or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and 1 or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Table 6: Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, Table 7 will be used.

Table 7: Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal Progression	Yes or No	PD
Any	Yes	PD

CCI

CCI

8.2 Appendix B: MedDRA Preferred Terms for Adverse Events of Special Interest

AESI Category MedDRA Level	**Preferred Terms**	**SMQ Scope**
Thrombocytopenia Event		
Haematopoietic cytopenias affecting more than one type of blood cell (SMQ) [20000028]	Megakaryocytes decreased	Narrow
	Platelet count decreased	Narrow
	Platelet maturation arrest	Narrow
	Platelet production decreased	Narrow
	Platelet toxicity	Narrow
	Thrombocytopenia	Narrow
	Megakaryocytes abnormal	Broad
	Platelet count abnormal	Broad
	Platelet disorder	Broad
	Plateletcrit abnormal	Broad
	Plateletcrit decreased	Broad
	Thrombocytopenia neonatal	Broad
Anemia Event:		
Haematopoietic erythropenia (SMQ) [20000029]	Anaemia macrocytic	Narrow
	Aplasia pure red cell	Narrow
	Aplastic anaemia	Narrow
	Erythroblast count decreased	Narrow
	Erythroid maturation arrest	Narrow
	Erythropenia	Narrow
	Hypoplastic anaemia	Narrow
	Microcytic anaemia	Narrow
	Proerythroblast count decreased	Narrow
	Red blood cell count decreased	Narrow
	Reticulocyte count decreased	Narrow
	Reticulocytopenia	Narrow
	Anaemia	Broad
	Anaemia neonatal	Broad
	Erythroblast count abnormal	Broad

AESI Category **MedDRA Level**	**Preferred Terms**	**SMQ Scope**
	Erythropoiesis abnormal	Broad
	Haematocrit abnormal	Broad
	Haematocrit decreased	Broad
	Haemoglobin abnormal	Broad
	Haemoglobin decreased	Broad
	Leukoerythroblastic anaemia	Broad
	Normochromic normocytic anaemia	Broad
	Proerythroblast count abnormal	Broad
	Red blood cell count abnormal	Broad
	Reticulocyte count abnormal	Broad
	Reticulocyte percentage decreased	Broad
Leukopenia Event Haematopoietic leukopenia (SMQ) [20000030]	Agranulocytosis	Narrow
	Band neutrophil count decreased*	Narrow
	Band neutrophil percentage decreased*	Narrow
	Basophil count decreased	Narrow
	Basophilopenia	Narrow
	B-lymphocyte count decreased	Narrow
	Cyclic neutropenia*	Narrow
	Eosinopenia	Narrow
	Eosinophil count decreased	Narrow
	Febrile neutropenia*	Narrow
	Granulocyte count decreased*	Narrow
	Granulocytes maturation arrest*	Narrow
	Granulocytopenia*	Narrow
	Idiopathic neutropenia*	Narrow
	Leukopenia	Narrow
	Lymphocyte count decreased	Narrow
	Lymphopenia	Narrow
	Metamyelocyte count decreased	Narrow
	Monoblast count decreased	Narrow
	Monocyte count decreased	Narrow
	Monocytopenia	Narrow
	Myeloblast count decreased	Narrow
	Myelocyte count decreased	Narrow
	Neutropenia*	Narrow

AESI Category **MedDRA Level**	**Preferred Terms**	**SMQ Scope**
	Neutropenic infection*	Narrow
	Neutropenic sepsis*	Narrow
	Neutrophil count decreased*	Narrow
	Promyelocyte count decreased	Narrow
	Pure white cell aplasia	Narrow
	Radiation leukopenia	Narrow
	T-lymphocyte count decreased	Narrow
	White blood cell count decreased	Narrow
	Basophil count abnormal	Broad
	Basophil percentage decreased	Broad
	B-lymphocyte abnormalities	Broad
	Differential white blood cell count abnormal*	Broad
	Eosinophil count abnormal	Broad
	Eosinophil percentage decreased	Broad
	Full blood count abnormal	Broad
	Granulocytes abnormal*	Broad
	Granulocytopenia neonatal*	Broad
	Leukopenia neonatal	Broad
	Lymphocyte count abnormal	Broad
	Lymphocyte percentage abnormal	Broad
	Lymphocyte percentage decreased	Broad
	Lymphocytopenia neonatal	Broad
	Monocyte count abnormal	Broad
	Monocyte percentage decreased	Broad
	Myeloblast percentage decreased	Broad
	Myelocyte percentage decreased	Broad
	Myeloid maturation arrest	Broad
	Neutropenia neonatal*	Broad
	Neutrophil count abnormal*	Broad
	Neutrophil percentage decreased*	Broad
	Plasma cell disorder	Broad
	Plasma cells absent	Broad
	T-lymphocyte count abnormal	Broad
	White blood cell analysis abnormal	Broad
	White blood cell count abnormal	Broad
	White blood cell disorder	Broad

AESI Category **MedDRA Level**	**Preferred Terms**	**SMQ Scope**
Pancytopenia Event: Haematopoietic cytopenias affecting more than one type of blood cell (SMQ) [20000028]	Aplastic anaemia	Narrow
	Autoimmune aplastic anaemia	Narrow
	Bicytopenia	Narrow
	Bone marrow failure	Narrow
	Cytopenia	Narrow
	Febrile bone marrow aplasia	Narrow
	Full blood count decreased	Narrow
	Pancytopenia	Narrow
	Panmyelopathy	Narrow
	Aspiration bone marrow abnormal	Broad
	Biopsy bone marrow abnormal	Broad
	Blood count abnormal	Broad
	Blood disorder	Broad
	Bone marrow disorder	Broad
	Bone marrow infiltration	Broad
	Bone marrow myelogram abnormal	Broad
	Bone marrow necrosis	Broad
	Bone marrow toxicity	Broad
	Congenital aplastic anaemia	Broad
	Haematotoxicity	Broad
	Myelodysplastic syndrome	Broad
	Myelodysplastic syndrome transformation	Broad
	Myelofibrosis	Broad
	Myeloid metaplasia	Broad
	Plasmablast count decreased	Broad
	Primary myelofibrosis	Broad
	Scan bone marrow abnormal	Broad
MDS/AML Event: MedDRA PTs as listed	Myelodysplastic syndrome	NA
	Myelodysplastic syndrome transformation	NA
	Myelodysplastic syndrome unclassifiable	NA
	Acute myeloid leukaemia	NA
	Acute myeloid leukaemia recurrent	NA
	Blast crisis in myelogenous leukaemia	NA
	Myeloid leukaemia	NA

AESI Category **MedDRA Level**	**Preferred Terms**	**SMQ Scope**
Fatigue Event:		
Asthenic Conditions HLT	Adult failure to thrive	NA
	Asthenia	NA
	Autonomic nervous system imbalance	NA
	Cachexia	NA
	Chronic fatigue syndrome	NA
	Decreased activity	NA
	Fatigue	NA
	Lethargy	NA
	Listless	NA
	Malaise	NA
	Sluggishness	NA
Pneumonitis Event:		
MedDRA PTs as listed	Pneumonitis	NA
	Acute interstitial pneumonitis	NA
Overdose Event:		
MedDRA PTs as listed	Overdose	NA
	Accidental overdose	NA

*Preferred terms are included in the Neutropenia Event AESI.

9. STATISTICAL TABLES, DATA LISTINGS, AND FIGURES

9.1 List of Tables and Listings

9.2 List of Proposed Figures

Figure 14.1.1 Time to Treatment Discontinuation (ITT Population)

Figure 14.1.2 Time to Study Discontinuation (ITT Population)

Figure 14.2.1 Waterfall Plot (ITT Population)

Figure 14.2.2A Progression-free Survival (ITT Population)

Figure 14.2.2B Progression-free Survival (PP Population)

Figure 14.2.3 Progression-free Survival – Sensitivity Analysis (Using Unstratified Log-Rank Test and Cox PH Model Using Treatment Only) (ITT Population)

Figure 14.2.4 Progression-free Survival – Sensitivity Analysis (Using Investigator Assessment of PFS) (ITT Population)

Figure 14.2.5 Progression-free Survival – Sensitivity Analysis [Using Central Review (per RECIST) Assessment of PFS] (ITT Population)

Figure 14.2.6 Progression-free Survival – Sensitivity Analysis (Including Initiation of Anti-Cancer Treatment, Discontinuation for Any Cause, and Missed Tumor Assessments as Events) (ITT Population)

Figure 14.2.7 Progression-free Survival by <subgroup> (ITT Population)

<Note: repeat for each of the subgroups defined in Section 6.4.8>

Figure 14.2.8 Hazard Ratio (95% CI) for Progression-free Survival – Overall and by Subgroup (ITT Population)

Figure 14.2.9 Hazard Ratio (95% CI) for Progression-free Survival – Sensitivity Analyses (ITT Population)

Figure 14.2.10A Overall Survival (ITT Population)

Figure 14.2.10B Overall Survival (PP Population)

Figure 14.2.11.1 Overall Survival by <subgroup> (ITT Population)

<Note: repeat for each of the subgroups defined in Section 6.4.8>

Figure 14.2.12 Hazard Ratio (95% CI) for Overall Survival – Overall and by Subgroup (ITT Population)

Figure 14.2.13 Progression-free Survival 2 (ITT Population)

Figure 14.2.14 Least Squares Means (95% CI) for Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI) Over Time (ITT Population)

Figure 14.2.15 Least Squares Means (95% CI) for EuroQol 5-Dimension 5-Level (EQ-5D-5L) Index Score Over Time (ITT Population)

Figure 14.2.16 Least Squares Means (95% CI) for EuroQol Visual Analog Scale (EQ VAS) Over Time (ITT Population)

9.3 Statistical Table Shells

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Table 14.1.1

Subject Disposition by Cohort (All Enrolled Subjects)

Cohort: gBRCA^{mut}

Parameter	Statistic (N=)	Niraparib (N=)	Placebo (N=)	Overall (N=)
Number of Subjects				
Enrolled	n	xx	xx	xx
Randomized	n	xx	xx	xx
Randomized but not treated	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Intent-to-treat (ITT) Population	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety (SAF) Population	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Per-protocol (PP) Population	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ongoing at data cutoff	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinuations from Treatment	n	xx	xx	xx
Adverse event	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Disease progression	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Risk to subject	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe non-compliance	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject request	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinuations from Study	n	xx	xx	xx
Withdrawal of consent	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Deaths	n	xx	xx	xx
On treatment	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
During follow-up	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At any time	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Percentages based on the number randomized.
Source: Data Listing 16.2.x

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General note for all tables: Cohort will be presented for gBRCA, somatic BRCAmut and HRD positive/BRCAwt,HRD negative, non-gBRCA Overall.

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Table 14.1.2

Major Protocol Deviations by Cohort

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Number of Subjects [1]				
Enrolled	n	xx	xx	xx
With at least one major protocol deviation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomized but not treated	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Consumed the incorrect study medication per randomization scheme	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Failed to meet eligibility criteria but entered study	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-compliant (<80% compliant with study medication)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Took prohibited medication	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Percentages based on the number enrolled.
Source: Data Listing 16.2.x

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Table 14.1.3

Demographic Characteristics by Cohort (ITT Population)

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Age (years) [1]	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Age Group (years)				
18 - 64	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
65 - 74	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 65	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 75	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race				
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or other Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity				
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] As collected on the Demography eCRF, based on age at time of informed consent.
Source: Data Listing 16.2.x

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Table 14.1.4

Baseline Characteristics by Cohort (ITT Population)

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Screening Weight (kg)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Screening Height (cm)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
BMI (kg/m^2)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Screening ECOG performance status				
0	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: BMI = body mass index, calculated as weight(kg)/[height(m)]^2.
ECOG = Eastern Cooperative Oncology Group:

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Source: Data Listing 16.2.x

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Table 14.1.5

Cancer Staging (Initial Diagnosis) by Cohort (ITT Population)

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Primary tumor site				
Ovarian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary Peritoneal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Fallopian Tube	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Duration (yrs) since diagnosis [1]	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Cancer Stage (FIGO) at Time of Initial Diagnosis				
0	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
I	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IA	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IB	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IC	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
II	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IIA	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IIB	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IIC	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
III	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IIIA	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IIIB	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IIIC	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
IV	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sites of metastatic disease				
Ascites or effusion	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CNS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...	...	...	...	...
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of metastatic disease sites				
<3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Duration since initial diagnosis of primary cancer (Ovarian) to randomization.
Source: Data Listing 16.2.x

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Table 14.1.6

Prior and Baseline Hematology by Cohort (ITT Population)

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Prior Thrombocytopenia	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CTC Grade 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CTC Grade 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CTC Grade 3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CTC Grade 4	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prior Leukopenia	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CTC Grade 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CTC Grade 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CTC Grade 3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CTC Grade 4	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prior Anemia	<as above>	<as above>	<as above>	<as above>
CTC Grade 1				
CTC Grade 2				
CTC Grade 3				
CTC Grade 4				
Prior Neutropenia	<as above>	<as above>	<as above>	<as above>
CTC Grade 1				
CTC Grade 2				
CTC Grade 3				
CTC Grade 4				
Baseline Platelet Count (10^9/L)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Baseline Hemoglobin (g/dL)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Baseline MPV (fL)	<as above>	<as above>	<as above>	<as above>

Note: MPV = mean platelet volume.
Source: Data Listing 16.2.x

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Table 14.1.7

Randomization Stratification Factors by Cohort (ITT Population)

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Time to progression [1]				
< 12 months	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 12 months	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Use of bevacizumab [2]				
Yes	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Best response [3]				
CR	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PR	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Time to progression after the penultimate (next to last) platinum therapy before study enrollment.
[2] Use of bevacizumab in conjunction with the penultimate or last platinum regimen.
[3] Best response during the last platinum regimen (Complete Response [CR] or Partial Response [PR]).
Source: Data Listing 16.2.x

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Table 14.1.8

Prior Ovarian Cancer Treatment (Chemotherapy, Surgery, Radiotherapy) by Cohort (ITT Population)

Cohort: $gBRCA^{mut}$

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Number of lines of platinum therapy (regimens)				
2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
> 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any surgeries/procedures related to the study indication				
Yes	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of surgeries related to study indication				
1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any radiotherapy prior to enrollment				
Yes	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Source: Data Listing 16.2.x

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Table 14.1.9

Ovarian Cancer Pathology by Cohort (ITT Population)

Cohort: gBRCA^{mut}

Method	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Histological	Histologic subtype [1]				
	Serous	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Endometrioid	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mucinous	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Tumor grade [2]				
	Low Grade	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Grade 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Grade 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Grade 3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	High Grade	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not assessable	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cytological	<as above>				

[1] Subjects are counted once within each reported subtype.
[2] Subjects are counted once at the maximum reported grade (Low < Grade 1 < Grade 2 < Grade 3 < High)
Source: Data Listing 16.2.x

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Table 14.1.10.1

Centralized (Myriad) Comprehensive BRCA Analysis (ITT Population – gBRCA^{mut} Cohort)

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
BRCA1 variant				
Yes	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Test result/interpretation				
Positive for deleterious mutation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Genetic variant, suspected deleterious	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Genetic variant, favor polymorphism	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Genetic variant, uncertain significance	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
BRCA2 variant				
Yes	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Test result/interpretation				
Positive for deleterious mutation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Genetic variant, suspected deleterious	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Genetic variant, favor polymorphism	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Genetic variant, uncertain significance	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
BRCA1 and/or BRCA2 rearrangement				
Yes	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not done	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Test result/interpretation				
Positive for deleterious mutation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Genetic variant, suspected deleterious	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Genetic variant, favor polymorphism	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Genetic variant, uncertain significance	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Source: Data Listing 16.2.x

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Repeat for (note that local summary will not include "rearrangement" portion of the table)
Table 14.1.10.2 Local BRCA Analysis (ITT Population – gBRCA^{mut} Cohort)

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Table 14.1.11

Medical History by Cohort, System Organ Class and Preferred Term (ITT Population)

Cohort: $gBRCA^{mut}$

System Organ Class Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Any condition or surgery	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 1				
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...				
SOC 2				
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...				
Etc.				

Note: Patients who report multiple occurrences of the same condition (preferred term) are included only once per SOC and preferred term.
Source: Data Listing 16.2.x

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Table 14.1.12

Physical Examination by Cohort and Body System (ITT Population)

Cohort: gBRCA^{mut}

Body System	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Any abnormality	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormalities reported for:				
General appearance	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Dermatologic	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
HEENT	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.				

Note: Counts are based on the number of subjects experiencing at least one abnormal result within a body system. Percentages are based on ITT population.
Source: Data Listing 16.2.x

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Table 14.1.13.1

Prior Medications by Cohort, Anatomic Therapeutic Class (ATC) and Preferred Term (ITT Population)

Cohort: gBRCA^{mut}

ATC (Level 3) Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Any prior medication	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...				
ATC 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...				
Etc.				

Note: Prior medications are those that start and stop prior to the date of first dose of study medication. Patients who report multiple occurrences of the same medication (preferred term) are included only once per ATC and preferred term.
Source: Data Listing 16.2.x

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Programming Note: Repeat for
Table 14.1.13.2 Concomitant Medications by Cohort, Anatomic Therapeutic Class (ATC) and Preferred Term (ITT Population)
Table 14.1.13.3 Prior and Concomitant Medications by Cohort, Anatomic Therapeutic Class (ATC) and Preferred Term (ITT Population)

Footnote as follows:
Note: Concomitant medications are those that start on or after the date of first dose of study medication. Patients who report multiple occurrences of the same medication (preferred term) are included only once per ATC and preferred term.

Note: Prior and concomitant medications are those that start and stop prior to the date of first dose of study medication and are subsequently resumed on or after the date of first dose, or those that are ongoing on the date of first dose. Patients who report multiple occurrences of the same medication (preferred term) are included only once per ATC and preferred term.

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Table 14.1.14

Prior Platinum Therapy by Cohort (ITT Population)

Cohort: $gBRCA^{mut}$

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Overall duration of prior platinum therapy (months) [1]	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Overall exposure to prior platinum therapy (months) [2]	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Time from completion of final platinum therapy to randomization (days) [3]	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx

[1] Total number of days on treatment (summed over all regimens) divided by 30.4375.
[2] Number of months from start date of first platinum to end date of last platinum.
[3] Number of days from last platinum end date to date of randomization.
Source: Data Listing 16.2.x

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Table 14.1.15

Prior Chemotherapy by Cohort (ITT Population)

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)	Overall (N=xx)
Number of lines of chemotherapy (regimens)				
1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 5	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total duration of last platinum based therapy (months)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Total duration of penultimate platinum based therapy (months)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
< 6 months	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 6 to < 12 months	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 12 months	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total duration of any chemotherapy (months)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx

Each summary is calculated as the total number of days on treatment divided by 30.4375.
Source: Data Listing 16.2.x

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Table 14.2.1.1

Progression-free Survival – gBRCA^{mut} Cohort (ITT Population)

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
Survival Distribution Function (SDF) [3]	SDF (95% CI)		
6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
12-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
...		...	...
<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
p-value [4]		0.xxx	
Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	xxx (xx.x, xx.x)	

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 5.1.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors.
[5] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Programming Note: Repeat for
Table 14.2.1.2 Progression-free Survival – gBRCA^{mut} Cohort (PP Population)

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Table 14.2.2.1

Progression-free Survival – non-gBRCA^{mut} Cohort (ITT Population)

Cohort Subset [1]	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
HRD positive	Progression-free Survival (months) [2] [3]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Survival Distribution Function (SDF) [4]	SDF (95% CI)		
	6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	12-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	...		...	...
	<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [5]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [6]	HR (95% CI)	xxx (xx.x, xx.x)	
Overall	<as above>			
HRD negative	<as above>			

[1] Hierarchical testing: HRD positive subset tested first at α=0.025 (1-sided). If HRD positive subset demonstrates statistical significance, overall cohort is then tested (also at 1-sided α=0.025). HRD negative is presented but is not part of the hierarchical testing.
[2] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 5.1.1 of the statistical analysis plan for censoring conventions.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[4] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[5] Based on stratified log-rank test using randomization stratification factors.
[6] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Programming Note: Repeat for
Table 14.2.2.2 Progression-free Survival – non-gBRCA^{mut} Cohort (PP Population)

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Table 14.2.3.1

Progression-free Survival – Sensitivity Analysis (using unstratified log-rank test and Cox PH model using treatment only) by Cohort
(ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Survival Distribution Function (SDF) [3]	SDF (95% CI)		
	6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	12-minth		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	...		...	...
	<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [4]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 5.1.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on unstratified log-rank test.
[5] Based on Cox Proportional Hazards Model using treatment only.
Source: Data Listing 16.2.x

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Table 14.2.3.2

Progression-free Survival – Sensitivity Analysis (using Investigator assessment of PFS) by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Survival Distribution Function (SDF) [3]	SDF (95% CI)		
	6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	12-minth		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	...		...	...
	<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [4]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 5.1.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors.
[5] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Table 14.2.3.3

Progression-free Survival – Sensitivity Analysis [using central review (per RECIST) assessment of PFS] by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Survival Distribution Function (SDF) [3]	SDF (95% CI)		
	6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	12-minth		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	...		...	...
	<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [4]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

Note: Clinical determination of PD is censored.
[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 5.1.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors.
[5] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Table 14.2.3.4

Progression-free Survival – Sensitivity Analysis (including initiation of anti-cancer treatment, discontinuation for any cause, and missed tumor assessments as events) by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Survival Distribution Function (SDF) [3]	SDF (95% CI)		
	6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	12-minth		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	...		...	...
	<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [4]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 5.1.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors.
[5] Based on Cox Proportional Hazards Model.
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Table 14.2.3.5

Progression-free Survival by Cohort and <subgroup> (ITT Population)

Cohort	<subgroup>	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	<level 1>	Progression-free Survival (months) [1] [2]	Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
		Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
		p-value [3]		0.xxx	
		Hazard Ratio, Niraparib:Placebo [4]	HR (95% CI)	xxx (xx.x, xx.x)	
	<level 2>	Progression-free Survival (months) [1] [2]	Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
		Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
		p-value [3]		0.xxx	
		Hazard Ratio, Niraparib:Placebo [4]	HR (95% CI)	xxx (xx.x, xx.x)	
	Overall	Treatment × <subgroup> interaction	p-value [4]	0.xxx	
Non-gBRCA^{mut}	<as above>				

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 5.1.1 of the statistical analysis plan for censoring conventions.
[2] Median PFS estimated from product-limit (Kaplan-Meier) method. Confidence interval from Brookmeyer and Crowley method with log-log transformation.
[3] Based on stratified log-rank test using randomization stratification factors.
[4] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Table 14.2.4.1

Overall Survival by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	Overall Survival (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Survival Distribution Function (SDF) [3]	SDF (95% CI)		
	6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	12-minth		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	...		...	...
	<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [4]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] OS is defined as the date of randomization to the date of death by any cause. Patients known to be alive were censored at the last known survival follow-up date.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors.
[5] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Table 14.2.4.2

Overall Survival – Sensitivity Analysis (using unstratified log-rank test and Cox PH model using treatment only) by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	Overall Survival (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Survival Distribution Function (SDF) [3]	SDF (95% CI)		
	6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	12-minth		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	...		...	...
	<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [4]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] OS is defined as the date of randomization to the date of death by any cause. Patients known to be alive were censored at the last known survival follow-up date.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on unstratified log-rank test.
[5] Based on Cox Proportional Hazards Model using treatment only.
Source: Data Listing 16.2.x

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Table 14.2.4.3

Overall Survival by Cohort and <subgroup> (ITT Population)

Cohort	<subgroup>	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA[mut]	<level 1>	Overall Survival (months) [1] [2]	Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
		Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
		p-value [3]		0.xxx	
		Hazard Ratio, Niraparib:Placebo [4]	HR (95% CI)	xxx (xx.x, xx.x)	
	<level 2>	Overall Survival (months) [1] [2]	Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
		Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
		p-value [3]		0.xxx	
		Hazard Ratio, Niraparib:Placebo [4]	HR (95% CI)	xxx (xx.x, xx.x)	
	Overall	Treatment × <subgroup> interaction	p-value [4]	0.xxx	
Non-gBRCA[mut]	<as above>				

[1] OS is defined as the date of randomization to the date of death by any cause. Patients known to be alive were censored at the last known survival follow-up date.
[2] Median PFS estimated from product-limit (Kaplan-Meier) method. Confidence interval from Brookmeyer and Crowley method with log-log transformation.
[3] Based on stratified log-rank test using randomization stratification factors.
[4] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Table 14.2.5.1

Progression-free Survival (PFS2) by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	PFS2 (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Survival Distribution Function (SDF) [3]	SDF (95% CI)		
	6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	12-minth		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	...		...	...
	<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [4]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] PFS2 is defined as the time in months from the date of randomization to progression or death. Progression or death that occurs subsequent to start of another anti-cancer therapy is counted as an event.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors.
[5] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Table 14.2.5.2

PFS2 – Sensitivity Analysis (using unstratified log-rank test and Cox PH model using treatment only) by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}		75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	PFS2 (months) [1] [2]			
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Survival Distribution Function (SDF) [3]	SDF (95% CI)		
	6-month		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	12-minth		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	...		...	...
	<as data allow>		xx (xx.x, xx.x)	xx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [4]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] PFS2 is defined as the time in months from the date of randomization to progression or death. Progression or death that occurs subsequent to start of another anti-cancer therapy is counted as an event.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on unstratified log-rank test.
[5] Based on Cox Proportional Hazards Model using treatment only.
Source: Data Listing 16.2.x

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Table 14.2.6

Assessment of Agreement between Central and Investigator Overall Response by Cohort and Visit (ITT Population)

Cohort: gBRCA^{mut}

Visit	Parameter	Niraparib (N=xx)	Placebo (N=xx)
Cycle 2	Number(%) of discordant observations	xx (xx.x)	xx (xx.x)
	Simple kappa coefficient	0.xx	0.xx
	95% CI	(0.xx, 0.xx)	(0.xx, 0.xx)
	p-value	0.xxx	0.xxx
Cycle 4	<as above>		

Source: Listing 16.2.x

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Table 14.2.7

Concordance of Companion HRD Diagnostic Test Compared to the Centralized gBRCA Mutation Test (ITT Population – gBRCA Positive Subjects)

	Centralized gBRCA Mutation Test
Companion HRD Diagnostic Test	Positive for gBRCA (N=xx)
Positive	xx (xx.x)
Negative	xx (xx.x)
Sensitivity [1]	
95% CI	

[1] Sensitivity is the proportion of positive candidate results out of total positive central results.
Note: Since it is very likely that the HRD test may show positive results due to genetic scarring that are not related to BRCA, specificity may not be possible to assess, therefore analysis of specificity was not performed.
Source: Listing 16.2.x

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Table 14.2.8.1

Functional Assessment of Cancer Therapy - Ovarian Symptom Index (FOSI) Completion Status by Cohort and Visit (ITT Population)

Cohort: $gBRCA^{mut}$

Visit	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Screening	Number of subjects completing FOSI	n (%)	xx (xx.x)	xx (xx.x)
	Reason for non-completion			
	1=Illness	n (%)	xx (xx.x)	xx (xx.x)
	2=Inconvenience	n (%)	xx (xx.x)	xx (xx.x)
	3=Language/illiteracy	n (%)	xx (xx.x)	xx (xx.x)
	4=Administrative failure	n (%)	xx (xx.x)	xx (xx.x)
	5=Other	n (%)	xx (xx.x)	xx (xx.x)
	Difference (95% CI) in non-completion rates [1]		xx.x (xx.x, xx.x)	
	p-value [2]		0.xxx	
Cycle 3 Day 1	<as above>			

[1] 95% confidence interval for difference in binomial proportions from Newcombe (hybrid-score) confidence limits.
[2] P-value from Fisher's exact test (2-sided).
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Programming Note: Repeat the preceding table for
Table 14.2.8.2 EuroQoL 5-Dimension 5-Level (EQ-5D-5L) Completion Status by Cohort and Visit (ITT Population)
Table 14.2.8.3 Neuropathy Questionnaire Completion Status by Cohort and Visit (ITT Population)

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Table 14.2.9.1

Analysis of Functional Assessment of Cancer Therapy - Ovarian Symptom Index (FOSI) by Cohort over Time (ITT Population)

Cohort: gBRCA^{mut}

Visit	Actual/ Change	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Baseline	Actual	n	xx	xx
		Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x, xx.x	xx.x, xx.x
		Min, Max	xx, xx	xx, xx
Cycle 3 Day 1	Actual	<as above>	<as above>	<as above>
	Change from BL	n	xx	xx
		Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x, xx.x	xx.x, xx.x
		Min, Max	xx, xx	xx, xx
		LS Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.x, xx.x	xx.x, xx.x
		Difference from placebo		
		LS Mean (SE)	xx.x (xx.xx)	
		95% CI	xx.x, xx.x	
		p-value	0.xxx	
Cycle 5 Day 1	<as above>			
...				
Overall	Change from BL	LS Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)
		95% CI	xx.x, xx.x	xx.x, xx.x
		Difference from placebo		
		LS Mean (SE)	xx.x (xx.xx)	
		95% CI	xx.x, xx.x	
		p-value	0.xxx	

Note: Least squares (LS) means, 95% CI and p-values from repeated measures model with stratification factors, treatment, visit, and treatment-by-visit interaction as fixed effects and baseline as a random effect.
Source: Data Listing 16.2.x

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Programming Note: Repeat the preceding table for
Table 14.2.9.2 Analysis of EuroQoL 5-Dimension 5-Level (EQ-5D-5L) by Cohort over Time (ITT Population)
Table 14.2.9.3 Analysis of EuroQoL Visual Analog Scale (EQ-VAS) by Cohort over Time (ITT Population)

