PASS INFORMATION

Title	**Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)**
Protocol version identifier	**3000-04-001 Version 5**
Date of last version of protocol	**May 2nd, 2019**
EU PAS register number	**TBD**
Active substance	**Niraparib**
Medicinal product	**ZEJULA®, 100 mg hard capsules**
Product reference	
Procedure number	**EMEA/H/C/004249/MEA/002**
Marketing authorisation holder(s)	**TESARO Bio Netherlands B.V.** **Joop Geesinkweg 901-999, 1114 AB** **Amsterdam-Duivendrecht,** **The Netherlands**
Joint PASS	**N/A**
Research question and objectives	**To determine the risk of developing myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and other second primary malignancies (SPMs) in patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer administered niraparib in the routine clinical setting.** **The objectives are as follows:** • Primary: To estimate the incidence rate of MDS/AML among a cohort of adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with niraparib who are in a complete or partial response to platinum-based chemotherapy

	• Secondary: To estimate the incidence rate of SPMs in the same cohort • Exploratory: To compare the incidence rate of MDS/AML and other SPMs in niraparib-treated patients with a retrospective cohort of patients with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received at least 2 lines of platinum-based chemotherapy but were not treated with any PARP inhibitor
Country(ies) of study	**European countries with approved use of ZEJULA®**
Author	**Dr. Dirk Schneider, MD** **International Medical Director** **Medical Affairs, TESARO**

SPONSOR SIGNATURE PAGE

Declaration of Sponsor

Title (Study Number): Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib) (3000-04-001)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

D. Schneider — 02. May 2019

Dr. Dirk Schneider, MD

International Medical Director
Medical Affairs, TESARO

2. MAY. 2019

Dr. **Jean-Paul Dutertre**, MD

Director, EU Qualified Person for
Pharmacovigilance
TESARO Bio France sas

INVESTIGATOR'S AGREEMENT

I have received and read the European Union [EU] summary of product characteristics (SmPC) released by the European Medicines Agency (EMA). I have read Protocol 3000-04-001 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
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2. LIST OF MAIN ABBREVIATIONS USED IN THE STUDY PROTOCOL

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
AML	acute myeloid leukemia
BRCA	breast cancer susceptibility gene
CBC	complete blood cell count
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
EAP	Expanded Access Program
eCRF	electronic case report form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FIGO	International Federation of Gynecology and Obstetrics
g*BRCA*mut	germline breast cancer susceptibility gene mutation
GCP	Good Clinical Practice
HRD	homologous recombination deficiency
HRDneg	homologous recombination deficiency negative
HRDpos	homologous recombination deficiency positive
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intended to treat
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
NCI	National Cancer Institute
NIH	National Institutes of Health

Abbreviation or Specialist Term	Explanation
NOVA	Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer
PARP	poly(ADP-ribose) polymerase
PASS	post-authorization safety study
PFS	progression-free survival
Q1	first quarter
Q2	second quarter
Q3	third quarter
Q4	fourth quarter
SAE	serious adverse event
SAP	statistical analysis plan
SEER	Surveillance, Epidemiology, and End Results
SIR	standardized incidence ratio
SmPC	summary of product characteristics
SPM	second primary malignancy
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UAT	User Acceptance Testing
US	United States

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3. ABSTRACT

3.1. Title

Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)

3.2. Rationale and Background

Niraparib is a poly(ADP-ribose) polymerase (PARP) inhibitor. A decision to grant marketing authorization was adopted by the European Commission on 16 November 2017 with the indication of monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy. The recommended starting dose for niraparib is three 100 mg hard capsules once daily, equivalent to a total daily dose of 300 mg.[1,2]

Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and other second primary malignancies (SPMs) have been observed in the context of PARP inhibitor treatments. The mechanism of action of PARP inhibition suggests that there may be a risk associated with the use of PARP inhibitors. Therefore, the specific evaluation of this potential risk has been included in the Risk Management Plan for niraparib.

The results from Phase 3 clinical studies using niraparib, olaparib, or rucaparib did not show any statistically significant correlation between the use of PARP inhibitors and the incidence of MDS/AML or SPMs.[1-6] It is important to note that all patients who received either niraparib, olaparib, or rucaparib had previously received chemotherapy with DNA-damaging agents and/or radiotherapy,[1-6] the use of which is known to be a risk factor associated with MDS/AML.

In the NOVA (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer) study, a Phase 3, randomized, double-blind study of maintenance treatment, comparing niraparib versus placebo in patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, the incidence of MDS/AML was similar in the niraparib arm (7 of 367 patients, 1.9%) and the placebo arm (2 of 179 patients, 1.1%).[5] In the same study, there was 1 case of SPM in the niraparib-treated group.

Patients treated with chemotherapy have an increased risk for MDS/AML. This has been shown in a study using information in the United States (US) Surveillance, Epidemiology, and End Results (SEER) database collected between 1975 and 2008.[6] Among 23,180 adult patients with ovarian cancer who had received chemotherapy, 72 cases of AML occurred. In this study, the standardized incidence ratios (SIRs) were calculated as the ratio of the observed-to-expected incidence of AML. The expected incidence of AML was computed considering age-, race-, sex-, and calendar year-specific incidence rates of AML from the general SEER population, multiplied by the appropriate patient-years at risk. The SIRs 2-sided, Poisson-based 95% confidence intervals (CIs) were also calculated. The overall SIR for treatment-related AML in this cohort was 8.68 (95% CI: 6.79, 10.94). The SIR was increased to 12.07 (95% CI: 8.77, 16.20) during the 4.9 years following the administration of chemotherapy. The cohort included in this study did not receive treatment with a PARP

inhibitor. Therefore, it is likely that the incidence of MDS/AML is elevated in patients with ovarian cancer who have been previously treated with chemotherapy compared with the general population. This is further supported by Shenolikar et al[7] through analysis of the US claims database MarketScan for the incidence of MDS/AML in 23,862 patients diagnosed with ovarian cancer between January 2000 and June 2014. The study reports that the incidence of MDS and AML was higher among patients exposed to DNA-damaging therapy, such as alkylating agents, antimetabolites, platinum-based antineoplastic agents, and topoisomerase inhibitors, and that duration of exposure to these agents was a significant risk factor for developing MDS and AML.[7]

Similarly, in an independent study using information in the US SEER database collected from 1992 to 2012,[8] among 41,073 women with a diagnosis of a histologically confirmed primary ovarian malignancy, a total of 1,831 women (4.5%) developed an SPM. The overall SIR for this cohort as compared to the general population was 0.978 (99% CI: 0.992, 1.036), suggesting that the cancer treatment received by these patients could be a risk factor for the development of other SPMs.[8]

To better characterize the risks of MDS/AML and SPMs associated with niraparib treatment, a post-authorization safety study (PASS) in patients receiving maintenance treatment with niraparib was agreed with the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use.

3.3. Research Question and Objectives

The objective of this PASS is to determine the risk of developing MDS/AML and SPMs in patients administered niraparib in the routine clinical setting.

The objectives are as follows:

- Primary Objective: To estimate the incidence rate of MDS/AML among a cohort of adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with niraparib who are in a complete or partial response to platinum-based chemotherapy
- Secondary Objective: To estimate the incidence rate of SPMs in the same cohort
- Exploratory Objective: To compare the incidence rate of MDS/AML and other SPMs in niraparib-treated patients with a retrospective cohort of patients with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received at least 2 lines of platinum-based chemotherapy but were not treated with any PARP inhibitor

3.4. Study Design

This PASS will be conducted as a prospective (primary data), noninterventional, single-arm study including patients who have received or are receiving niraparib through the European Expanded Access Program (EAP) and patients treated post-approval in routine clinical practice. The EAP was offered—in alignment with local rules and regulations—as preapproval or pre-reimbursement access to patients within the expected European Union [EU] summary of product characteristics (SmPC) for niraparib (NOVA study).[1] In general, access was granted to patients who did not have a treatment alternative, including the participation in a clinical study. Patients who receive niraparib post-approval in routine clinical practice who will weigh less than 58 kg will most likely initiate niraparib treatment (in accordance with the European Union [EU] SmPC) at a lower dose (200 mg instead of 300

mg) than those that were treated during the EAP; this dose adjustment is expected to result in decreased thrombocytopenia, anemia, and other treatment-emergent adverse events.

To validate the data, a retrospective, secondary data analysis will be performed from patients who were diagnosed with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer and were treated with 2 or more lines of platinum-based chemotherapy between years 2005 and 2010, and have survived for at least 6 months following the last platinum-based chemotherapy. These patients would have been eligible for treatment with niraparib but did not receive such treatment as it was not approved. The standard of care for these patients would have been very similar to what they would receive today except for the addition of a PARP inhibitor as maintenance treatment. In addition, to ensure that the secondary data analysis reflects the primary data analysis, patients included for the secondary data analysis will have similar clinical profiles to the patients in the cohort used for the primary data analysis with respect to: age, anticancer chemo- and radiotherapy received, and follow-up period.

3.5. Population

Cohort for primary data collection: Adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are receiving or have received niraparib after response (complete or partial) to platinum-based chemotherapy.

Cohort for secondary data collection: Adult patients diagnosed with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who received at least 2 lines of platinum-based chemotherapy between years 2005 and 2010 and were followed for at least 6 months after second-line treatment but were not treated with any PARP inhibitor.

3.5.1. Inclusion Criteria for Primary Data Analysis

1. Patient must be female, aged 18 or older.
2. Patient must have a diagnosis of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.
3. Patient treated with niraparib is eligible if one of the following criteria is met:
    a. The patient received niraparib as monotherapy for the maintenance treatment of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy as part of the EAP, regardless of whether the patient is receiving niraparib at the time of enrollment.
    b. The patient received niraparib as monotherapy for the maintenance treatment of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy as part of clinical practice, regardless of whether the patient is receiving niraparib at the time of enrollment.
    c. The patient received niraparib following European Union [EU] SmPC guidelines as monotherapy for the maintenance treatment of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy as part of the

control arm of a clinical trial, regardless of whether the patient is receiving niraparib at the time of enrollment.

d. The patient will initiate the treatment with niraparib within 4 weeks of enrollment as monotherapy for the maintenance treatment of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy as part of clinical practice.

