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 epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)**
Protocol version identifier	**3000-04-001 (GSK 213705) Version 8**
Date of last version	**June, 08th, 2021**
Sponsor	**Tesaro (GlaxoSmithKline company)** 1250 South Collegeville Road Collegeville, PA 19126
EU PAS register number	**EUPAS29407**
Active substance	**Niraparib**
Medicinal product	**ZEJULA®, 100 mg hard capsules**
Product reference	**Not applicable**
Procedure number	**EMEA/H/C/004249/MEA/002**
Marketing authorisation holder(s)	**GlaxoSmithKline (Ireland) Limited** **12 Riverwalk** **Citywest Business Campus** **Dublin 24** **Ireland**
Joint PASS	**Not applicable**
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:** **- epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy** **or**

	- platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial to platinum-based chemotherapy **To whom niraparib is administered in the routine clinical setting.** **The objectives are as follows:** • **Primary:** To estimate the incidence rate of MDS/AML, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients: 1) with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy or 2) with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy, treated with niraparib • **Secondary:** To estimate the incidence rate of SPMs, and the distribution of these events across different risk factors for SPMs, in the same cohorts • **Exploratory:** CCI [redacted] CCI [redacted]
Country(ies) of study	**European countries with approved use of ZEJULA®**
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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 epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib) (3000-04-001; GSK 213705)

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 Pharmacovigilance Practice.

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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(GSK 213705) 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

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Table 1 Table of Contents

LIST OF TABLES

2. LIST OF MAIN ABBREVIATIONS USED IN THE STUDY PROTOCOL

Table 2 Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADR	adverse drug reaction
AE	adverse event
AML	acute myeloid leukemia
BICR	Blinded independent central review
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
GVP	Good Pharmacovigilance Practices
HA	Health authority
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
MAA	Marketing Authorisation Application
MCV	mean corpuscular volume

Abbreviation or Specialist Term	Explanation
MDS	myelodysplastic syndrome
NCI	National Cancer Institute
NIH	National Institutes of Health
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
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	risk management plan
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
TEAE	treatment-emergent adverse event
UAT	User Acceptance Testing
US	United States

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Lynparza
MarketScan
Rubraca
SAS

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 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 for niraparib 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.

On 17 September 2020 GSK received European Commission approval of Zejula (niraparib) as first-line monotherapy maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and other second primary malignancies (SPMs) have been observed in the context of PARP inhibitor treatments. However, 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. The mechanism of action of PARP inhibition suggests that there may be a risk of MDS/AML and SPM 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.

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, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients with:
  - advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR

- 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, and the distribution of these events across different risk factors for SPMs, in the same cohorts.
- **Exploratory Objective**: CCI [redacted] CCI

3.4. Study Design

This PASS will be conducted as a prospective (referred as 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.

To generate baseline incidence rates of MDS/AML and SPMs, analyses using a retrospective, secondary data will be performed including patients who have similar clinical profiles to the patients in the primary cohort with respect to ovarian cancer diagnosis, age, anticancer chemo- and radiotherapy received and follow up period. These patients would have been eligible for treatment with niraparib but did not receive such treatment. The retrospective analysis will be performed using data from a European healthcare database.

3.5. Population

Cohort for primary data collection: Adult patients diagnosed with:

- advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy or,
- 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

Cohort for secondary data collection: Adult patients with a similar clinical profile as the patients in the primary analysis cohort who were not treated with niraparib.

3.6. Data Collected

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. The baseline data will include patient demographic characteristics, tumor characteristics, medical and treatment history. During the follow-up period, data will be collected on treatment with chemotherapeutic agents, adverse events and study outcomes (MDS, AML and SPM). **Secondary data cohort:** Patients will be followed from the last date of the first-line or second-line chemotherapy. Baseline information that will be collected prior to the index date will include patient demographic characteristics, tumor characteristics,

medical and treatment history. During the follow-up period data on the treatment with chemotherapy agents and study outcomes will be collected.

3.7. Data Sources

This primary cohort will prospectively collect data from patients who have received or are receiving niraparib through the European Expanded Access Program (EAP), in a clinical trial, and patients treated post-approval in routine clinical practice. Primary data will be sourced from patients' electronic health records. The participating physicians will document the measures taken in the web-based documentation sheet (eCRF) of this noninterventional study on a quarterly basis. The secondary data will be derived from either an electronic medical record (non-claims) European healthcare database. The database will be selected based on the population coverage at a national level to maximize the representativeness of the study results to the ovarian cancer patient population, availability of patient longitudinal data with a follow-up period that will be similar to the primary data collection cohort and the availability of data to define the key study variables. A feasibility assessment will be conducted select the most appropriate database for the analysis. The extraction of the analysis database will be based on the coding system used in the database.