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Table 14.2.10

Analysis of EQ-5D-5L Dimension Scores by Cohort and Visit (ITT Analysis Set)

Cohort: gBRCA^{mut}

Visit	EQ-5D Dimension	Response Level	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Screening	Mobility	Level 1	n (%)	xx (xx.x)	xx (xx.x)
		Level 2	n (%)	xx (xx.x)	xx (xx.x)
		Level 3	n (%)	xx (xx.x)	xx (xx.x)
		Level 4	n (%)	xx (xx.x)	xx (xx.x)
		Level 5	n (%)	xx (xx.x)	xx (xx.x)
			p-value [1]		0.xxx
	Self-Care	Level 1	n (%)	xx (xx.x)	xx (xx.x)
		Level 2	n (%)	xx (xx.x)	xx (xx.x)
		Level 3	n (%)	xx (xx.x)	xx (xx.x)
		Level 4	n (%)	xx (xx.x)	xx (xx.x)
		Level 5	n (%)	xx (xx.x)	xx (xx.x)
			p-value [1]		0.xxx
	Etc.				
Cycle 3 Day 1	<as above>				

Note: Level 1 denotes no problem. Level 5 denotes inability to function or extreme pain/discomfort or anxiety/depression.
[1] P-value from Pearson chi-square test of association between treatment and ordinal response level.
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Table 14.2.11

Analysis of Neuropathy Questionnaire by Cohort and Visit (ITT Analysis Set)

Cohort: gBRCA^{mut}

Visit	Tingling/ Numbness in	Response Level	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Screening	Hands	0 CCI	n (%)	xx (xx.x)	xx (xx.x)
		1	n (%)	xx (xx.x)	xx (xx.x)
		2	n (%)	xx (xx.x)	xx (xx.x)
		3	n (%)	xx (xx.x)	xx (xx.x)
		4	n (%)	xx (xx.x)	xx (xx.x)
			p-value [1]		0.xxx
	Feet	0 CCI	n (%)	xx (xx.x)	xx (xx.x)
		1	n (%)	xx (xx.x)	xx (xx.x)
		2	n (%)	xx (xx.x)	xx (xx.x)
		3	n (%)	xx (xx.x)	xx (xx.x)
		4	n (%)	xx (xx.x)	xx (xx.x)
			p-value [1]		0.xxx
Cycle 3 Day 1	<as above>				

[1] P-value from Pearson chi-square test of association between treatment and ordinal response level.
Source: Listing 16.2.x

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Table 14.2.12

Functional Assessment of Cancer Therapy - Ovarian Symptom Index (FOSI) Worsening by Cohort and Visit (ITT Population)

Cohort: gBRCA^{mut}

Visit	MID Status	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Cycle 3 Day 1	CCI	n (%)	xx (xx.x) xx (xx.x) xx (xx.x)	xx (xx.x) xx (xx.x) xx (xx.x)
	Difference (95% CI) in percentage "Worsened" [1] [2]		xx.x (xx.x, xx.x)	
	p-value [2]		0.xxx	
	Cumulative percentage "Worsened" [3]	n (%)	xx (xx.x)	xx (xx.x)
	Treatment group difference (95% CI) [2]		xx.x (xx.x, xx.x)	
	p-value [4]		0.xxx	
Cycle 5 Day 1	<as above>			

Note: MID = minimally important difference, defined as >2 point change from baseline in FACT-O Symptom Index (FOSI) score.
Improved (Worsened) is defined as >2 point increase (decrease) from baseline.
[1] By visit percentages based on the number of subjects with a FOSI score at the visit.
[2] 95% confidence interval from normal approximation to difference in binomial proportions.
[3] Cumulative percentages based on the number of subjects in the ITT population in each treatment group (N).
[4] P-value from chi-square test.
Source: Data Listing 16.2.x

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Table 14.2.13

Time to FOSI Symptom Worsening by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	Time to symptom worsening (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [3]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [4]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] Time to symptom worsening for subjects without a worsening FOSI score post-baseline are censored at the date of the last FOSI assessment or death/discontinuation. Subjects without baseline and/or post-baseline FOSI assessments are censored at the date of randomization. Worsening is defined as >2 point decrease from baseline.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] Based on stratified log-rank test using randomization stratification factors.
[4] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Table 14.2.14

Chemotherapy-free interval (CFI) by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	CFI (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [3]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [4]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] CFI is defined as the time in months from the last prior platinum dose until initiation of the next anticancer therapy (excluding maintenance therapy). Subjects not experiencing another anticancer therapy are censored at the last known assessment date.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] Based on stratified log-rank test using randomization stratification factors.
[4] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Table 14.2.15

Time to CA-125 Progression by Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
gBRCA^{mut}	Time to CA-125 progression (months) [1] [2]	75th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		Median (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
		25th Percentile (95% CI)	xxx (xx.x, xx.x)	xxx (xx.x, xx.x)
	Censored Observations	N (%)	xx (xx.x)	xx (xx.x)
	Event Rate, Overall	N (%)	xx (xx.x)	xx (xx.x)
	p-value [3]		0.xxx	
	Hazard Ratio, Niraparib:Placebo [4]	HR (95% CI)	xxx (xx.x, xx.x)	
Non-gBRCA^{mut}	<as above>			

[1] Time to CA-125 progression is defined as the time in months from the date of randomization to the date of progression as defined by CA-125 (see table 3.1.1 in the statistical analysis plan).
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] Based on stratified log-rank test using randomization stratification factors.
[4] Based on Cox Proportional Hazards Model.
Source: Data Listing 16.2.x

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Table 14.2.16

PPD (ITT Population)

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
CCI	n (%)	xx (xx.x)	xx (xx.x)
		xx (xx.x)	xx (xx.x)
		xx (xx.x)	xx (xx.x)
		xx (xx.x)	xx (xx.x)
		0.xxx	
	n (%)	xx (xx.x)	xx (xx.x)
		xx.x (xx.x, xx.x)	
		0.xxx	

[1] 95% confidence interval from normal approximation to difference in binomial proportions.
[2] P-value from Cochran-Mantel-Haenszel test stratified by randomization factors.
Source: Data Listing 16.2.x

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Table 14.3.1.1A

Summary of Number of Subjects with Adverse Events by Cohort (SAF Population)

Cohort: gBRCA^{mut}

Characteristic	Statistic	Nirparib (N=xx)	Placebo (N=xx)
Total number of TEAEs	n	n	n
Any TEAE	n (%)	n (xx.x)	n (xx.x)
Any Related TEAE	n (%)	n (xx.x)	n (xx.x)
Any TEAE with CTCAE Toxicity Grade ≥3	n (%)	n (xx.x)	n (xx.x)
Any Related TEAE with CTCAE Toxicity Grade ≥3	n (%)	n (xx.x)	n (xx.x)
Any Serious TEAE	n (%)	n (xx.x)	n (xx.x)
Any Related Serious TEAE	n (%)	n (xx.x)	n (xx.x)
Any TEAE leading to treatment discontinuation	n (%)	n (xx.x)	n (xx.x)
Any TEAE leading to death	n (%)	n (xx.x)	n (xx.x)

Note: AE = Adverse Event; TEAE = Treatment-Emergent Adverse Event. Toxicity is graded using NCI CTCAE version 4.02. Subjects with more than 1 event of the same Preferred Term are counted only once for the event with the highest CTCAE grade. AEs with missing relationship are assumed to be treatment related.
Source: Listing 16.2.x

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Table 14.3.1.1B

Summary of Number of Subjects with Adverse Events for Subgroups by Cohort: Age (SAF Population)

Cohort: gBRCA^{mut}

	Statistic	Nirparib (N=xx)		Placebo (N=xx)	
Characteristic		< 65 years	>=65 years	< 65 years	>=65 years
Total Number of TEAEs	n	n	n	n	n
Any TEAE	n (%)	n (xx.x)	n (xx.x)	n (xx.x)	n (xx.x)
Any Related TEAE	n (%)	n (xx.x)	n (xx.x)	n (xx.x)	n (xx.x)
Any TEAE with CTCAE Toxicity Grade ≥3	n (%)	n (xx.x)	n (xx.x)	n (xx.x)	n (xx.x)
Any Related TEAE with CTCAE Toxicity Grade ≥3	n (%)	n (xx.x)	n (xx.x)	n (xx.x)	n (xx.x)
Any Serious TEAE	n (%)	n (xx.x)	n (xx.x)	n (xx.x)	n (xx.x)
Any Related Serious TEAE	n (%)	n (xx.x)	n (xx.x)	n (xx.x)	n (xx.x)
Any TEAE leading to treatment discontinuation	n (%)	n (xx.x)	n (xx.x)	n (xx.x)	n (xx.x)
Any TEAE leading to death	n (%)	n (xx.x)	n (xx.x)	n (xx.x)	n (xx.x)

Note: AE = Adverse Event; TEAE = Treatment-Emergent Adverse Event. Toxicity is graded using NCI CTCAE version 4.02. Subjects with more than 1 event of the same Preferred Term are counted only once for the event with the highest CTCAE grade. AEs with missing relationship are assumed to be treatment related.
Source: Listing 16.2.x

Programming Note: Repeat the preceding table for
Table 14.3.1.1C Summary of Number of Subjects with Adverse Events for Subgroups by Cohort: Race (SAF Population)
Table 14.3.1.1D Summary of Number of Subjects with Adverse Events for Subgroups by Cohort: Number of Prior Platinum Therapies (SAF Population)
Table 14.3.1.1E Summary of Number of Subjects with Adverse Events for Subgroups by Cohort: Duration of Penultimate Platinum Therapy (SAF Population)
Table 14.3.1.1F Summary of Number of Subjects with Adverse Events for Subgroups by Cohort: Cancer Subtype (SAF Population)

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Table 14.3.1.2

Summary of Treatment-Emergent Adverse Events by Cohort, MedDRA System Organ Class and Preferred Term (SAF Population)

Cohort: $gBRCA^{mut}$

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)

Etc.

Note: If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Source: Listing 16.2.x

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Table 14.3.1.3A

Treatment-Emergent Adverse Events Reported in >=5% of Subjects in Either Treatment Group by Cohort and MedDRA Preferred Term
(SAF Population)

Cohort: $gBRCA^{mut}$

Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
PT 2	n (%)	xx (xx.x)	xx (xx.x)

Etc.

Note: If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Source: Listing 16.2.x

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Programming Note: Repeat the preceding table for
Table 14.3.1.3B Treatment-Emergent Adverse Events Reported in >10% of Subjects in Either Treatment Group by Cohort and MedDRA Preferred Term (SAF Population)
Table 14.3.1.4 Treatment-Emergent Adverse Events With Incidence >10% in Niraparib versus Placebo Treatment Group, by Cohort and MedDRA Preferred Term (SAF Population)

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Table 14.3.1.5

Related Treatment-Emergent Adverse Events by Cohort, MedDRA System Organ Class and Preferred Term (SAF Population)

Cohort: $gBRCA^{mut}$

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
Etc.			

Note: If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Source: Listing 16.2.x

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Table 14.3.1.6

Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (SAF Population)

Cohort: gBRCA^{mut}

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)

Etc.

Note: If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Source: Listing 16.2.x

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Table 14.3.1.7

Related Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (SAF Population)

Cohort: $gBRCA^{mut}$

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)

Etc.

Note: If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Source: Listing 16.2.x

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Table 14.3.1.8

Treatment-Emergent Adverse Events by Cohort, MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade (SAF Population)

System Organ Class Preferred Term CTCAE Grade	Statistic	Niraparib (N=xx)	Placebo (N=xx)
SOC 1			
Grade 1	n (%)	xx (xx.x)	xx (xx.x)
Grade 2	n (%)	xx (xx.x)	xx (xx.x)
Grade 3	n (%)	xx (xx.x)	xx (xx.x)
Grade 4	n (%)	xx (xx.x)	xx (xx.x)
Grade 5	n (%)	xx (xx.x)	xx (xx.x)
PT 1			
Grade 1	n (%)	xx (xx.x)	xx (xx.x)
Grade 2	n (%)	xx (xx.x)	xx (xx.x)
Grade 3	n (%)	xx (xx.x)	xx (xx.x)
Grade 4	n (%)	xx (xx.x)	xx (xx.x)
Grade 5	n (%)	xx (xx.x)	xx (xx.x)
PT 2			
Grade 1	n (%)	xx (xx.x)	xx (xx.x)
Grade 2	n (%)	xx (xx.x)	xx (xx.x)
Grade 3	n (%)	xx (xx.x)	xx (xx.x)
Grade 4	n (%)	xx (xx.x)	xx (xx.x)
Grade 5	n (%)	xx (xx.x)	xx (xx.x)
SOC2			
Etc.			

Note: Toxicity is graded using NCI CTCAE version 4.02. Subjects with more than 1 event of the same Preferred Term are counted only once for the event with the highest CTCAE grade.
Source: Listing 16.2.x

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Programming Note: Sort by decreasing overall frequency (i.e., combined treatment groups, combined grades).

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Table 14.3.1.9

Related Treatment-Emergent Adverse Events by Cohort, MedDRA SOC and Preferred Term by Maximum Toxicity Grade (SAF Population)

Preferred Term CTCAE Grade	Statistic	Niraparib (N=xx)	Placebo (N=xx)
SOC 1			
Grade 1	n (%)	xx (xx.x)	xx (xx.x)
Grade 2	n (%)	xx (xx.x)	xx (xx.x)
Grade 3	n (%)	xx (xx.x)	xx (xx.x)
Grade 4	n (%)	xx (xx.x)	xx (xx.x)
Grade 5	n (%)	xx (xx.x)	xx (xx.x)
PT 1			
Grade 1	n (%)	xx (xx.x)	xx (xx.x)
Grade 2	n (%)	xx (xx.x)	xx (xx.x)
Grade 3	n (%)	xx (xx.x)	xx (xx.x)
Grade 4	n (%)	xx (xx.x)	xx (xx.x)
Grade 5	n (%)	xx (xx.x)	xx (xx.x)
PT 2			
Grade 1	n (%)	xx (xx.x)	xx (xx.x)
Grade 2	n (%)	xx (xx.x)	xx (xx.x)
Grade 3	n (%)	xx (xx.x)	xx (xx.x)
Grade 4	n (%)	xx (xx.x)	xx (xx.x)
Grade 5	n (%)	xx (xx.x)	xx (xx.x)
Etc.			

Note: Toxicity is graded using NCI CTCAE version 4.02. Subjects with more than 1 event of the same Preferred Term are counted only once for the event with the highest CTCAE grade.
Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Source: Listing 16.2.x

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Programming Note: Sort by decreasing overall frequency (i.e., combined treatment groups, combined grades).

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Table 14.3.1.10

CTCAE Grade ≥3 TEAEs by Cohort and MedDRA System Organ Class and Preferred Term (SAF Population)

Cohort: gBRCA^{mut}

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)

Etc.

Note: Toxicity is graded using NCI CTCAE version 4.02. Subjects with more than 1 event of the same Preferred Term are counted only once for the event with the highest CTCAE grade.
Source: Listing 16.2.x

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Table 14.3.1.11

Related CTCAE Grade ≥3 TEAEs by Cohort and MedDRA System Organ Class and Preferred Term (SAF Population)

Cohort: gBRCA^{mut}

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)

Etc.

Note: Toxicity is graded using NCI CTCAE version 4.02. Subjects with more than 1 event of the same Preferred Term are counted only once for the event with the highest CTCAE grade.
Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Source: Listing 16.2.x

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Table 14.3.1.12

TEAEs Resulting in Death by Cohort and MedDRA System Organ Class and Preferred Term (SAF Population)

Cohort: $gBRCA^{mut}$

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
Etc.			

Note: If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Source: Listing 16.2.x

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Programming Note: Repeat the preceding table for
Table 14.3.1.13 TEAEs Resulting in Study Drug Interruption by Cohort and MedDRA System Organ Class and Preferred Term (SAF Population)
Table 14.3.1.14 TEAEs Resulting in Study Drug Dose Reduction by Cohort and MedDRA System Organ Class and Preferred Term (SAF Population)
Table 14.3.1.15 TEAEs Resulting in Withdrawal of Study Drug by Cohort and MedDRA System Organ Class and Preferred Term (SAF Population)

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Table 14.3.1.16A

Treatment-Emergent Adverse Events of Special Interest by Cohort (SAF Population)

Cohort: gBRCA^{mut}

AESI Category Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Thrombocytopenia Event	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
Anemia Event	n (%)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)
Etc.			

Note: If a subject experienced more than 1 event in a given AESI category, that subject is counted once for the category. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Source: Listing 16.2.x

Programming Note: See Appendix B of SAP for a complete list of PTs to be included in each AESI category.

Programming Note: Repeat the preceding table for
Table 14.3.1.16B ≥Grade 3 AESIs by Cohort (SAF Population)
Table 14.3.1.16C AESIs Reported as SAEs by Cohort and MedDRA System Organ Class and Preferred Term (SAF Population)
Table 14.3.1.16D AESIs Resulting in Study Drug Interruption by Cohort (SAF Population)
Table 14.3.1.16E AESIs Resulting in Study Drug Dose Reduction by Cohort (SAF Population)
Table 14.3.1.16F AESIs Resulting in Withdrawal of Study Drug by Cohort (SAF Population)
Table 14.3.1.16G ≥Grade 3 AESIs Resulting in Withdrawal of Study Drug by Cohort (SAF Population)

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Table 14.3.1.17

Relationship of Myelosuppression AESIs with Prior Myelosuppression by Cohort (SAF Population)

Cohort: gBRCA^{mut}

AESI Category Prior Myelosuppression Category	Statistic	Nirparib (N=xx)	Placebo (N=xx)
Any Myelosuppression Event*	n (%)	n (xx.x)	n (xx.x)
Prior History of Myelosuppression			
Yes	n (%)	n (xx.x)	n (xx.x)
No	n (%)	n (xx.x)	n (xx.x)
Any Thrombocytopenia Events	n (%)	n (xx.x)	n (xx.x)
By Baseline Platelet Count			
<100 x 10^9/L	n (%)	n (xx.x)	n (xx.x)
>=100 - <125 x 10^9/L	n (%)	n (xx.x)	n (xx.x)
>=125 – 150 x 10^9/L	n (%)	n (xx.x)	n (xx.x)
>=150 x 10^9/L	n (%)	n (xx.x)	n (xx.x)
By Prior History of Thrombocytopenia			
Yes	n (%)	n (xx.x)	n (xx.x)
Grade 1	n (%)	n (xx.x)	n (xx.x)
Grade 2	n (%)	n (xx.x)	n (xx.x)
Grade 3	n (%)	n (xx.x)	n (xx.x)
Grade 4	n (%)	n (xx.x)	n (xx.x)
No	n (%)	n (xx.x)	n (xx.x)
Any Anemia Events			
By Baseline Hemoglobin	n (%)	n (xx.x)	n (xx.x)
<8 g/dL	n (%)	n (xx.x)	n (xx.x)
>=8 - <10 g/dL	n (%)	n (xx.x)	n (xx.x)
>=10 – 12 g/dL	n (%)	n (xx.x)	n (xx.x)
>=12 g/dL	n (%)	n (xx.x)	n (xx.x)

Cohort: gBRCA^{mut}

AESI Category Prior Myelosuppression Category	Statistic	Nirparib (N=xx)	Placebo (N=xx)
By Prior History of Anemia			
Yes	n (%)	n (xx.x)	n (xx.x)
Grade 1	n (%)	n (xx.x)	n (xx.x)
Grade 2	n (%)	n (xx.x)	n (xx.x)
Grade 3	n (%)	n (xx.x)	n (xx.x)
Grade 4	n (%)	n (xx.x)	n (xx.x)
No	n (%)	n (xx.x)	n (xx.x)
Any Leukopenia Events			
By Prior History of Leukopenia			
Yes	n (%)	n (xx.x)	n (xx.x)
No	n (%)	n (xx.x)	n (xx.x)
Any Neutropenia Events	n (%)	n (xx.x)	n (xx.x)
By Prior History of Neutropenia			
Yes			
Grade 1	n (%)	n (xx.x)	n (xx.x)
Grade 2	n (%)	n (xx.x)	n (xx.x)
Grade 3	n (%)	n (xx.x)	n (xx.x)
Grade 4	n (%)	n (xx.x)	n (xx.x)
No			
Any Pancytopenia Events	n (%)	n (xx.x)	n (xx.x)
Prior History of Myelosuppression			
Yes			
No			
Any MDS/AML Events	n (%)	n (xx.x)	n (xx.x)
Prior History of Myelosuppression			
Yes			
No			

Source: Listing 16.2.x
*Includes AESI categories of thrombocytopenia, anemia, leukopenia, neutropenia, pancytopenia and MDS/AML

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Table 14.3.1.18A

Time to Onset of First Occurrence of Treatment-Emergent Adverse Events of Special Interest by Cohort (SAF Population)

Cohort: $gBRCA^{mut}$

AESI Category	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Anemia Event	N	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	SEM	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Thrombocytopenia Event	N	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	SEM	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Leukopenia Event	N	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	SEM	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Neutropenia Event	N	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	SEM	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Etc. for remaining AESI			
	<as above>	<as above>	<as above>

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Repeat for:
Table 14.3.1.18B Time to Onset of First Occurrence of Grade≥3 Treatment-Emergent Adverse Events of Special Interest by Cohort (SAF Population)

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Table 14.3.1.19A

Duration of Treatment-Emergent Adverse Events of Special Interest by Cohort (SAF Population)

Cohort: gBRCA^{mut}

AESI Category	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Anemia Event	N	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	SEM	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Thrombocytopenia Event	N	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	SEM	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Leukopenia Event	N	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	SEM	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Neutropenia Event	N	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	SEM	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Etc. for remaining AESI			
	<as above>	<as above>	<as above>

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Repeat for:
Table 14.3.1.19B Duration of Grade≥3 Treatment-Emergent Adverse Events of Special Interest by Cohort (SAF Population)

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Table 14.3.1.20

Incidence by Duration of Selected Treatment-Emergent Adverse Events of Special Interest by Cohort (SAF Population)

Cohort: gBRCA^{mut}

AESI Category [1]	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Anemia Event of ≥28 Days Duration[1]			
No Events	n (%)	xx (xx.x)	xx (xx.x)
1 Event	n (%)	xx (xx.x)	xx (xx.x)
2 Events	n (%)	xx (xx.x)	xx (xx.x)
3 Events	n (%)	xx (xx.x)	xx (xx.x)
4 Events	n (%)	xx (xx.x)	xx (xx.x)
>4 Events	n (%)	xx (xx.x)	xx (xx.x)
Grade ≥3 Anemia Event of ≥28 Days Duration			
No Events	n (%)	xx (xx.x)	xx (xx.x)
1 Event	n (%)	xx (xx.x)	xx (xx.x)
2 Events	n (%)	xx (xx.x)	xx (xx.x)
3 Events	n (%)	xx (xx.x)	xx (xx.x)
4 Events	n (%)	xx (xx.x)	xx (xx.x)
>4 Events	n (%)	xx (xx.x)	xx (xx.x)
Fatigue Event of ≥28 Days Duration[1]			
No Events	n (%)	xx (xx.x)	xx (xx.x)
1 Event	n (%)	xx (xx.x)	xx (xx.x)
2 Events	n (%)	xx (xx.x)	xx (xx.x)
3 Events	n (%)	xx (xx.x)	xx (xx.x)
4 Events	n (%)	xx (xx.x)	xx (xx.x)
>4 Events	n (%)	xx (xx.x)	xx (xx.x)
Grade ≥3 Fatigue Event of ≥28 Days Duration			
No Events	n (%)	xx (xx.x)	xx (xx.x)
1 Event	n (%)	xx (xx.x)	xx (xx.x)
2 Events	n (%)	xx (xx.x)	xx (xx.x)
3 Events	n (%)	xx (xx.x)	xx (xx.x)
4 Events	n (%)	xx (xx.x)	xx (xx.x)
>4 Events	n (%)	xx (xx.x)	xx (xx.x)
≥Grade 2 hematologic toxicities [2] ≥28 days with any grade anemia ≥28 days			
Etc.			

[1] Events in this table are counted if the continuous duration of a given event is ≥28 days.
[2] Hematologic toxicity is defined as AESI of thrombocytopenia, leukopenia, neutropenia, or pancytopenia events
Source: Listing 16.2.x

Programming Note: See Appendix B of SAP for a complete list of PTs to be included in each AESI category.

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Table 14.3.1.21

Treatment-Emergent Adverse Event Rates per Patient-Exposure Year[1] by Cohort, by MedDRA SOC and Preferred Term (SAF Population)

Cohort: $gBRCA^{mut}$

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)	Placebo (N=xx)
System Organ Class 1			
Preferred Term 1	rate (xx.xx)	xx.xx	xx.xx
Preferred Term 2	rate (xx.xx)	xx.xx	xx.xx
Etc.	rate (xx.xx)	xx.xx	xx.xx
System Organ Class 2			
Preferred Term 1	rate (xx.xx)	xx.xx	xx.xx
Preferred Term 2	rate (xx.xx)	xx.xx	xx.xx
Etc.	rate (xx.xx)	xx.xx	xx.xx

[1] Incidence rates per patient-exposure year = the number of patients experiencing an event in the numerator, and the total exposure time in patient-exposure years (PEY) at the time of first occurrence of the AE for each patient with the AE, including the total exposure for patients without the AE, in the denominator. Patients count at most once per PT.

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Table 14.3.1.22A

Incidence of Treatment-Emergent Adverse Events of Special Interest and Select Gastrointestinal Events by Cohort, by Cycle of First Occurrence[1] (SAF Population)

Cohort: gBRCA^{mut}

		Niraparib (N = xx)					
AESI Category/ GI Event	Statistic	Cycle 1 (N=xx)	Cycle 2 (N=xx)	Cycle 3 (N=xx)	Cycle 4 (N=xx)	Cycle 5 (N=xx)	Cycle ≥6 (N=xx)
Anemia Event	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Thrombocytopenia Event	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc for AESI categories							
Nausea	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vomiting	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] AEs are included only in the month in which they first occurred; duplicate AEs are not included. If a patient experienced more than 1 event in a given System Organ Class, that patient is counted once for the class. If a patient experienced more than 1 event within a given preferred term, that patient is counted only once for that term. An AE is assigned to the month if the start date of the AE occurs within the month. For recurrent events, the event is included only in the first month reported.
Source: Listing 16.xx

Programming note: repeat for placebo

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:

Table 14.3.1.22B Prevalence of Treatment-Emergent Adverse Events of Special Interest and Select Gastrointestinal Events by Cohort, by Cycle of Any Occurrence[1]: Ovarian Cancer Treatment Pool

[1] AEs are included that are evident within any month, not just events that have their first start date within the month. Events that continue throughout a month, i.e., the start date is prior to the month and the stop date (or continuing) is after the end of that month, are considered as occurring within the month.

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Table 14.3.1.23A

Incidence of Treatment-Emergent Adverse Events of Special Interest and Select Gastrointestinal Events per Patient-Exposure Year by Cohort, by Cycle of First Occurrence[1] (SAF Population)

Cohort: gBRCA^{mut}

		Niraparib (N = xx)					
AESI Category/ GI Event	Statistic	Cycle 1 (N=xx)	Cycle 2 (N=xx)	Cycle 3 (N=xx)	Cycle 4 (N=xx)	Cycle 5 (N=xx)	Cycle ≥6 (N=xx)
Anemia Event	rate (xx.xx)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Thrombocytopenia Event	rate (xx.xx)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Etc for AESI categories							
Nausea	rate (xx.xx)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Vomiting	rate (xx.xx)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

[1] AEs are included only in the month in which they first occurred; duplicate AEs are not included. If a patient experienced more than 1 event in a given System Organ Class, that patient is counted once for the class. If a patient experienced more than 1 event within a given preferred term, that patient is counted only once for that term. An AE is assigned to the month if the start date of the AE occurs within the month. For recurrent events, the event is included only in the first month reported.
Source: Listing 16.xx

Programming note: repeat for placebo

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:

Table 14.3.1.23B Prevalence of Treatment-Emergent Adverse Events of Special Interest and Select Gastrointestinal Events per Patient-Exposure Year by Cohort, by Cycle of Any Occurrence[1]: Ovarian Cancer Treatment Pool

[1] AEs are included that are evident within any month, not just events that have their first start date within the month. Events that continue throughout a month, i.e., the start date is prior to the month and the stop date (or continuing) is after the end of that month, are considered as occurring within the month.

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Table 14.3.1.24A

Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Age
(SAF Population)

Cohort: gBRCA^{mut}

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx) <65 years	Niraparib (N=xx) ≥65 years	Placebo (N=xx) <65 years	Placebo (N=xx) ≥65 years
SOC 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Etc.