4. Patient must be able and agree to sign a consent form.

3.5.2. Exclusion Criterion for Primary Data Analysis

1. Patient receiving niraparib for use that is not approved according to authorized indication.

3.5.3. Inclusion Criteria for Secondary Data Analysis

1. Female patients who had a diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer at the age of 18 or older.
2. Patients who received 2 or more lines of platinum-based chemotherapy in years 2005 through 2010.
3. Patients who had a treatment follow-up for at least 6 months to 5 years from initiation of second-line platinum-based chemotherapy

3.5.4. Exclusion Criterion for Secondary Data Analysis

1. Patients who were exposed to any PARP inhibitor during the treatment and follow-up period used for the analysis.

3.6. Data Collected

To determine whether the occurrence of MDS/AML and SPMs is associated with niraparib treatment and not with other potential risk factors, three types of data will be collected:

1) Data for variables that are critical and moderate risk factors for MDS/AML and SPMs as described in Section 8.3.
2) Data for variables that are not described as risk factors for MDS/AML and other SPMs, but that are described as associated with early stages of development of these events as well as with adverse events related to treatment with niraparib as described in Section 8.3.
3) Data to confirm use of niraparib according to European Union [EU] SmPC guidelines.

For the secondary data cohort, only data for variables that are critical risk factors for MDS/AML and SPMs will be collected. For the primary data cohort, additional AEs and SAEs will be collected through TESARO pharmacovigilance and reported as described in Section 10.

For the primary data cohort, data will be collected at 2 different time periods: 1) baseline data (at initiation of niraparib treatment) and 2) follow-up data (collection occurs quarterly during a maximum 5-year clinical follow-up of the patient after niraparib initiation). For patients who start niraparib treatment before being enrolled in the study, the baseline data will be collected retrospectively from the time when niraparib treatment was initiated. For patients

who start niraparib treatment at time of enrollment, baseline data will be collected prospectively at time of enrollment. If a patient will not initiate treatment with niraparib for any reason after being enrolled in the study, baseline data will still be collected and included in the analysis, whenever this is feasible.

- Baseline data for the primary data cohort will include the following:
  - Tumor diagnosis (histological type, grade, International Federation of Gynecology and Obstetrics [FIGO] stage, primary location)
  - Age at diagnosis (derived from date of birth till date of diagnosis)
  - Age at study entry (derived from date of birth till date of enrollment)
  - Height
  - Weight
  - If available: germline and/or somatic breast cancer susceptibility gene (*BRCA*) status
  - Prior chemotherapy medications and radiations (indication, dose, and duration of treatment)
  - Other treatment received for cancer (indication, dose, and duration of treatment)
  - Niraparib exposure: dose and duration (start and stop dates and interruptions)
  - Other PARP inhibitor use: dose and duration (specify which PARP inhibitor, start and stop dates, and interruptions)
  - Patient's history of other cancers (type of cancer and date at diagnosis)
  - Patient's family history of cancer (type of cancer and family member)
  - Smoker (no/yes–frequency/quantity)
  - Patient's exposure to oncogenic chemicals/heavy metals
  - Alcohol use (no/yes–frequency/quantity)
  - Patient's history of autoimmune diseases
  - Prior history of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, and neutropenia
  - Complete blood cell count (CBC) abnormalities
  - MDS/AML and SPM events (type of event and date of diagnosis)
- Follow-up data for the primary data cohort will include the following:
  - Weight
  - Chemotherapy/radiotherapy and/or other cancer treatments (indication, dose, and duration of treatment)
  - Niraparib exposure (dose, dates of dose changes and interruptions, and date of discontinuation and reason)
  - Use of other PARP inhibitor (specify which PARP inhibitor, dose, and duration)

  - Patient's exposure to oncogenic chemicals/heavy metals
  - New occurrence of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, and neutropenia
  - New occurrences of MDS/AML and SPMs (type of event and date of diagnosis)

The participating physicians will document the measures taken in the web-based documentation sheet (electronic case report form [eCRF]) of this noninterventional study on a quarterly basis.

- Secondary data for the analysis of the comparator arm will include the following:
  - Age at diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer (derived from date of birth till date of diagnosis)
  - History of other cancers (type of cancer and date of diagnosis)
  - Chemotherapy/radiotherapy and/or other cancer treatments (indication, dose, and duration of treatment)
  - Other treatment received for cancer (indication, dose, and duration of treatment)
  - Follow-up period (derived from date of diagnosis till one of the following events, whichever comes first: patient death, end of health plan enrollment, or end of study)
  - MDS/AML and SPM events (type of event and date of diagnosis)

The rationale for selected risk factors associated with MDS/AML and SPMs in both the primary data and secondary data cohorts, including discussion of the respective limitations, are discussed in Sections 8.2.3 and 8.3.

3.7. Data Sources

TESARO is currently providing niraparib through an EAP to patients in the EU including several cohort programs. Patients who participated in this program will be approached by their physicians in Q4 2019 and will be offered the opportunity to participate in this prospective, noninterventional PASS. To reach the requested target of 1,000 patient-years of observation, with up to 5-years follow-up time for the patients that reach this survival milestone, and an overall average of 2.5 years of follow-up, the majority of patients enrolled will have started treatment with niraparib following commercialization of the drug in the individual European countries.

The secondary data source will be derived from the US claims database MarketScan. MarketScan is a longitudinal US database with over 240 million patients with claims records containing inpatient and outpatient data, specialty pharmacy and mail-order prescriptions, laboratory, medical records, and hospital claims data. This database provides high-quality data on anticancer therapies used by US patients and includes a long follow-up period, allowing the capture of the most critical risk factors influencing the incidence of MDS/AML and other SPMs in patients diagnosed with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer. MarketScan was successfully used by Shenolikar et al[7] to evaluate the incidence of MDS and AML in patients diagnosed with ovarian and breast cancer. The

study suggested that occurrence of these secondary malignancies is mainly induced by the DNA-damaging anticancer treatments to which patients with ovarian and breast cancer are exposed.[7] The current study provides an opportunity for an independent validation of the results previously described.[7]

By performing the analysis using data entered from 2005-2010, it will be possible to select patients that received the same chemotherapy regimens as the ones received by patients enrolled for collection of primary data but who were not exposed to any PARP inhibitor. In addition, this time frame allows for at least 5 years of follow-up data to be collected for each individual patient.

The use of a US population in the comparator arm for a study performed in a European population is justified by 2 different indirect evidences that suggest similar incidence of MDS/AML and other SPMs between these 2 populations following a diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer:

- Patients in the US and EU receive the same platinum-based chemotherapies, which are considered to be the major risk factors for developing MDS, AML, and SPMs in this patient population.[6,7]
- Age-adjusted incidence rates from the US SEER database[9] indicate that the risk for developing AML or MDS following a diagnosis with ovarian cancer is 3.6 and 4.9 per 100,000 women annually, respectively. For Europe no data are available following a diagnosis with ovarian cancer, but the age adjusted incidence rate of AML or MDS in the general population of women is comparable to the incidence rate observed in the USA (3.7 and 5.4 per 100,000 women annually for AML and MDS, respectively) as reported by the International Agency for Research on Cancer EU database (EU component of GLOBOCAN)[10]. Note that the GLOBOCAN database is managed in France; however, the data collected is representative of the EU population.

The use of the US FLATIRON database was excluded as it has limited capacity to track the development of secondary MDS/AML and other SPMs in patients diagnosed with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer.

3.8. Study Size

The mean duration of follow-up among 372 intended to treat (ITT) patients randomized into the NOVA study niraparib arms was 26.9 months (as the data cutoff of 03/26/2018). This represents approximately 834 patient-years of observation. Seven cases of MDS/AML were reported in the niraparib group in the main portion of this study, which represents an incidence rate of approximately 0.84 per 100 patient-years, with a 95% CI of 0.34 to 1.73 per 100 patient-years. One case of SPM was reported in the niraparib group in the main portion of this study, which represents an incidence rate of approximately 0.12 per 100 patient-years, with a 95% CI of 0.003 to 0.67 per 100 patient-years. Thus, the minimum data required to achieve a quantifiable number of MDS/AML and SPM events is 1,000 patient years with approximately 2.5 years of average follow-up.

To allow for the necessary time required for development of a secondary malignancy, patients will be followed for up to 5 years from treatment initiation. Survival and observational data from Olaparib Study 19 suggest that with maximum 5-years follow- from treatment initiation it is possible to achieve an average of approximately 2.5 years of follow-

up per patient,[11] confirming the data collected from the NOVA study which indicate 26.9 months follow-up over a period of 3 years-follow-up from the first dose of the last patient enrolled.

Given the high risk for missing data and for loosing patients to follow-up in a non-interventional study within a real world setting, it is planned to recruit up to 800 patients for a maximum of 5 years of follow-up per patient so that up to 2,000 patient-years of observation data can be reached. This sample size allows adequate patient data to compensate for a large incidence of missing data given that we expect to observe a significant incidence of MDS/AML and SPMs when data for 1,000 patient-years are collected over a maximum follow-up period of 5 years and an overall average follow-up pf 2.5 years.

Table 3 below provides the 95% CIs for different numbers of observed events of MDS/AML during this follow-up period.

Table 3: Confidence Intervals for Observed Events of MDS/AML for 1,000 Patient-Years

Observed Number of Events	Rate (per 100 patient-years)	Lower 95% Confidence Limit (per 100 patient-years)	Upper 95% Confidence Limit (per 100 patient-years)
5	0.5	0.16	1.2
10	1.0	0.48	1.8
15	1.5	0.84	2.5
20	2.0	1.2	3.1
25	2.5	1.6	3.7

3.9. Data Analysis

Details of the statistical analyses presented below will be provided in Section 8.7. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol.

The analysis population for all analyses is the safety population, defined as all patients who receive any amount of niraparib (at least 1 dose). All analyses will be performed using SAS statistical software v9.4 or later and will include summary statistics, including the number and percentage for categorical variables and the number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Further details will be provided in the statistical analysis plan (SAP).

Analyses will be descriptive; no hypothesis will be tested. Distributions of patient and tumor characteristics will be summarized. Incidence rates of MDS/AML and other SPMs and their respective 95% CIs per 100 person-time units will be estimated. For the primary data, a sensitivity analysis will be performed on the group of patients who have never received PARP inhibitor treatments prior to study enrollment. In addition, a descriptive comparison on baseline characteristics of those patients who did not receive/initiate niraparib after initial enrollment versus those who did receive the treatment will be performed.