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 of 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.

The sample size was not revised following the addition to the study population patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. It is anticipated that the exposure to Niraparib will be similar in the two populations based on the data from the NOVA and PRIMA clinical studies. Given the high risk for missing data and for losing patients to follow-up in a non-interventional study in 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 of 2.5 years.

3.9. Data Analysis

The study 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.

3.10. Milestones

Detailed milestones are listed Section 5 below.

4. TABLE OF AMENDMENTS AND UPDATES

Table 3 Table of Revisions

Number	Date	Section of the study protocol	Amendment or update	Reason
1	7 December 2020	Title	Platinum sensitive relapsed, high grade serous has been removed from the title	The study population has been updated to include patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy due to the EMA approval for use of niraparib as first line maintenance therapy. The title has been revised to include the new study population
2	7 December 2020	Pass Information	• Revised the contact Details for the Market Authorisation Holder, author and names for the sponsor signature page • Research question and objectives have been updated to include patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy due to the EMA approval for use of niraparib as first line maintenance therapy.	• Revised to most current contact details for GSK following transition from Legacy Tesaro • To include the new indication for niraparib approved by the EMA
3	7 December 2020	Section 3.1-3.10	• Most of the text that was included in the abstract was also included in the main protocol. Therefore, the text that was repeated in the main	• The abstract was revised to streamline the protocol to allow sites to easily follow the protocols to

Number	Date	Section of the study protocol	Amendment or update	Reason
			protocol has been deleted in the abstract • The study population has also been updated to include patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy • The data source for the secondary data cohort has been revised to a non-claims EU healthcare database	improve site adherence to protocol procedures • To include the new indication for niraparib approved by the EMA • The secondary data source has been revised to identify a data source that will enable creation of a more comparable cohort to the primary data cohort, due to availability of more granular details to define the characteristics of the patient population, and to allow for a similar follow up period to measure study outcomes as the average follow-up period in MarketScan approximately 2 years.
4	7 December 2020	Section 4	• The list of amendments to the protocol	• Included the list of amendments implemented in the protocol
5	7 December 2020	Section 5	• Some of the text that was included in primary data collection section was also included in the other sections of the protocol (study setting and sample size calculation). This text has now been deleted. • The text has been revised for the secondary data collection due to	• The protocol was revised to be more streamlined to allow sites to easily follow the protocols to improve on adherence to protocol procedures.

Number	Date	Section of the study protocol	Amendment or update	Reason
			changes proposed data secondary data source and the study period • The end of enrollment period has been extended to Q4 2021	• The proposed secondary data source has been revised to include a data source that will identify a more comparable cohort to the primary data cohort and to allow for a similar follow up period to measure study outcomes • This is account for the impact of COVID on the recruitment
6	7 December 2020	Section 6	• Updated background information on the occurrence of study outcomes using more recent data and added background information on the new population that will be included in the study i.e. patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy	• To include the new indication for niraparib approved by the EMA
7	7 December 2020	Section 7	• Updated the study objectives to include patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy	• To include the new indication for niraparib approved by the EMA
8	7 December 2020	Section 8.1-Section 8.8	• The text in the methods section has been revised. This includes removing text that was repeated in multiple sections or moving texts to more relevant sections. Details for	The revisions were implemented to streamline the protocol to allow sites to easily follow the protocols to

Number	Date	Section of the study protocol	Amendment or update	Reason
			the revisions in each section are provided below.	improve on adherence to study procedures
		Section 8.2.1	• Inclusion of patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in the selection criteria • Inclusion criteria providing clarification that patients who are part of a clinical trial arm will be excluded if this is GSK trial	• To include the new indication for niraparib approved by the EMA • To avoid duplication in the reporting of adverse events
		Section 8.2.2	• The selection criteria for the second data collection has also been updated	• To include the new indication for niraparib approved by the EMA and to ensure the study population is similar to the primary data collection cohort
		Section 8.2.3	• Weight to be collected within 3 months of study enrolment • To collect data on Homologous Recombination Deficiency (HRD) status • Collect the latest complete blood count data prior to niraparib initiation	• To ensure that the weight reflects that weight the time of niraparib initiation • The HRD status data will be used to characterize the patient population • This is to ensure the baseline data reflects the status of the patient at the time of niraparib initiation
		Section 8.3.2	• Replacing the secondary data source from MarketScan database to either	• The secondary data source has been