Note: If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Source: Listing 16.2.x

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Programming Note: Repeat the preceding table for
Table 14.3.1.24B Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Race (SAF Population)
Table 14.3.1.24C Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Number of Prior Platinum Therapies (SAF Population)
Table 14.3.1.24D Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Duration of Penultimate Platinum Therapy (SAF Population)
Table 14.3.1.24E Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Cancer Subtype (SAF Population)

Table 14.3.1.25A Treatment Emergent Adverse Events Reported in >=5% of Subjects in Either Treatment Group for Subgroups by Cohort, MedDRA SOC and Preferred Term: Age (SAF Population)
Table 14.3.1.25B Treatment Emergent Adverse Events Reported in >=5% of Subjects in Either Treatment Group for Subgroups by Cohort, MedDRA SOC and Preferred Term: Race (SAF Population)
Table 14.3.1.25C Treatment Emergent Adverse Events Reported in >=5% of Subjects in Either Treatment Group for Subgroups by Cohort, MedDRA SOC and Preferred Term: Number of Prior Platinum Therapies (SAF Population)
Table 14.3.1.25D Treatment Emergent Adverse Events Reported in >=5% of Subjects in Either Treatment Group for Subgroups by Cohort, MedDRA SOC and Preferred Term: Duration of Penultimate Platinum Therapy (SAF Population)
Table 14.3.1.25E Treatment Emergent Adverse Events Reported in >=5% of Subjects in Either Treatment Group for Subgroups by Cohort, MedDRA SOC and Preferred Term: Cancer Subtype (SAF Population)

Table 14.3.1.26A Treatment Emergent Serious Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Age (SAF Population)
Table 14.3.1.26B Treatment Emergent Serious Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Race (SAF Population)

Table 14.3.1.26C Treatment Emergent Serious Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Number of Prior Platinum Therapies (SAF Population)
Table 14.3.1.26D Treatment Emergent Serious Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Duration of Penultimate Platinum Therapy (SAF Population)
Table 14.3.1.26E Treatment Emergent Serious Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Cancer Subtype (SAF Population)

Table 14.3.1.27A Grade ≥3 Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Age (SAF Population)
Table 14.3.1.27B Grade ≥3 Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Race (SAF Population)
Table 14.3.1.27C Grade ≥3 Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Number of Prior Platinum Therapies (SAF Population)
Table 14.3.1.27D Grade ≥3 Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Duration of Penultimate Platinum Therapy (SAF Population)
Table 14.3.1.27E Grade ≥3 Treatment Emergent Adverse Events for Subgroups by Cohort, MedDRA SOC and Preferred Term: Cancer Subtype (SAF Population)

Table 14.3.1.28A Treatment Emergent Adverse Events Resulting in Withdrawal of Study Drug for Subgroups by Cohort, MedDRA SOC and Preferred Term: Age (SAF Population)
Table 14.3.1.28B Treatment Emergent Adverse Events Resulting in Withdrawal of Study Drug for Subgroups by Cohort, MedDRA SOC and Preferred Term: Race (SAF Population)
Table 14.3.1.28C Treatment Emergent Adverse Events Resulting in Withdrawal of Study Drug for Subgroups by Cohort, MedDRA SOC and Preferred Term: Number of Prior Platinum Therapies (SAF Population)
Table 14.3.1.28D Treatment Emergent Adverse Events Resulting in Withdrawal of Study Drug for Subgroups by Cohort, MedDRA SOC and Preferred Term: Duration of Penultimate Platinum Therapy (SAF Population)
Table 14.3.1.28E Treatment Emergent Adverse Events Resulting in Withdrawal of Study Drug for Subgroups by Cohort, MedDRA SOC and Preferred Term: Cancer Subtype (SAF Population)

Table 14.3.1.29A

Treatment-Emergent Adverse Events of Special Interest for Patients Subgroups by Cohort: Age (SAF Population)

Cohort: gBRCA^{mut}

	Statistic	Niraparib (N=xx)		Placebo (N=xx)	
AESI Category		<65 years	≥65 years	<65 years	≥65 years
Thrombocytopenia Event	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Anemia Event	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.					

Note: If a subject experienced more than 1 event in a given AESI category, that subject is counted once for the category. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.
Source: Listing 16.2.x

Programming Note: See Appendix B of SAP for a complete list of PTs to be included in each AESI category.

Programming Note: Repeat the preceding table for
Table 14.3.1.29B Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Race (SAF Population)
Table 14.3.1.29C Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Number of Prior Platinum Therapies (SAF Population)
Table 14.3.1.29D Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Duration of Penultimate Platinum Therapy (SAF Population)
Table 14.3.1.29E Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Cancer Subtype (SAF Population)
Table 14.3.1.29F Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Prior Myelosuppression (SAF Population)

Table 14.3.1.30A Grade ≥3 Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Age (SAF Population)
Table 14.3.1.30B Grade ≥3 Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Race (SAF Population)
Table 14.3.1.30C Grade ≥3 Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Number of Prior Platinum Therapies (SAF Population)
Table 14.3.1.30D Grade ≥3 Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Duration of Penultimate Platinum Therapy (SAF Population)
Table 14.3.1.30E Grade ≥3 Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Cancer Subtype (SAF Population)
Table 14.3.1.30F Grade ≥3 Treatment-Emergent Adverse Events of Special Interest for Patient Subgroups by Cohort, MedDRA SOC and Preferred Term: Prior Myelosuppression (SAF Population)

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Table 14.3.1.31

Summary of Time to First Onset of AESI by Cohort (SAF Population)

Cohort: gBRCA^{mut}

Time to first onset of:	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Thrombocytopenia Events	n	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx
	Median [1]	xx.x	xx.x
	95% CI	xx.x, xx.x	xx.x, xx.x
Anemia Events	<as above>		
Leukopenia Events	<as above>		
Etc.			

[1] Median and 95% confidence interval estimated from product-limit (Kaplan-Meier) method.
Source: Data Listing 16.2.x

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Table 14.3.2.1

Listing of Treatment-Emergent AEs Leading to Death (SAF Population)

Cohort: $gBRCA^{mut}$
Treatment: Niraparib

Subject Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date (Rel Day [1])	Date of Death	Action Taken Regarding Study Agent	Concomitant Medication Given for AE? Yes/No	Relationship

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.2.2

Listing of Serious Treatment-Emergent AEs (SAF Population)

Cohort: gBRCA^{mut}
Treatment: Niraparib

Subject Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome
			DDMMMYYYY/ Ongoing	-xx					

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.2.3

Listing of Treatment-Emergent AEs Resulting in Study Drug Interruption (SAF Population)

Cohort: gBRCA^{mut}
Treatment: Niraparib

Subject Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Concomitant Medication Given?	Relationship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx					

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.2.4

Listing of Treatment-Emergent AEs Resulting in Study Drug Dose Reduction (SAF Population)

Cohort: gBRCA^{mut}
Treatment: Niraparib

Subject Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Concomitant Medication Given?	Relationship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx					

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.2.5

Listing of Treatment-Emergent AEs Resulting in Withdrawal of Study Drug (SAF Population)

Cohort: gBRCA^{mut}
Treatment: Niraparib

Subject Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Concomitant Medication Given?	Relationship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx					

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.4.1

Listing of Abnormal Laboratory Values (SAF Population)

Cohort: gBRCA^{mut}
Treatment: Niraparib

Subject Number	Age/ Race/ Weight	Group	Laboratory Test (unit)	Visit	Visit Date (Rel Day [1])	Result	CTCAE Grade [2]	Reference Range Low	Reference Range High
		Hematology							
		Chemistry							

[1] Rel Day is calculated as visit date minus first dose date (plus 1 day if visit date is on or after first dose date).
[2] CTCAE Grade: 1=…

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Programming Note: Repeat the preceding table for
Table 14.3.4.2 Listing of Laboratory Values with CTCAE Severity Grade ≥3 (SAF Population)
Table 14.3.4.3 Listing of Clinically Significant Laboratory Values (SAF Population)

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Table 14.3.5.1

Summary and Change from Baseline for Hematology Parameters by Time Point, and by Cohort (SAF Population)

Cohort: $gBRCA^{mut}$

Parameter	Time Point	Actual/ Change	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Parameter 1	Baseline	Actual	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
	Greatest Increase	Actual	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
		Change	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
	Greatest Decrease	<as above>			
	End of Treatment	<as above>			
Parameter 2	<as above>				

Source: Data Listing 16.2.x

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Programming Note: Repeat the preceding table for
Table 14.3.5.2 Summary and Change from Baseline for Chemistry Parameters by Time Point, by Cohort (SAF Population)

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Table 14.3.5.3

Summary of Shifts in Hematology Parameters from Baseline to Maximum CTCAE Grade by Cohort (SAF Population)
Cohort: gBRCA^{mut}

				Maximum Post-Baseline CTCAE Grade						
Parameter	Treatment Group	Statistic	Baseline CTCAE Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Parameter 1	Niraparib	n (%)	Grade 0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Placebo		<as above>							
Parameter 2	<as above>									

Note: Toxicity is graded using NCI CTCAE version 3.0.
Source: Listing 16.2.x

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Programming Note: Repeat the preceding table for
Table 14.3.5.4 Shifts in Chemistry Parameters from Baseline to Maximum CTCAE Grade by Cohort (SAF Population)

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Table 14.3.5.5

Summary of Shift from Baseline in Hematology Parameters by Time Point, and by Cohort (SAF Population)
Cohort: $gBRCA^{mut}$

					Post-Baseline			
Parameter	Time Point	Treatment Group	Statistic	Baseline	Low	Normal	High	Total
Parameter 1	Smallest post-baseline value	Niraparib	n (%)	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			n (%)	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			n (%)	High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			n (%)	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Placebo	n (%)	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			n (%)	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			n (%)	High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			n (%)	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Largest post-baseline value	<as above>						
	End of treatment value	<as above>						
Parameter 2	<as above>							

Note: Only subjects with a baseline and post-baseline value are included for a given parameter.
Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Programming Note: Repeat the preceding table for
Table 14.3.5.6 Shift from Baseline in Chemistry Parameters by Time Point, by Cohort (SAF Population)

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Table 14.3.5.7

Shift from Baseline in Platelet Count Categories by Time Point, by Cohort (SAF Population)

Cohort: gBRCA^{mut}

Time Point	Treatment Group	Statistic	Baseline Category	Post-Baseline Category 1	2	3	4	Total
Smallest post-baseline value	Niraparib	n (%)	1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Placebo	n (%)	1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		p-value [1]	0.xxx					
Largest post-baseline value	<as above>							
End of treatment value	<as above>							

[1] p-value from Cochran-Mantel Haenszel test stratified by treatment group.
Note: Only subjects with a baseline and post-baseline value are included. Categories are as follows:

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Source: Listing 16.2.x

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Table 14.3.5.8

Summary of Shift from Baseline in CTCAE Grade for Platelet Counts, Hemoglobin and ANC by Time Point, and by Cohort (SAF Population)

Cohort: gBRCA^{mut}
Parameter: Platelet Counts <repeat for Hemoglobin and Absolute Neutrophil Count>

				Post-Baseline CTCAE Grade					
Time Point	Treatment Group	Statistic	Baseline CTCAE Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Smallest post-baseline value	Niraparib	n (%)	Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Placebo	n (%)	Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		p-value [1]	0.xxx						
Largest post-baseline value	<as above>								
End of treatment value	<as above>								

[1] p-value from Cochran-Mantel Haenszel test stratified by treatment group.
Note: Only subjects with a baseline and post-baseline value are included.
Source: Listing 16.2.x

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Table 14.3.5.9

Summary and Change from Baseline for Vital Signs by Visit, by Cohort (SAF Population)

Cohort: gBRCA^{mut}

Parameter	Visit	Actual/ Change	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Parameter 1	Baseline	Actual	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
	Cycle 1 Day 15	Actual	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
		Change	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
	Cycle 2	<as above>			
	Etc.				
Parameter 2	<as above>				

Source: Data Listing 16.2.x

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Table 14.3.5.10

Summary and Change from Baseline for Vital Signs by Time Point, by Cohort (SAF Population)

Cohort: gBRCA^{mut}

Parameter	Time Point	Actual/ Change	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Parameter 1	Baseline	Actual	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
	Greatest Increase	Actual	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
		Change	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
	Greatest Decrease	<as above>			
	End of Treatment	<as above>			
Parameter 2	<as above>				

Source: Data Listing 16.2.x

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Table 14.3.5.11

Summary and Change from Baseline for ECG Parameters by Time Point, by Cohort (SAF Population)

Cohort: gBRCA^{mut}

Parameter	Time Point	Actual/ Change	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Parameter 1	Baseline	Actual	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
	Greatest Increase	Actual	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
		Change	n	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx
	Greatest Decrease	<as above>			
	End of Treatment	<as above>			
Parameter 2	<as above>				

Source: Data Listing 16.2.x

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Table 14.3.5.12

Summary and Change from Baseline for ECG Parameters by Time Point (SAF Population – QTc Subset)

Time Point	Actual/ Change	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Pre-dose	Actual	n	xx	xx
		Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x, xx.x	xx.x, xx.x
		Min, Max	xx, xx	xx, xx
One hour post dose	Actual	n	xx	xx
		Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x, xx.x	xx.x, xx.x
		Min, Max	xx, xx	xx, xx
	Change	n	xx	xx
		Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x, xx.x	xx.x, xx.x
		Min, Max	xx, xx	xx, xx
1.5 hours post dose	<as above>			
<repeat for remaining post dose time points>				

Source: Data Listing 16.2.x

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Table 14.3.5.13

Summary of Maximum QTc Interval Prolongation and Change from Baseline in QTc Interval, by Cohort (SAF Population)

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Maximum post-baseline QTc Interval			
> 450 ms	n (%)	xx (xx.x)	xx (xx.x)
> 480 ms	n (%)	xx (xx.x)	xx (xx.x)
> 500 ms	n (%)	xx (xx.x)	xx (xx.x)
Change from baseline to maximum post-baseline QTc Interval			
> 30 ms	n (%)	xx (xx.x)	xx (xx.x)
> 60 ms	n (%)	xx (xx.x)	xx (xx.x)
Change from baseline to minimum post-baseline QTc Interval			
> 30 ms	n (%)	xx (xx.x)	xx (xx.x)
> 60 ms	n (%)	xx (xx.x)	xx (xx.x)

Note: Only subjects with a baseline and post-baseline value are included for a given parameter.
Source: Listing 16.2.x

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Table 14.3.5.14

Summary of Overall Exposure to Study Drug, by Cohort (SAF Population)

Cohort: $gBRCA^{mut}$

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Number of Cycles Started			
1	n (%)	xx (xx.x)	xx (xx.x)
2	n (%)	xx (xx.x)	xx (xx.x)
...	...	...	...
> 12	n (%)	xx (xx.x)	xx (xx.x)
Number of Cycles Started	n	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx
Total Study Duration [1]	<as above>		
Overall Treatment Exposure [2]	<as above>		
Treatment Duration [3]	<as above>		
Dose Intensity (mg/day) [4]	<as above>		
Relative Dose Intensity [5]	<as above>		

[1] Total study duration is calculated as last visit date or date of death minus randomization date plus one.
[2] Overall treatment exposure is calculated as last dose date minus first dose date plus one.
[3] Treatment duration is calculated as last dose date - first dose date minus any skipped or interrupted doses + 1)
[4] Dose intensity is calculated as sum of the daily doses actually consumed divided by total duration.
[5] Relative dose intensity is calculated as dose intensity (mg/day) divided by intended dose intensity (mg/day) multiplied by 100, where intended dose is 300 mg/day.
Source: Listing 16.2.x

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Table 14.3.5.15

Summary of Study Drug Compliance by Cohort, and by Cycle and Overall (SAF Population)

Cohort: gBRCA^{mut}

Cycle	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Overall	Compliance	n	xx	xx
		Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x, xx.x	xx.x, xx.x
		Min, Max	xx, xx	xx, xx
	Compliance Rate	n (%)	xx (xx.x)	xx (xx.x)
	<80% compliant	n (%)	xx (xx.x)	xx (xx.x)
	>120% compliant	n (%)	xx (xx.x)	xx (xx.x)
Cycle 1	Compliance	n	xx	xx
		Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x, xx.x	xx.x, xx.x
		Min, Max	xx, xx	xx, xx
	Compliance Rate	n (%)	xx (xx.x)	xx (xx.x)
	<80% compliant	n (%)	xx (xx.x)	xx (xx.x)
	>120% compliant	n (%)	xx (xx.x)	xx (xx.x)

Etc.

Note: Compliance is calculated as the number of capsules prescribed (per dose prescribed) minus the number of capsules returned by the patient divided by the number of capsules prescribed during the same period multiplied by 100. Compliance rate is the number and percentage of subjects 80% to 120% compliant.
Source: Listing 16.2.x

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Table 14.3.5.16

Summary of Dose Interruptions and Dose Reductions by Cycle and Overall, by Cohort (SAF Population)

Cohort: $gBRCA^{mut}$

Cycle	Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
At Any Time	Dose Interruptions			
	Dose interruption for any reason	n (%)	xx (xx.x)	xx (xx.x)
	Dose interruption due to AE	n (%)	xx (xx.x)	xx (xx.x)
	Dose Reductions			
	Dose reduction for any reason	n (%)	xx (xx.x)	xx (xx.x)
	Dose reduction due to AE	n (%)	xx (xx.x)	xx (xx.x)
Cycle 1	Dose Interruptions			
	Dose interruption for any reason	n (%)	xx (xx.x)	xx (xx.x)
	Dose interruption due to AE	n (%)	xx (xx.x)	xx (xx.x)
	Dose Reductions			
	Dose reduction for any reason	n (%)	xx (xx.x)	xx (xx.x)
	Dose reduction due to AE	n (%)	xx (xx.x)	xx (xx.x)
Cycle 2	<as above>			

Source: Listing 16.2.x

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Table 14.3.5.17

Summary of Follow-Up Anti-Cancer Therapy, by Cohort (SAF Population)

Cohort: gBRCA^{mut}

Parameter	Statistic	Niraparib (N=xx)	Placebo (N=xx)
Number of Follow-Up Therapies			
1	n (%)	xx (xx.x)	xx (xx.x)
2	n (%)	xx (xx.x)	xx (xx.x)
...	...	...	...
<as data allow>	n (%)	xx (xx.x)	xx (xx.x)
Type of Follow-Up Therapy [1]			
Chemotherapy	n (%)	xx (xx.x)	xx (xx.x)
Hormonal therapy	n (%)	xx (xx.x)	xx (xx.x)
PARP	n (%)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)
Time to follow-up therapy [2]	n	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx
	Median (95% CI) [4]	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Duration of follow-up therapy [3]	n	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx
	Median (95% CI) [4]	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
CCI			
	n (%)	xx (xx.x)	xx (xx.x)
	n (%)	xx (xx.x)	xx (xx.x)
	n (%)	xx (xx.x)	xx (xx.x)
	n (%)	xx (xx.x)	xx (xx.x)
	n (%)	xx (xx.x)	xx (xx.x)
	n (%)	xx (xx.x)	xx (xx.x)
	n (%)	xx (xx.x)	xx (xx.x)
Dose Limiting Toxicity			
Yes	n (%)	xx (xx.x)	xx (xx.x)
No	n (%)	xx (xx.x)	xx (xx.x)

[1] Subjects are counted once per reported type of therapy, but may be captured more than once across therapy types.
[2] Time to follow-up therapy is defined as the last dose date of study treatment to the first dose of follow-up anti-cancer therapy.
[3] Duration of follow-up therapy is calculated as last dose date minus first dose date plus 1 (all types combined).
[4] Median and 95% confidence interval estimated from product-limit (Kaplan-Meier) method.
Source: Listing 16.2.x
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9.4 Data Listing Shells

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Listing 16.2.1.1

Discontinuation from Treatment

Cohort:
Treatment Group:

Subject Number	Date of Treatment Discontinuation	Date of First Dose	Date of Last Dose	Number of Days on Treatment[1]	Primary Reason for Treatment Discontinuation
					Other: <specify>
					Patient request: <specify>

[1] Days on treatment = Last dose date – first dose date + 1.

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Listing 16.2.1.2

Discontinuation from Study

Cohort:
Treatment Group:

Subject Number	Date of Discontinuation	Date of Randomization	Number of Days on Study [1]	Reason for Discontinuation	Cause of Death	Date of Death

[3] Days on study = Last assessment date – randomization date + 1.

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Listing 16.2.1.3

Survival Assessment

Cohort:
Treatment Group:

Subject Number	Current Subject Status	Date Last Known to be Alive	New Diagnosis Since Completing Study Treatment

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Listing 16.2.2.1

Inclusion/Exclusion Criteria: Main Study

Cohort:
Treatment Group:

Subject Number	Did the Subject Satisfy all Inclusion/Exclusion Criteria?	Inclusion/Exclusion Criterion Number	Inclusion/Exclusion Criterion Text

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.2.2

Protocol Violations

Cohort:
Treatment Group:

Subject Number	Type of Violation	Description of Violation	Date

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Listing 16.2.3.1

Study Populations

Cohort:
Treatment Group:

Subject Number	Included in ITT Population	Included in Per Protocol Population	Included in Safety Population
	Yes	No	Yes

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Listing 16.2.3.2

Subjects Excluded from Per-protocol Population

Cohort:
Treatment Group:

Subject Number	Reason for Exclusion

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Listing 16.2.4.1

Demographics

Cohort:
Treatment Group:

Subject Number	Age (yr)	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2)	Screening ECOG Performance Status

Note: BMI = Body Mass Index. BMI (kg/m^2) = weight (kg) / [height (m)]^2

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Listing 16.2.4.2

Medical History

Cohort:
Treatment Group:

Subject Number	Any Conditions or Surgeries	System Organ Class [1]/ Preferred Term [1]/ Condition	Start Date	Ongoing at Study Start?	Stop Date

[3] Coding was done using MedDRA version 17.1.

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Listing 16.2.4.3

Prior Hematology

Cohort:
Treatment Group:

Subject Number	Test	CTCAE Grade	Start Date/ End Date(days)	Which Prior Regimen	Treatment Given
	(e.g., Thrombocytopenia)				

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Listing 16.2.4.4A

Ovarian Cancer Treatment: Part 1

Cohort:
Treatment Group:

Subject Number	Prior History of Myelosuppression	Regimen Number	Chemotherapy Course	Cancer Type	Reason for Administration	Start Date/ Stop Date	Best Response	Progression Date	Discontinuation Reason

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Listing 16.2.4.4B

Ovarian Cancer Treatment: Part 2

Cohort:
Treatment Group:

			Beginning of Regimen			Completion of Regimen		
Subject Number	Regimen Number	Agent Name	CA-125 Collect Date	CA-125 Value (U/ml)	ULN Range (U/ml)	CA-125 Collect Date	CA-125 Value (U/ml)	ULN Range (U/ml)
		Bond, James						

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Listing 16.2.4.5

Other Cancer History

Cohort:
Treatment Group:

Subject Number	Cancer History Unrelated to Study Indication?	Cancer Type	Date Last Treated

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Listing 16.2.4.6

Ovarian Cancer Pathology

Cohort:
Treatment Group:

Subject Number	Biopsy Date	Method of Diagnosis	Histologic Subtype	Tumor Grade

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Listing 16.2.4.7

Cancer Staging

Cohort:
Treatment Group:

Subject Number	Primary Tumor Site	Initial Diagnosis Date	Cancer Stage (FIGO) at Time of Initial Diagnosis	Sites of Metastatic Disease

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Listing 16.2.4.8

Prior Surgery for Study Indication

Cohort:
Treatment Group:

Subject Number	Any Surgeries/ Procedures?	Surgery/Procedure	Anatomical Location	Indication	Date of Surgery/ Procedure

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Listing 16.2.4.9

Previous Radiotherapy

Cohort:
Treatment Group:

Subject Number	Any Prior Radiotherapy	Site and Region	Radiotherapy Start Date	Radiotherapy Stop Date	Total Grays

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Listing 16.2.4.10

Centralized (Myriad) Comprehensive BRCA Analysis

Cohort:
Treatment Group:

			BRCA 1		BRCA 2		BRCA 1 and/or BRCA 2	
Subject Number	Specimen Blood Draw Date	Report Date	Variant Results/ Interpretation	Specific Variant Result	Variant Results/ Interpretation	Specific Variant Result	Rearrangement Specification	Results/ Interpretation

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.4.11

Local BRCA Mutation Testing

Cohort:
Treatment Group:

Subject Number	Name of Lab	City/Country	Specimen Draw Date	Report Date	Test Results/ Interpre-tation	BRCA 1		BRCA 2		
						Variant Interpre-tation	Specific Variant Result	Variant Interpre-tation	Specific Variant Result	Test Results

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Listing 16.2.4.12

Randomization Factors

Cohort:
Treatment Group:

Subject Number	Underwent Triplicate ECG?	All Randomization Factors Entered?	Date of Randomization	Randomization ID	Was Bevacizumab used in Conjunction with Penultimate Platinum or Last Chemotherapy Regimen?	Best Response during Last Platinum Regimen?	Time to Progression after Penultimate Platinum Therapy

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Listing 16.2.5.1A

Study Medication and Dispensation: Part 1

Cohort:
Treatment Group:

Subject Number	Visit	Bottle from Previous Cycle Returned?	Bottle Number Returned	Number of Unused Capsules Returned	Bottle Number Dispensed	Dose Prescribed at this Visit (mg)	Date:Time of Administration	Was Full Dose Taken No <specify reason>

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Listing 16.2.5.1B

Study Medication and Dispensation: Part 2

Cohort:
Treatment Group:

Subject Number	Visit	Dose Modified During Previous Cycle?	Start Date	Stop Date	Dose (mg)	Reason for Change	Action Taken	Any Missed Doses
						Other <specify>		Yes <explain>

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Listing 16.2.5.2

Study Medication and Dispensation: First Dose

Cohort:
Treatment Group:

Subject Number	Dose Administration Date:Time	Bottle Number Dispensed	Dose Prescribed (mg)	Full Dose Consumed?	Amount Consumed	Reason Full Dose Not Consumed

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Listing 16.2.5.3

Study Medication Compliance

Cohort:
Treatment Group:

Subject Number	Visit	Number of Capsules Prescribed [1]	Number of Capsules Returned [2]	Percent Compliance [3]	Overall Compliance [4]
		xxx	yyy	100*(xxx-yyy)/xxx	

[1] Number of capsules expected to have been consumed since previous cycle, accounting for dose interruptions and reductions.
[2] Unused capsules not returned and not reported as missed doses will be assumed to have been consumed.
[3] The number of capsules prescribed (per dose prescribed) minus the number of capsules returned by the patient divided by the number of capsules prescribed during the same period multiplied by 100.
[4] The total number of capsules prescribed (per dose prescribed) minus the total number of capsules returned by the patient divided by the total number of capsules prescribed multiplied by 100.

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Listing 16.2.6.1

Overall Survival, Disease Progression (Central Review), and Date of Last Contact

Cohort:
Treatment Group:

Subject Number	Disease Progression (DP)	Date of DP	Study Day	Clinical Progression (CP)	Date of CP	Study Day	Death	Date of Death	Study Day	Date of Last Contact	Study Day
	Yes			Yes			Yes				
	No			No			No				

Note: Study day is calculated as date of interest minus date of randomization plus one.

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Listing 16.2.6.2

Centralized Evaluation of Response (RECIST)

Cohort:
Treatment Group:

Subject Number	Visit	Date of Radiological Scan or Assessment	Target Lesion(s) Response	Non Target Lesion(s) Response	New Lesion Progression	Overall Response	Date of Progression [1]

[1] Earlier of the date of progression per oncologist review or the date of first reported overall response of PD per radiological review.
Note: CR=Complete Response, PR=Partial Response, SD=Stable Disease, (U)PD=(Unequivocal) Progressive Disease, NN=Non-CR/Non-PD, NE=Not Evaluable, ND=No Disease

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Listing 16.2.6.3

Investigator Evaluation of Response (RECIST)

Cohort:
Treatment Group:

Subject Number	BOR with last platinum therapy	Visit	Date of Radiological Scan or Assessment)	Target Lesion(s) Response	Non Target Lesion(s) Response	New Lesions?	Overall Response
				NE <specify reason>			

Note: CR=Complete Response, PR=Partial Response, SD=Stable Disease, (U)PD=(Unequivocal) Progressive Disease, NN=Non-CR/Non-PD, NE=Not Evaluable, ND=No Disease, NA=Not Applicable

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Listing 16.2.6.4A

Progressive Disease

Cohort:
Treatment Group:

Subject Number	Determined Date of Progressive Disease	Study Day	Criteria Met for Progressive Disease	Clinical Signs and Symptoms

Note: Study day is calculated as date of interest minus date of randomization plus one.

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Listing 16.2.6.4B

Diagnostic Tests Performed that Lead to Diagnosis of Progressive Disease

Cohort:
Treatment Group:

Subject Number	Diagnostic Test	Diagnostic Test Date	Study Day	Describe Results
	Other: <specify>			

Note: Study day is calculated as date of interest minus date of randomization plus one.

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Listing 16.2.6.5

Centralized Tumor Identification

Cohort:
Treatment Group:

Subject Number	Visit	Assessment Date	Lesion Number [1]	Tumor Type	Location	Method	Adjudicated Record
			R1-T01	Target			Y
			R2-NT01	Non-target			N
			R1-NEW01	New			

[1] R1 = Reader 1, R2 = Reader2, Txx = target lesion #xx, NTxx = non-target lesion #xx, NEWxx = new lesion #xx

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Listing 16.2.6.6A

Centralized Target Lesion Assessment – Part 1

Cohort:
Treatment Group:

Subject Number	Visit	Assessment Date	Lesion Number [1]	Diameter (mm)	Sum of Diameters (mm)	Sum of Diameters (NLND)[2] (mm)	% Change from Baseline	Change from Nadir	% Change from Nadir	Adjudicated Record

[1] R1 = Reader 1, R2 = Reader2, Txx = target lesion #xx
[2] NLND = Non-Lymph Node Tumors

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Listing 16.2.6.6B

Centralized Target Lesion Assessment – Part 2

Cohort:
Treatment Group:

Subject Number	Visit	Assessment Date	Lesion Number [1]	All Target Lymph Nodes Non-pathological	Tumor State	Adjudicated Record
				N	Present	

[1] R1 = Reader 1, R2 = Reader2, Txx = target lesion #xx

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Listing 16.2.6.7

Centralized Non-Target and New Lesion Assessment

Cohort:
Treatment Group:

Subject Number	Visit	Assessment Date	Lesion Number [1]	Tumor State	Non-target Status	Adjudicated Record

[1] R1 = Reader 1, R2 = Reader2, NTxx = non-target lesion #xx, NEWxx = new lesion #xx

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Listing 16.2.6.8

Investigator Target Lesion Assessment

Cohort:
Treatment Group:

Subject Number	Visit	Assessment Date	Lesion Number	Site	Location	Method	Longest Dimension (mm)	Short Axis (Lymph Nodes Only) (mm)	Lesion Status

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Listing 16.2.6.9

Investigator Non Target Lesion Assessment

Cohort:
Treatment Group:

Subject Number	Visit	Assessment Date	Lesion Number	Site	Location	Method	Lesion Status

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Listing 16.2.6.10

Investigator New Lesion Assessment

Cohort:
Treatment Group:

Subject Number	Visit	Assessment Date	Lesion Number	Site	Location	Method

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Listing 16.2.6.11

Functional Assessment of Cancer Therapy - Ovarian Symptom Index (FOSI)

Cohort:
Treatment Group:

					Response as it Applied to Past 7 Days							
Subject Number	Visit	Reason Form Not Received from Subject	Assessment Date	Study Day	Lack of Energy	Vomiting	Pain	Nausea	Swelling in Stomach Area	Worry Condition will Worsen	Content with Quality of Life	Cramps in Stomach Area

Note: Study day is calculated as date of interest minus date of randomization plus one.