A descriptive analysis will also be performed on the secondary data collected retrospectively from patients who were not treated with niraparib. The incidence rates of MDS/AML and other SPMs and their respective 95% CIs per 100 person-time units will be reported.

The primary analysis on both primary and secondary cohorts will be performed using all events of either MDS/AML or other SPMs without considering the risk factors associated with these events. In addition, given the descriptive nature of this analysis, no formal statistical testing will be conducted between the primary and secondary data cohorts.

The initial analysis will then be followed by an evaluation of how MDS/AML and SPM events detected either in the primary or secondary data cohort are distributed with respect to the variables collected for each group. This analysis will be more detailed in the primary data cohort, due to the possibility of collecting a broader number of variables associated with patients diagnosed with platinum-sensitive, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. For the secondary data cohort, this analysis will focus on the critical factors impacting MDS/AML and SPMs in this patient population, such as age at diagnosis, anticancer chemo- and radiotherapy received, follow-up period, and history of other cancers.

3.10. Milestones

Detailed milestones are listed in Table 4 of Section 5 below.

4. TABLE OF AMENDMENTS AND UPDATES

None to date.

5. MILESTONES

5.1. Data Collection

Primary data collection will start at the time of each patient enrollment. For patients who have been exposed to niraparib prior to enrollment in the study, data collection will be initially captured retrospectively from the beginning of niraparib treatment and continued prospectively throughout a maximum 5-year follow-up period counting from the first dose on niraparib. For patients who start niraparib treatment at the time of enrollment, data will be captured only prospectively.

Patients treated for a diagnosis of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer usually visit the clinic at least on a quarterly basis. Thus, data will be collected from the medical charts of each patient quarterly until study end. The average duration of observation per patient will be recorded to validate that there will be an average of approximately 2.5 years of follow-up per patient.

Study end: Data collection will continue until fulfillment of the target observation plan for at least 1,000 patient-years and maximum 5 years of follow-up for those patients who achieve this survival milestone, with an overall average patients follow-up of 2.5 years. This is expected to be by Q3 2026.

Secondary data collection will start in Q3 2023, or after the interim analysis of 500 patient-years, to ensure that the results from the midterm analysis will guide the selection of a retrospective patient population that mirrors the prospective cohort in terms of age of patients at time of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis, anticancer chemo- and radiotherapy received, and follow-up period.

The secondary data will be collected from Q3 2023 to Q3 2026. To avoid bias during data analysis, secondary data analysis will be performed in parallel with the primary data analysis from Q4 2026 through Q1 2027.

Table 4: Detailed Study Milestones

Milestone	Planned Date
Start of data collection (primary data)	Q4 2019
End of enrollment	Q3 2021
Interim report (primary data) and start secondary data collection	Q3 2023
End of primary and secondary data collection and start of analysis	Q3 2026
Registration in the EU PAS register	Q2 2019
Final report of study results	Q1 2027

Abbreviations: EU = European Union; PAS = Post-Authorization Studies; Q1= first quarter; Q3 = third quarter; Q4 = fourth quarter.

6. RATIONALE AND BACKGROUND

Niraparib is a potent, orally active poly(ADP-ribose) polymerase (PARP)1 and PARP2 inhibitor.

In the randomized, double-blind, Phase 3 NOVA (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer) study,[5] a total of 553 patients were randomized at 107 centers worldwide. Patients were categorized according to the presence or absence of a germline breast cancer susceptibility gene (*BRCA*) mutation (g*BRCA*mut cohort and non-g*BRCA*mut cohort) and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily. In the non-g*BRCA*mut cohort, testing for homologous recombination deficiency (HRD) was performed using an HRD test on tumor tissue obtained at the time of initial diagnosis or at the time of recurrence. The primary endpoint was progression-free survival (PFS). The study enrolled 203 patients in the g*BRCA*mut cohort and 350 patients in the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut cohort, 162 had tumors that were identified as HRD positive (HRDpos), and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined for 54 patients.

Demographic and baseline characteristics were well balanced. Table 5 below shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (ie, g*BRCA*mut cohort, HRDpos cohort, and overall non-g*BRCA*mut cohort). In addition, median PFS in patients with HRDneg tumors was 6.9 months (95% confidence interval [CI]: 5.6, 9.6) in the niraparib arm versus 3.8 months (95% CI: 3.7, 5.6) in the placebo arm, with a hazard ratio of 0.58 (95% CI: 0.361, 0.922) (p = 0.0226).

Table 5: Progression-Free Survival in Ovarian Cancer Patients in NOVA[5]

	g*BRCA*mut Cohort		**Non-g*BRCA*mut Cohort (regardless of HRD status)**		**HRDpos (within non-g*BRCA*mut cohort)**	
	Niraparib (n = 138)	**Placebo (n = 65)**	**Niraparib (n = 234)**	**Placebo (n = 116)**	**Niraparib (n = 106)**	**Placebo (n = 56)**
Median PFS, months (95% CI)	21.0 (12.9, NE)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value	< 0.0001		< 0.0001		< 0.0001	
HR (niraparib: placebo) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	

Abbreviations: CI = confidence interval; g*BRCA*mut = germline breast cancer gene mutation; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NE = not estimable; PFS = progression-free survival.
PFS is defined as the time in months from the date of first dose to progression or death.
Source: ZEJULA® US Prescribing Information.

All 367 patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut cohorts. In the overall safety population, for the niraparib versus placebo treatment arms, the incidences of Grade 3 or 4 TEAEs (74% versus 23%), serious adverse events (SAEs) (30% versus 15%), TEAEs leading to treatment interruption (67% versus 15%), TEAEs leading to dose reduction (69%

versus 5%), and TEAEs leading to treatment discontinuation (15% versus 2%) were higher for niraparib than for placebo. There were no on-treatment deaths reported.

The most commonly observed nonhematologic TEAEs (all grades) in niraparib-treated compared with placebo-treated patients were nausea (74% versus 35%), fatigue (46% versus 32%), constipation (40% versus 20%), and vomiting (34% versus 16%). The majority of the nonhematologic TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (all grades) in niraparib-treated compared with placebo-treated patients were anemia (49% versus 7%), thrombocytopenia (46% versus 3%), decreased platelet count (20% versus 2%), and neutropenia (18% versus 3%). Although Grade 3 or 4 hematologic laboratory adverse events (AEs) were common at the initiation of study treatment, no severe clinical sequelae were observed, and relatively few patients discontinued study treatment due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these AEs beyond Cycle 3. In the NOVA study, niraparib dose adjustment tended to occur early with most patients reaching their individual adjusted dose level at the end of Month 3 (ie, Cycle 3) of treatment.

6.1. MDS/AML

Myelodysplastic syndrome (MDS) is a group of bone marrow failure disorders characterized by ineffective hematopoiesis in one or more of the lineages of the bone marrow.[12] MDS can evolve from a refractory anemia to acute myeloid leukemia (AML), which is associated with a decrease in intramedullary apoptosis and a block in myeloid differentiation. The incidence is 5 per 100,000 and increases to 21 per 100,000 among persons aged 70 or older.[13] The association of MDS with age suggests genetic damage caused by hazardous exposure or inherited susceptibility. The diagnostic classification currently in use by the World Health Organization recognizes 6 distinct entities of MDS based on morphologic quantitative and qualitative evaluation of the peripheral blood and bone marrow using basic hematological techniques.[14]

6.1.1. Reported Cases of MDS/AML With PARP Inhibitors

In total, 11 cases of MDS/AML were reported across all studies included as of the data cutoff dates reported in the Risk Management Plan as of March 26, 2018. These included the following: a) 8 cases of MDS (7 niraparib and 1 placebo) and 1 case of AML (placebo) in the NOVA main study, b) 1 case of MDS (niraparib) in the food effect substudy, and c) 1 case of MDS/AML (niraparib) in the QUADRA study.

In the NOVA main study, the incidence of MDS/AML was similar in the niraparib arm (7 of 367 patients, 1.9%) and the placebo arm (2 of 179 patients, 1.1%).[5] The overall incidence of MDS/AML in niraparib-treated subjects is 0.7% (9 of 1,214 subjects) in TESARO-sponsored studies as of the data cutoff (Investigator's brochure [IB] version 7.0). One case of MDS has been reported in the niraparib investigator-sponsored trial program as well (IB version 7.0).

In addition, in 4,452 patients treated per clinical care using a commercial supply of niraparib, a total of 8 cases of MDS/AML were reported, 2 of which were in patients that did not present indication for niraparib treatment as per European Union [EU] summary of product characteristics (SmPC) guidelines (Risk Management Plan as of 26 March 2018).

According to the Lynparza® (olaparib) Product Information, the incidence of MDS/AML in patients treated with olaparib monotherapy in clinical studies, including long-term follow-up, was <1.5% (21 of 1,680).[3] All of these patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Some patients

also had a history of previous cancer or bone marrow dysplasia.[3] According to the Rubraca® (rucaparib) Product Information, MDS/AML was reported in 0.5% (2 of 377) of patients with ovarian cancer treated with rucaparib. Patients who experienced MDS/AML after treatment with rucaparib had all received prior treatment with platinum and other DNA-damaging agents.[4]

6.1.2. Risk Factors Associated With MDS/AML

Risk factors for MDS/AML include age, chemotherapy and/or radiation therapy, family history of MDS/AML, smoking, alcohol use, autoimmune diseases, genetic syndromes, and exposure to certain chemicals and heavy metals.[6,13,15-30] In addition, the incidence of MDS/AML was found to be associated with gender (more common in the male population), weight, platelet transfusions, anemia, renal and/or hepatic insufficiency, and mean corpuscular volume (MCV) abnormalities.

The mechanism of action of PARP inhibitors suggests that these agents may induce development of MDS/AML.[31] Results from Phase 3 clinical studies using niraparib, olaparib, or rucaparib have failed to show any statistically significant correlation between the use of PARP inhibitors and the incidence of MDS/AML or second primary malignancies (SPMs). It is important to note that all patients who received either niraparib, olaparib, or rucaparib had previously received chemotherapy with DNA-damaging agents and/or radiotherapy,[1-4] the use of which is known to be a risk factor associated with MDS/AML.