Number	Date	Section of the study protocol	Amendment or update	Reason
			a non-claims European healthcare database	revised to identify a data source that will enable creation of a more comparable cohort to the primary data cohort, due to availability of more granular details to define the characteristics of the patient population, and to allow for a similar follow up period to measure study outcomes as the average follow-up period in MarketScan approximately 2 years.
		Section 8.5	• The data management for the secondary data has been updated	• This is to provide more details on how the secondary data will be managed
		Section 8.6	• Data analysis to include stratification of data analysis by the two ovarian cancer populations based on the use of niraparib either as first-line or second-line maintenance therapy	• This is due to the inclusion of the study population with the new indication for niraparib approved by the EMA
		Section 8.7.3	• Updating the duration of archiving study documents from 2 years to 10 years after finalization of the study report	• Updated to align with the GSK archiving processes
		Section 8.7.7	• Study monitoring included additional information on how the study monitoring will be implemented and considering the COVID-19 pandemic	• To ensure compliance with study procedures
		Section 8.8	• Limitation of the research methods: deleted the limitations associated	• This is due to changes in the

Number	Date	Section of the study protocol	Amendment or update	Reason
			with the MarketScan databases and updated with information on the new proposed secondary data sources	proposed data source for the secondary data collection
		Section 10	• Management and reporting of adverse events/adverse reactions: Hospitalizations for planned elective treatment for pre-existing conditions will not be considered a severe adverse event, Deleted pneumonitis as an AE of special interest and will now be reported as an AE, , updated the sponsor contact details from Tesaro to GSK and included the COVID-19 infection assessment form	• To align with the GSK pharmacovigilance processes
9	7 December 2020	Annex 1	• Deleted	• This information is already included in the protocol Section 8.2.1

5. MILESTONES

Primary data collection: Data collection will start at the time of enrolment of the first patient into the study in fourth quarter (Q4) 2019. Data collection will continue until fulfillment of the target observation period of at least 1,000 patient-years and maximum 5 years of follow-up for those patients who achieve this survival milestone, with an expected average patient follow-up of 2.5 years. This is expected to be achieved by the third quarter (Q3) of 2026.

Secondary data collection: The secondary database will be selected such that the study period is to the primary data collection period i.e., Q4 2019 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 the first quarter (Q1) of 2027.

Details of the key study milestones are provided in Table 4 below.

Table 4 Detailed Study Milestones

Milestone	Planned Date
Start of data collection (primary data)	Q4 2019
End of enrollment	Q3/4 2021
Interim report (primary data)	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; Q2 = second 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 a 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 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 (i.e. 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% 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 (HR) 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; HR=hazard ratio; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NE = not estimable; PFS = progression-free survival; US=United States.
Note: 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 incidence of Grade 3 or 4 TEAEs (74% versus 23%), 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 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.

The efficacy results in the PRIMA (PR-30-5017-C) study demonstrated a statistically significant and clinically meaningful benefit of niraparib treatment in the overall population of patients with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) who had responded to front-line platinum-based therapy. Median progression free survival (PFS) was significantly longer in subjects who received niraparib compared to those who received placebo, with corresponding favourable hazard ratio (HR). The PRIMA study met the primary endpoint in subjects with HRD tumours; median PFS as determined by Blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1) was 21.9 months in the niraparib arm and 10.4 months in the placebo arm (HR 0.43; [95% CI: 0.310,0.588]; p<0.0001). For the overall population, median PFS for subjects randomised to niraparib was 13.8 months versus 8.2 months on placebo (HR 0.62 [95% CI: 0.50 to 0.76]; p<0.0001). A reduction of risk to progression of disease or death during study was demonstrated for subjects in the niraparib arm compared to subjects in placebo arm, for subjects with homologous recombination proficient tumors (HR 0.68 [95% CI: 0.492,0.944]; p=0.0203) as well. Safety outcomes were consistent with those seen in the NOVA study, specifically thrombocytopenia of any grade and grade≥3. Initiation of the individualised starting dose of niraparib in the PRIMA study (i.e. initial starting dose of 200 mg or 300 mg based on the subject's baseline body weight and/or baseline platelet count) decreased the incidence of myelosuppression events.