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Listing 16.2.6.12

EuroQoL 5-Dimension 5-Level (EQ-5D-5L)

Cohort:
Treatment Group:

Subject Number	Visit	Reason Form Not Received from Subject	Assessment Date	Study Day	Describe Your Health Today					Index Score	Health Number (EQ-VAS)
					Mobility	Self-Care	Usual Activities	Pain/ Discomfort	Anxiety/ Depression		
					5	5	5	5	5	-1.09	0.00

Note: Study day is calculated as date of interest minus date of randomization plus one.
Dimension scores range from CCI to CCI e is calculated using the United States value set.
EQ-VAS ranges from CCI to CCI .

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Listing 16.2.6.13

Neuropathy Questionnaire

Cohort:
Treatment Group:

					Response as it Applied to Past 7 Days	
Subject Number	Visit	Reason Form Not Received from Subject	Assessment Date	Study Day	Feet Numb or Prickling/Tingling Feelings	Hands Numb or Prickling/Tingling Feelings
					0 - CCI	4 - CCI

Note: Study day is calculated as date of interest minus date of randomization plus one.

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Listing 16.2.6.14

ECOG Performance Status

Cohort:
Treatment Group:

Subject Number	Visit	Was Assessment Performed?	Date	Study Day	Performance Status [1]

Note: Study day is calculated as date of interest minus date of randomization plus one.
[1] CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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Listing 16.2.6.15

Serum CA-125

Cohort:
Treatment Group:

Subject Number	Reason Not Performed	Sampling Date	Study Day	Completion Date	Study Day	Result Evaluation	Result

Note: Study day is calculated as date of interest minus date of randomization plus one.

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Listing 16.2.7.1

Adverse Events Sorted by Subject

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Preferred Term/ Verbatim Term	Start Date/ Stop Date	Rel Day [1]	TEAE [2]	CTCAE Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx	No						

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] TEAE = treatment emergent adverse event

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Listing 16.2.7.2

Adverse Events Sorted by System Organ Class (SOC), Preferred Term and Subject

Cohort:
Treatment Group:

System Organ Class/ Preferred Term/ Verbatim Term	Subject Number	Age/ Race/ Weight (kg)	Start Date/ Stop Date	Rel Day [1]	TEAE [2]	CTCAE Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome	SAE?

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] TEAE = treatment emergent adverse event

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Listing 16.2.7.3

Thrombocytopenic Adverse Events Sorted by Subject

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Adverse Event	Start Date/ Stop Date	Rel Day [1]	TEAE [2]	CTCAE Grade	Platelet Count	Action Taken	Concomitant Medication Given?	Relationship	Outcome	SAE?

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] TEAE = treatment emergent adverse event

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Listing 16.2.7.4

Glossary of Adverse Events

System Organ Class	Preferred Term	Verbatim Term

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Listing 16.2.8.1A

Laboratory Results: Hematology Part 1

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	Hemoglobin (unit)	MCV (unit)	Platelets (unit)	MPV (unit
							xx L2-CS (xx, xx)	

Note: MCV = mean corpuscular volume, MPV = mean platelet volume, H = High relative to normal range, L = Low relative to normal range. CTCAE grade appended if applicable. CS = clinically significant (per investigator), normal ranges are from local lab.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Programming Note: In the platelet example above, xx is the value in SI units, L2 indicates a CTCAE grade 2 low value, CS is clinically significant, (xx, xx) is the normal range reported by the local lab.
Please note carefully that all reported values, CTCAE grading, flagging of values relative to normal range, and normal range values are from original lab dataset, not normalized values.
Do not flag normal values, just present the value and normal range, e.g., xx (xx, xx)

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Listing 16.2.8.1B

Laboratory Results: Hematology Part 2

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	WBC (unit)	ANC (unit)	Lymphocytes (unit)	Monocytes (unit)

Note: WBC = white blood cell (count), ANC = absolute neutrophil count, H = High relative to normal range, L = Low relative to normal range. CTCAE grade appended if applicable. CS = clinically significant (per investigator), normal ranges are from local lab.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.8.1C

Laboratory Results: Hematology Part 3

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	Eosinophils (unit)	Basophils (unit)	APTT (unit)	INR

Note: APTT = activated partial thromboplastin time, INR = international normalized ratio, H = High relative to normal range, L = Low relative to normal range. CTCAE grade appended if applicable. CS = clinically significant (per investigator), normal ranges are from local lab.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.8.2A

Laboratory Results: Chemistry Part 1

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	Sodium (unit)	Potassium (unit)	Chloride (unit)	Calcium (unit)

Note: H = High relative to normal range, L = Low relative to normal range. CTCAE grade appended if applicable. CS = clinically significant (per investigator), normal ranges are from local lab.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.8.2B

Laboratory Results: Chemistry Part 2

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	Magnesium (unit)	Glucose (unit)	Creatinine (unit)	BUN (unit)

Note: BUN = blood urea nitrogen, H = High relative to normal range, L = Low relative to normal range. CTCAE grade appended if applicable. CS = clinically significant (per investigator), normal ranges are from local lab.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.8.2C

Laboratory Results: Chemistry Part 3

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	AST (unit)	ALT (unit)	ALP (unit)	Total Bilirubin (unit)

Note: AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, H = High relative to normal range, L = Low relative to normal range. CTCAE grade appended if applicable. CS = clinically significant (per investigator), normal ranges are from local lab.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.8.2D

Laboratory Results: Chemistry Part 4

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	GGT (unit)	Total Protein (unit)	Albumin (unit)	LDH (unit)	Amylase (unit)

Note: GGT = gamma glutamyl transferase, LDH = lactic dehydrogenase, H = High relative to normal range, L = Low relative to normal range. CTCAE grade appended if applicable. CS = clinically significant (per investigator), normal ranges are from local lab.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.8.3A

Laboratory Results: Urinalysis Part 1

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	Specific Gravity	Urobilinogen	Leukocyte Esterase	Nitrite	Blood

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.8.3B

Laboratory Results: Urinalysis Part 2

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	Protein	Glucose	Ketones	Bilirubin

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.8.4

Laboratory Results: Liver Function Tests – Potential Hy's Law Cases

Cohort:
Treatment Group:

Subject Number	Age/ Race/ Weight (kg)	Visit	Sample Collection Date	Rel Day [1]	Laboratory Analyte (result/xULN) ALT (U/L)	AST (U/L)	Total Bilirubin (umol/L)	ALP (U/L)	INR
					150/3.3	100/2.7	40/2.3	100/0.7	1

Note: ALT=alanine aminotransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase, INR=international normalized ratio
ULN=upper limit of normal
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Programming note: Include all visits for any subjects with ALT or AST >3xULN, or bilirubin >2xULN at any time post baseline.

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Listing 16.2.8.5

Pregnancy Test

Cohort:
Treatment Group:

Subject Number	Menopause or Surgical Sterilization?	Reason Serum Pregnancy Test Not Performed	Date Sample Taken	Rel Day [1]	Result	Contraception Practice Confirmed

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.9.1

Vital Signs

Cohort:
Treatment Group:

Subject Number	Visit	Reason Not Performed	Assessment Date	Rel Day [1]	Height (cm)	Weight (kg)	Temperature (°C)	Pulse (beats/min)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.9.2

Physical Examination

Cohort:
Treatment Group:

Subject Number	Visit	Date Performed	Rel Day [1]	Body System	Status	Abnormality Description

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.9.3

Electrocardiogram

Cohort:
Treatment Group:

Subject Number	Visit	Time Point	Date:Time of Assessment	Rel Day [1]	Heart Rate (bpm)	RR (sec)	PR (msec)	QRS (msec)	QT (msec)	QTcB (msec)	QTcF (msec)

Note: (N)CS = (Not) Clinically Significant
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.9.4

Overall Electrocardiogram Interpretation

Cohort:
Treatment Group:

Subject Number	Visit	Time Point	Date:Time of Assessment	Rel Day [1]	Specify Sinus Rhythm	ECG Interpretation

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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~~Listing 16.2.9.5~~

~~Electrocardiogram – QTc Subset~~

Cohort:
Treatment Group:

Subject Number	Visit	Time Point	Date:Time of Assessment	Rel Day [1]	Heart Rate (bpm)	RR (sec)	PR (msec)	QRS (msec)	QT (msec)	QTcB (msec)	QTcF (msec)

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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~~Listing 16.2.9.6~~

~~Abnormal Electrocardiogram Findings - QTc Subset~~

Cohort:
Treatment Group:

Subject Number	Visit	Time Point	Date:Time of Assessment	Rel Day [1]	Classification	Comments
					Abnormal, Potentially Clinically Significant	SINUS RHYTHM 1ST DEGREE AV BLOCK *** ***

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.9.5

Surgeries/Procedures

Cohort:
Treatment Group:

Subject Number	Any Surgeries or Procedures	Surgery/Procedure while on study	Date	Rel Day [1]

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.6

Follow-up Surgery and Radiotherapy

Cohort:
Treatment Group:

	Follow-up Surgery for Cancer			Follow-up Radiotherapy					
Subject Number	Surgical Procedure Name	Surgery/ Procedure Date	Rel Day [1]	Anatomical Areas Radiated	Start Date	Rel Day [1]	End Date	Rel Day [1]	Total Grays

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.7

Follow-up Anti-Cancer Therapy

Cohort:
Treatment Group:

Subject Number	ATC/ Generic Name/ Verbatim Name	Type of Therapy	Start/ Stop Date	Rel Day [1]	Disease Progression Encountered?	Date of Progression	Best Response	DLT?	Description of DLT
		Other <clarify>							

[1] Rel Day is calculated as start date minus last dose date of randomized treatment. Rel Day is signed positive for events with onset after last dose date of randomized treatment.

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Listing 16.2.9.8

Previous and Concomitant Medications

Cohort:
Treatment Group:

Subject Number	ATC/ Generic Name/ Verbatim Name	Total Dose	Dose Units	Frequency	Indication	Route of Administration	Start/ Stop Date	Rel Day [1]

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.9

Cytology/Histology

Cohort:
Treatment Group:

Subject Number	Cytology/Histology Test	Date	Rel Day [1]	Results

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

STATISTICAL ANALYSIS PLAN

A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib versus Placebo in Patients with Platinum Sensitive Ovarian Cancer (Food Effect Safety Substudy)

Protocol PR-30-5011-C (Food Effects Substudy)

Protocol Number:	PR-30-5011-C (Food Effects Substudy)
Protocol Version and Date:	Amendment 6: 9 March 2016 Amendment 5: 11 September 2015 Amendment 4: 4 December 2014 Amendment 3: 9 April 2014 Amendment 2: 3 March 2014 (amendment 2 never issued) Amendment 1: 3 May 2013 Original: 21 March 2013
Name of Test Drug:	Niraparib capsules
Phase:	Phase 3
Methodology:	An open-label substudy to assess the effect of a high-fat meal on the pharmacokinetics (PK) of a single 300 mg dose of niraparib in patients with ovarian cancer
Sponsor:	TESARO Inc. 1000 Winter Street, Suite 3300 Waltham, MA 02451 Tel: (339) 970-0900
Sponsor Representative:	Shefali Agarwal, MD, MPH Senior Medical Director
Analysis Plan Date:	13 May 2016
Analysis Plan Version:	Final Version 2.0

APPROVAL SIGNATURE PAGE

Protocol Title: A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

Sponsor: TESARO Inc.
1000 Winter Street, Suite 3300
Waltham, MA 02451

Protocol Number: PR-30-5011-C (Food Effects Substudy)

Document Date / Version: 13 May 2016 / Final Version 2.0

Veristat, Inc. Author:

PPD MS
Principal Biostatistician
Veristat, LLC
118 Turnpike Road
Suite 200
Southborough, MA 01772

Signature: PPD

Date:

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report. PPD

Sponsor Signatory:

Mohammed Al-Adhami, PhD
Director, Biostatistics
TESARO Inc.

Signature: PPD

Date:

Sponsor Signatory:

Shefali Agarwal, MD, MPH
Senior Medical Director
TESARO Inc.

Signature: PPD

Date:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BUN	Blood urea nitrogen
CA-125	Cancer antigen 125
CBC	Complete blood count
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
FE	Food effect
FIGO	International Federation of Gynecology and Obstetrics
GGT	Gamma glutamyl transferase
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPV	Mean platelet volume
NCI	National Cancer Institute
PK	Pharmacokinetic
Q_1	First quartile
Q_3	Third quartile

Abbreviation	Definition
QD	Once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
Rel Day	Relative study day
SAE	Serious adverse event
SAP	Statistical analysis plan
SI	*Système International d'Unités*
SOC	System Organ Class (MedDRA)
StdDev	Standard deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WBC	White blood count
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

At selected sites in the United States (US), approximately 12 patients will be enrolled into a 14-day, open-label, 2-treatment, crossover substudy to evaluate the effect of a high-fat meal on niraparib (single dose) exposure. For this food-effect (FE) substudy, entry criteria will be broadened to include patients with ovarian cancer, regardless of platinum sensitivity and burden of disease, as long as no standard therapy exists or the patient has refused standard therapy.

Upon completion of the 14-day FE substudy, participating patients will then conform to the schedule in the main study on Cycle 1/Day 1 (approximately 2 weeks after the start of the FE substudy) and will begin dosing with open-label niraparib at 300 mg once daily (QD). These 12 patients will only be assessed for safety for the duration of the study and may continue until Investigator-determined disease progression.

1.1.2. Study Objectives

Study objectives are to assess the effect of a high-fat meal on the PK of a single 300 mg dose of niraparib in patients with ovarian cancer, and to evaluate the safety and tolerability of niraparib.

This statistical analysis plan (SAP) outlines the methods to be used in the analysis of study safety data. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide safety results to be presented in the clinical study report (CSR) for this trial. This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

A separate population pharmacokinetic (PK) analysis plan will be prepared for the other primary objective, to characterize the PK of niraparib under fed and fasted conditions. This analysis plan is being developed by Biomedical Systems.

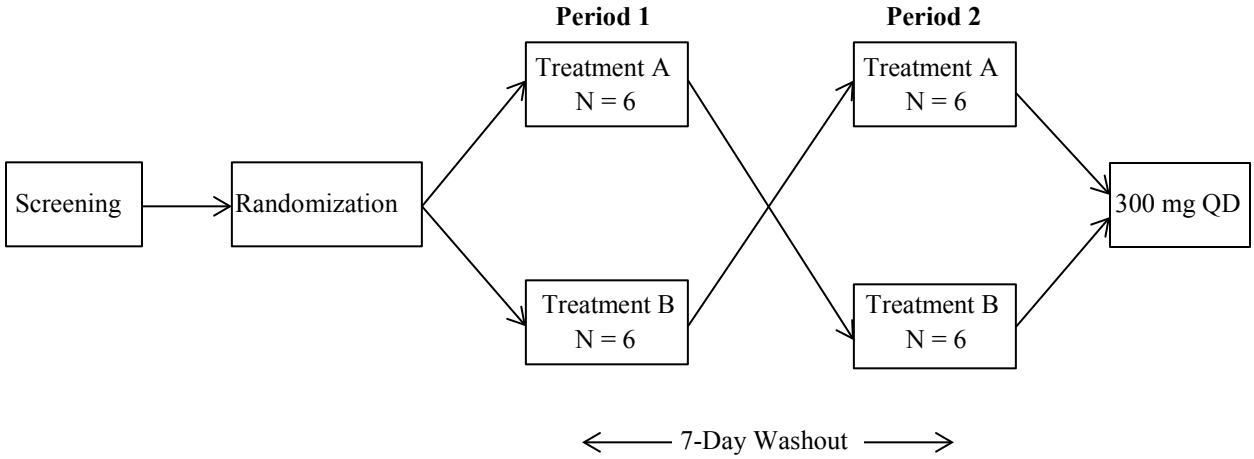
1.2. Study Design

1.2.1. Synopsis of Study Design

The 12 patients chosen for enrollment into the substudy will be randomized to either Sequence Group A or Sequence Group B, with 6 patients assigned to each group. In Group A, patients will fast (nothing to eat or drink except water) for at least 10 hours before receiving a single dose of 300 mg niraparib; patients will continue to fast for at least 2 hours following the dose. In Group B, patients will fast for at least 10 hours before consuming a high-fat meal. Within 5 minutes of finishing the meal, a single dose of 300 mg niraparib will be administered orally and patients will resume fasting for at least 4 hours. After a 7-day PK assessment and washout period, all patients will receive their second single dose of niraparib on Day 8 under the opposite (fasting versus high-fat meal) circumstance: the previous 6 patients in Group A will receive their single dose of niraparib after a high-fat meal and patients in Group B will receive their second single dose of niraparib under fasting conditions.

A schematic of the study design is provided in Figure 1.

Figure 1: Schematic Study Diagram



Treatment A = Single oral dose of niraparib under fasting condition
Treatment B = Single oral dose of niraparib under fed condition

The high-fat (approximately 50% of total caloric content of the meal) and high calorie (approximately 800–1,000 calories) meal is recommended for food-effect bioavailability and fed bioequivalence studies.

Niraparib will be administered in the clinical facility. If emesis should occur within 4 hours of dosing, the substudy patient will be considered non-evaluable from a PK perspective and will need to be replaced.

FE substudy patients will undergo intensive (triplicate) electrocardiogram (ECG) monitoring on FE Days 1 and 8 at baseline (predose) and 1, 1.5, 2, 3, 4, 6, and 8 hours postdose to coincide with blood sampling for PK determination. Triplicate ECGs should be performed between 2 and 5 minutes apart and should be performed prior to PK blood draws. The average of each of the triplicate measures will be used for analysis. Additional blood samples for PK will be collected at 12, 24, 48, 72, 96, and 120 hours postdose on FE Days 1 and 8; predose and 2 hours postdose on Cycle 1/Day 1 and Cycle 2/Day 1; and predose (only) on Cycle 4/Day 1 and Cycle 8/Day 1.

As stated in Section 1.1.1, when the substudy completes, participating patients will follow the schedule in the main study on Cycle 1/Day 1 (approximately 2 weeks after the start of the FE substudy), will begin dosing with open-label niraparib at 300 mg QD, and will be assessed for safety only for the duration of the study. They may continue participation in the main study until Investigator-determined disease progression.

1.2.2. Randomization Methodology

Patients will be randomized into 2 sequence groups (Group A or Group B) with 6 patients per sequence group, 12 patients in total.

1.2.3. Stopping Rules and Unblinding

There are no formal plans for early stopping. Unblinding is not applicable to this open-label substudy.

1.2.4. Study Procedures

The schedule of assessments is outlined in Table 1.

Table 1: Schedule of Events – Open-Label Food Effect Substudy (Study Completed)

	Screening	14-Day Food Effect		Cycle[1]			Subsequent Cycles[2]	Treatment Discontinuation (within 7 days of last dose)
				C1		C2		
Day	**-28 to -1**	**FE 1**	**FE 8**	**1**	**15**	**1**	**Cycle n, Day 1**	
Informed consent	X							
Demographics	X							
Medical, cancer, surgical, medication history	X							
Pregnancy test	X[3]			X[3]				
Randomization	X[4]							
Study treatment dispensed/collected		X[5]	X[5]	X		X	X	X[6]
Consumption of high-fat meal, as applicable		X	X					
Physical examination	X	X		X	X	X	X	X
Vital signs, height[7], weight	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X		X	X	X
Hematology/serum chemistry	X	X	X	X	X	X	X	X
Urinalysis[8]	X							
12-lead ECG[9]	X	X[10]	X[10]	X		X		X
Blood sample for PK[11]		X	X	X		X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X[12]

	Screening	14-Day Food Effect		Cycle[1]			Subsequent Cycles[2]	Treatment Discontinuation (within 7 days of last dose)
				C1		C2		
Day	**-28 to -1**	**FE 1**	**FE 8**	**1**	**15**	**1**	**Cycle n, Day 1**	
Concomitant medications	X	X	X	X	X	X	X	X
Bone marrow aspirate and biopsy and sample collection (whole blood) for cytogenetic analysis		X[13]						
Note: Patients in food effect substudy will receive a single oral dose of niraparib 300 mg on FE Days 1 and 8. Upon completion of the 14-day substudy, patients will then start open-label treatment with daily niraparib (300 mg QD) on Day 1/Cycle 1 (approximately 2 weeks after start of food effect substudy) and will be followed using the main study visit schedule for safety.								

Abbreviations: AML = acute myeloid leukemia C = cycle; FE = food effect; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MDS = Myelodysplastic syndrome; PK = pharmacokinetic(s); QD = once daily; SAE = serious adverse event.

[1] Treatment cycles are 28 days long, visits on Day 1 of each cycle unless otherwise specified.

[2] Visits continue every 4 weeks until study treatment discontinuation.

[3] Negative serum pregnancy test required within 72 hours prior to study treatment for females of childbearing potential; repeated every 3 months for duration of study (eg, Cycle 4, Cycle 7).

[4] Patients will be randomized in a crossover design within 72 hours prior to FE Day 1 (first single dose).

[5] Patients receive a single oral dose of niraparib 300 mg on FE Days 1 and 8.

[6] No new capsules dispensed.

[7] Height obtained at screening only.

[8] Urinalysis parameters must include: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen, and bilirubin.

[9] 12-lead ECG at Screening, Cycle 1/Day 1 (predose and 2 hours postdose), Cycle 2/Day 1 (predose and 2 hours postdose), and at treatment discontinuation. ECG monitoring is to be performed prior to PK blood draws.

[10] Triplicate ECG monitoring to coincide with PK on FE Days 1 and 8 at baseline (predose) and at 1, 1.5, 2, 3, 4, 6, and 8 hours postdose. Triplicate ECGs should be performed between 2-5 minutes apart and prior to PK blood draws.

[11] Blood samples for PK will be taken on FE Days 1 and 8 at baseline (within 30 minutes prior to dosing) and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours postdose. Additional blood samples will be collected predose and 2 hours postdose on Day 1 of Cycles 1 and 2 and predose only on Day 1 of Cycles 4 and 8. The exact time of the PK blood draw will be recorded and PK blood draws are to be completed after ECG monitoring.

[12] SAEs recorded up to 30 days after study treatment discontinuation.

[13] For any suspected myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization [WHO] criteria) and other sample testing results related to MDS/AML.

1.2.5. Pharmacokinetic and Safety Parameters

1.2.5.1. Pharmacokinetic Parameters

The PK endpoints are defined in a separate population PK analysis plan.

1.2.5.2. Safety Parameters

Safety evaluations performed during the study include physical examinations, measurement of vital signs, 12-lead ECGs, clinical laboratory evaluations including hematology, serum chemistry, and urinalysis, and monitoring of adverse events (AEs) and concomitant medications.

The safety endpoints are:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory parameters:
    - Complete blood count (CBC): hemoglobin, platelets, mean platelet volume (MPV) (optional), mean corpuscular volume, white blood cell (WBC) count, absolute lymphocyte count, percent lymphocytes, absolute neutrophil count, and percent neutrophils
    - Coagulation factors: activated partial thromboplastin time (aPTT) and international normalized ratio (INR)
    - Serum chemistry assessments for safety include: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea or blood urea nitrogen (BUN), total protein, albumin, lactate dehydrogenase (LDH), and amylase
    - Urinalysis: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen, and bilirubin
    - Serum cancer antigen 125 (CA-125)
    - Serum pregnancy testing
- Physical examination and vital signs:
    - Weight
    - Height (Screening only)
    - Blood pressure
    - Pulse
    - Temperature
- Eastern Cooperative Oncology Group (ECOG) performance status
- ECG
- Concomitant medications

Additional safety parameters include study treatment exposure and compliance.

2. PATIENT POPULATION

2.1. Population Definitions

The Safety population is defined as all patients who are randomized and who received at least 1 dose of study treatment. The Safety population is the primary population for the analysis of safety endpoints.

2.2. Protocol Violations

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Approximately 12 patients will be enrolled into the open-label FE substudy. If the number of evaluable patients (defined as completing both the fasted and fed portions) falls below 10, patients may be replaced at the discretion of the Sponsor. This is a descriptive substudy and no formal sample size calculations were performed.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pretreatment and on-treatment study days are numbered relative to the day of the first dose of study medication during the QD dosing phase, which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study medication is designated with an "L" (eg, Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, and so on. Similarly, during the crossover phase, study days are numbered relative to the day of the first dose of study medication during the crossover phase, which is designated as FE Day 1.

All output will be incorporated into Microsoft Word or Excel files or Adobe Acrobat PDF files, sorted, and labeled according to the International Conference on Harmonisation (ICH) recommendations[1], and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, and safety parameters.

Demographic, baseline, and disposition data will be presented by sequence (AB and BA) and overall. Safety data, including AEs, laboratory values, vital signs, and ECG data, will be summarized by treatment condition (fasted/fed) and overall for the crossover phase. Safety data from the QD dosing phase will be summarized overall.

For categorical variables, summary tabulations of the number and percentage of patients within each category of the parameter will be presented. Percentages will be based on the patients with a non-missing parameter. Percentages will be reported to 1 decimal place. Percentages will not be presented for zero counts.

For continuous variables, the number of patients, mean, standard deviation (StdDev), median, first quartile (Q_1), third quartile (Q_3), minimum, and maximum values will be presented. Mean, median, Q_1, and Q_3 will be reported to 1 more decimal place than the raw data, while the StdDev will be reported to 2 more decimal places than the raw data.

This study is primarily descriptive in nature; therefore, there are no formal statistical hypothesis tests planned.

3.3. Computing Environment

All statistical analyses will be performed using SAS statistical software v9.3 or later, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v18.0. Laboratory parameter changes will be described using shift tables relative to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.02. Concomitant medications will be coded using the latest version of the WHO Anatomical Therapeutic Chemical (ATC) classification.

3.4. Baseline Definitions

For safety summaries during the crossover phase, baseline will be defined as the dosing day for each treatment condition (fasting or fed). For each treatment condition, summaries will be provided for Day 1, Day 8, and change from Day 1 to Day 8. In particular, FE Day 8 will serve as Day 1 for the respective treatment condition and Cycle 1/Day 1 (QD dosing phase) will serve as Day 8 for the respective treatment condition.

For safety summaries during the QD dosing phase (ie, all treatment administered), baseline is defined as the most recent measurement prior to the first administration of study drug (ie, the latest assessment on or before FE Day 1).

3.5. Methods of Pooling Data

Data will be pooled across study sites. In addition, safety data under the same treatment condition of each treatment sequence (AB or BA) will be pooled for tabulation.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

3.8. Subpopulations

No analyses of subject subgroups are planned.

3.9. Withdrawals, Dropouts, Loss to Follow-up

If the number of evaluable patients falls below 10, patients may be replaced at the discretion of the Sponsor.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the electronic case report form (eCRF) will be included in data listings that will accompany the CSR.

When tabulating AE data, partial dates will be handled as follows: if the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution. Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, the Rel Day of all dates will be presented.

3.12. Interim Analyses

No interim analyses are planned for this study.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated overall and by treatment sequence (AB or BA) and will include the number of patients who: were randomized, treated, included in each analysis set, received treatment under fasted and fed conditions, discontinued treatment and reason(s) for discontinuation, withdrew prior to completing the study and the reason(s) for withdrawal, and the number of patient deaths and primary cause of death.

A by-subject listing of study completion information, including the reason for premature treatment discontinuation or study withdrawal, if applicable, will be presented. Entry criteria, protocol deviations, and inclusion/exclusion for analysis sets will be listed.

4.2. Demographics and Baseline Characteristics

Demographics, baseline characteristics, and medical history information will be summarized by treatment sequence and overall for the safety population using descriptive statistics.

Demographic and baseline data for each patient will be provided in data listings.

The demographic and baseline characteristics tables will include the following variables:

- Age at time of informed consent (years), calculated as date of informed consent minus date of birth / 365.25
- Age categories (18 to 64, 65 to 74, ≥65, and ≥75)
- Race (White, Black/African American, Asian, American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, Other, Unknown, and Not Reported)
- Ethnicity (Hispanic/Latino, non-Hispanic/Latino, Unknown, and Not Reported)
- Screening height, weight, and body mass index (BMI)
- ECOG performance status

Medical history will be coded using MedDRA v18.0 or later. All medical history data will be provided in a data listing.

4.3. Pharmacokinetic Evaluations

Details of the population PK and intensive PK analyses, including combined analyses of the ECG variables and PK parameters, will be contained in a separate analysis plan.

4.4. Safety Analyses

Safety analyses will be conducted using the Safety population. During the crossover phase, safety summaries will be presented by treatment condition (fasted or fed) and overall. During the QD dosing phase, summaries will be presented overall.