Patients treated with chemotherapy have an increased risk for MDS/AML. This has been shown in a study using information from the United States (US) Surveillance, Epidemiology, and End Results (SEER) database collected between 1975 and 2008.[6] Among 23,180 adult patients with ovarian cancer who received initial chemotherapy, 72 cases of AML occurred. In this study, the standardized incidence ratios (SIRs) were calculated as the ratio of the observed-to-expected incidence of AML. The expected incidence of AML was computed considering age-, race-, sex-, and calendar year-specific incidence rates of AML from the general SEER population, multiplied by the appropriate patient-years at risk. The 2-sided, Poisson-based 95% CIs for SIRs were also calculated. The overall SIR for treatment-related AML in this cohort was 8.68 (95% CI: 6.79, 10.94). The SIR was increased to 12.07 (95% CI: 8.77, 16.20) during the 4.9 years following the administration of chemotherapy. The cohort included in this study did not receive treatment with a PARP inhibitor. Therefore, it is likely that the incidence of MDS/AML is elevated in patients with ovarian cancer who have been previously treated with chemotherapy compared with the general population.

This is supported by Shenolikar et al[7] through analysis of the US claims database MarketScan for the incidence of MDS/AML in 23,862 patients diagnosed with ovarian cancer between January 2000 and June 2014. The study reports that the incidence of MDS and AML was higher among patients exposed to DNA-damaging therapy, such as alkylating agents, antimetabolites, platinum-based antineoplastic agents, and topoisomerase inhibitors, and that duration of exposure to these agents was a significant risk factor for developing MDS and AML.[7]

6.2. Second Primary Malignancies

The mechanism of action of PARP inhibitors suggests that these agents may induce development of SPMs.[32] SPMs are cancers that develop after a primary cancer was diagnosed and treated in the same individual. Based on a study using information from the US SEER database collected from 1992 to 2012,[8] among 41,073 women with a diagnosis of a

histologically confirmed primary ovarian malignancy, a total of 1,831 women (4.5%) developed an SPM. The overall SIR for this cohort as compared to the general population was 0.978 (99% CI: 0.992, 1.036). Race and age of diagnosis may impact the subsequent risk of developing SPM. Studies have shown that women could be at risk of developing subsequent cancers including breast, gastrointestinal, lung, and gynecological cancers, as well as leukemia.[8,33,34]

6.2.1. Reported SPMs in Patients Treated With Niraparib

Three subjects out of a total of 1,214 subjects treated with niraparib have reported an SPM other than MDS/AML, which has a cumulative incidence of 0.2%. The types of SPMs reported in these 3 subjects were undifferentiated sarcoma, intestinal carcinoma, and lymphocytic leukemia.

One patient out of 181 patients in the placebo group of the NOVA study also reported an SPM event (breast cancer).

In addition, as of 26 March 2018, there were 12 reports of SPMs in 4,452 patients treated with niraparib after marketing approval of niraparib.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this post-authorization safety study (PASS) is to determine the risk of developing MDS/AML and SPMs in patients administered niraparib in the routine clinical setting.

The objectives are as follows:

- Primary Objective: To estimate the incidence rate of MDS/AML among a cohort of adult patients with platinum-sensitive, relapsed, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer treated with niraparib who are in a complete or partial response to platinum-based chemotherapy
- Secondary Objective: To estimate the incidence rate of SPMs in the same cohort
- Exploratory Objective: To compare the incidence rate of MDS/AML and other SPMs in niraparib-treated patients with a retrospective cohort of patients with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received at least 2 lines of platinum-based chemotherapy but were not treated with any PARP inhibitor

8. RESEARCH METHODS

8.1. Study Design

This PASS will be conducted as a prospective, noninterventional, single-arm study including patients that have received or are receiving niraparib through the European Expanded Access Program (EAP) and those in routine clinical practice.

The mean duration of follow-up among 372 intended to treat (ITT) patients randomized into the NOVA study niraparib arms was 26.9 months (as the data cutoff of 03/26/2018). This represents approximately 834 patient-years of observation. Seven cases of MDS/AML were reported in the niraparib group in the main portion of this study, which represents an incidence rate of approximately 0.84 per 100 patient-years, with a 95% CI of 0.34 to 1.73 per 100 patient-years. One case of SPM was reported in the niraparib group in the main portion of this study, which represents an incidence rate of approximately 0.12 per 100 patient-years, with a 95% CI of 0.003 to 0.67 per 100 patient-years. Thus, the minimum data required to achieve a quantifiable number of MDS/AML and SPM events is 1,000 patient years with approximately an average of 2.5 years of follow-up.

To allow for the necessary time required for development of a secondary malignancy, patients will be followed for up to 5 years from treatment initiation. Survival and observational data from Olaparib Study 19 suggest that with maximum 5-years follow- from treatment initiation it is possible to achieve an average of approximately 2.5 years of follow-up per patient,[11] confirming the data collected from the NOVA study which indicate 26.9 months follow-up over a period of 3 years-follow-up from the first dose of the last patient enrolled.

Given the high risk for missing data and for loosing patients to follow-up in a non-interventional study within a real world setting, it is planned to recruit up to 800 patients for a maximum of 5 years of follow-up per patient so that up to 2,000 patient-years of observation data can be reached. This sample size allows adequate patient data to compensate for a large incidence of missing data given that we expect to observe a significant incidence of MDS/AML and SPMs when 1,000 patient-years are reached over a maximum follow-up period of 5 years with an overall average of 2.5 years follow-up..

To validate the data, a retrospective, secondary data analysis will be performed from patients who were diagnosed with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer, were treated with 2 or more lines of platinum-based chemotherapy between years 2005 and 2010, and have survived for at least 6 months following the last platinum-based chemotherapy. These patients would have been eligible for treatment with niraparib but did not receive such treatment as it was not approved. The standard of care for these patients would have been very similar to what they would receive today except for the addition of a PARP inhibitor as maintenance treatment. In addition, to ensure that the secondary data analysis fully reflects the primary data analysis, patients included for the secondary data analysis will have similar clinical profiles to the patients in the cohort used for the primary data analysis with respect to: age, anticancer chemo- and radiotherapy received, and follow-up period.

The incidence of MDS/AML and SPMs will be analyzed as described in Section 8.7.

8.2. Setting

All patients diagnosed with platinum-sensitive, relapsed, high-grade serous epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer, who are receiving or have received treatment with niraparib as part of routine clinical practice and following the European Medicines Agency (EMA)-approved SmPC indications, are eligible to participate in the study; this includes the following: 1) patients who received niraparib as part of the EAP, regardless of whether they continue using niraparib following enrollment in this study, 2) patients who started receiving niraparib in routine clinical practice before enrollment in this study, regardless of whether they continue treatment following enrollment, and 3) patients will initiate the treatment within 4 weeks of enrollment in this study (see inclusion and exclusion criteria for more enrollment eligibility details). In the latter case, it is important to note that the decision for the physician to prescribe the drug is made by the treating physician before the decision to include the patient in the study and is independent of the decision to include the patient in the study.

Patients will be identified and notified of the study by their treating physician. Signed consent from interested patients will then be obtained by the physician or a designated representative. The incidence of MDS/AML and SPMs will be collected by the physician at the time of enrollment and quarterly thereafter for a maximum period of 5 years (Table 7). For patients who were exposed to niraparib treatment before being enrolled in the study, retrospective data starting from the beginning of niraparib treatment will be collected. All patients capable of understanding and signing the consent form will be included in the study.

Patients will be enrolled in 5 European countries (Germany, The Netherlands, France, Italy and Spain; Table 6), all of which will have niraparib treatment approved for reimbursement by the time local enrollment will start. A total of 100 to 120 sites will be engaged to reach the targeted data collection within a period of 5 years. The sites will be selected for inclusion in the study based on the following parameters:

1. Sites using niraparib per European Union [EU] SmPC indication
2. Number of patients visiting the site with the correct indication for use of niraparib as maintenance treatment
3. Sites with an organized and compliant infrastructure for global clinical research
4. Sites participating in the EAP will be preferred to collect the outcome of patients participating in this early treatment program, but sites that did not participate in the EAP will also be included to meet the enrollment goal for this project.

Table 6: Countries and Dates of Reimbursement Approval for ZEJULA®

Country	Reimbursement Approval	Number of Expected Sites
Germany	Q1 2018	30
The Netherlands	Q2 2018	20
France	Q1 2019	20
Italy	Q4 2018	25
Spain	Q2 2019	15

Abbreviations: Q1 = first quarter; Q2 = second quarter; Q4 = fourth quarter.

The control group will include secondary data from adult patients diagnosed with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who were treated with at least 2 lines of platinum-based chemotherapy in the years between 2005 and 2010 and were

followed for at least 6 months after second-line treatment, but were not treated with any PARP inhibitor. These patients would have been eligible for treatment with niraparib but did not receive such treatment as it was not approved/available. The standard of care for these patients would have been very similar to what they would receive today except for the addition of a PARP inhibitor as maintenance treatment. In addition, to ensure that the secondary data analysis fully reflects the primary data analysis, patients included for the secondary data analysis will be selected to have a similar clinical profile to the patients in the cohort used for the primary data analysis with respect to: age at diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer, anticancer chemo- and radiotherapy received, and follow-up period.

8.2.1. Inclusion/Exclusion Criteria

Inclusion criteria for primary data analysis

1. Patient must be female, aged 18 or older.
2. Patient must have a diagnosis of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.
3. Patient is eligible if one of the following criteria is met:
    a. The patient received niraparib as monotherapy for the maintenance treatment of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy as part of the EAP, regardless of whether the patient is receiving niraparib at the time of enrollment.
    b. The patient received niraparib as monotherapy for the maintenance treatment of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy as part of clinical practice, regardless of whether the patient is receiving niraparib at the time of enrollment.
    c. The patient received niraparib following European Union [EU] SmPC guidelines as monotherapy for the maintenance treatment of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy as part of the control arm of a clinical trial, regardless of whether the patient is receiving niraparib at the time of enrollment.
    d. The patient will initiate the treatment with niraparib within 4 weeks of enrollment as monotherapy for the maintenance treatment of platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy as part of clinical practice.
4. Patient must be able and agree to sign a consent form.

Exclusion criterion for primary data analysis

1. Patient receiving niraparib for use that is not approved according to authorized indication.

Inclusion criteria for secondary data analysis

1. Female patients who had a diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer at the age of 18 or older.

2. Patients who received 2 or more lines of platinum-based chemotherapy in years 2005 through 2010.
3. Patients who had a treatment follow-up for at least 6 months to 5 years from initiation of second-line platinum-based chemotherapy.