4.4.1. Study Drug Exposure

Extent of treatment during the QD dosing phase will be summarized as follows:

- Number and percent of patients beginning 1, 2, 3, …, 12, and >12 cycles
- Overall treatment exposure (months), defined as the [last dose date - first dose date + 1] / 30.4375, will be summarized as a continuous variable
- Time on study (months), defined as [last visit date or date of death - first dose date + 1] / 30.4375, will be summarized as a continuous variable

Duration and intensity of study treatment:

- Dose intensity (mg/day), defined as sum of the daily doses actually consumed divided by overall treatment exposure (converted to days), will be summarized as a continuous variable
- Relative dose intensity, defined as dose intensity (mg/day) divided by intended dose intensity (mg/day) multiplied by 100, where intended dose is 300 mg × overall treatment exposure (converted to days), will be summarized as a continuous variable

Dose reductions and dose interruptions:

- Number and percentage of patients with a dose reduction, defined as the dose consumed being less than the dose prescribed, for any reason and due to an AE (overall and by cycle)
- Number and percentage of patients with a dose interruption, defined as the dose consumed being 0 mg, for any reason and due to an AE (overall and by cycle)

Dosing information for each patient will be presented in a data listing.

4.4.2. Study Drug Compliance

Patient compliance with the study drug will be assessed via pill counts for the QD dosing phase. Study drug compliance will be defined by the dosing compliance ratio: the number of capsules prescribed (per dose prescribed) minus the number of capsules returned by the patient, divided by the number of capsules prescribed during the same period multiplied by 100. Unused capsules not returned and not reported as missed doses will be assumed to have been consumed.

A patient is evaluated as compliant if the patient has taken 80% to 120% of the expected capsules during participation in the study. Overall compliance rate, proportion of patients considered compliant, and compliance rate by cycle will be summarized.

4.4.3. Adverse Events

All AEs will be classified using MedDRA v18.0. The severity of the toxicities will be graded according to the NCI CTCAE v4.02. Any AEs leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.02 Grade 3 or higher, study treatment-related events, and serious adverse events (SAEs) will be presented. Related TEAEs are defined as TEAEs considered at least possibly related to treatment as judged by the Investigator. Any AEs for which the relationship to study drug is missing will be considered as related to study treatment. Tables will be produced for both the crossover phase (by treatment sequence and overall) and for the QD dosing phase (over all treatment).

Any TEAE will be defined as:

- Any new AE (one that was not seen prior to the start of treatment) that occurs for the first time after at least 1 dose of study treatment has been administered; or
- A pre-existing condition (one that was seen prior to the start of treatment) that worsens in severity after at least 1 dose of study treatment has been administered; or
- A pre-existing condition that is subsequently deemed related to study treatment.

Note: If the start date is missing for an AE and the actual start date cannot be determined from a partial date, the AE will be considered treatment-emergent.

All AEs will be collected from the time of signing the main informed consent form (ICF) through the end of treatment (EOT) visit. New SAEs (including deaths) will be collected for 30 days after the EOT visit. Any AEs recorded in the database that occur from the time of informed consent to first dose will be listed only and not included in safety analyses. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

The number and percentage of patients reporting a TEAE will be summarized by SOC and preferred term. If a patient experienced more than 1 event within a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event within a given preferred term, that patient is counted only once for that preferred term.

A high-level overview of TEAEs will be presented in a summary table. This table will include the number and percentage of patients for the following categories: any TEAE, any grade ≥3 TEAE, any related TEAE, any AE leading to treatment discontinuation/study termination, any treatment-emergent SAEs, any treatment-related SAEs, pregnancies, and deaths. The following lists the AE tables to be displayed:

- Overview of AEs
- TEAEs by SOC and preferred term
- Related TEAEs by SOC and preferred term
- Treatment-emergent SAEs by SOC and preferred term
- Related treatment-emergent SAEs by SOC and preferred term
- Grade ≥3 TEAEs by SOC and preferred term
- Related grade ≥3 TEAEs by SOC and preferred term
- TEAEs of special interest (see Section 7)
- TEAEs resulting in death by SOC and preferred term
- TEAEs resulting in study drug interruption by SOC and preferred term
- TEAEs resulting in study drug dose reduction by SOC and preferred term
- TEAEs resulting in study drug withdrawn by SOC and preferred term

Tables structured as listings will be provided for the following:

- Deaths
- Serious AEs
- TEAEs resulting in study drug interruption
- TEAEs resulting in study drug dose reduction
- TEAEs resulting in study drug withdrawn
- Adverse events of special interest

AE summaries will be ordered in decreasing frequency for SOC (alphabetically for SOCs with the same number of AEs reported), and decreasing frequency for preferred term within SOC (alphabetically for preferred terms with the same number of AEs reported within a SOC).

4.4.4. Laboratory Data

Laboratory assessments will be performed locally at each center's laboratory by means of their established methods. All laboratory values will be converted to the International System of Units, universally abbreviated SI (from the French *Le Système International d'Unités*) and classified as normal, low, or high based on normal ranges supplied by the local laboratories and upon employing standardization, as described below.

When local laboratories report different reference ranges for a particular test, these results will be normalized prior to calculating changes from baseline.[[2]] The reference range used by the majority of laboratories will be used as the "standard reference range" for a particular test. If 2 or more reference ranges are used by an equal number of laboratories, or no majority exists, the widest reference range will be used as the "standard reference range." Results from laboratories that use a reference range different from the "standard reference range" will be converted using the following formula:

$$x' = \max\left(0,\ \frac{x - \text{lLLN}}{\text{lULN} - \text{lLLN}} \times (\text{sULN} - \text{sLLN}) + \text{sLLN}\right),$$

where x is the result reported by the local laboratory; x' is the normalized result; lLLN and lULN are the lower and upper limits of normal from the local laboratory, respectively; and sLLN and sULN are the lower and upper limits of normal from the "standard reference range."

Normalized laboratory values will be used to calculate summary statistics; however, shift analyses and patient listings of laboratory data will be based on the values and normal ranges reported by the local laboratories, expressed in SI units.

Hematologic and chemistry laboratory results will be graded according to the cut points defined in the NCI CTCAE v4.02 severity grade. Laboratory results will be summarized by maximum CTCAE grade, as available. Continuous results will be analyzed using change from baseline and shift values.

Observed values and change from baseline will be summarized by visit. Graphical line mean changes over time may be provided.

Shift from baseline to the maximum CTCAE grade will be tabulated for hematology parameters.

In order to investigate possible drug-induced liver injury (DILI) a listing of potential Hy's Law cases (patients with AST or ALT >3 × ULN in combination with bilirubin >2 ×ULN) will also be presented. Additionally a Hy's Law plot will be produced which plots peak ALT and peak total bilirubin in 1 panel and peak AST and peak total bilirubin in a second panel.

A by-patient listing of all laboratory data will be provided, with laboratory reference ranges and abnormal values highlighted, and including center, patient identifier, and visit. Tables in the form of by-patient listings are also provided for abnormal lab values, CTCAE grade ≥3, and clinically significant lab findings, as reported by the investigator or local lab.

4.4.5. Vital Signs

Summaries of vital signs parameters (systolic and diastolic blood pressures, pulse rate, and temperature), height at Screening only, weight, and BMI will be presented by visit. Summary statistics will be produced for both observed and change from baseline values, for each parameter.

Vital sign measurements and physical examination findings will be presented for each patient in a data listing.

4.4.6. Electrocardiogram

Routine 12-lead ECGs will be performed for patients at Screening, Cycle 1/Day 1 (predose and 2 hours postdose), Cycle 2/Day 1 (predose and 2 hours postdose), and at treatment discontinuation.

Routine ECG results will be summarized descriptively, including the number and percentage of patients with normal, abnormal, and clinically significant abnormal results at Screening and each study visit.

For the primary analysis of QTcF, interpretation using Fridericia's (QTcF) method will be used. A summary of the number and percentage of patients with QTc interval exceeding predefined upper limits (eg, >450 ms, >480 ms, >500 ms) will be provided. A summary of the number and percentage of patients with change from Screening in QTc interval exceeding predefined upper limits (eg, >30 ms, >60 ms) will be provided. A separate summary will be provided which includes the change from predose to 2 hours postdose at Cycle1/Day 1 and Cycle 2/Day 1.

All routine 12-lead ECG data for each patient will be provided in a data listing.

Summaries and analyses of intensive ECG monitoring at FE Day 1 and FE Day 8 are discussed in a separate population PK analysis plan.

4.4.7. Concomitant Medications

All medications will be coded using the March 2015 or later version of the WHO Drug Dictionary (WHODD).

The use of concomitant medications will be included in a by-patient data listing.

5. CHANGES TO PLANNED ANALYSES

As of the date of this final SAP, there have been no changes between the protocol-defined statistical analyses for this sub-study and those presented in this SAP.

If any modifications in the experimental design, dosages, parameters, patient selection, or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approval from the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

6. REFERENCES

1 US Federal Register. International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D 0174]. Federal Register Volume 63, Number, pages 49583 49598. September 16, 1998.

2 Chuang-Stein C. Some Issues Concerning the Normalization of Laboratory Data Based on Reference Ranges. Therapeutic Innovation and Regulatory Science (Impact Factor 0.46). 2001; 35(1):153-156.

7. APPENDIX 1: TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST

AESI Category **MedDRA Level**	**Preferred Terms**
Thrombocytopenia Event Haematopoietic cytopenias affecting more than one type of blood cell (SMQ) [20000028]	Megakaryocytes decreased Platelet count decreased Platelet maturation arrest Platelet production decreased Platelet toxicity Thrombocytopenia Megakaryocytes abnormal Platelet count abnormal Platelet disorder Plateletcrit abnormal Plateletcrit decreased Thrombocytopenia neonatal
Anemia Event: Haematopoietic erythropenia (SMQ) [20000029]	Anaemia macrocytic Aplasia pure red cell Aplastic anaemia Erythroblast count decreased Erythroid maturation arrest Erythropenia Hypoplastic anaemia Microcytic anaemia Proerythroblast count decreased Red blood cell count decreased Reticulocyte count decreased Reticulocytopenia Anaemia Anaemia neonatal Erythroblast count abnormal Erythropoiesis abnormal Haematocrit abnormal Haematocrit decreased Haemoglobin abnormal Haemoglobin decreased Leukoerythroblastic anaemia Normochromic normocytic anaemia Proerythroblast count abnormal Red blood cell count abnormal Reticulocyte count abnormal Reticulocyte percentage decreased

AESI Category **MedDRA Level**	**Preferred Terms**
Leukopenia Event	
Haematopoietic leukopenia (SMQ) [20000030]	Agranulocytosis Band neutrophil count decreased* Band neutrophil percentage decreased* Basophil count decreased Basophilopenia B-lymphocyte count decreased Cyclic neutropenia* Eosinopenia Eosinophil count decreased Febrile neutropenia* Granulocyte count decreased* Granulocytes maturation arrest* Granulocytopenia* Idiopathic neutropenia* Leukopenia Lymphocyte count decreased Lymphopenia Metamyelocyte count decreased Monoblast count decreased Monocyte count decreased Monocytopenia Myeloblast count decreased Myelocyte count decreased Neutropenia* Neutropenic infection* Neutropenic sepsis* Neutrophil count decreased* Promyelocyte count decreased Pure white cell aplasia Radiation leukopenia T-lymphocyte count decreased White blood cell count decreased Basophil count abnormal Basophil percentage decreased B-lymphocyte abnormalities Differential white blood cell count abnormal* Eosinophil count abnormal Eosinophil percentage decreased Full blood count abnormal Granulocytes abnormal* Granulocytopenia neonatal* Leukopenia neonatal Lymphocyte count abnormal

AESI Category **MedDRA Level**	**Preferred Terms**
	Lymphocyte percentage abnormal Lymphocyte percentage decreased Lymphocytopenia neonatal Monocyte count abnormal Monocyte percentage decreased Myeloblast percentage decreased Myelocyte percentage decreased Myeloid maturation arrest Neutropenia neonatal* Neutrophil count abnormal* Neutrophil percentage decreased* Plasma cell disorder Plasma cells absent T-lymphocyte count abnormal White blood cell analysis abnormal White blood cell count abnormal White blood cell disorder
Pancytopenia Event: Haematopoietic cytopenias affecting more than one type of blood cell (SMQ) [20000028]	Aplastic anaemia Autoimmune aplastic anaemia Bicytopenia Bone marrow failure Cytopenia Febrile bone marrow aplasia Full blood count decreased Pancytopenia Panmyelopathy Aspiration bone marrow abnormal Biopsy bone marrow abnormal Blood count abnormal Blood disorder Bone marrow disorder Bone marrow infiltration Bone marrow myelogram abnormal Bone marrow necrosis Bone marrow toxicity Congenital aplastic anaemia Haematotoxicity Myelodysplastic syndrome Myelodysplastic syndrome transformation Myelofibrosis Myeloid metaplasia Plasmablast count decreased Primary myelofibrosis

AESI Category **MedDRA Level**	**Preferred Terms**
	Scan bone marrow abnormal
MDS/AML Event: MedDRA PTs as listed	Myelodysplastic syndrome Myelodysplastic syndrome transformation Myelodysplastic syndrome unclassifiable Acute myeloid leukaemia Acute myeloid leukaemia recurrent Blast crisis in myelogenous leukaemia Myeloid leukaemia
Fatigue Event: Asthenic Conditions HLT	Adult failure to thrive Asthenia Autonomic nervous system imbalance Cachexia Chronic fatigue syndrome Decreased activity Fatigue Lethargy Listless Malaise Sluggishness
Pneumonitis Event: MedDRA PTs as listed	Pneumonitis Acute interstitial pneumonitis
Overdose Event: MedDRA PTs as listed	Overdose Accidental overdose

*Preferred terms are included in the Neutropenia Event AESI.

8. CLINICAL STUDY REPORT APPENDICES

8.1. List of Statistical Tables, Figures, and Data Listings

8.2. Table and Figure Shells

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Table 14.1.1

Patient Enrollment and Disposition by Treatment Sequence and Overall

Parameter	Statistic	Sequence Group A	Sequence Group B	Overall
Number of Patients				
Randomized	n	xx	xx	xx
Treated	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treated in Fasted Period	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treated in Fed Period	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Population				
Discontinuations from Treatment	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse event	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Disease progression	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Risk to patient	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe non-compliance	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient request	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinuations from Study	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of consent	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Deaths	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
On treatment	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
During follow-up	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At any time	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Main Cause of Death	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Disease progression	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse event	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
Note: Percentages based on the number randomized.
Source: Data Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.1.2

Demographic Characteristics by Treatment Sequence and Overall (Safety Population)

Parameter	Statistic	Sequence Group A (N=xx)	Sequence Group B (N=xx)	Overall (N=xx)
Age (years) [1]	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Age Group (years)				
18 - 64	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
65 - 74	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 65	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 75	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race				
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black/African American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or other Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Reported	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity				
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Reported	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
Note: Percentages based on the number of patients in the Safety population.
[1] As collected on the Demography eCRF, based on age at time of informed consent.
Source: Data Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.1.3

Baseline Characteristics by Treatment Sequence and Overall (Safety Population)

Parameter	Statistic	Sequence Group A (N=xx)	Sequence Group B (N=xx)	Overall (N=xx)
Screening Weight (kg)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Screening Height (cm)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Screening BMI (kg/m^2)	n	xx	xx	xx
	Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
ECOG performance status				
0	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

[2]

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Source: Data Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.3.1.1A

Summary of Number and Percentage of Patients with Adverse Events by Treatment Condition and Overall: Crossover Phase
(Safety Population)

		Treatment Condition		
Characteristic	Statistic	Fasted (N=xx)	Fed (N=xx)	Overall (N=xx)
Total number of TEAEs	n	xx	xx	xx
Any TEAE	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any related TEAE	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any TEAE with CTCAE Toxicity Grade ≥3	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any serious TEAE	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any treatment-related serious TEAE	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any pregnancy	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any AE leading to treatment discontinuation	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any TEAE leading to death	n (%)	n (xx.x)	n (xx.x)	n (xx.x)

Note: AE = Adverse Event; TEAE = Treatment-Emergent Adverse Event. Toxicity is graded using NCI CTCAE version 4.02. Patients with more than 1 event of the same preferred term are counted only once for the event with the highest CTCAE grade.
Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (overall column only):
Table 14.3.1.1B Summary of Number of Patients with Adverse Events: QD Dosing Phase Overall (Safety Population)

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Table 14.3.1.2A

Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Treatment Condition and Overall: Crossover Phase (Safety Population)

		Treatment Condition		
MedDRA System Organ Class Preferred Term	Statistic	Fasted (N=xx)	Fed (N=xx)	Overall (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.				

Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (overall column only):

Table 14.3.1.2B Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)

Programming Note: For all tables displaying SOC and PT: AE summaries will be ordered in decreasing frequency for SOC (alphabetically for SOCs with the same number of AEs reported), and decreasing frequency for preferred term within SOC (alphabetically for preferred terms with the same number of AEs reported within a SOC).

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Table 14.3.1.3A

Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Treatment Condition and Overall: Crossover Phase (Safety Population)

		Treatment Condition		
MedDRA System Organ Class Preferred Term	Statistic	Fasted (N=xx)	Fed (N=xx)	Overall (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Etc.

Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (overall column only):
Table 14.3.1.3B Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)

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Table 14.3.1.4A

Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term by Treatment Condition and Overall: Crossover Phase (Safety Population)

		Treatment Condition		
MedDRA System Organ Class Preferred Term	Statistic	Fasted (N=xx)	Fed (N=xx)	Overall (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.

Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (overall column only):

Table 14.3.1.4B Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)

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Table 14.3.1.5A

Related Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term by Treatment Condition and Overall: Crossover Phase (Safety Population)

		Treatment Condition		
MedDRA System Organ Class Preferred Term	Statistic	Fasted (N=xx)	Fed (N=xx)	Overall (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Etc.

Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (overall column only):
Table 14.3.1.5B Related Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)

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Table 14.3.1.6A

CTCAE Grade ≥3 TEAEs by MedDRA System Organ Class and Preferred Term by Treatment Condition and Overall: Crossover Phase (Safety Population)

		Treatment Condition		
MedDRA System Organ Class Preferred Term	Statistic	Fasted (N=xx)	Fed (N=xx)	Overall (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.				

Note: Toxicity is graded using NCI CTCAE version 4.02. Patients with more than 1 event of the same preferred term are counted only once for the event with the highest CTCAE grade.
Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (overall column only):
Table 14.3.1.6B CTCAE Grade ≥3 TEAEs by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)

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Table 14.3.1.7A

Related CTCAE Grade ≥3 TEAEs by MedDRA System Organ Class and Preferred Term by Treatment Condition and Overall: Crossover Phase (Safety Population)

		Treatment Condition		
MedDRA System Organ Class Preferred Term	Statistic	Fasted (N=xx)	Fed (N=xx)	Overall (N=xx)
SOC 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Etc.

Note: Toxicity is graded using NCI CTCAE version 4.02. Patients with more than 1 event of the same preferred term are counted only once for the event with the highest CTCAE grade.
Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (overall column only):
Table 14.3.1.7B Related CTCAE Grade ≥3 TEAEs by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)

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Table 14.3.1.8

TEAEs Resulting in Death by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)

MedDRA System Organ Class Preferred Term	Statistic	Overall (N=xx)
SOC 1	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)

Etc.

Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (overall column only):
- Table 14.3.1.9 TEAEs Resulting in Study Drug Interruption by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)
- Table 14.3.1.10 TEAEs Resulting in Study Drug Dose Reduction by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)
- Table 14.3.1.11 TEAEs Resulting in Withdrawal of Study Drug by MedDRA System Organ Class and Preferred Term: QD Dosing Phase Overall (Safety Population)

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Table 14.3.1.12A

Overview of Treatment Emergent Adverse Events of Special Interest by Treatment Condition and Overall: Crossover Phase (Safety Population)

		Treatment Condition		
Characteristic	Statistic	Fasted (N=xx)	Fed (N=xx)	Overall (N=xx)
Any thrombocytopenia event	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any Grade ≥3 thrombocytopenia event	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any Serious thrombocytopenia event	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any thrombocytopenia event resulting in dose reduction	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any thrombocytopenia event leading to discontinuation	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any anemia event	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any Grade ≥3 anemia	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any Serious anemia event	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any anemia resulting in dose reduction	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any anemia event leading to discontinuation	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any neutropenia event	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any Grade ≥3 neutropenia	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any Serious neutropenia event	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any neutropenia resulting in dose reduction	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any neutropenia event leading to discontinuation	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any leukopenia event	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any Grade ≥3 leukopenia	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any Serious leukopenia event	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any leukopenia resulting in dose reduction	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
Any leukopenia event leading to discontinuation	n (%)	n (xx.x)	n (xx.x)	n (xx.x)
<continue with all defined AESIs>				

Note: Toxicity is graded using NCI CTCAE version 4.02. Patients with more than 1 event of the same preferred term are counted only once for the event with the highest CTCAE grade.
Source: Listing 16.2.x

Programming note: for MedDRA preferred terms to be included in the AESI, see Section 7.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (overall column only):
Table 14.3.1.12B Overview of Treatment Emergent Adverse Events of Special Interest: QD Dosing Phase Overall (Safety Population)

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Table 14.3.2.1

Listing of Treatment-Emergent Adverse Events Leading to Death (Safety Population)

Sequence Group A

Patient Number	Treatment Condition	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date (Rel Day [1])	Date of Death	Severity Grade	Action Taken Regarding Study Agent	Concomitant Medication Given for AE? Yes/No	Relationship

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
Note: AEs leading to death are those AEs with a fatal outcome or CTCAE grade 5.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.3.2.2

Listing of Serious Treatment-Emergent Adverse Events (Safety Population)

Sequence Group A

Patient Number	Treatment Condition	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome
				DDMMMYYYY/ Ongoing	-xx					

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.3.2.3

Listing of Treatment-Emergent Adverse Events Resulting in Study Drug Interruption (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Concomitant Medication Given?	Relationship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx					

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.3.2.4

Listing of Treatment-Emergent Adverse Events Resulting in Study Drug Dose Reduction (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Concomitant Medication Given?	Relationship	Outcome	SAE?	Dose After Reduction
			DDMMMYYYY/ Ongoing	-xx						

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.3.2.5

Listing of Treatment-Emergent Adverse Events Resulting in Withdrawal of Study Drug (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Concomitant Medication Given?	Relationship	Outcome	SAE?	Date Study Drug Withdrawn
			DDMMMYYYY/ Ongoing	-xx						

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.3.2.6

Listing of Treatment-Emergent Adverse Events of Special Interest (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Action Taken	Concomitant Medication Given?	Relation-ship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx						

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.3.4.1

Listing of Abnormal Laboratory Values (Safety Population)

Sequence Group A

Patient Number	Treatment Condition	Age/ Race/ Weight	Group	Laboratory Test (unit)	Visit	Visit Date (Rel Day [1])	Result	CTCAE Grade [2]	Reference Range Low	Reference Range High
			Hematology							
			Chemistry							

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
[1] Rel Day is calculated as visit date minus first dose date (plus 1 day if visit date is on or after first dose date).
[2] CTCAE Grade: 1=…

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for:
Table 14.3.4.2 Listing of Laboratory Values with CTCAE Severity Grade ≥3 (Safety Population)
Table 14.3.4.3 Listing of Clinically Significant Laboratory Values (Safety Population)

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Table 14.3.5.1A

Summary and Change from Baseline for Hematology Parameters by Visit, by Treatment Condition and Overall: Crossover Phase
(Safety Population)

				Treatment Condition		
Parameter	Visit	Actual/ Change	Statistic	Fasted (N=xx)	Fed (N=xx)	Overall (N=xx)
Parameter 1	Day 1	Actual	n	xx	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx	xx, xx
	Day 8	Actual	n	xx	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx	xx, xx
		Change	n	xx	xx	xx
			Mean (StdDev)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x	xx.x
			Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
			Min, Max	xx, xx	xx, xx	xx, xx
Parameter 2	<as above>					

Source: Data Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Repeat for (tables with "B" suffix present overall column only):
Table 14.3.5.1B Summary and Change from Baseline for Hematology Parameters by Visit: QD Dosing Phase Overall (Safety Population)
Table 14.3.5.2 Summary and Change from Baseline for Chemistry Parameters by Visit Overall (Safety Population)

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Table 14.3.5.3

Summary of Shifts in CTCAE Grade - Hematology Parameters: QD Dosing Phase Overall (Safety Population)

				Post-Screening CTCAE Grade					
Parameter	Post-Screening Value	Statistic	Screening CTCAE Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Parameter 1	Maximum CTCAE Grade	n (%)	Grade 0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	End of Treatment		<as above>						
Parameter 2	Maximum CTCAE Grade		<as above>						
	End of Treatment		<as above>						

Note: Toxicity is graded using NCI CTCAE version 3.0.
Source: Listing 16.2.x

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Table 14.3.5.4

Summary and Change from Baseline for Vital Signs by Visit: QD Dosing Phase Overall (Safety Population)

Parameter	Visit	Actual/ Change	Statistic	Overall (N=xx)
Parameter 1	Day 1	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
	Day 8	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
		Change	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
Parameter 2	<as above>			

Source: Data Listing 16.2.x

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Table 14.3.5.5

Summary of QTcF Interval Prolongation and Change from Pre-dose in QTc Interval (Safety Population)

Visit	Parameter	Statistic	Overall (N=xx)
Cycle 1 Day 1	Post-dose QTcF Interval		
	> 450 msec	n (%)	xx (xx.x)
	> 480 msec	n (%)	xx (xx.x)
	> 500 msec	n (%)	xx (xx.x)
	Change from pre-dose to post-dose QTcF Interval		
	> 30 msec	n (%)	xx (xx.x)
	> 60 msec	n (%)	xx (xx.x)
Cycle 2 Day 1	<as above>		

Source: Listing 16.2.x

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Table 14.3.5.6

Summary of Overall ECG Interpretation (Safety Population)

Visit	Time Point	Interpretation	Statistic	Overall (N=xx)
Screening		Normal	n (%)	xx (xx.x)
		Abnormal, not clinically significant	n (%)	xx (xx.x)
		Abnormal, clinically significant	n (%)	xx (xx.x)
Cycle 1 Day 1	Pre-dose	<as above>		
	Post-dose	<as above>		
Cycle 2 Day 1	<as above>			
End of Treatment		<as above>		

Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.3.5.7

Summary of Overall Exposure to Study Drug: QD Dosing Phase (Safety Population)

Parameter	Statistic	Overall (N=xx)
Number of Cycles Started		
1	n (%)	xx (xx.x)
2	n (%)	xx (xx.x)
...	...	...
> 12	n (%)	xx (xx.x)
Total Study Duration [2]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
	Median (95% CI) [1]	xx.x (xx.x, xx.x)
Overall Treatment Exposure [3]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
	Median (95% CI) [1]	xx.x (xx.x, xx.x)
Dose Intensity (mg/day) [4]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Relative Dose Intensity [5]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx

[1] Median and 95% confidence interval estimated from product-limit (Kaplan-Meier) method.
[2] Total study duration is calculated as last visit date or date of death minus enrollment date plus one.
[3] Overall treatment exposure is calculated as last dose date minus first dose date plus one.
[4] Dose intensity is calculated as sum of the daily doses actually consumed divided by total duration.
[5] Relative dose intensity is calculated as dose intensity (mg/day) divided by intended dose intensity (mg/day) multiplied by 100, where intended dose is 300 mg x total duration.
Source: Listing 16.2.x

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Table 14.3.5.8

Summary of Study Drug Compliance by Cycle and Overall: QD Dosing Phase (Safety Population)

Cycle	Parameter	Statistic	Overall (N=xx)
Overall	Compliance	n	xx
		Mean (StdDev)	xx.x (xx.xx)
		Median	xx.x
		Q1, Q3	xx.x, xx.x
		Min, Max	xx, xx
	Compliance Rate	n (%)	xx (xx.x)
	<80% compliant	n (%)	xx (xx.x)
	>120% compliant	n (%)	xx (xx.x)
Cycle 1	Compliance	n	xx
		Mean (StdDev)	xx.x (xx.xx)
		Median	xx.x
		Q1, Q3	xx.x, xx.x
		Min, Max	xx, xx
	Compliance Rate	n (%)	xx (xx.x)
	<80% compliant	n (%)	xx (xx.x)
	>120% compliant	n (%)	xx (xx.x)
Etc.			

Note: Compliance is calculated as the number of capsules prescribed (per dose prescribed) minus the number of capsules returned by the patient divided by the number of capsules prescribed during the same period multiplied by 100. Compliance rate is the number and percentage of patients 80% to 120% compliant.
Source: Listing 16.2.x

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Table 14.3.5.9

Summary of Dose Interruptions and Dose Reductions by Cycle: QD Dosing Phase (Safety Population)

Cycle	Parameter	Statistic	Overall (N=xx)
At Any Time	Dose Interruptions		
	Dose interruption for any reason	n (%)	xx (xx.x)
	Dose interruption due to AE	n (%)	xx (xx.x)
	Dose Reductions		
	Dose reduction for any reason	n (%)	xx (xx.x)
	Dose reduction due to AE	n (%)	xx (xx.x)
Cycle 1	Dose Interruptions		
	Dose interruption for any reason	n (%)	xx (xx.x)
	Dose interruption due to AE	n (%)	xx (xx.x)
	Dose Reductions		
	Dose reduction for any reason	n (%)	xx (xx.x)
	Dose reduction due to AE	n (%)	xx (xx.x)
Cycle 2	<as above>		

Source: Listing 16.2.x

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8.3. Data Listing Shells

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Listing 16.2.1.1

Discontinuation from Treatment

Sequence Group A

Patient Number	Date of Treatment Discontinuation	Date of First Dose	Date of Last Dose	Number of Days on Treatment[1]	Primary Reason for Treatment Discontinuation
					Other: <specify>
					Patient request: <specify>

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
[1] Days on treatment = Last dose date – first dose date + 1.

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Listing 16.2.1.2

Discontinuation from Study

Sequence Group A

Patient Number	Date of Discontinuation	Date of Informed Consent	Number of Days on Study [1]	Reason for Discontinuation	Cause of Death	Date of Death

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
[1] Days on study = Last assessment date – date of informed consent + 1.