Exclusion criterion for secondary data analysis

1. Patients who were exposed to any PARP inhibitor during the treatment and follow-up period used for the analysis.

8.2.2. Data Collection

To determine whether the occurrence of MDS/AML and SPMs is associated with niraparib treatment and not with other potential risk factors, three types of data will be collected:

1) Data for variables that are critical and moderate risk factors for MDS/AML and SPMs as described in Section 8.3.
2) Data for variables that are not described as risk factors for MDS/AML and other SPMs, but that are described as associated with early stages of development of these events as well as with adverse events related to treatment with niraparib as described in Section 8.3.
3) Data to confirm use of niraparib according to European Union [EU] SmPC guidelines.

For the secondary data cohort, only data for variables that are critical risk factors for MDS/AML and SPMs will be collected.

For the primary data cohort, data will be collected at 2 different time periods: 1) baseline data (at initiation of niraparib treatment) and 2) follow-up data (collection occurs quarterly during a maximum 5-year clinical follow-up of the patient after niraparib initiation). For patients who start niraparib treatment before being enrolled in the study, the baseline data will be collected retrospectively from the time when niraparib treatment was initiated. For patients who start niraparib treatment at time of enrollment, baseline data will be collected prospectively at time of enrollment. If a patient will not initiate treatment with niraparib for any reason after being enrolled in the study, baseline data will still be collected and included in the analysis, whenever this is feasible.

8.2.3. Variables Collected

- Baseline data for the primary data cohort will include the following:
  - Tumor diagnosis (histological type, grade, International Federation of Gynecology and Obstetrics [FIGO] stage, primary location)
  - Age at diagnosis (derived from date of birth till date of diagnosis)
  - Age at study entry (derived from date of birth till date of enrollment
  - Height
  - Weight
  - If available: germline and/or somatic breast cancer susceptibility gene (*BRCA*) status
  - Prior chemotherapy medications and radiations (indication, dose, and duration of treatment)

  - Other treatment received for cancer (indication, dose, and duration of treatment)
  - Niraparib exposure: dose and duration (start and stop dates and interruptions)
  - Other PARP inhibitor use: dose and duration (specify which PARP inhibitor, start and stop dates, and interruptions)
  - Patient's history of other cancers (type of cancer and date at diagnosis)
  - Patient's family history of cancer (type of cancer and family member)
  - Smoker (no/yes–frequency/quantity)
  - Patient's exposure to oncogenic chemicals/heavy metals
  - Alcohol use (no/yes–frequency/quantity)
  - Patient's history of autoimmune diseases
  - Prior history of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, and neutropenia
  - Complete blood cell count (CBC) abnormalities
  - MDS/AML and SPM events (type of event and date of diagnosis)
- Follow-up data for the primary data cohort will include the following:
  - Weight
  - Chemotherapy/radiotherapy and/or other cancer treatments (indication, dose, and duration of treatment)
  - Niraparib exposure (dose, dates of dose changes and interruptions, and date of discontinuation and reason)
  - Use of other PARP inhibitor (specify which PARP inhibitor, dose, and duration)
  - Patient's exposure to oncogenic chemicals/heavy metals
  - New occurrence of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, and neutropenia
  - New occurrences of MDS/AML and SPMs (type of event and date of diagnosis)

The participating physicians will document the measures taken in the web-based documentation sheet (electronic case report form [eCRF]) of this noninterventional study on a quarterly basis.

Additional AEs and SAEs observed during the study will be collected through TESARO pharmacovigilance and reported as described in Section 10.

- Secondary data for the analysis of the comparator arm will include the following:
  - Age at diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer (derived from date of birth till date of diagnosis)
  - History of other cancers (type of cancer and date of diagnosis)

- Chemotherapy/radiotherapy and/or other cancer treatments (indication, dose, and duration of treatment)
- Other treatment received for cancer (indication, dose, and duration of treatment)
- Follow-up period (derived from date of diagnosis till one of the following events, whichever comes first: patient death, end of health plan enrollment, or end of study)
- MDS/AML and SPM events (type of event and date of diagnosis)

The data collected for the secondary data cohort represent critical risk factors associated with the incidence of secondary malignancies after diagnosis and treatment of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer, which can be captured through the MarketScan database.

Previous publications have shown that exposure to DNA-damaging therapies and the length of exposure to these therapies are critical risk factors to developing secondary malignancies in this population[6,7]. Generation of a new malignancy is a complex and lengthy process that is observed more frequently in an elderly population[13,15] and over a longer follow-up period after treatment with DNA-damaging agents. Data relating to both of these risk factors will be captured by describing the age of the patient at diagnosis, all cancer treatments received by the patient at specific dates, exposure time to each cancer treatment, and the follow-up period (derived from date of diagnosis till one of the following events, whichever comes first: patient death, end of health plan enrollment, or end of study). Patients who have a history of multiple cancers are often genetically more likely to develop secondary malignancies following diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer. The anticancer treatment history to which each patient has been exposed will also provide the individual history of cancers that have occurred in each patient before diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Additional critical risk factors associated with the incidence of secondary malignancies after diagnosis and treatment of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer that are not collected by MarketScan and thus will not be available in the analysis of the comparator arm include: tobacco use[20-22,30] and exposure to other carcinogenic factors.[27,28,30] The incidence of tobacco use has a significant but also similar impact in both the primary and secondary data cohorts. Independent reports published by the Centers for Disease Control and Prevention and the European Commission indicate similar cancer-related mortality rates in a US versus EU population (141 deaths per 100,000 people versus 138 deaths per 100,000 people, respectively),[35-37] and no data were reported suggesting that smoking-induced incidence of MDS/AML or other SPMs is different between a US versus EU population. Exposure to specific carcinogenic factors that significantly increase the risk for MDS/AML and other SPMs is most likely similarly very low in both the primary and secondary data cohorts.

Alcohol use and previous history of autoimmune diseases are also not collected by MarketScan and will not be available for the analysis of secondary data. These variables are considered as only moderate risk factors for MDS/AML and other SPMs.[24-26,30] In addition, the incidence of these risk factors is most likely similarly distributed between the primary and secondary data cohorts.

Additional variables that are associated with MDS/AML or other SPMs, but are not described as risk factors for these malignancies, include weight,[38] CBC abnormalities,[39] and prior history of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, or neutropenia.[40,41] These variables will be collected in the primary data cohort, as they are also associated or represent adverse reactions to niraparib treatment, but will not be available for the analysis of the secondary data cohort as they are not collected by MarketScan.

Different histotypes of ovarian cancer present distinct cytological aspects and genetic mutations, but none have been directly associated with other malignancies. Information on tumor histotypes will be collected for the patients enrolled in the prospective part of the study to validate that these patients received niraparib treatment per European Union [EU] SmPC indication (platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer). While MarketScan does not provide any information on the specific histology and grade of ovarian, fallopian tube, or primary peritoneal cancer, this is not a limitation for the analysis of the secondary data as histotype itself is not a known risk factor for MDS/AML or other SPMs. It is to note that all histotypes of ovarian, fallopian tube, or primary peritoneal cancer are treated with platinum-based chemotherapy.[42,43]

Further details on the risk factors associated with MDS/AML and SPMs are reported in Section 8.3.

Table 7: Schedule of Events

Study Procedures	Enrollment Day 1	Interval Data Collection Quarterly Follow-up[b]	Interim Report[a]	Interval Data Collection Quarterly Follow-up[b]	End of Study 5-year Follow-up[a]
Informed consent[c]	X				
Inclusion/exclusion criteria	X				
Collection of baseline data	X				
Collection of interval data		X		X	
MDS/AML and SPM interim analysis and report (primary data only)			X		
Collection of secondary data[d]				X	
MDS/AML and SPM final analysis and report (primary and secondary data)					X

Abbreviations: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; Q1 = first quarter; Q3 = third quarter; SPM = second primary malignancy.

[a] Midterm report will be submitted when data from 500 patient-years have been collected. This is expected to be by Q3 2023. The full study report will be submitted at study end (1,000 patient-years of observation and 5-year follow-up, with an average follow-up period of 2.5 years) expected to be by Q1 2027.

[b] Interval data will be collected quarterly from the medical charts obtained during scheduled routine visits of the patient to the clinical site.

[c] The patient will be informed about the study and the consent form at least 24 hours before obtaining consent on Day 1.

[d] Secondary data collection will be performed after interim data is complete to mirror the primary data profile. Analysis of secondary data will be performed at end of study in parallel with the primary data analysis to avoid analysis bias between the 2 cohorts.

8.3. Variables

The scope of the study is to evaluate the incidence of MDS/AML and SPMs in patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer who receive maintenance treatment with niraparib per regulatory guidelines. Information will be collected on the patients' ovarian cancer diagnosis (stage, grade, histotype, and date of diagnosis) and therapy received, including detailed use of niraparib and other PARP inhibitors. To determine the risk of developing MDS/AML and SPMs in this patient population following exposure to niraparib, the following variables were described to be critical or moderate risk factors for MDS/AML or SPM, or simply associated with early stage of MDS/AML development:

- Critical risk factors for MDS/AML and other SPMs
    1. **Age:** It is well established that both MDS and other SPMs are more likely to occur in the elderly. The incidence of MDS is 5 per 100,000 and increases to 21 per 100,000 among persons aged 70 or older.[13,15]

2. **Prior chemotherapy medications and radiation:** Patients who receive a certain type of chemotherapy and radiation treatment for cancers are at increased risk of developing MDS, AML, and/or SPMs.[6,7,16-18] Three groups of chemotherapy agents are known to cause treatment-related MDS/AML, including alkylating agents, topoisomerase II inhibitors, and antimetabolites.[6] In addition, cisplatin chemotherapy has been shown to increase the risk for MDS/AML.[19] Combining these agents with radiation therapy further increases the risk of MDS and AML.
3. **Smoking:** An association between smoking and MDS and/or SPM risk was found to be significant in most studies.[20-22,30] The risk seems to be related to intensity and duration of smoking with a greater risk of MDS being observed among former and current smokers who smoked more than 1 pack of cigarettes per day.[21-23]
4. **Chemicals and other environmental hazards:** Patients exposed to occupational and environmental chemicals are at increased risk of developing MDS. Solvents, including benzene, and agricultural chemicals[20,21,29] are classes of chemicals most often reported as linked with MDS.[27,28,30]

- Moderate risk factors for MDS/AML and other SPMs

5. **Alcohol use:** Daily alcohol consumption may be associated with increased risk of MDS and/or SPM.[30] Data indicated an increased risk for MDS in individuals who consumed ≥10 g/day versus those who consumed <10 g/day.[24]
6. **Patient's history of autoimmune diseases:** Recent studies suggest an increased risk of MDS or AML among patients with autoimmune diseases. Specifically, AML was associated with rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, hemolytic anemia, systemic vasculitis, ulcerative colitis, pernicious anemia, and giant cell arthritis.[25] MDS is associated with hypothyroidism, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, polymyalgia rheumatica, chronic rheumatic heart disease, polyarteritis nodosa, discoid lupus erythematosus, pernicious anemia, and psoriasis.[25,26]

- Factors associated with MDS/AML and SPMs but that are not considered risk factors for these malignancies

7. **Weight:** An association between increased weight and AML risk was found, including overweight (25 to 29.9 kg/m^2) and obese (≥30 kg/m^2) patients.[38]
8. **Prior history of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, and neutropenia:** Anemia, thrombocytopenia, and neutropenia are common cytopenias associated with MDS[40,41] and are prognostic factors for diagnosing MDS.[44]
9. **CBC abnormalities:** Elevated levels of MCV is associated with early stages of MDS[39] and can be evaluated by conducting a CBC with leukocyte differentials.