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Listing 16.2.2.1

Inclusion/Exclusion Criteria

Sequence Group A

Patient Number	Did the Patient Satisfy all Inclusion/Exclusion Criteria?	Inclusion/Exclusion Criterion Number	Inclusion/Exclusion Criterion Text

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.2.2

Protocol Violations

Sequence Group A

Patient Number	Type of Violation	Description of Violation	Date

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.3.1

Study Populations

Sequence Group A

Patient Number	Included in Safety Population
	Yes
	No: Reason for exclusion

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.4.1

Demographics

Sequence Group A

Patient Number	Age (yr)	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2)	Screening ECOG Performance Status

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
Note: BMI = Body Mass Index. BMI (kg/m^2) = weight (kg) / [height (m)]^2

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Listing 16.2.4.2

Medical History

Sequence Group A

Patient Number	Any Conditions or Surgeries	System Organ Class [1]/ Preferred Term [1]/ Condition	Start Date	Ongoing at Study Start?	Stop Date

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
[1] Coding was done using MedDRA version 17.1.

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Listing 16.2.4.3

Prior Hematology

Sequence Group A

Patient Number	Event	CTCAE Grade	Start Date/ End Date(days)	Which Prior Regimen	Treatment Given
	(e.g., Thrombocytopenia)				

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.4.4A

Ovarian Cancer Treatment: Part 1

Sequence Group A

Patient Number	Regimen Number	Chemotherapy Course	Cancer Type	Reason for Administration	Start Date/ Stop Date	Best Response	Progression Date	Discontinuation Reason

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.4.4B

Ovarian Cancer Treatment: Part 2

Sequence Group A

			Beginning of Regimen			Completion of Regimen		
Patient Number	Regimen Number	Agent Name	CA-125 Collect Date	CA-125 Value (U/ml)	ULN Range (U/ml)	CA-125 Collect Date	CA-125 Value (U/ml)	ULN Range (U/ml)

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.4.5

Other Cancer History

Sequence Group A

Patient Number	Cancer History Unrelated to Study Indication?	Cancer Type	Date Last Treated

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.4.6

Ovarian Cancer Pathology

Sequence Group A

Patient Number	Biopsy Date	Method of Diagnosis	Subtype	Tumor Grade

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.4.7

Cancer Staging

Sequence Group A

Patient Number	Primary Tumor Site	Initial Diagnosis Date	Cancer Stage (FIGO) at Time of Initial Diagnosis	Sites of Metastatic Disease

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.4.8

Prior Surgery for Study Indication

Sequence Group A

Patient Number	Any Surgeries/ Procedures?	Surgery/Procedure	Anatomical Location	Indication	Date of Surgery/ Procedure

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.4.9

Previous Radiotherapy

Sequence Group A

Patient Number	Any Prior Radiotherapy	Site and Region	Radiotherapy Start Date	Radiotherapy Stop Date	Total Grays

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.5.1A

Study Medication: Part 1

Sequence Group A

Patient Number	Visit	Bottle from Previous Cycle Returned?	Bottle Number Returned	Number of Unused Capsules Returned	Bottle Number Dispensed	Dose Prescribed at this Visit (mg)	Date:Time of Administration	Was Full Dose Taken
								No <specify reason>

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.5.1B

Study Medication: Part 2

Sequence Group A

Patient Number	Visit	Dose Modified During Previous Cycle?	Start Date	Stop Date	Dose (mg)	Reason for Change	Action Taken	Any Missed Doses
						Other <specify>		Yes <explain>

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.5.2

Study Medication: First Dose

Sequence Group A

Patient Number	Visit	Dose Administration Date:Time	Bottle Number Dispensed	Dose Prescribed (mg)	Full Dose Consumed?	Amount Consumed	Reason Full Dose Not Consumed
	FE Day 1						
	FE Day 8						
	Cycle 1 Day 1						

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

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Listing 16.2.5.3

Study Medication Compliance

Sequence Group A

Patient Number	Visit	Number of Capsules Prescribed [1]	Number of Capsules Returned [2]	Percent Compliance [3]	Overall Compliance [4]
		xxx	yyy	100*(xxx-yyy)/xxx	

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted
[1] Number of capsules expected to have been consumed since previous cycle, accounting for dose interruptions and reductions.
[2] Unused capsules not returned and not reported as missed doses will be assumed to have been consumed.
[3] The number of capsules prescribed (per dose prescribed) minus the number of capsules returned by the patient divided by the number of capsules prescribed during the same period multiplied by 100.
[4] The total number of capsules prescribed (per dose prescribed) minus the total number of capsules returned by the patient divided by the total number of capsules prescribed multiplied by 100.

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Listing 16.2.6.6

ECOG Performance Status

Sequence Group A

Patient Number	Visit	Was Assessment Performed?	Date	Study Day	Performance Status [1]

Sequence Group A: Fasted->Fed
Sequence Group B: Fed->Fasted

Note: Study day is calculated as date of interest minus date of informed consent plus one.
[1] CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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Listing 16.2.7.1

Adverse Events Sorted by Patient

Treatment Condition: Fasted

Patient Number	Preferred Term/ Verbatim Term	Start Date/ Stop Date	Rel Day [1]	TEAE [2]	CTCAE Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome	SAE?
		DDMMMYYYY/ Ongoing	-xx	No						

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] TEAE = treatment emergent adverse event

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Programming Note: Repeat for Fed condition and QD dosing period

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Listing 16.2.7.2

Adverse Events Sorted by System Organ Class (SOC), Preferred Term and Patient

Treatment Condition: Fasted

System Organ Class/ Preferred Term/ Verbatim Term	Patient Number	Start Date/ Stop Date	Rel Day [1]	TEAE [2]	CTCAE Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome	SAE?

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] TEAE = treatment emergent adverse event

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Programming Note: Repeat for Fed condition and QD dosing period

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Listing 16.2.7.3

Adverse Events of Special Interest Sorted by Patient

Treatment Condition: Fasted

Patient Number	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/ Stop Date	Rel Day [1]	TEAE [2]	CTCAE Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome	SAE?

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] TEAE = treatment emergent adverse event

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Programming Note: Repeat for Fed condition and QD dosing period

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Listing 16.2.7.4

Glossary of Adverse Events

System Organ Class	Preferred Term	Verbatim Term

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Listing 16.2.8.1

Laboratory Results: Hematology

Treatment Condition: Fasted

Patient Number	Visit	Sample Collection Date	Rel Day [1]	Laboratory Test	Result	Units	Flag [2]	Normal Range

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] H = High relative to normal range, L = Low relative to normal range. CTCAE grade appended if applicable. CS = clinically significant (per investigator).

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Programming Note: Repeat for Fed condition and QD dosing period

Repeat for:
- Listing 16.2.8.2 Laboratory Results: Chemistry
- Listing 16.2.8.3 Laboratory Results: Urinalysis
- Listing 16.2.8.4 Laboratory Results: Coagulation

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Listing 16.2.8.5

Laboratory Results: Liver Function Tests – Potential Hy's Law Cases

Treatment Condition: Fasted

				Laboratory Analyte (result/xULN)				
Patient Number	Visit	Sample Collection Date	Rel Day [1]	ALT (U/L)	AST (U/L)	Total Bilirubin (umol/L)	ALP (U/L)	INR
				150/3.3	100/2.7	40/2.3	100/0.7	1

Note: ALT=alanine aminotransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase, INR=international normalized ratio, ULN=upper limit of normal.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

Programming Note: Include all visits for any patients with ALT or AST >3xULN, or bilirubin >2xULN at any time post Screening.
Programming Note: Repeat for Fed condition and QD dosing period

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Listing 16.2.8.6

Pregnancy Test

Patient Number	Age	Menopause or Surgical Sterilization?	Visit	Reason Serum Pregnancy Test Not Performed	Date Sample Taken	Rel Day [1]	Result	Contraception Practice Confirmed

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.1

Vital Signs

Treatment Condition: Fasted

Patient Number	Visit	Reason Not Performed	Assessment Date	Rel Day [1]	Height (cm)	Weight (kg)	Temperature (°C)	Pulse (beats/min)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Programming Note: Repeat for Fed condition and QD dosing period

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Listing 16.2.9.2

Physical Examination

Treatment Condition: Fasted

Patient Number	Visit	Date Performed	Rel Day [1]	Body System	Status	Abnormality Description

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Programming Note: Repeat for Fed condition and QD dosing period

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Listing 16.2.9.3

Electrocardiogram

Patient Number	Visit	Time Point	Date:Time of Assessment	Rel Day [1]	Heart Rate (bpm)	RR (sec)	PR (msec)	QRS (msec)	QT (msec)	QTcB (msec)	QTcF [2] (msec)

Note: (N)CS = (Not) Clinically Significant
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] Values flagged with a single asterisk are changes from baseline >30. Values flagged with two asterisks are changes from baseline >60.

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Listing 16.2.9.4

Overall Electrocardiogram Interpretation

Patient Number	Age (yrs)	Visit	Time Point	Date:Time of Assessment	Rel Day [1]	Specify Sinus Rhythm	ECG Interpretation

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.5

Surgeries/Procedures

Patient Number	Any Surgeries or Procedures	Surgery/Procedure while on study	Date	Rel Day [1]

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.6

Follow-up Surgery and Radiotherapy

	Follow-up Surgery for Cancer			Follow-up Radiotherapy					
Patient Number	Surgical Procedure Name	Surgery/ Procedure Date	Rel Day [1]	Anatomical Areas Radiated	Start Date	Rel Day [1]	End Date	Rel Day [1]	Total Grays

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.7

Previous and Concomitant Medications

Patient Number	ATC/ Generic Name/ Verbatim Name	Total Dose	Dose Units	Frequency	Indication	Route of Administration	Start/ Stop Date	Rel Day [1]

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.8

Cytology/Histology

Patient Number	Cytology/Histology Test	Date	Rel Day [1]	Results

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

STATISTICAL ANALYSIS PLAN

A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

Protocol PR-30-5011-C QTc Safety Substudy

Protocol Number:	PR-30-5011-C
Protocol Version and Date:	Amendment 5: 11 September 2015 Amendment US 2: 11 September 2015 Amendment US 1: 10 March 2015 Amendment 4: 4 December 2014 Amendment 3: 9 April 2014 Amendment 2: 3 March 2014 (amendment 2 never issued) Amendment 1: 3 May 2013 Original: 21 March 2013
Name of Test Drug:	Niraparib capsules
Phase:	Phase 3
Methodology:	An open-label substudy to evaluate corrected QT interval in a subset of ovarian cancer patients treated with niraparib
Sponsor:	TESARO Inc. 1000 Winter Street, Suite 3300 Waltham, MA 02451 Tel: (339) 970-0900
Sponsor Representative:	Shefali Agarwal, MD, MPH Senior Medical Director
Analysis Plan Date:	01 June 2016
Analysis Plan Version:	Final Version 2.0

APPROVAL SIGNATURE PAGE

Protocol Title: A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

Sponsor: TESARO Inc.
1000 Winter Street, Suite 3300
Waltham, MA 02451

Protocol Number: PR-30-5011-C QTc Safety Substudy

Document Date / Version: 01 June 2016/ Final Version 2.0

Veristat, Inc. Author:

PPD MS
Principal Biostatistician
Veristat, LLC
118 Turnpike Road
Suite 200
Southborough, MA 01772

Signature: PPD

Date: PPD

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

Mohammed Al-Adhami, PhD
Director, Biostatistics
TESARO Inc.

Signature: PPD

Date: PPD

Sponsor Signatory:

Shefali Agarwal, MD, MPH
Senior Medical Director
TESARO Inc.

Signature: PPD

Date: PPD

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BUN	Blood urea nitrogen
CA-125	Cancer antigen 125
CBC	Complete blood count
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
FIGO	International Federation of Gynecology and Obstetrics
GCIG	Gynecologic Cancer Intergroup
GGT	Gamma glutamyl transferase
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPV	Mean platelet volume

Abbreviation	Definition
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Objective response rate
PD	Progressive disease
PET	Positron emission tomography
PK	Pharmacokinetic
PR	Partial response
Q_1	First quartile
Q_3	Third quartile
QD	Every day
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
Rel Day	Relative study day
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SI	*Système International d'Unités*
SOC	System Organ Class (MedDRA)
StdDev	Standard deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WBC	White blood count
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

This open-label substudy will evaluate QT interval corrected for heart rate (QTc) in approximately 20 patients with ovarian cancer. QTc, objective response rate (ORR), duration of response, and exploratory biomarkers will be assessed in this subset of niraparib-treated patients with ovarian cancer.

1.1.2. Study Objectives

The objectives of the study are to evaluate QTc; to evaluate antitumor activity and durability of response; and to explore potential biomarkers such as those related to deoxyribonucleic acid (DNA) repair deficiency following treatment with niraparib in patients who have ovarian cancer.

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

A separate population pharmacokinetic (PK) analysis plan describes the analyses of electrocardiogram (ECG) variables and PK parameters. This analysis plan is being developed by Biomedical Science.

1.2. Study Design

1.2.1. Synopsis of Study Design

At selected sites in the United States (US), approximately 20 patients will undergo intensive ECG monitoring to coincide with PK evaluation on Day 1 as part of the open-label QTc substudy. Triplicate ECGs will be performed between 2 and 5 minutes apart and will be performed prior to PK blood draws. These patients will remain in the clinic on Day 1 and will have triplicate ECG testing performed predose and at 1, 1.5, 2, 3, 4, 6, and 8 hours postdose (Day 1 only). Patients will be supine and rested for approximately 2 minutes before ECGs are recorded. The average of each of the triplicate measures will be used for analysis. These QTc substudy patients will undergo all assessments outlined in the QTc substudy schedule of assessments as detailed in Table 1.

In the QTc substudy, niraparib 300 mg (3 × 100 mg niraparib capsules) will be administered orally every day (QD) continuously. Patients will be instructed to take their dose at the same time of the day, preferably in the morning. The first dose will be administered at the site. Dose interruption (no longer than 28 days) or dose reduction (no more than 2 dose reductions) will be allowed based on treatment side effects (refer to section 5.3 of the protocol for further details). Dose reductions to 2 capsules QD (200 mg QD) and subsequently to 1 capsule QD (100 mg QD) will be allowed. No further dose reductions will be allowed. The timing of study evaluations will not be modified for patients who require a dose interruption or reduction.

Clinic visits will occur in each cycle (4 weeks ± 3 days). Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) will be used for tumor assessment via a computed tomography (CT) or magnetic resonance imaging (MRI) scan of abdomen/pelvis and clinically indicated areas, which is required at the end of every 2 cycles (8 weeks with a window of ± 7 days from date of visit) through Cycle 14 (56 weeks), then at the end of every 3 cycles (12 weeks with a window of ± 7 days) until disease progression. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for a reason other than disease progression or death, withdrawal of consent, or being lost to follow-up, scans should continue at the specified intervals. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and cancer antigen 125 (CA-125) testing should continue at the specified intervals until disease progression is confirmed or until the start of subsequent anticancer treatment.

1.2.2. Randomization Methodology

Randomization is not applicable to this open-label substudy.

1.2.3. Stopping Rules and Unblinding

There are no formal plans for early stopping for efficacy or safety. Unblinding is not applicable to this open-label substudy.

1.2.4. Study Procedures

The schedule of assessments is outlined in Table 1.

Table 1: Schedule of Events – QTc Substudy

	Screening	**Cycle 1**[1]				**Cycle 2**	**Subsequent Cycles**[2]	**Treatment Discontinuation (within 7 days of last dose)**
Day	**-28 to -1**	**1**[3]	**8**	**15**	**21**	**1**	**Cycle n, Day 1**	
Informed consent	X							
Demographics	X							
Medical, cancer, surgical, medication history	X							
Archival tumor sample[4]	X							
Blood sample for exploratory biomarkers (eg, DNA repair deficiency)		X[5]						
Tumor assessment (RECIST)[6]	X						X	X
Chest CT/MRI[7]	X							
Pregnancy test	X[8]						X[8]	
Study treatment dispensed/collected		X				X	X	X[9]
Physical examination	X	X		X		X	X	X
Vital signs, height,[10] weight	X	X		X		X	X	X
ECOG performance status	X	X				X	X	X
CBC[11]	X	X[12]	X	X	X	X	X	X
Coagulation/serum chemistry	X	X[12]		X		X	X	X
Urinalysis[13]	X							
Serum CA-125	X[14]	X				X	X	X
12-lead ECG[15]	X					X		X

	Screening	**Cycle 1**[(1)]				**Cycle 2**	**Subsequent Cycles**[(2)]	**Treatment Discontinuation (within 7 days of last dose)**
Day	**-28 to -1**	**1**[(3)]	**8**	**15**	**21**	**1**	**Cycle n, Day 1**	
Triplicate ECG		X[(16)]						
Blood sample for PK		X[(17)]				X[(18)]	X[(18)]	
Adverse event monitoring	X	X		X		X	X	X[(19)]
Concomitant medications	X	X		X		X	X	X
Bone marrow aspirate and biopsy and sample collection (whole blood) for cytogenetic analysis		X[(20)]						

Abbreviations: AML = Acute myeloid leukemia; CA-125 = cancer antigen 125; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ICF = informed consent form; MDS = myelodysplastic syndrome; MRI = magnetic resonance imaging; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event, WHO = World Health Organization.

(1) Treatment cycles are 28 days long, visits on Day 1 of each cycle unless otherwise specified.

(2) Visits continue every 4 weeks until study treatment discontinuation. All applicable assessments in this column are to be completed on Day 1 of each cycle unless otherwise indicated below (eg, RECIST, pregnancy testing, PK).

(3) Cycle 1/Day 1 is day of first dose.

(4) Formalin-fixed, paraffin-embedded tumor sample consisting of a 100-micron thickness of sections (≥80-micron minimum) or unsectioned paraffin block.

(5) Blood samples will be collected for all patients on Cycle 1/Day 1 predose (within 30 minutes) for the exploratory evaluation of biomarkers such as those related to DNA repair deficiency.

(6) RECIST tumor assessment via CT or MRI of abdomen/pelvis and clinically indicated areas required at Screening, every 8 weeks (±7 days) for 6 months, and then every 12 weeks until disease progression; at this point, a final follow-up set of images is required. Positron emission tomography (PET)/CT may be used according to RECIST guidelines. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for a reason other than disease progression or death, withdrawal of consent, or loss to follow up, scans and CA-125 testing should continue at the specified intervals. If a patient had a CT/MRI of the abdomen/pelvis and clinically indicated areas within the 28-day screening window before Cycle 1/Day 1 but prior to signing the informed consent form (ICF), the patient is not required to complete an additional CT/MRI scan for study screening. CT/MRI scans completed during Screening prior to signing the ICF must have been performed and be able to be submitted per the image acquisition guidelines.

(7) Chest CT/MRI if not done as part of RECIST tumor assessment at Screening. If the chest CT/MRI is clear at Screening, repeat chest imaging is not required in the absence of lesions to be followed or in the absence of clinical indication requiring follow-up.

(8) Negative serum pregnancy test required within 72 hours prior to study treatment for females of childbearing potential; repeated every 3 months for duration of study (eg, Cycle 4, Cycle 7).

(9) No new capsules dispensed.

(10) Height obtained at Screening only.

(11) If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored until the adverse event (AE) resolves, and to ensure safety of the new dose, weekly blood draws for CBC will also be required for an additional 4 weeks after the adverse event has been resolved to the specified levels, after which monitoring every 4 weeks may resume.

(12) If Screening laboratory testing (serum chemistry, CBC, coagulation) performed within 72 hours of Day 1, repeat testing not required.

(13) Urinalysis parameters must include: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen, and bilirubin.

(14) CA-125 sample within 72 hours of dose on Cycle 1/Day 1.

(15) Patients will have a 12-lead ECG at Screening, Cycle 2/Day 1 (predose and 2 hours postdose, within 30 minutes), and at treatment discontinuation. ECG monitoring is to be performed prior to PK blood draws.

(16) At selected sites, patients (approximately 20) will undergo triplicate ECG testing on Day 1 only at baseline (predose) and 1, 1.5, 2, 3, 4, 6 and 8 hours postdose. Triplicate ECGs should be performed between 2-5 minutes apart and should be performed prior to PK blood draws.

(17) At selected sites, patients (approximately 20) undergoing intensive PK on Day 1 will have samples collected at baseline (within 30 minutes predose) and 1, 1.5, 2, 3, 4, 6 and 8 hours (± 2 minutes at all time points) postdose. Note: The exact time of the PK blood draw will be recorded and PK blood draws are to be completed after ECG monitoring.

(18) Blood samples for PK collected on Cycle 2/Day 1 predose (within 30 minutes) and 2 hours postdose (± 15 minutes) as well as on Cycle 4/Day 1 and Cycle 8/Day 1 at predose (trough) within 30 minutes only. Note: The exact time of the PK blood draw will be recorded and ECG monitoring is to be completed prior to the PK blood draw.

(19) Serious adverse events (SAEs) recorded up to 30 days after study treatment discontinuation.

(20) For any suspected myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) case reported while a patient is receiving treatment or being followed for post-treatment assessments, bone marrow aspirate and biopsy testing must be completed by a local hematologist. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings (which must include a classification according to World Health Organization (WHO) criteria and other sample testing results related to MDS/AML.

1.2.5. Efficacy, Pharmacokinetic, and Safety Parameters

1.2.5.1. Efficacy Parameters

Efficacy endpoints include the following:

- The ORR, defined as the proportion of patients achieving complete response (CR) or partial response (PR), as assessed by the Investigator per RECIST (v1.1). Tumor assessments after the initiation of further anticancer therapy are excluded for the assessment of best overall response.
- Duration of response, which is defined as the time from first documentation of CR or PR until the time of first documentation of progressive disease (PD), as assessed by the Investigator per RECIST (v1.1) or clinical criteria.

1.2.5.2. Pharmacokinetic Parameters

The PK endpoints are defined in a separate population PK analysis plan.

1.2.5.3. Safety Parameters

Safety evaluations performed during the study include physical examinations, measurement of vital signs, 12-lead ECGs, clinical laboratory evaluations including hematology, serum chemistry, and urinalysis, and monitoring of adverse events (AEs) and concomitant medications.

The safety endpoints are:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory parameters:
    - Complete blood count (CBC): hemoglobin, platelets, mean platelet volume (optional), mean corpuscular volume, white blood cell (WBC) count, absolute lymphocyte count, percent lymphocytes, absolute neutrophil count, and percent neutrophils
    - Coagulation factors: activated partial thromboplastin time (aPTT) and international normalized ratio (INR)
    - Serum chemistry assessments for safety include: sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea or blood urea nitrogen (BUN), total protein, albumin, lactate dehydrogenase (LDH), and amylase
    - Urinalysis: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen, and bilirubin
    - Serum CA-125
    - Serum pregnancy testing

- Physical examination and vital signs:
    - Weight
    - Height (Screening visit only)
    - Blood pressure
    - Pulse
    - Temperature
- Eastern Cooperative Oncology Group (ECOG) performance status
- ECG
- Concomitant medications

Additional safety parameters include study treatment exposure and compliance.

2. PATIENT POPULATION

2.1. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: All patients who received at least 1 dose of study treatment
- Safety Population: All patients who received at least 1 dose of study treatment

The ITT population is the primary population for the analysis of efficacy parameters. The Safety population is the primary population for the analysis of safety endpoints. Even though the ITT and Safety populations are defined identically, when discussing efficacy analyses, the term "ITT population" will be used, and when discussing safety analyses, the term "Safety population" will be used.

2.2. Protocol Violations

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Approximately 20 patients will be enrolled into the open-label QTc substudy. If the number of evaluable patients falls below 20, replacement patients may be used at the discretion of the Sponsor. This is a descriptive substudy and no formal sample size calculations were performed.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pretreatment and on-treatment study days are numbered relative to the day of the first dose of study medication, which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study medication is designated with an "L" (eg, Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, for example.

All output will be incorporated into Microsoft Word or Excel files or Adobe Acrobat PDF files, sorted, and labeled according to the International Conference on Harmonisation (ICH) recommendations[1], and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number (n) and percentage (%) of patients within each category of the parameter will be presented. Percentages will be based on the patients with a non-missing parameter. Percentages will be reported to 1 decimal place. Percentages will not be presented for zero counts.

For continuous variables, the number of patients (n), mean, standard deviation (StdDev), median, first quartile (Q_1), third quartile (Q_3), minimum, and maximum values will be presented. Mean, median, Q_1, and Q_3 will be reported to 1 more decimal place than the raw data, while the StdDev will be reported to 2 more decimal places than the raw data.

Time-to-event data will be analyzed using the product-limit (Kaplan-Meier [KM]) methodology using quartile estimates of the survival distribution function, with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations.

This study is primarily descriptive in nature; therefore, there are no formal statistical hypothesis tests planned.

3.3. Computing Environment

All statistical analyses will be performed using SAS statistical software v9.3 or later, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v18.0 or later. Laboratory parameter changes will be described using shift tables relative to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.02. Concomitant medications will be coded using the latest version of the World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) classification, version Sept2015.

3.4. Baseline Definitions

For all analyses except ECG, baseline is defined as the most recent measurement prior to the first administration of study drug. For ECG analyses, baseline will be defined as the average of the closest triplicate (if triplicates were collected) readings prior to dosing on the first day that study drug is administered.

3.5. Methods of Pooling Data

Data will be pooled across study sites.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

3.8. Subpopulations

Analysis of results may be evaluated in patient subgroups as needed for regulatory submission purposes.

3.9. Withdrawals, Dropouts, Loss to Follow-up

If the number of evaluable patients falls below 20, replacement patients may be used at the discretion of the Sponsor.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the electronic case report form (eCRF) will be included in data listings that will accompany the CSR.

When tabulating AE data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution. Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

3.12. Interim Analyses

No interim analyses are planned for this study.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated and include the number enrolled, the total number treated, the number in each patient population for analysis, the number who discontinued treatment and reason(s) for discontinuation, the number who withdrew prior to completing the study and reason(s) for withdrawal, and the number of patient deaths and primary cause of death.

A by-patient data listing of study completion information, including the reason for premature treatment discontinuation or study withdrawal, if applicable, will be presented.

4.2. Demographics and Baseline Characteristics

Demographics, baseline characteristics, and medical history information will be summarized for the ITT population using descriptive statistics.

Demographic and baseline data for each patient will be provided in data listings.

The demographic and baseline characteristics tables will include the following variables:

- Age at time of informed consent (years) calculated as date of informed consent minus date of birth / 365.25
- Age categories (18 to 64, 65 to <75, ≥65, and ≥75)
- Race (White, Black/African American, Asian, American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, and Other)
- Ethnicity (Hispanic and non-Hispanic)
- Primary tumor site (ovarian, primary peritoneal, or fallopian tube)
- Time from first diagnosis to informed consent (years) calculated as the date of informed consent minus date of first diagnosis / 365.25
- International Federation of Gynecology and Obstetrics (FIGO) stage at time of initial diagnosis
- Sites of metastatic disease
- Screening height, weight, and body mass index (BMI)
- ECOG performance status at baseline
- History of thrombocytopenia and grade (repeated for leukopenia, anemia, and neutropenia)
- Baseline platelet count, baseline hemoglobin, and baseline mean platelet volume (MPV)
- Prior ovarian cancer treatment, including number of prior platinum courses, number of previous chemotherapy regimens, any surgeries/procedures related to the study indication, number of surgeries, and any radiotherapy prior to enrollment
- Time since last platinum therapy
- Histology and grade of disease at diagnosis and most recent biopsy, if additional biopsy performed

Medical history will be coded using MedDRA v18.0 or later, and the number and percentage of patients experiencing at least 1 such diagnosis by MedDRA System Organ Class (SOC) and preferred term will be reported.

Baseline physical examination findings will be summarized by presenting the number and percentage of patients with abnormalities for each eCRF-defined body system.

4.3. Efficacy Evaluation

4.3.1. Objective Response Rate

The ORR is defined as the proportion of patients achieving CR or PR as assessed by the Investigator per RECIST (v1.1) criteria. Tumor assessments after the initiation of further anticancer therapy are excluded for the assessment of best overall response.

PD will also be determined using non-RECIST criteria if at least 1 of the following is met:

- Additional diagnostic tests (eg, histology/cytology, ultrasound techniques, endoscopy, positron emission tomography [PET]) identify new lesions or determine existing lesions qualify for unequivocal PD and CA-125 progression according to Gynecologic Cancer Intergroup (GCIG) criteria
- Definitive clinical signs and symptoms of PD unrelated to nonmalignant or iatrogenic causes ([a] intractable cancer-related pain; [b] malignant bowel obstruction/worsening dysfunction; or [c] unequivocal symptomatic worsening of ascites or pleural effusion) and CA-125 progression according to GCIG criteria.

The response criteria by RECIST (v1.1) are listed in Appendix 2 of the protocol.

Per RECIST, a confirmatory assessment of CR or PR must be made at least 4 weeks following initial response in order to determine a best overall response of CR or PR. Similarly, for a best overall response of stable disease (SD), SD must be documented at least once, at least 4 weeks from Day 1. For analysis purposes, the best overall response (CR > PR > SD > PD) observed after Day 1 until the earliest of disease progression, treatment with any anticancer therapy other than study drug, or premature study discontinuation will be determined for each patient.

Patient response will be summarized for each cycle by presenting the numbers and percentages of patients at each response level (CR, PR, SD, or PD). A similar summary will be presented for best overall response. A point estimate and associated 95% CI (based on the Wilson score method) will be presented for the ORR.