Not all of these variables are available from MarketScan and will thus not be available for analysis of the comparator arm. The secondary data cohort will include only those patients that: a) were diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer, b) received at least 2 lines of platinum-based chemotherapy (indicating tumor relapse), and c) for which there is evidence that they were followed for at least 6 months after second-line treatment (suggesting platinum sensitivity). For all these patients, it will be possible to collect age at time of diagnosis for the specified indication, other cancer history, and detailed data on patients' exposure to cancer treatments. Altogether, it will be possible to select a

retrospective cohort with an indication very similar to the prospective patient cohort and to collect information on all the most critical risk factors for MDS/AML and other SPMs in this patient population.[6,7]

8.4. Data Sources

TESARO is currently providing niraparib through an EAP to patients in the European Union (EU) including several cohort programs. Patients who participated in this program will be approached by their physicians in Q4 2019 and will be offered the opportunity to participate in this prospective, noninterventional PASS. To reach the requested target of 1,000 patient-years of observation, maximum follow-up of 5 years for those patients who achieve this milestone, and overall 2.5 years of average follow-up, the majority of patients that will be enrolled will have started treatment with niraparib following commercialization of the drug in individual European countries.

Data collection will start at the time of each patient enrollment. For each patient, data will be collected quarterly until 5 years of follow-up from the first dose of niraparib is achieved or until the patient's death, whichever occurs first. The average duration of observation per patient will be recorded to validate that there will be an average of approximately 2.5 years of follow-up per patient.

Termination of data collection will occur once sufficient data are gathered to fulfill the target observation plan for 1,000 patient-years and when data for 5 years of follow-up are collected for patients who reach this milestone, with an overall average follow-up of 2.5 years.

The secondary data source will be derived from the US claims database MarketScan. MarketScan is a longitudinal US database with over 240 million patients with claims records containing inpatient and outpatient data, specialty pharmacy and mail-order prescriptions, laboratory, medical records, and hospital claims data. This database provides high-quality data on anticancer therapies used by US patients and includes a long follow-up period, allowing the capture of the most critical risk factors influencing the incidence of MDS/AML and other SPMs in patients diagnosed with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer. MarketScan was successfully used by Shenolikar et al[7] to evaluate the incidence of MDS and AML in patients diagnosed with ovarian and breast cancer. The study suggested that occurrence of these secondary malignancies is mainly induced by the DNA-damaging anticancer treatments to which patients with ovarian and breast cancer are exposed.[7] The current study provides an opportunity for an independent validation of the results previously described.[7]

By performing the analysis using data entered from 2005-2010, it will be possible to select patients that received the same chemotherapy regimens as the ones received by patients enrolled for collection of primary data but who were not exposed to any PARP inhibitor. In addition, this time frame allows for up to 5 years of follow-up data to be collected for each individual patient.

The use of a US population in the comparator arm for a study performed in a European population is justified by 2 different indirect evidences that suggest similar incidence of MDS/AML and other SPMs between these 2 populations following a diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer:

- Patients in the US and EU receive the same platinum-based chemotherapies, which are considered to be the major risk factors for developing MDS, AML, and SPMs in this patient population.[6,7]
- Age-adjusted incidence rates from the US SEER database[9] indicate that the risk for developing AML or MDS following a diagnosis with ovarian cancer is 3.6 and 4.9 per 100,000 women annually, respectively. For Europe no data are available following a diagnosis with ovarian cancer, but the age adjusted incidence rate of AML or MDS in the general population of women is comparable to the incidence rate observed in the USA (3.7 and 5.4 per 100,000 women annually for AML and MDS, respectively) as reported by the International Agency for Research on Cancer EU database: (EU component of GLOBOCAN)[10]. Note that the GLOBOCAN database is managed in France; however, the data collected is representative of the EU population.

The use of the US FLATIRON database was excluded as it has limited capacity to track the development of secondary MDS/AML and other SPMs in patients diagnosed with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer.

8.5. Study Size

The mean duration of follow-up among 372 ITT patients randomized into the NOVA study niraparib arms was 26.9 months (as the data cutoff of 03/26/2018). This represents approximately 834 patient-years of observation. Seven cases of MDS/AML were reported in the niraparib group in the main portion of this study, which represents an incidence rate of approximately 0.84 per 100 patient-years, with a 95% CI of 0.34 to 1.73 per 100 patient-years. One case of SPM was reported in the niraparib group in the main portion of this study, which represents an incidence rate of approximately 0.12 per 100 patient-years, with a 95% CI of 0.003 to 0.67 per 100 patient-years. Thus, the minimum data required to achieve a quantifiable number of MDS/AML and SPM events is 1,000 patient years with approximately 2.5 years of average follow-up.

To allow for the necessary time required for development of a secondary malignancy, patients will be followed for up to 5 years from treatment initiation. Survival and observational data from Olaparib Study 19 suggest that with maximum 5-years follow- from treatment initiation it is possible to achieve an average of approximately 2.5 years of follow-up per patient,[11] confirming the data collected from the NOVA study which indicate 26.9 months follow-up over a period of 3 years-follow-up from the first dose of the last patient enrolled.

Given the high risk for missing data and for loosing patients to follow-up in a non-interventional study within a real world setting, it is planned to recruit up to 800 patients for a maximum of 5 years of follow-up per patient so that up to 2,000 patient-years of observation data can be reached. This sample size allows adequate patient data to compensate for a large incidence of missing data given that it is expected to observe a significant incidence of MDS/AML and SPMs when 1,000 patient-years are reached over a maximum follow-up period of 5 years and an overall average follow-up of 2.5 years.

Table 8 below provides the 95% CIs for different numbers of observed events of MDS/AML during this follow-up period.

Table 8: Confidence Intervals for Observed Events of MDS/AML for 1,000 Patient-Years

Observed Number of Events	Rate (per 100 patient-years)	Lower 95% Confidence Limit (per 100 patient-years)	Upper 95% Confidence Limit (per 100 patient-years)
5	0.5	0.16	1.2
10	1.0	0.48	1.8
15	1.5	0.84	2.5
20	2.0	1.2	3.1
25	2.5	1.6	3.7

8.6. Data Management

The data are entered by the staff at each clinical site into the data input mask of a web-based, password-protected documentation system (eCRF). The data entered manually for each patient are validated online and stored via a secure internet connection (https) in the central study database in the secure computer center of the contract research organization (see Section 8.8.1 for complete data quality assurance). Every data entry and every data change are automatically provided with a user and date (audit trail). De-identified data collected for each patient will be accessible through a secure web system by TESARO in line with local regulations.

Missing data will be identified via a standard listing in the clinical database called the Missing Page Report. The study database is designed to capture forms and visits per the defined schedule in the protocol. If a visit or form is available for entry in the database but not completed by the site, it will be identified as missing in the Missing Page Report.

Once all edit/validation checks applicable to the study protocol are identified and approved by the clinical study team, they are programmed to help identify any missing data and data discrepancies. Queries are placed on the discrepant data within the electronic data capture (EDC) system for the site to respond and make any necessary corrections to the data. All derivation and validation procedures are fully tested and documented in User Acceptance Testing (UAT) scripts. Details regarding the edit checks are listed in the Data Validation Specifications, an appendix of the Data Management Plan.

In addition, a clinical monitoring plan has been established to include scheduled monitoring calls every 6 months with each site and yearly in-person visits with each site. Any missing data will be addressed during these interactions with the sites. The plan also includes the option of having additional ad hoc calls with sites where data collection presents persistent problems.

A full midterm report will be prepared and distributed to the competent local agencies where the study is performed and to the EMA. All statistical analyses will be performed on variables listed in Section 8.3 as well as additional adverse reactions that will be identified during the study. All adverse reactions will be reported both in the study analysis and in the pharmacovigilance database (see also Section 10). Analysis will be performed using SAS statistical software v9.4 or later, unless otherwise noted.

8.7. Data Analysis

Details of the statistical analyses presented below will be provided in the study's statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol.

The analysis population for all analyses is the safety population, defined as all patients who receive any amount of niraparib (at least 1 dose). All analyses will be performed using SAS statistical software v9.4 or later and will include summary statistics, including the number and percentage for categorical variables and the number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Further details will be provided in the SAP.

Analyses will be descriptive; no hypothesis will be tested. Distributions of patient and tumor characteristics will be summarized. Incidence rates of MDS/AML and other SPMs and their respective 95% CIs per 100 person-time units will be estimated. For the primary data, a sensitivity analysis will be performed on the group of patients who have never received PARP inhibitor treatments prior to study enrollment. In addition, a descriptive comparison on baseline characteristics of those patients who did not receive/initiate niraparib after initial enrollment versus those who did receive the treatment will be performed.

A descriptive analysis will also be performed on the secondary data collected retrospectively from patients who were not treated with niraparib. The incidence rates of MDS/AML and other SPMs and their respective 95% CIs per 100 person-time units will be reported.

The primary analysis on both primary and secondary cohorts will be performed using all events of either MDS/AML or other SPMs without considering the risk factors associated with these events. In addition, given the descriptive nature of this analysis, no formal statistical testing will be conducted between the primary and secondary data cohorts.

This initial analysis will then be followed by an evaluation of how MDS/AML and SPM events detected either in the primary or secondary data cohort are distributed with respect to the variables collected for each group. This analysis will be more detailed in the primary data cohort, due to the possibility of collecting a broader number of variables associated with patients diagnosed with platinum-sensitive, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.

For the primary data cohort, standardized incidence of MDS/AML and SPMs will be performed across various critical and moderate risk factors for MDS/AML and SPMs, such as age, anticancer chemo- and radio-therapy received, history of other cancers, family history of cancers, presence of autoimmune disorders, use of alcohol and/or tobacco, exposure to certain chemicals and heavy metals, other non-DNA damaging anti-cancer treatments, and use of other PARP inhibitors (for a complete explanation of variables analyzed during the study, see Section 8.3). For the secondary data cohort, this analysis will focus on the critical factors impacting MDS/AML and SPMs in this patient population, such as age at diagnosis, anticancer chemo- and radiotherapy received, follow-up period, and history of other cancers.

Thus, while not all variables will be available for both the primary data and secondary data cohorts, this discrepancy will not affect the analysis since the most important variables affecting MDS/AML and SPM events in this patient population, such as age, anticancer chemo- and radiotherapy, follow-up time, and history of other cancers will be collected for both cohorts. In addition, no statistical comparison will be performed between the 2 cohorts.

8.8. Quality Control

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 8.8.8 for more details regarding the audit process.

8.8.1. Data Quality Assurance

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and standard operating procedures for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator or designee.

8.8.2. Access to Source Data/Documents

An electronic data capture system to manage data collection will be utilized during this study. The electronic data capture system is a software tool designed to ensure quality assurance and facilitate data capture during clinical studies.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail of all data changes will be maintained. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Sponsor and the Investigators will follow the EU General Data Protection Regulation that replaces the Data Protection Directive 95/46/EC and that was designed to harmonize data privacy laws across Europe, to protect and empower all EU citizens' data privacy, and to reshape the way organizations across the region approach data privacy.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the Institutional Review Board (IRB) to have direct access to all documents pertaining to the study.

8.8.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. According to International Conference on Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a

marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

8.8.4. Good Clinical Practice

This study will be conducted in accordance with ICH GCP and the Declaration of Helsinki (version 2008), as well as with the guideline on Good Pharmacovigilance Practices – Module VIII (Rev 3) EMA/813938/2011 Rev 3.[45] The clinical study will also be carried out in keeping with national and local regulatory requirement(s).

8.8.5. Informed Consent

Before each patient is enrolled in this safety study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, in such a manner that the patient is aware of the potential risks and inconveniences. The patient should be informed that he/she is free to withdraw from the study at any time. The patient will receive all information that is required by regulatory authorities and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB/Independent Ethics Committee (IEC)-approved informed consent form (ICF), as required by each country's regulatory agency, prior to the start of the study.

If an ICF is required, the ICF must be signed and dated; one copy will be given to the patient, and the Investigator will retain 1 copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all patients subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

8.8.6. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the responsible IRB/IEC/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

8.8.7. Study Monitoring

A monitor commissioned by the Sponsor can randomly check the data collection by matching the data stored in the eCRF with the medical records. Patients are informed about this aspect before participation in this noninterventional study and asked for their consent. Only patients who have given their informed consent can be observed in the noninterventional study.

All study materials will be returned to the Sponsor after the study has been completed.

8.8.8. Audits and Inspections

Responsible IRB/IEC/Competent Authorities and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

8.8.9. Ethical Considerations

The study will be conducted in accordance with the ethical principles founded in the Declaration of Helsinki (version 2008). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

8.9. Limitations of the Research Methods

This is an observational, noninterventional prospective study aimed at collecting specific AEs that may be associated with niraparib. The study does not address efficacy of the drug. In addition, no comparisons of the incidence of events of interest are planned. Lack of randomization does not allow establishing causality between niraparib and MDS/AML and SPM incidence.

Inclusion of a retrospective comparator arm of patients with the indication to receive niraparib treatment that will not be treated with niraparib is limited by the low number of these potential cases and scientifically confounding, and therefore not feasible. Because eligible patients would not be denied a treatment that is commercially available, patients who do not receive treatment would be systematically different, as there is quite probably some characteristic related to the patient's health status or medical history that resulted in the physician not prescribing a PARP inhibitor for that patient. Hence, selection bias is likely to confound any analysis that is conducted based on a comparator group of patients not treated with a PARP inhibitor that is recruited in parallel. In addition, given the availability of different PARP inhibitors for patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer, it is expected that very few patients would not receive at least one of such treatments, thus further limiting the possibility of achieving a significant comparator cohort.

To compensate for the lack of a parallel comparator arm of patients with the indication for treatment with niraparib, but who did not receive such treatment, the study will include the analysis of historical data of patients presenting the indication for treatment with niraparib, but who did not receive such treatment, or treatment with any other PARP inhibitor, as it was not widely available.

To increase the chances of detecting events of MDS/AML or SPM, attempts will be made to follow-up with patients for up to 5 years from first dose exposure to niraparib and accrue data for an average of 2.5 years follow-up. However, due to the poor prognosis of the disease, it is expected that such an observational time frame will be applicable to less than 30% of patients enrolled, as per historical data reporting overall survival from diagnosis of high-grade, advanced stage ovarian cancer. In addition, while in a clinical trial setting it was possible to achieve an average follow-up of 2.5 years with approximately 400 patients receiving

niraparib, in the real world setting the risk for losing the patients to follow-up is much greater. It is expected that up to 17 events will be observed for MDS/AML and up to 3 events for SPM at up to 2,000 patient-years of observation that can be achieved through this extended research design, which is twice as much the minimum data collection required to observe a quantifiable number of MDS/AML and other SPM, which is 1,000 patient years for up to 5-years follow-up and 2.5 years of average follow up.

The treating physician may not be able to collect exposure to environmental factors, such as heavy metals and other polluters known to be associated with various malignancies. Finally, not all risk factors that could be associated with the diverse SPMs are known and/or can be accurately captured by this study. Collection of risk factors for MDS/AML and other SPMs will be more limited for the secondary data than for the primary data because some variables are not collected by MarketScan and will thus not be available. This limitation will not impact the primary analysis considering the occurrence of all MDS/AML and SPM events irrespective of the associated risk factors. In addition, the most significant variables affecting MDS/AML and SPMs in this patient population will be available for both cohorts as discussed in Sections 3.6 and 8.3. In fact, MarketScan was successfully used by Shenolikar et al[7] for a similar analysis, and the current study provides an opportunity to independently validate these published data.

The current study also aims at including patients who have been exposed to niraparib before the time of enrollment. Some of these patients may have terminated niraparib treatment but will still be considered eligible for the study. The observation period for incidence of MDS/AML or SPMs in these patients will include the time from the beginning of niraparib treatment, thus providing a time advantage in assessing safety of niraparib treatment. However, inclusion of this patient population may introduce a potential bias of patient selection by leaving aside those who have received niraparib and died before the study start. The incidence of this bias should be minimal as this patient population includes patients who participate in the EAP for whom it is known that no mortality has occurred. Thus, the potential bias is accepted to provide patients a safety assessment of niraparib treatment in a shorter time.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

The study will be conducted in accordance with the ethical principles founded in the Declaration of Helsinki (version 2008). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained.

Discontinuation from the study

Specific reasons for discontinuing from the study include the following:

- Withdrawal of consent by the patient, who is at any time free to discontinue participation in the study, without prejudice to further treatment
- Loss to follow-up
- Death from any cause
- Sponsor decision to terminate study

If a patient is thought to be lost to follow-up, or discontinues the study, attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are thought to be lost to follow-up, at least 3 documented attempts, including 1 attempt via certified mail, should be made to contact the patient before the patient is deemed lost to follow-up.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Definitions

10.1.1. Adverse Events

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including clinically significant laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time after the signing of the informed consent, including baseline or washout periods, even if no study treatment has been administered. (See Section 10.3 for information about AE collecting and reporting.)

10.1.2. Serious Adverse Events

An SAE is any untoward medical occurrence, that, at any dose

- Results in death
- Is life-threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization* or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event**

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be captured in the medical history section in the eCRF. Complications experienced during these hospitalizations must be reported as AEs (or SAEs, if hospitalization is prolonged due to the AE).

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered SAEs; an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug. (See Section 10.4 for information about SAE reporting.)

10.1.3. Treatment-Emergent Adverse Events

A TEAE is any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.

10.1.4. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for niraparib are the following:

- MDS and AML
- Second primary cancers (new malignancies [other than MDS or AML])
- Pneumonitis
- Embryo-fetal toxicity

10.1.5. Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- **Abuse:** The persistent or sporadic, intentional excessive use of the study treatment, which is accompanied by harmful physical or psychological effects.
- **Misuse:** Medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** Any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** A deliberate or accidental administration of study treatment to a study patient at a dose greater than that assigned to the patient per the study protocol and under the direction of the Investigator. If an overdose occurs, the Investigator and the Sponsor should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose should be documented on the applicable sections within the eCRF. An overdose (including an AE or SAE resulting from the overdose, if any) will be reported as described in Section 10.4.4.
- **Accidental/occupational exposure:** The unintentional exposure to a study treatment as a result of one's professional or nonprofessional occupation, or accidental exposure to a nonprofessional to whom exposure was not intended (ie, study product given to wrong patient).

10.2. Assessment of Adverse Events

10.2.1. Severity Assessment

All AEs will be assessed by the Investigator for severity* according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03, 14 June 2010, National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity Grades 1 through 5 provide unique clinical descriptions of the severity of each AE. The CTCAE v4.03 is available on the NCI/NIH website.