4.3.2. Duration of Response

For patients who respond to treatment, duration of response (in months) is defined as the initial response date of confirmed CR or PR to the earliest date of PD and will be calculated as:

[Earliest Date of PD – First Date of Response for Patients with Confirmed Response + 1] / 30.4375

Censoring for duration of response may occur for a variety of reasons:

1. Patients known to be alive and known not to have started new (non-protocol) anticancer treatment, progression-free, and who have a baseline and at least 1 post-dosing radiological assessment, will be censored at the date of the last radiological assessment that verified lack of PD

2. Patients starting new anticancer treatment prior to disease progression will be censored at the date of last radiological assessment documenting no disease progression prior to the new treatment
3. Documentation of disease progression or death after an unacceptably long interval (>17 weeks for the first 6 months on study and >25 weeks after 6 months on study, ie, 2 consecutive missed or indeterminate overall response assessments) since the last radiological assessment will be censored at the date of last radiological assessment documenting no disease progression
4. Patients who die will be censored at the date of death

A time-to-event analysis of duration of response will be performed using the KM method. Summaries will include quartile estimates of the survival distribution function and associated 95% CIs. A KM plot will be produced.

4.4. Pharmacokinetic Evaluations

Details of the population PK and intensive PK analyses, including combined analyses of the ECG variables and PK parameters, will be contained in a separate analysis plan.

4.5. Safety Analyses

Safety analyses will be conducted using the Safety population.

4.5.1. Study Drug Exposure

Extent of treatment will be summarized as follows:

- Number and percent of patients beginning 1, 2, 3, …, 12, and >12 cycles
- Overall treatment exposure (months), defined as the [last dose date - first dose date + 1] / 30.4375, will be summarized as a continuous variable
- Time on study (months), defined as [last visit date or date of death - first dose date + 1] / 30.4375, will be summarized as a continuous variable

Duration and intensity of study treatment:

- Dose intensity (mg/day), defined as sum of the daily doses actually consumed divided by overall treatment exposure (converted to days), will be summarized as a continuous variable
- Relative dose intensity, defined as dose intensity (mg/day) divided by intended dose intensity (mg/day) multiplied by 100, where intended dose is 300 mg × overall treatment exposure (converted to days), will be summarized as a continuous variable

Dose reductions, dose interruptions, and missed doses:

- Number and percentage of patients with a dose reduction, defined as the dose consumed is less than the dose prescribed, for any reason and due to an AE (overall and by cycle)
- Number and percentage of patients with a dose interruption, defined as the dose consumed is 0 mg, for any reason and due to an AE (overall and by cycle)

Dosing information for each patient will be presented in a data listing.

4.5.2. Study Drug Compliance

Patient compliance with the study drug will be assessed via pill counts. Study drug compliance will be defined by the dosing compliance ratio: the number of capsules prescribed (per dose prescribed) minus the number of capsules returned by the patient divided by the number of capsules prescribed during the same period multiplied by 100. Unused capsules not returned and not reported as missed doses will be assumed to have been consumed.

A patient is evaluated as compliant if the patient has taken 80% to 120% of the expected capsules during participation in the study. Overall compliance rate, proportion of patients considered compliant, and compliance rate by cycle will be summarized.

4.5.3. Adverse Events

All AEs will be classified using MedDRA v18.0 or later. The severity of the toxicities will be graded according to the NCI CTCAE v4.03. Any AEs leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade 3 or higher, study treatment-related events, and serious adverse events (SAEs) will be presented.

Any TEAE will be defined as:

- Any new AE (one that was not seen prior to the start of treatment) that occurs for the first time after at least 1 dose of study treatment has been administered; or
- A pre-existing condition (one that was seen prior to the start of treatment) that worsens in severity after at least 1 dose of study treatment has been administered; or
- A pre-existing condition that is subsequently deemed related to study treatment.

Note: If the start date is missing for an AE and the actual start date cannot be determined from a partial date, the AE will be considered treatment-emergent.

All AEs will be collected from the time of signing the main informed consent form (ICF) through the end of treatment (EOT) visit. New SAEs (including deaths) will be collected for 30 days after the EOT visit. Any AEs recorded in the database that occur from the time of informed consent to first dose will be listed only and not included in safety analyses. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

Related TEAEs are defined as TEAEs considered at least possibly related to treatment as judged by the Investigator. Any AEs for which the relationship to study drug is missing will be considered as related to study treatment.

The number and percentage of patients reporting a TEAE will be summarized by SOC, preferred term, toxicity grade, and relationship to study drug. Within the same preferred term, only the most severe AE for each patient will be counted in tabulations by severity, and only the highest ranked relationship to treatment for each patient will be counted in tabulations related to treatment. Within an SOC, patients with more than 1 preferred term will be counted only once using the most severe AE reported for tabulations by severity and the highest ranked relationship to treatment for tabulations related to treatment. The imputation for a missing relationship or severity will take place prior to determining the most related or severe AE within an SOC or preferred term for a given patient.

A high-level overview of TEAEs will be presented in a summary table. This table will include the number and percentage of patients for the following categories: any TEAE, any grade ≥3 TEAE, any related TEAE, any AE leading to treatment discontinuation/study termination, any treatment-emergent SAEs, pregnancies, and deaths. The following lists the AE tables to be displayed:

- Overview of AEs
- TEAEs by SOC and preferred term
- Related TEAEs by SOC and preferred term
- Treatment-emergent SAEs by SOC and preferred term
- Related treatment-emergent SAEs by SOC and preferred term
- Grade ≥3 TEAEs by SOC and preferred term
- Related grade ≥3 TEAEs by SOC and preferred term
- TEAEs of special interest (see Section 7)
- TEAEs in ≥10% of patients by SOC and preferred term
- TEAEs by preferred term and maximum toxicity grade
- Related TEAEs by preferred term and maximum toxicity grade
- TEAEs resulting in death by SOC and preferred term
- TEAEs resulting in study drug interruption by SOC and preferred term
- TEAEs resulting in study drug dose reduction by SOC and preferred term
- TEAEs resulting in study drug withdrawn by SOC and preferred term

Tables structured as listings will be provided for the following:

- Deaths
- Serious AEs
- TEAEs resulting in study drug interruption
- TEAEs resulting in study drug dose reduction
- TEAEs resulting in study drug withdrawal
- TEAEs of special interest

AE summaries will be ordered in decreasing frequency for SOC (alphabetically for SOCs with the same number of AEs reported), and decreasing frequency for preferred term within SOC (alphabetically for preferred terms with the same number of AEs reported within a SOC).

4.5.4. Laboratory Data

Laboratory assessments will be performed locally at each center's laboratory by means of their established methods. All laboratory values will be converted to the International System of Units, universally abbreviated SI (from the French *Le Système International d'Unités*) and classified as normal, low, or high based on normal ranges supplied by the local laboratories and upon employing standardization, as described below.

When local laboratories report different reference ranges for a particular test, these results will be normalized prior to calculating changes from baseline.[2] The reference range used by the majority of laboratories will be used as the "standard reference range" for a particular test. If 2 or more reference ranges are used by an equal number of laboratories, or no majority exists, the widest reference range will be used as the "standard reference range." Results from laboratories which use a reference range different from the "standard reference range" will be converted using the following formula:

$$x' = \max\left(0,\ \frac{x - \mathrm{lLLN}}{\mathrm{lULN} - \mathrm{lLLN}} \times (\mathrm{sULN} - \mathrm{sLLN}) + \mathrm{sLLN}\right),$$

where x is the result reported by the local laboratory; x' is the normalized result; lLLN and lULN are the lower and upper limits of normal from the local laboratory, respectively; and sLLN and sULN are the lower and upper limits of normal from the "standard reference range."

Normalized laboratory values will be used to calculate summary statistics; however, shift analyses and patient listings of laboratory data will be based on the values and normal ranges reported by the local laboratories, expressed in SI units.

Hematologic and chemistry laboratory results will be graded according to the cut points defined in the NCI CTCAE v4.03 severity grade. Laboratory results will be summarized by maximum CTCAE grade as available. Continuous results will be analyzed using change from baseline and shift values.

Observed values and change from baseline will be summarized by visit. Graphical line mean changes over time may be provided.

Shift from baseline to the smallest post-baseline value, largest postbaseline value, and EOT value will be reported using number and percentage of patients. Baseline and postbaseline results will be categorized as low, normal, or high relative to the normal range, or by CTCAE grade as applicable.

In order to investigate possible drug-induced liver injury (DILI), a listing of potential Hy's Law cases (patients with AST or ALT >3 × ULN in combination with bilirubin >2 ×ULN) will also be presented. Additionally, a Hy's Law plot will be produced that plots peak ALT and peak total bilirubin in 1 panel and peak AST and peak total bilirubin in a second panel.

A by-patient listing of all laboratory data will be provided, with laboratory reference ranges and abnormal values highlighted, and including center, patient identifier, and visit. Tables in the form of by-patient listings are also provided for abnormal lab values, CTCAE grade ≥3, and clinically significant lab findings, as reported by the investigator or local laboratory.

4.5.5. Vital Signs

Summaries of vital signs parameters (systolic and diastolic blood pressures, pulse rate, and temperature), weight, and BMI will be presented by visit. Summary statistics will be produced for both observed and change from baseline values, for each parameter.

Vital sign measurements and physical examination findings will be presented for each patient in a data listing.

4.5.6. Electrocardiogram

Routine 12-lead ECGs will be performed for patients at Screening, Cycle 2/Day 1 (predose and 2 hours postdose), and at treatment discontinuation. Triplicate ECGs will be performed to coincide with PK evaluation on Cycle 1/Day 1.

Routine ECG results will be summarized descriptively, including the number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each study visit. Baseline will be defined as the Screening assessment. Summary statistics will be provided for continuous ECG parameters, and will be presented for each scheduled visit. Change from predose to 2 hours postdose at Cycle 2/Day 1 will also be included.

For the primary analysis of QTcF, interpretation using Fridericia's (QTcF) method will be used. A summary of the number and percentage of patients with QTc interval exceeding FDA suggested upper limits (eg, >450 ms, >480 ms, >500 ms) will be provided.[3] A summary of the number and percentage of patients with change from baseline in QTc interval exceeding FDA suggested upper limits (eg, >30 ms, >60 ms) will be provided. A separate summary will be provided which includes the change from predose to 2 hours postdose at Cycle 2/Day 1.

All routine 12-lead ECG data for each patient will be provided in a data listing. Summaries and analyses of intensive ECG monitoring at Cycle 1/Day 1 are discussed in a separate population PK analysis plan.

4.5.7. Concomitant Medications

All medications will be coded using the September 2015 of the WHO Drug Dictionary (WHODD). Medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the treatment withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study drug will be classified as Prior only. If a medication starts before the date of first dose of study drug and stops on or after the date of first dose of study drug then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study drug. Concomitant medication will be summarized by ATC level 3 and preferred term in frequency tables. Patients with more than 1 medication in a given ATC level and preferred term will be counted only once in that category.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study drug. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study drug. If there is clear evidence to suggest that the medication started prior to the first dose of study drug, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study drug. If there is clear evidence to suggest that the medication stopped prior to the first dose of study drug, the medication will be assumed to be Prior only. The following lists the concomitant medication tables to be displayed:

- Number and percentage with at least 1 concomitant medication by ATC level 3 and preferred term

- Number and percentage with at least 1 prior medication by ATC level 3 and preferred term
- Number and percentage with at least 1 prior or concomitant medication by ATC level 3 and preferred term

The use of concomitant medications will be included in a by-patient data listing.

5. CHANGES TO PLANNED ANALYSES

As of the date of this final SAP, there have been no changes between the protocol-defined statistical analyses and those presented in this SAP.

If any modifications in the experimental design, dosages, parameters, patient selection, or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approval from the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

6. REFERENCES

1 US Federal Register. International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D 0174]. Federal Register Volume 63, Number, pages 49583 49598. September 16, 1998.

2 Chuang-Stein C. Some Issues Concerning the Normalization of Laboratory Data Based on Reference Ranges. Therapeutic Innovation and Regulatory Science (Impact Factor 0.46). 2001; 35(1):153-156.

3 Food and Drug Administration. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Guidance for Industry. October 2005; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073153.pdf

7. APPENDIX 1: TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST

AESI Category **MedDRA Level**	**Preferred Terms**
Thrombocytopenia Event Haematopoietic cytopenias affecting more than one type of blood cell (SMQ) [20000028]	Megakaryocytes decreased Platelet count decreased Platelet maturation arrest Platelet production decreased Platelet toxicity Thrombocytopenia Megakaryocytes abnormal Platelet count abnormal Platelet disorder Plateletcrit abnormal Plateletcrit decreased Thrombocytopenia neonatal
Anemia Event: Haematopoietic erythropenia (SMQ) [20000029]	Anaemia macrocytic Aplasia pure red cell Aplastic anaemia Erythroblast count decreased Erythroid maturation arrest Erythropenia Hypoplastic anaemia Microcytic anaemia Proerythroblast count decreased Red blood cell count decreased Reticulocyte count decreased Reticulocytopenia Anaemia Anaemia neonatal Erythroblast count abnormal Erythropoiesis abnormal Haematocrit abnormal Haematocrit decreased Haemoglobin abnormal Haemoglobin decreased Leukoerythroblastic anaemia Normochromic normocytic anaemia Proerythroblast count abnormal Red blood cell count abnormal Reticulocyte count abnormal Reticulocyte percentage decreased

AESI Category **MedDRA Level**	**Preferred Terms**
Leukopenia Event	
Haematopoietic leukopenia (SMQ) [20000030]	Agranulocytosis Band neutrophil count decreased* Band neutrophil percentage decreased* Basophil count decreased Basophilopenia B-lymphocyte count decreased Cyclic neutropenia* Eosinopenia Eosinophil count decreased Febrile neutropenia* Granulocyte count decreased* Granulocytes maturation arrest* Granulocytopenia* Idiopathic neutropenia* Leukopenia Lymphocyte count decreased Lymphopenia Metamyelocyte count decreased Monoblast count decreased Monocyte count decreased Monocytopenia Myeloblast count decreased Myelocyte count decreased Neutropenia* Neutropenic infection* Neutropenic sepsis* Neutrophil count decreased* Promyelocyte count decreased Pure white cell aplasia Radiation leukopenia T-lymphocyte count decreased White blood cell count decreased Basophil count abnormal Basophil percentage decreased B-lymphocyte abnormalities Differential white blood cell count abnormal* Eosinophil count abnormal Eosinophil percentage decreased Full blood count abnormal Granulocytes abnormal* Granulocytopenia neonatal* Leukopenia neonatal Lymphocyte count abnormal

AESI Category **MedDRA Level**	**Preferred Terms**
	Lymphocyte percentage abnormal Lymphocyte percentage decreased Lymphocytopenia neonatal Monocyte count abnormal Monocyte percentage decreased Myeloblast percentage decreased Myelocyte percentage decreased Myeloid maturation arrest Neutropenia neonatal* Neutrophil count abnormal* Neutrophil percentage decreased* Plasma cell disorder Plasma cells absent T-lymphocyte count abnormal White blood cell analysis abnormal White blood cell count abnormal White blood cell disorder
Pancytopenia Event: Haematopoietic cytopenias affecting more than one type of blood cell (SMQ) [20000028]	Aplastic anaemia Autoimmune aplastic anaemia Bicytopenia Bone marrow failure Cytopenia Febrile bone marrow aplasia Full blood count decreased Pancytopenia Panmyelopathy Aspiration bone marrow abnormal Biopsy bone marrow abnormal Blood count abnormal Blood disorder Bone marrow disorder Bone marrow infiltration Bone marrow myelogram abnormal Bone marrow necrosis Bone marrow toxicity Congenital aplastic anaemia Haematotoxicity Myelodysplastic syndrome Myelodysplastic syndrome transformation Myelofibrosis Myeloid metaplasia Plasmablast count decreased Primary myelofibrosis

AESI Category **MedDRA Level**	**Preferred Terms**
	Scan bone marrow abnormal
MDS/AML Event: MedDRA PTs as listed	Myelodysplastic syndrome Myelodysplastic syndrome transformation Myelodysplastic syndrome unclassifiable Acute myeloid leukaemia Acute myeloid leukaemia recurrent Blast crisis in myelogenous leukaemia Myeloid leukaemia
Fatigue Event: Asthenic Conditions HLT	Adult failure to thrive Asthenia Autonomic nervous system imbalance Cachexia Chronic fatigue syndrome Decreased activity Fatigue Lethargy Listless Malaise Sluggishness
Pneumonitis Event: MedDRA PTs as listed	Pneumonitis Acute interstitial pneumonitis
Overdose Event: MedDRA PTs as listed	Overdose Accidental overdose

*Preferred terms are included in the Neutropenia Event AESI.

8. CLINICAL STUDY REPORT APPENDICES

8.1. List of Statistical Tables, Figures, and Data Listings

8.2. Table and Figure Shells

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Protocol PR-30-5011-C (QTc substudy)

Table 14.1.1

Patient Enrollment and Disposition

Parameter	Statistic (N=)	Niraparib (N=)
Number of Patients [1]		
Enrolled	n	xx
Treated	n (%)	xx (xx.x)
Ongoing at the time of data cutoff	n (%)	xx (xx.x)
Intent-to-treat (ITT) Population	n (%)	xx (xx.x)
Safety Population	n (%)	xx (xx.x)
Discontinuations from Treatment [2]	n	xx
Adverse event	n (%)	xx (xx.x)
Disease progression	n (%)	xx (xx.x)
Risk to patient	n (%)	xx (xx.x)
Severe non-compliance	n (%)	xx (xx.x)
Patient request	n (%)	xx (xx.x)
Pregnancy	n (%)	xx (xx.x)
Lost to follow-up	n (%)	xx (xx.x)
Death	n (%)	xx (xx.x)
Other	n (%)	xx (xx.x)
Discontinuations from Study [3]	n	xx
Withdrawal of consent	n (%)	xx (xx.x)
Lost to follow-up	n (%)	xx (xx.x)
Death	n (%)	xx (xx.x)
Other	n (%)	xx (xx.x)
Number of Deaths [1]	n	xx
On treatment	n (%)	xx (xx.x)
During follow-up	n (%)	xx (xx.x)
At any time	n (%)	xx (xx.x)
Main Cause of Death[3]	n	xx
Disease progression	n (%)	xx (xx.x)
Adverse event	n (%)	xx (xx.x)
Unknown	n (%)	xx (xx.x)
Other	n (%)	xx (xx.x)

Note: Percentages based on the number of patients in the ITT population.
[1] Percentages based on the number enrolled.
[2] Percentages based on the number of treatment discontinuations.
[3] Percentages based on the number of study discontinuations.
Source: Data Listing 16.2.x

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Table 14.1.2

Protocol Deviations

Parameter	Statistic	Niraparib (N=)
Number of Patients [1]		
Treated	n	xx
With at least one protocol deviation	n (%)	xx (xx.x)
Failed to meet eligibility criteria but entered study	n (%)	xx (xx.x)
Non-compliant (<80% compliant with study medication)	n (%)	xx (xx.x)
Took prohibited medication	n (%)	xx (xx.x)

Note: Percentages based on the number of patients in the ITT population.
[1] Percentages based on the number treated.
Source: Data Listing 16.2.x

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Table 14.1.3

Demographic Characteristics (ITT Population)

Parameter	Statistic	Niraparib (N=xx)
Age (years) [1]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Age Group (years)		
18 - 64	n (%)	xx (xx.x)
65 - 74	n (%)	xx (xx.x)
≥ 65	n (%)	xx (xx.x)
≥ 75	n (%)	xx (xx.x)
Race		
White	n (%)	xx (xx.x)
Black/African American	n (%)	xx (xx.x)
Asian	n (%)	xx (xx.x)
American Indian or Alaska Native	n (%)	xx (xx.x)
Native Hawaiian or other Pacific Islander	n (%)	xx (xx.x)
Other	n (%)	xx (xx.x)
Unknown	n (%)	xx (xx.x)
Not Reported	n (%)	xx (xx.x)
Ethnicity		
Hispanic or Latino	n (%)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)
Unknown	n (%)	xx (xx.x)
Not Reported	n (%)	xx (xx.x)

Note: Percentages based on the number of patients in the ITT population.
[1] As collected on the Demography eCRF, based on age at time of informed consent.
Source: Data Listing 16.2.x

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Table 14.1.4

Cancer Staging (Initial Diagnosis) (ITT Population)

Parameter	Statistic	Niraparib (N=xx)
Primary tumor site		
Ovarian	n (%)	xx (xx.x)
Primary Peritoneal	n (%)	xx (xx.x)
Fallopian Tube	n (%)	xx (xx.x)
Duration (years) since diagnosis [1]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Cancer stage (FIGO)		
0	n (%)	xx (xx.x)
I	n (%)	xx (xx.x)
IA	n (%)	xx (xx.x)
IB	n (%)	xx (xx.x)
IC	n (%)	xx (xx.x)
II	n (%)	xx (xx.x)
IIA	n (%)	xx (xx.x)
IIB	n (%)	xx (xx.x)
IIC	n (%)	xx (xx.x)
III	n (%)	xx (xx.x)
IIIA	n (%)	xx (xx.x)
IIIB	n (%)	xx (xx.x)
IIIC	n (%)	xx (xx.x)
IV	n (%)	xx (xx.x)
Sites of metastatic disease		
Ascites or effusion	n (%)	xx (xx.x)
CNS	n (%)	xx (xx.x)
...	...	...
Other	n (%)	xx (xx.x)

Note: Percentages based on the number of patients in the ITT population.
[1] Duration since initial diagnosis of primary cancer (Ovarian) to enrollment (date of informed consent).
Source: Data Listing 16.2.x

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Table 14.1.5

Baseline Characteristics (ITT Population)

Parameter	Statistic	Niraparib (N=xx)
Screening Weight (kg)	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Screening Height (cm)	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
BMI (kg/m^2)	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Screening ECOG performance status		
0	n (%)	xx (xx.x)
1	n (%)	xx (xx.x)
2	n (%)	xx (xx.x)
3	n (%)	xx (xx.x)
4	n (%)	xx (xx.x)

Note: Percentages based on the number of patients in the ITT population.
Note: BMI = body mass index, calculated as weight(kg)/[height(m)]^2.
ECOG = Eastern Cooperative Oncology Group:

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Source: Data Listing 16.2.x

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Table 14.1.6

Prior and Baseline Hematology (ITT Population)

Parameter	Statistic	Niraparib (N=xx)
Prior Thrombocytopenia	n (%)	xx (xx.x)
CTC Grade 1	n (%)	xx (xx.x)
CTC Grade 2	n (%)	xx (xx.x)
CTC Grade 3	n (%)	xx (xx.x)
CTC Grade 4	n (%)	xx (xx.x)
Prior Leukopenia	n (%)	xx (xx.x)
CTC Grade 1	n (%)	xx (xx.x)
CTC Grade 2	n (%)	xx (xx.x)
CTC Grade 3	n (%)	xx (xx.x)
CTC Grade 4	n (%)	xx (xx.x)
Prior Anemia	<as above>	<as above>
CTC Grade 1		
CTC Grade 2		
CTC Grade 3		
CTC Grade 4		
Prior Neutropenia	<as above>	<as above>
CTC Grade 1		
CTC Grade 2		
CTC Grade 3		
CTC Grade 4		
Baseline Platelet Count (10^9/L)	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Baseline Hemoglobin (g/dL)	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Baseline MPV (fL)	<as above>	<as above>

Note: Percentages based on the number of patients in the ITT population.
Note: MPV = mean platelet volume.
Source: Data Listing 16.2.x

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Table 14.1.7

Prior Ovarian Cancer Treatment (Chemotherapy, Surgery, Radiotherapy) (ITT Population)

Parameter	Statistic	Niraparib (N=xx)
Number of prior platinum courses		
1	n (%)	xx (xx.x)
2	n (%)	xx (xx.x)
3	n (%)	xx (xx.x)
4	n (%)	xx (xx.x)
≥ 5	n (%)	xx (xx.x)
Number of prior chemotherapy courses		
1	n (%)	xx (xx.x)
2	n (%)	xx (xx.x)
3	n (%)	xx (xx.x)
4	n (%)	xx (xx.x)
≥ 5	n (%)	xx (xx.x)
Any surgeries/procedures related to the study indication		
Yes	n (%)	xx (xx.x)
No	n (%)	xx (xx.x)
Number of surgeries		
1	n (%)	xx (xx.x)
2	n (%)	xx (xx.x)
≥ 3	n (%)	xx (xx.x)
Any radiotherapy prior to enrollment		
Yes	n (%)	xx (xx.x)
No	n (%)	xx (xx.x)
Time since last platinum therapy (months)	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx

Note: Percentages based on the number of patients in the ITT population.
Source: Data Listing 16.2.x

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Table 14.1.8

Ovarian Cancer Pathology (ITT Population)

Method	Parameter	Statistic	Niraparib (N=xx)
Histological	Histologic subtype [1]		
	Serous	n (%)	xx (xx.x)
	Endometrioid	n (%)	xx (xx.x)
	Mucinous	n (%)	xx (xx.x)
	Other	n (%)	xx (xx.x)
	Tumor grade [2]		
	Low Grade	n (%)	xx (xx.x)
	Grade 1	n (%)	xx (xx.x)
	Grade 2	n (%)	xx (xx.x)
	Grade 3	n (%)	xx (xx.x)
	High Grade	n (%)	xx (xx.x)
	Not assessable	n (%)	xx (xx.x)
Cytological	<as above>		

Note: Percentages based on the number of patients in the ITT population.
[1] Patients are counted once within each reported subtype.
[2] Patients are counted once at the maximum reported grade (Low < Grade 1 < Grade 2 < Grade 3 < High)
Source: Data Listing 16.2.x

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Table 14.1.9

Medical History by MedDRA System Organ Class and Preferred Term (ITT Population)

System Organ Class Preferred Term	Statistic	Niraparib (N=xx)
Any condition or surgery	n (%)	xx (xx.x)
SOC 1		
Preferred Term 1	n (%)	xx (xx.x)
Preferred Term 2	n (%)	xx (xx.x)
...		
SOC 2		
Preferred Term 1	n (%)	xx (xx.x)
Preferred Term 2	n (%)	xx (xx.x)
...		
Etc.		

Note: MedDRA Version 18.8.
Note: Percentages based on the number of patients in the ITT population.
Note: If a patient experienced more than 1 condition within a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 condition within a given preferred term, that patient is counted only once for that preferred term.
Source: Data Listing 16.2.x

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Table 14.1.10

Baseline Physical Examination by Body System (ITT Population)

Body System	Statistic	Niraparib (N=xx)
Any abnormality	n (%)	xx (xx.x)
Abnormalities reported for:		
General appearance	n (%)	xx (xx.x)
Dermatologic	n (%)	xx (xx.x)
HEENT	n (%)	xx (xx.x)
Etc.		

Note: Percentages based on the number of patients in the ITT population.
Note: Counts are based on the number of patients experiencing at least one abnormal result within a body system. Percentages are based on ITT population.
Source: Data Listing 16.2.x

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Table 14.1.11

Prior Medications by Anatomic Therapeutic Class (ATC) and Preferred Term (ITT Population)

ATC (Level 3) Preferred Term	Statistic	Niraparib (N=xx)
Any prior medication	n (%)	xx (xx.x)
ATC 1	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
Preferred Term 2	n (%)	xx (xx.x)
...		
ATC 2	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
Preferred Term 2	n (%)	xx (xx.x)
...		
Etc.		

Note: Percentages based on the number of patients in the ITT population.
Note: Prior medications are those that start and stop prior to the date of first dose of study medication. Patients who report multiple occurrences of the same medication (preferred term) are included only once per ATC and preferred term.
Source: Data Listing 16.2.x

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Repeat for:
Table 14.1.12 Concomitant Medications by Anatomic Therapeutic Class (ATC) and Preferred Term (ITT Population)
Table 14.1.13 Prior and Concomitant Medications by Anatomic Therapeutic Class (ATC) and Preferred Term (ITT Population)

Footnotes as follows:

Note: Concomitant medications are those that start on or after the date of first dose of study medication. Patients who report multiple occurrences of the same medication (preferred term) are included only once per ATC and preferred term.

Note: Prior and concomitant medications are those that start and stop prior to the date of first dose of study medication and are subsequently resumed on or after the date of first dose, or those that are ongoing on the date of first dose. Patients who report multiple occurrences of the same medication (preferred term) are included only once per ATC and preferred term.

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Table 14.1.14

Prior Platinum Therapy (ITT Population)

Parameter	Statistic	Niraparib (N=xx)
Months on prior platinum [1]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Total months on prior platinum [2]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Months since last platinum [3]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx

[1] Total number of days on treatment divided by 30.4375.
[2] Number of months from start date of first platinum to end date of last platinum.
[3] Number of months from last platinum end date to enrollment (date of informed consent).
Source: Data Listing 16.2.x

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Table 14.1.15

Prior Chemotherapy (ITT Population)

Parameter	Statistic	Niraparib (N=xx)
Number of chemotherapy courses		
1	n (%)	xx (xx.x)
2	n (%)	xx (xx.x)
3	n (%)	xx (xx.x)
4	n (%)	xx (xx.x)
≥ 5	n (%)	xx (xx.x)
Months on last platinum based regimen	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Months on penultimate platinum based regimen	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Months on other chemotherapy	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Total months on any chemotherapy	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx

Note: Each summary is calculated as the total number of days on treatment divided by 30.4375.
Note: Percentages based on the number of patients in the ITT population.
Source: Data Listing 16.2.x

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Table 14.2.1

Objective Response Rate (ITT Population)

Parameter	Statistic	Niraparib (N=xx)
Objective Response Rate (ORR)		
Evaluable [1]	n (%)	xx (xx.x)
ORR: CR or PR [2]	n (%)	xx (xx.x)
	Proportion	0.xxx
	95% CI [3]	0.xxx, 0.xxx
Disease Control Rate (DCR)		
Evaluable [1]	n (%)	xx (xx.x)
DCR: CR, PR or SD [2]	n (%)	xx (xx.x)
	Proportion	0.xxx
	95% CI [3]	0.xxx, 0.xxx
Best Overall Response		
CR [2]	n (%)	xx (xx.x)
PR [2]	n (%)	xx (xx.x)
SD [2]	n (%)	xx (xx.x)
PD [2]	n (%)	xx (xx.x)

Note: CR = Complete responder, PR = Partial responder, SD = Stable disease, PD = Progressive disease
Note: Percentages based on the number of patients in the ITT population.
[1] Evaluable excludes patients with no Investigator Evaluation of Response or with an assessment of non-evaluable.
Percent is out of the number of patients in the ITT population.
[2] Percent is out of the number of patients evaluable in the ITT population.
[3] Based on Wilson Score method.
Source: Listing 16.2.6.1

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Table 14.2.2

Overall Response by Visit (ITT Population)

Visit	Response	Statistic	Niraparib (N=xx)
Week 8	CR	n (%)	xx (xx.x)
	PR	n (%)	xx (xx.x)
	SD	n (%)	xx (xx.x)
	PD	n (%)	xx (xx.x)
Etc.			