*Note that there is a distinction between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 10.1.2. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

10.2.2. Relationship to Study Data Collection

The Investigator must provide a causality assessment regarding the relationship of the event with the niraparib treatment prescribed to the patient for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- Related: A causal relationship between the medicinal product and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE. Positive rechallenge/dechallenge is supportive.
- Not related: A causal relationship between the medicinal product and AE is not a reasonable possibility. There is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

10.3. Collecting and Recording Adverse Events

AEs may be volunteered spontaneously by the study patient or discovered by the study staff during physical examinations or by asking an open, nonleading question such as, “How have you been feeling since your last study visit?” The Investigator will document the nature of the AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All SAEs will be collected from the signing of the ICF for this study up to the end of study or the patient’s death for any cause and recorded in the eCRF and sent to TESARO Pharmacovigilance as described in Section 10.4.

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, electrocardiogram, or reported by patient), and that are not already known to be related to the presence and/or progression of the disease, will be collected and recorded in the

eCRF for each patient from the signing of the ICF for this study until the end of study or patient's death for any cause, whichever comes first. SAEs will be reported to TESARO Pharmacovigilance as described in Section 10.4. AEs known to be associated with the presence and standard treatment of high-grade serous ovarian, fallopian tube, and primary peritoneal cancer are listed in Table 9. These should be recorded in the eCRF but should not be reported.

Table 9: Common Disease-Related Events That Are Expected in Ovarian Cancer Population

MedDRA Preferred Term	Frequency in the Placebo Arm of NOVA (N = 179), n (%)
Any TEAE	**171 (95.5)**
Nausea	63 (35.2)
Fatigue	58 (32.4)
Constipation	36 (20.1)
Vomiting	29 (16.2)
Headache	17 (9.5)
Decreased appetite	26 (14.5)
Insomnia	13 (7.3)
Abdominal pain	53 (29.6)
Dyspnoea	15 (8.4)
Diarrhoea	37 (20.7)
Dizziness	13 (7.3)
Asthenia	16 (8.9)
Back pain	21 (11.7)
Arthralgia	22 (12.3)
Dyspepsia	17 (9.5)
Nasopharyngitis	13 (7.3)
Urinary tract infection	11 (6.1)
Dysgeusia	7 (3.9)
Myalgia	18 (10.1)
Abdominal distension	22 (12.3)
In addition to the signs and symptoms associated with progression of the underlying ovarian cancer do not need to be reported as TEAEs	

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.

MDS/AML and SPMs are AESIs that are being analyzed within the scope of this study, and the incidence of these events will be fully described in the eCRF form and analyzed per the study objectives and design. Other AESIs, such as pneumonitis and embryo-fetal toxicities, will have to be recorded and reported following the same requirements as for SAEs.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the treatment period. Pre-existing conditions will be recorded as medical history in the eCRF and on the SAE Report Form.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal) and should not be reported. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 10.4.

10.3.1. Follow-Up of Adverse Events

All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

If an Investigator becomes aware of an SAE after the specified follow-up period and considers the SAE related to the study drug, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs described in Section 10.4.

10.4. Reporting

The Investigator must report all SAEs and all follow-up information to the Sponsor through the eCRF within 24 hours of becoming aware of the initial event or follow-up information. AEs that are not commonly known to be associated with a high-grade serous ovarian, fallopian tube, or primary peritoneal cancer must be reported to the Sponsor within 90 days through the eCRF.

It is the responsibility of the Investigator to review source documentation and describe pertinent information on the eCRF. If supporting documentation is requested (eg, hospital reports, consultant reports, death certificates, autopsy reports), the Investigator should highlight all relevant and pertinent information within such documents, ensure that any patient's personal identifiers (including medical record number) are removed, and submit the documents to the Sponsor. The Sponsor (or designee) will return a confirmation of receipt within 1 business day. If no acknowledgment of receipt is received, the Investigator or designee should resubmit the eCRF or query the sponsor to confirm the reporting route.

After receipt of the initial eCRF, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information. The Investigator must promptly respond to queries from the Sponsor.

Collection of secondary data will not require reporting of any AEs or SAEs as it will be assumed that this was done during the treatment of the patient when these events occurred.

All AEs and SAEs collected through primary data collection as part of the study design will be reported annually through to interim safety analyses as well as in the final safety report to the competent authority of each country where the study is being conducted.

10.4.1. Submission and Distribution of Serious Adverse Event Reports

Per regulatory requirements, if an event is assessed by the Sponsor (TESARO, Inc.) as a suspected unexpected serious adverse reaction (SUSAR), it is the responsibility of the Sponsor, and not of the Investigator, to submit the SUSAR to Regulatory Authorities according to applicable regulations.

In addition, the SUSAR will be distributed to the Investigators/sites, utilizing a Council for International Organizations of Medical Sciences Report Form or the MedWatch 3500A form.

10.4.2. Adverse Events of Special Interest

AESIs should be collected and reported as follows:

- MDS and AML, along with other second cancers, are collected as part of the study design as described in Section 8. Evaluation of the incidence of these AESIs constitutes the primary and second objectives of the current study.
- Pneumonitis should be reported to the Sponsor through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first).
- Embryo-fetal toxicity should be reported as outlined in Section 10.4.3.

10.4.3. Pregnancy

The Investigator must report all pregnancies and the outcomes to the Sponsor. The Sponsor has the responsibility to monitor the outcome of all pregnancies reported during the clinical study.

The details of the pregnancy or other associated event (eg, elective abortion) should be captured in the eCRF as appropriate and reported to the Sponsor through the eCRF. Pregnancy is not an AE and therefore does not need to be reported as an AE in the eCRF unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. The Investigator must follow up all pregnancies, document the course and the outcome, and report this information to the Sponsor within 24 hours of becoming aware—even if the patient was withdrawn from the study or the study has finished.

An elective abortion without complications should not be regarded as an AE; however, it should be reported as the outcome to the pregnancy eCRF page. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the pregnancy outcome eCRF page and as an AE in the eCRF. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

10.4.4. Special Situations

All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported through the eCRF to the Sponsor regardless of whether an AE or SAE has occurred. The form should be submitted as soon as possible, and if there is no AE or SAE, it should be indicated that “no AE has occurred.” If the abuse, misuse, medication error, overdose, or accidental/occupational exposure is associated with an SAE, an SAE must be submitted to the Sponsor within 24 hours of awareness through the eCRF.

10.4.5. Reporting Contact Information

Any queries and/or follow-up communication regarding safety reporting should be addressed to:

Email: tesaropv@ubc.com

Fax: 1-866-433-3038

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The noninterventional PASS will be registered in the EU PASS register via the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website (www.encepp.eu) before the study commences.

The study protocol will be uploaded after finalization and prior to the start of data collection (EMA/613603/2012 EU PAS Register Guide).

An annual progress report (including status of patients' enrollment, eventual protocol deviations, and/or other problems encountered) and a midterm interim report of data analysis will be submitted to the competent authority of each country where the study is being conducted. A final study report will be submitted to the EMA and to the competent authority of each country where the study is being conducted.

The interim and final report will include descriptive statistical analysis, performed as described in Section 8.7, of variables collected as described in Section 8.3 and other eventual adverse reactions collected during the study and reported in the pharmacovigilance database.

TESARO retains the right to publish the results from this study.

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ANNEX 1. COUNTRIES AND SITES PARTICIPATING IN THE STUDY

The study will be performed in the following countries of the European Union: Germany, the Netherlands, France, Italy, and Spain. In all of these countries, niraparib is expected to be approved for reimbursement by the time patient enrollment will begin (Table 10). The sites will be selected for inclusion in the study based on the following parameters:

1) Sites using niraparib per summary of product characteristics indication
2) Number of patients visiting the site with the correct indication for use of niraparib as maintenance treatment
3) Sites participating in the Extended Access Program
4) Sites with an organized and compliant infrastructure for global clinical research

Table 10: Countries and Dates of Reimbursement Approval for ZEJULA®

Country	Reimbursement Approval	Number of Expected Sites
Germany	Q1 2018	30
The Netherlands	Q2 2018	20
France	Q1 2019	20
Italy	Q4 2018	25
Spain	Q1 2019	15

Abbreviations: Q1 = first quarter; Q2 = second quarter; Q4 = fourth quarter.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer "N/A" (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)

Study reference number:

3000-04-001

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
	☒	☐	☐	5
	☒	☐	☐	5 and 8
	☐	☐	☒	5 and 8

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.1 Start of data collection[1]	☒	☐	☐	5 and 8
1.1.2 End of data collection[2]	☒	☐	☐	5 and 8
1.1.3 Study progress report(s)	☒	☐	☐	5 and 8
1.1.4 Interim progress report(s)				
1.1.5 Registration in the EU PAS register				
1.1.6 Final report of study results.				

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	3.2 and 7
2.1.2 The objective(s) of the study?	☒	☐	☐	3.3 and 7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	3.5 and 8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is not a hypothesis-driven study. This type of safety data collection was not done before

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	3.4 and 8
.3.2 Does the protocol specify whether the study is based on primary, second or combined data collection?	☒	☐	☐	3.4 and 8.2
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	3.8 and 8.5

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	3.5, 3.7, and 8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	5.0 and 8.2
4.2.2 Age and sex?	☒	☐	☐	3.5 and 8.2
4.2.3 Country of origin?	☒	☐	☐	3.5 and 8.2
4.2.4 Disease/indication?	☒	☐	☐	3.5 and 8.2
4.2.5 Duration of follow-up?	☒	☐	☐	3.5 and 8.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	3.5, 3.7, and 8.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	3.7 and 8.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	3.7, 3.8, and 8.2
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	3.7, 3.8, and 8.2

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and second (if applicable) outcome(s) to be investigated?	☒	☐	☐	3.9 and 8.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	3.6 and 8.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	8.2 and 8.3
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	8.9
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	8.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☐	8.2, 8.3, and 8.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	3.7, 8.2, 8.3, and 8.9

Comments:

The rationale for study covariates is justified from published literature

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	3.7 and 8.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	3.6, 8.2, and 8.3
9.1.3 Covariates?	☒	☐	☐	3.6, 8.2, and 8.3
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	3.7 and 8.4
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	3.6, 8.2, and 8.3
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	3.6, 8.2, and 8.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.6

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	3.9 and 8.7
10.2 Are descriptive analyses included?	☒	☐	☐	3.9 and 8.7
10.3 Are stratified analyses included?	☐	☒	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	3.9, 8.7, and 8.9
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	8.6
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	3.8 and 8.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6 and 8.8
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	8.9
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.1

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8.8
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	8.8
13.3 Have data protection requirements been described?	☒	☐	☐	8.8

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: Dr. Dirk Schneider, MD

Date: 22.05.2019

Signature: _____