Note: CR = Complete responder, PR = Partial responder, SD = Stable disease, PD = Progressive disease
Note: Percentages based on the number of patients in the ITT population.

Source: Listing 16.2.6.1

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Table 14.2.3

Duration of Response (ITT Population)

Parameter	Statistic	Niraparib (N=xx)
Duration of Response (months) [1, 2]	75th percentile (95% CI)	xxx (xx.x, xx.x)
	Median (95% CI)	xxx (xx.x, xx.x)
	25th percentile (95% CI)	xxx (xx.x, xx.x)
Survival Distribution Function (SDF) [3]		
6-month	SDF (95% CI)	xxx (xx.x, xx.x)
12-month		
...		
<As data allows>		
Censored Observations	n (%)	xx (xx.x)
Event Rate	n (%)	xx (xx.x)

Note: Percentages based on the number of patients in the ITT population.
[1] Duration of response is defined as the time in months from the first date of complete or partial response (later confirmed) to disease progression. See section 4.3.2 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.

Source: Listing 16.2.x

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Figure 14.2.3

KM Curve: Duration of Response (ITT Population)

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Table 14.3.1.1

Summary of Number and Percentage of Patients with Adverse Events (Safety Population)

Characteristic	Statistic	Nirparib (N=xx)
Total number of TEAEs	n	xx
Any TEAE	n (%)	x (xx.x)
Any related TEAE	n (%)	x (xx.x)
Any TEAE with CTCAE Toxicity Grade ≥3	n (%)	x (xx.x)
Any serious TEAE	n (%)	x (xx.x)
Any treatment-related serious TEAE	n (%)	x (xx.x)
Any pregnancy	n (%)	x (xx.x)
Any AE leading to treatment discontinuation	n (%)	x (xx.x)
Any TEAE leading to death	n (%)	x (xx.x)

Note: AE = Adverse Event; TEAE = Treatment-Emergent Adverse Event. Toxicity is graded using NCI CTCAE version 4.02. Patients with more than 1 event of the same preferred term are counted only once for the event with the highest CTCAE grade. AEs with missing relationship are imputed to be related.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.1.2

Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)
SOC 1	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
Etc.		

Note: MedDRA Version 18.8.
Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.1.3

Treatment-Emergent Adverse Events Reported in >=10% of Patients by MedDRA Preferred Term (Safety Population)

Preferred Term	Statistic	Niraparib (N=xx)
Preferred Term 1	n (%)	xx (xx.x)
Preferred Term 2	n (%)	xx (xx.x)
Etc.		

Note: MedDRA Version 18.8.
Note: If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.1.4

Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)
SOC 1	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
Etc.		

Note: MedDRA Version 18.8.
Note: Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.1.5

Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)
SOC 1	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
Etc.		

Note: MedDRA Version 18.8.
Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.1.6

Related Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)
SOC 1	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
Etc.		

Note: MedDRA Version 18.8.
Note: Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.1.7

Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum Toxicity Grade (Safety Population)

Preferred Term	Statistic	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Preferred Term 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.						

Note: MedDRA Version 18.8.
Note: Toxicity is graded using NCI CTCAE version 4.02. Patients with more than 1 event of the same preferred term are counted only once for the event with the highest CTCAE grade.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Programming Note: Sort by decreasing frequency (ie, combined grades within preferred term).

Repeat for:
Table 14.3.1.8 Related Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum Toxicity Grade (Safety Population)

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Table 14.3.1.9

CTCAE Grade ≥3 TEAEs by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)
SOC 1	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
Etc.		

Note: MedDRA Version 18.8.
Note: Toxicity is graded using NCI CTCAE version 4.02. Patients with more than 1 event of the same preferred term are counted only once for the event with the highest CTCAE grade.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.1.10

Related CTCAE Grade ≥3 TEAEs by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)
SOC 1	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
Etc.		

Note: MedDRA Version 18.8.
Note: Related events are those identified as likely related or related per investigator. Missing relationship is imputed as related.
Note: Toxicity is graded using NCI CTCAE version 4.02. Patients with more than 1 event of the same preferred term are counted only once for the event with the highest CTCAE grade.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.1.11

TEAEs Resulting in Death by MedDRA System Organ Class and Preferred Term (Safety Population)

MedDRA System Organ Class Preferred Term	Statistic	Niraparib (N=xx)
SOC 1	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
SOC 2	n (%)	xx (xx.x)
Preferred Term 1	n (%)	xx (xx.x)
Etc.		

Note: MedDRA Version 18.8.
Note: If a patient experienced more than 1 event in a given SOC, that patient is counted once for the SOC. If a patient experienced more than 1 event with a given preferred term, that patient is counted only once for that preferred term.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Repeat for:
Table 14.3.1.12 TEAEs Resulting in Study Drug Interruption by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.13 TEAEs Resulting in Study Drug Dose Reduction by MedDRA System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.14 TEAEs Resulting in Withdrawal of Study Drug by MedDRA System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.15

Overview of Treatment-Emergent Adverse Events of Special Interest (Safety Population)

Characteristic	Statistic	Nirparib (N=xx)
Any thrombocytopenia event	n (%)	n (xx.x)
Any Grade ≥3 thrombocytopenia event	n (%)	n (xx.x)
Any Serious thrombocytopenia event	n (%)	n (xx.x)
Any thrombocytopenia event resulting in dose reduction	n (%)	n (xx.x)
Any thrombocytopenia event leading to discontinuation	n (%)	n (xx.x)
Any anemia	n (%)	n (xx.x)
Any Grade ≥3 anemia event	n (%)	n (xx.x)
Any Serious thrombocytopenia event	n (%)	n (xx.x)
Any anemia resulting in dose reduction	n (%)	n (xx.x)
Any thrombocytopenia event leading to discontinuation	n (%)	n (xx.x)
Any neutropenia	n (%)	n (xx.x)
Any Grade ≥3 neutropenia event	n (%)	n (xx.x)
Any Serious neutropenia event	n (%)	n (xx.x)
Any neutropenia resulting in dose reduction	n (%)	n (xx.x)
Any neutropenia event leading to discontinuation	n (%)	n (xx.x)
Any leukopenia event	n (%)	n (xx.x)
Any Grade ≥3 leukopenia event	n (%)	n (xx.x)
Any Serious leukopenia event	n (%)	n (xx.x)
Any leukopenia resulting in dose reduction	n (%)	n (xx.x)
Any leukopenia event leading to discontinuation	n (%)	n (xx.x)
<continue with all defined AESIs>		

Note: MedDRA Version 18.8.
Note: Toxicity is graded using NCI CTCAE version 4.03. Patients with more than 1 event of the same Preferred Term are counted only once for the event with the highest CTCAE grade.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

Programming note: for MedDRA preferred terms to be included in the AESI, see Section 7.

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Table 14.3.2.1

Listing of Treatment-Emergent Adverse Events Leading to Death (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class Preferred Term Verbatim Term	Start Date (Rel Day [1])	Date of Death	Severity Grade	Action Taken Regarding Study Agent	Concomitant Medication Given for AE? Yes/No	Relationship

Note: MedDRA Version 18.8.
Note: AEs leading to death are those AEs with a fatal outcome or CTCAE grade 5.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.2.2

Listing of Serious Treatment-Emergent Adverse Events (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class/ Preferred Term/ Verbatim Term/	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome
			DDMMMYYYY/ Ongoing	-xx					

Note: MedDRA Version 18.8.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.2.3

Listing of Treatment-Emergent Adverse Events Resulting in Study Drug Interruption (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class/ Preferred Term/ Verbatim Term/	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Concomitant Medication Given?	Relationship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx					

Note: MedDRA Version 18.8.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.2.4

Listing of Treatment-Emergent Adverse Events Resulting in Study Drug Dose Reduction (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class/ Preferred Term/ Verbatim Term/	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Concomitant Medication Given?	Relationship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx					

Note: MedDRA Version 18.8.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.2.5

Listing of Treatment-Emergent Adverse Events Resulting in Withdrawal of Study Drug (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class/ Preferred Term/ Verbatim Term/	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Concomitant Medication Given?	Relationship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx					

Note: MedDRA Version 18.8.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.2.6

Listing of Treatment-Emergent Adverse Events of Special Interest (Safety Population)

Patient Number	Age/ Race/ Weight (kg)	System Organ Class/ Preferred Term/ Verbatim Term/	Start Date/ Stop Date	Rel Day [1]	Severity Grade	Action Taken	Concomitant Medication Given?	Relation-ship	Outcome	SAE?
			DDMMMYYYY/ Ongoing	-xx						

Note: MedDRA Version 18.8.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Table 14.3.4.1

Listing of Abnormal Laboratory Values (Safety Population)

Patient Number	Age/ Race/ Weight	Group	Laboratory Test (unit)	Visit	Visit Date (Rel Day [1])	Result	CTCAE Grade [2]	Reference Range Low	Reference Range High
		Hematology							
		Chemistry							

[1] Rel Day is calculated as visit date minus first dose date (plus 1 day if visit date is on or after first dose date).
[2] CTCAE Grade: 1=…

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Repeat for:
Table 14.3.4.2 Listing of Laboratory Values with CTCAE Severity Grade ≥3 (Safety Population)
Table 14.3.4.3 Listing of Clinically Significant Laboratory Values (Safety Population)

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Table 14.3.5.1

Summary and Change from Baseline for Hematology Parameters by Visit (Safety Population)

Parameter	Visit	Actual/ Change	Statistic	Niraparib (N=xx)
Parameter 1	Baseline	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
	Cycle 1 Day 8	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
		Change	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
	Etc.	<as above>		
	End of Treatment	<as above>		
Parameter 2	<as above>			

Source: Data Listing 16.2.x

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Repeat for:
Table 14.3.5.2 Summary and Change from Baseline for Chemistry Parameters by Time Point (Safety Population)

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Table 14.3.5.3

Summary of Shifts in CTCAE Grade - Hematology Parameters (Safety Population)

				Post-Baseline CTCAE Grade					
Parameter	Post-Baseline Value	Statistic	Baseline CTCAE Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Parameter 1	Maximum CTCAE Grade	n (%)	Grade 0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	End of Treatment		<as above>						
Parameter 2	Maximum CTCAE Grade		<as above>						
	End of Treatment		<as above>						

Note: Toxicity is graded using NCI CTCAE version 3.0.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Repeat for:
Table 14.3.5.4 Summary of Shifts in CTCAE Grade – Chemistry Parameters (Safety Population)

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Table 14.3.5.5

Summary of Shift from Baseline in Hematology Parameters (Safety Population)

				Post-Baseline			
Parameter	Post-Baseline Value	Statistic	Baseline	Low	Normal	High	Total
Parameter 1	Smallest post-baseline value	n (%)	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Largest post-baseline value						
	End of treatment value						
Parameter 2	<as above>						

Note: Only patients with a baseline and post-baseline value are included for a given parameter.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Repeat for:
Table 14.3.5.6 Summary of Shift from Baseline in Chemistry Parameters (Safety Population)

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Table 14.3.5.7

Summary and Change from Baseline for Vital Signs by Visit (Safety Population)

Parameter	Visit	Actual/ Change	Statistic	Niraparib (N=xx)
Parameter 1	Baseline	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
	Cycle 1 Day 15	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
		Change	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
	Cycle 2	<as above>		
	Etc.			
Parameter 2	<as above>			

Source: Data Listing 16.2.x

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Table 14.3.5.8

Summary and Change from Baseline (Screening) in ECG Parameters (Safety Population)

Parameter	Visit	Actual/ Change	Statistic	Niraparib (N=xx)
Parameter 1	Screening	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
	End of Treatment	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
		Change	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
Parameter 2	<as above>			

Source: Data Listing 16.2.x

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Table 14.3.5.9

Summary and Change from Pre-dose in ECG Parameters – Cycle 2 Day 1 (Safety Population)

Parameter	Time Point	Actual/ Change	Statistic	Niraparib (N=xx)
Parameter 1	Pre-dose	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
	2 hours post-dose	Actual	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
		Change	n	xx
			Mean (StdDev)	xx.x (xx.xx)
			Median	xx.x
			Q1, Q3	xx.x, xx.x
			Min, Max	xx, xx
Parameter 2	<as above>			

Source: Data Listing 16.2.x

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Table 14.3.5.10

Summary of Maximum QTcF Interval Prolongation and Change from Baseline in QTc Interval, by Baseline Category (Safety Population)

Baseline Category	Parameter	Statistic	Niraparib (N=xx)
Overall	Maximum post-baseline QTcF Interval		
	> 450 msec	n (%)	xx (xx.x)
	> 480 msec	n (%)	xx (xx.x)
	> 500 msec	n (%)	xx (xx.x)
	Change from baseline to maximum post-baseline QTcF Interval		
	> 30 msec	n (%)	xx (xx.x)
	> 60 msec	n (%)	xx (xx.x)
Baseline QTcB interval > 450 msec	<as above>		
Baseline QTcB interval <= 450 msec	<as above>		

Note: Only patients with a baseline and post-baseline value are included for a given parameter.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.5.11

Summary of QTcF Interval Prolongation and Change from Pre-dose in QTc Interval – Cycle 2 Day 1 (Safety Population)

Parameter	Statistic	Niraparib (N=xx)
Post-dose QTcF Interval		
> 450 msec	n (%)	xx (xx.x)
> 480 msec	n (%)	xx (xx.x)
> 500 msec	n (%)	xx (xx.x)
Change from pre-dose to post-dose QTcF Interval		
> 30 msec	n (%)	xx (xx.x)
> 60 msec	n (%)	xx (xx.x)

Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.5.12

Summary of Overall ECG Interpretation (Safety Population)

Visit	Time Point	Interpretation	Statistic	Niraparib (N=xx)
Screening		Normal	n (%)	xx (xx.x)
		Abnormal, not clinically significant	n (%)	xx (xx.x)
		Abnormal, clinically significant	n (%)	xx (xx.x)
Cycle 2 Day 1	Pre-dose	<as above>		
	Post-dose	<as above>		
End of Treatment		<as above>		

Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.5.13

Summary of Overall Exposure to Study Drug (Safety Population)

Parameter	Statistic	Niraparib (N=xx)
Number of Cycles Started		
1	n (%)	xx (xx.x)
2	n (%)	xx (xx.x)
...	...	...
> 12	n (%)	xx (xx.x)
Total Study Duration [2]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
	Median (95% CI) [1]	xx.x (xx.x, xx.x)
Overall Treatment Exposure [3]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
	Median (95% CI) [1]	xx.x (xx.x, xx.x)
Dose Intensity (mg/day) [4]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx
Relative Dose Intensity [5]	n	xx
	Mean (StdDev)	xx.x (xx.xx)
	Median	xx.x
	Q1, Q3	xx.x, xx.x
	Min, Max	xx, xx

Note: Percentages based on the number of patients in the ITT population.
[1] Median and 95% confidence interval estimated from product-limit (Kaplan-Meier) method.
[2] Total study duration is calculated as last visit date or date of death minus enrollment date plus one.
[3] Overall treatment exposure is calculated as last dose date minus first dose date plus one.
[4] Dose intensity is calculated as sum of the daily doses actually consumed divided by total duration.
[5] Relative dose intensity is calculated as dose intensity (mg/day) divided by intended dose intensity (mg/day) multiplied by 100, where intended dose is 300 mg x total duration.
Source: Listing 16.2.x

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Table 14.3.5.14

Summary of Study Drug Compliance by Cycle and Overall (Safety Population)

Cycle	Parameter	Statistic	Niraparib (N=xx)
Overall	Compliance	n	xx
		Mean (StdDev)	xx.x (xx.xx)
		Median	xx.x
		Q1, Q3	xx.x, xx.x
		Min, Max	xx, xx
	Compliance Rate	n (%)	xx (xx.x)
	<80% compliant	n (%)	xx (xx.x)
	>120% compliant	n (%)	xx (xx.x)
Cycle 1	Compliance	n	xx
		Mean (StdDev)	xx.x (xx.xx)
		Median	xx.x
		Q1, Q3	xx.x, xx.x
		Min, Max	xx, xx
	Compliance Rate	n (%)	xx (xx.x)
	<80% compliant	n (%)	xx (xx.x)
	>120% compliant	n (%)	xx (xx.x)
Etc.			

Note: Compliance is calculated as the number of capsules prescribed (per dose prescribed) minus the number of capsules returned by the patient divided by the number of capsules prescribed during the same period multiplied by 100. Compliance rate is the number and percentage of patients 80% to 120% compliant.
Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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Table 14.3.5.15

Summary of Dose Interruptions and Dose Reductions by Cycle (Safety Population)

Cycle	Parameter	Statistic	Niraparib (N=xx)
At Any Time	Dose Interruptions		
	Dose interruption for any reason	n (%)	xx (xx.x)
	Dose interruption due to AE	n (%)	xx (xx.x)
	Dose Reductions		
	Dose reduction for any reason	n (%)	xx (xx.x)
	Dose reduction due to AE	n (%)	xx (xx.x)
Cycle 1	Dose Interruptions		
	Dose interruption for any reason	n (%)	xx (xx.x)
	Dose interruption due to AE	n (%)	xx (xx.x)
	Dose Reductions		
	Dose reduction for any reason	n (%)	xx (xx.x)
	Dose reduction due to AE	n (%)	xx (xx.x)
Cycle 2	<as above>		

Note: Percentages based on the number of patients in the ITT population.
Source: Listing 16.2.x

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8.3. Data Listing Shells

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Listing 16.2.1.1

Discontinuation from Treatment

Patient Number	Date of Treatment Discontinuation	Date of First Dose	Date of Last Dose	Number of Days on Treatment[1]	Primary Reason for Treatment Discontinuation
					Other: <specify>
					Patient request: <specify>

[1] Days on treatment = Last dose date – first dose date + 1.

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Listing 16.2.1.2

Discontinuation from Study

Patient Number	Date of Discontinuation	Date of Informed Consent	Number of Days on Study [1]	Reason for Discontinuation	Cause of Death	Date of Death

[3] Days on study = Last assessment date – date of informed consent + 1.

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Listing 16.2.2.1

Inclusion/Exclusion Criteria

Patient Number	Did the Patient Satisfy all Inclusion/Exclusion Criteria?	Inclusion/Exclusion Criterion Number	Inclusion/Exclusion Criterion Text

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Listing 16.2.2.2

Protocol Violations

Patient Number	Type of Violation	Description of Violation	Date

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.3.1

Study Populations

Patient Number	Included in ITT Population	Included in Safety Population
	Yes	Yes
	No: Reason for exclusion	No: Reason for exclusion

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Listing 16.2.4.1

Demographics

Patient Number	Age (yr)	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2)	Screening ECOG Performance Status

Note: BMI = Body Mass Index. BMI (kg/m^2) = weight (kg) / [height (m)]^2

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Listing 16.2.4.2

Medical History

Patient Number	Any Conditions or Surgeries	System Organ Class [1]/ Preferred Term [1]/ Condition	Start Date	Ongoing at Study Start?	Stop Date

[3] Coding was done using MedDRA version 17.1.

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Listing 16.2.4.3

Prior Hematology

Patient Number	Event	CTCAE Grade	Start Date/ End Date(days)	Which Prior Regimen	Treatment Given
	(eg, Thrombocytopenia)				

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Listing 16.2.4.4A

Ovarian Cancer Treatment: Part 1

Patient Number	Regimen Number	Chemotherapy Course	Cancer Type	Reason for Administration	Start Date/ Stop Date	Best Response	Progression Date	Discontinuation Reason

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.4.4B

Ovarian Cancer Treatment: Part 2

			Beginning of Regimen			Completion of Regimen		
Patient Number	Regimen Number	Agent Name	CA-125 Collect Date	CA-125 Value (U/ml)	ULN Range (U/ml)	CA-125 Collect Date	CA-125 Value (U/ml)	ULN Range (U/ml)

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.4.5

Other Cancer History

Patient Number	Cancer History Unrelated to Study Indication?	Cancer Type	Date Last Treated

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Listing 16.2.4.6

Ovarian Cancer Pathology

Patient Number	Biopsy Date	Method of Diagnosis	Subtype	Tumor Grade

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Listing 16.2.4.7

Cancer Staging

Patient Number	Primary Tumor Site	Initial Diagnosis Date	Cancer Stage (FIGO) at Time of Initial Diagnosis	Sites of Metastatic Disease

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Listing 16.2.4.8

Prior Surgery for Study Indication

Patient Number	Any Surgeries/ Procedures?	Surgery/Procedure	Anatomical Location	Indication	Date of Surgery/ Procedure

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Listing 16.2.4.9

Previous Radiotherapy

Patient Number	Any Prior Radiotherapy	Site and Region	Radiotherapy Start Date	Radiotherapy Stop Date	Total Grays

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.5.1A

Study Medication: Part 1

Patient Number	Visit	Bottle from Previous Cycle Returned?	Bottle Number Returned	Number of Unused Capsules Returned	Bottle Number Dispensed	Dose Prescribed at this Visit (mg)	Date:Time of Administration	Was Full Dose Taken
								No <specify reason>

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Listing 16.2.5.1B

Study Medication: Part 2

Patient Number	Visit	Dose Modified During Previous Cycle?	Start Date	Stop Date	Dose (mg)	Reason for Change	Action Taken	Any Missed Doses
						Other <specify>		Yes <explain>

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Listing 16.2.5.2

Study Medication: First Dose

Patient Number	Dose Administration Date:Time	Bottle Number Dispensed	Dose Prescribed (mg)	Full Dose Consumed?	Amount Consumed	Reason Full Dose Not Consumed

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Listing 16.2.5.3

Study Medication Compliance

Patient Number	Visit	Number of Capsules Prescribed [1]	Number of Capsules Returned [2]	Percent Compliance [3]	Overall Compliance [4]
		xxx	yyy	100*(xxx-yyy)/xxx	

[1] Number of capsules expected to have been consumed since previous cycle, accounting for dose interruptions and reductions.
[2] Unused capsules not returned and not reported as missed doses will be assumed to have been consumed.
[3] The number of capsules prescribed (per dose prescribed) minus the number of capsules returned by the patient divided by the number of capsules prescribed during the same period multiplied by 100.
[4] The total number of capsules prescribed (per dose prescribed) minus the total number of capsules returned by the patient divided by the total number of capsules prescribed multiplied by 100.

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Listing 16.2.6.1

Investigator Evaluation of Response (RECIST)

Patient Number	Visit	Date of Radiological Scan (or Assessment)	Target Lesion(s) Response	Non Target Lesion(s) Response	New Lesions?	Overall Response
			NE <specify reason>			

Note: CR=Complete Response, PR=Partial Response, SD=Stable Disease, (U)PD=(Unequivocal) Progressive Disease, NN=Non-CR/Non-PD, NE=Not Evaluable, ND=No Disease

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Listing 16.2.6.2A

Investigator Determination of Progressive Disease

Patient Number	Determined Date of Progressive Disease	Study Day	Criteria Met for Progressive Disease	Clinical Signs and Symptoms

Note: Study day is calculated as date of interest minus date of informed consent plus 1.

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Listing 16.2.6.2B

Diagnostic Tests Performed that Lead to Diagnosis of Progressive Disease

Patient Number	Diagnostic Test	Diagnostic Test Date	Study Day	Describe Results
	Other: <specify>			

Note: Study day is calculated as date of interest minus date of informed consent plus one.

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Listing 16.2.6.3

Investigator Target Lesion Assessment

Patient Number	Visit	Assessment Date	Lesion Number	Site	Location	Method	Longest Dimension (mm)	Short Axis (Lymph Nodes Only) (mm)	Lesion Status

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Listing 16.2.6.4

Investigator Non-Target Lesion Assessment

Patient Number	Visit	Assessment Date	Lesion Number	Site	Location	Method	Lesion Status

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Listing 16.2.6.5

Investigator New Lesion Assessment

Patient Number	Visit	Assessment Date	Lesion Number	Site	Location	Method

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Listing 16.2.6.6

ECOG Performance Status

Patient Number	Visit	Was Assessment Performed?	Date	Study Day	Performance Status [1]

Note: Study day is calculated as date of interest minus date of informed consent plus one.
[1] CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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Listing 16.2.7.1

Adverse Events Sorted by Patient

Patient Number	Preferred Term/ Verbatim Term	Start Date/ Stop Date	Rel Day [1]	TEAE [2]	CTCAE Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome	SAE?
		DDMMMYYYY/ Ongoing	-xx	No						

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] TEAE = treatment emergent adverse event

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Listing 16.2.7.2

Adverse Events Sorted by System Organ Class (SOC), Preferred Term and Patient

System Organ Class/ Preferred Term/ Verbatim Term	Patient Number	Start Date/ Stop Date	Rel Day [1]	TEAE [2]	CTCAE Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome	SAE?

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] TEAE = treatment emergent adverse event

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Listing 16.2.7.3

Adverse Events of Special Interest Sorted by Patient

Patient Number	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/ Stop Date	Rel Day [1]	TEAE [2]	CTCAE Grade	Action Taken	Concomitant Medication Given?	Relationship	Outcome	SAE?

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] TEAE = treatment emergent adverse event

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Listing 16.2.7.4

Glossary of Adverse Events

System Organ Class	Preferred Term	Verbatim Term

PROGRAM NAME: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX DATE: HH:MM/DDMMMYYYY

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Listing 16.2.8.1

Laboratory Results: Hematology

Patient Number	Visit	Sample Collection Date	Rel Day [1]	Laboratory Test	Result	Units	Flag [2]	Normal Range

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] H = High relative to normal range, L = Low relative to normal range. CTCAE grade appended if applicable. CS = clinically significant (per investigator).

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Repeat for:
Listing 16.2.8.2 Laboratory Results: Chemistry
Listing 16.2.8.3 Laboratory Results: Urinalysis
Listing 16.2.8.4 Laboratory Results: Coagulation

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Listing 16.2.8.5

Laboratory Results: Liver Function Tests – Potential Hy's Law Cases

Patient Number	Visit	Sample Collection Date	Rel Day [1]	Laboratory Analyte (result/xULN) ALT (U/L)	AST (U/L)	Total Bilirubin (umol/L)	ALP (U/L)	INR
				150/3.3	100/2.7	40/2.3	100/0.7	1

Note: ALT=alanine aminotransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase, INR=international normalized ratio, ULN=upper limit of normal.
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Programming Note: Include all visits for any patients with ALT or AST >3xULN, or bilirubin >2xULN at any time post baseline.

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Listing 16.2.8.6

Pregnancy Test

Patient Number	Age	Menopause or Surgical Sterilization?	Reason Serum Pregnancy Test Not Performed	Date Sample Taken	Rel Day [1]	Result	Contraception Practice Confirmed

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.1

Vital Signs

Patient Number	Visit	Reason Not Performed	Assessment Date	Rel Day [1]	Height (cm)	Weight (kg)	Temperature (°C)	Pulse (beats/min)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)

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Listing 16.2.9.2

Physical Examination

Patient Number	Visit	Date Performed	Rel Day [1]	Body System	Status	Abnormality Description

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.3

Electrocardiogram

Patient Number	Visit	Time Point	Date:Time of Assessment	Rel Day [1]	Heart Rate (bpm)	RR (sec)	PR (msec)	QRS (msec)	QT (msec)	QTcB (msec)	QTcF [2] (msec)

Note: (N)CS = (Not) Clinically Significant
[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.
[2] Values flagged with a single asterisk are changes from baseline >30. Values flagged with two asterisks are changes from baseline >60.

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Listing 16.2.9.4

Overall Electrocardiogram Interpretation

Patient Number	Age	Visit	Time Point	Date:Time of Assessment	Rel Day [1]	Specify Sinus Rhythm	ECG Interpretation

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.5

Surgeries/Procedures

Patient Number	Any Surgeries or Procedures	Surgery/Procedure while on study	Date	Rel Day [1]

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.6

Follow-up Surgery and Radiotherapy

	Follow-up Surgery for Cancer			Follow-up Radiotherapy					
Patient Number	Surgical Procedure Name	Surgery/ Procedure Date	Rel Day [1]	Anatomical Areas Radiated	Start Date	Rel Day [1]	End Date	Rel Day [1]	Total Grays

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.7

Previous and Concomitant Medications

Patient Number	ATC/ Generic Name/ Verbatim Name	Total Dose	Dose Units	Frequency	Indication	Route of Administration	Start/ Stop Date	Rel Day [1]

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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Listing 16.2.9.8

Cytology/Histology

Patient Number	Cytology/Histology Test	Date	Rel Day [1]	Results

[1] Rel Day is calculated as start date minus first dose date (plus 1 if start date ≥ first dose date). Rel Day for events with a start date after last dose date is calculated using last dose date. Rel Day is signed negative for events with onset prior to first dose date. Rel Day is signed positive for events with onset after last dose date. Otherwise Rel Day is unsigned.

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