On 17 Sep 2020 GSK received European Commission approval of Zejula (niraparib) as first-line monotherapy maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

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 of MDS 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

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received niraparib monotherapy in clinical trials. In 1,785 patients treated with niraparib in clinical trials, MDS/AML occurred in 15 patients (0.8%). Of these 15 patients, 1 patient was treated in PRIMA, 11 patients in NOVA, and 3 patients in QUADRA. The duration of niraparib treatment in patients prior to developing MDS/AML varied from 1 month to > 4 years. The cases were typical of secondary, cancer therapy related MDS/AML. All patients had received platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia. Additional cases of MDS/AML have been documented in patients treated with Zejula in combination studies and in post-marketing reports. (according to Niraparib General Datasheet Version 2.0 Version Date: 14 SEP 2020; also in USPI 2020)
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 1.08% (30 out of 2783 patients).[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 1.7% (20 out of 1146) of patients with ovarian cancer treated with rucaparib. Patients who experienced MDS/AML after treatment with rucaparib had all received prior treatment with platinum agents 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 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 US SEER database collected between 1975 and 2008.[6] In this study, among 23,180 adult patients with ovarian cancer who received initial chemotherapy, 72 cases of AML occurred. 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. For the SIRs, 2-sided Poisson-based 95% 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 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 a study 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

In 1357 patients treated with niraparib in ovarian cancer monotherapy clinical trials (NOVA, PRIMA, QUADRA), SPM other than MDS/AML occurred in 17 patients (1.25%). (Niraparib Investigator Brochure v.11, 17 June 2020). The types of SPMs reported were undifferentiated sarcoma, intestinal carcinoma, lymphocytic leukemia, basal cell carcinoma, squamous cell carcinoma of skin, invasive ductal breast carcinoma, intraductal proliferative breast carcinoma, breast cancer, thyroid cancer, papillary thyroid cancer (RMP v.5 26 Aug 2020). There were additional cases of SPM documented in patients treated with Zejula in combination studies and in post-marketing reports.

7. 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, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients with:
  - Advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
  - Platinum-sensitive, relapse, 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, and the distribution of these events across different risk factors for SPMs, in the same cohorts
- **Exploratory Objective**: CCI [redacted] CCI [redacted]

8. RESEARCH METHODS

8.1. Study Design

This PASS will be conducted as a prospective, noninterventional, single-arm study will estimate the incidence rate of MDS/AML and SPMs in patients with advanced (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy or patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, that have received or are receiving niraparib through the expanded access program (EAP), a clinical trial and in routine clinical practice.

To allow for the necessary time required for development of a secondary malignancy, patients will be followed for up to 5 years from niraparib treatment initiation. Baseline characteristics of the patients will be collected at study enrollment. During the follow-up period, data on treatment with niraparib and other chemotherapeutic agents, and study outcomes (MDS/AML and SPMs) and AEs will be collected.

To obtain data on the baseline incidence rate of MDS/AML and SPMs in patients with ovarian cancer, a retrospective, secondary data analysis using an electronic medical records (non-claims) European healthcare database will be performed. This retrospective analysis will include a cohort of patients who would have been eligible for treatment with niraparib or other PARPis but did not receive such treatment. The cohort of patients included in 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. Patients will be followed from the index date (defined as the date of completion of a first or second line of chemotherapy treatment) to the first of 5 years of follow-up, initiation of any PARPi, death or loss to follow-up. Baseline characteristics will be defined at the index date. Information on treatment received and cases of MDS/AML and SPMs will be identified during the follow-up period.

8.2. Setting

Primary Data Collection Cohort

Patients will be enrolled in up to 5 European countries, 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 sample size 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 EU SmPC guidelines
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.

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 baseline characteristics, the study outcomes of MDS/AML and SPMs and any other

relevant data variables will be recorded in an electronic data capture (EDC) system by the physician or study staff at the time of enrollment and quarterly thereafter for a maximum period of 5 years (Table 6). 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.

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 (i.e., if the patients miss at least 3 of the expected visits for management based on standard clinical practice guidelines), 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.

8.2.1. Inclusion/Exclusion Criteria

Patients will be eligible for enrolment into this cohort if they fulfill ALL of the following criteria at the time of enrollment into the study:

1. Patient must be a female, aged 18 years or older.
2. Patient must have a diagnosis of:
   - advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
   - platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
3. The patient received niraparib:
   a. as part of the EAP, regardless of whether the patient is receiving niraparib at the time of enrollment.
   b. as part of clinical practice, within 4 weeks of enrollment regardless of whether the patient is receiving niraparib at the time of enrollment.
   c. as part of the control arm of a clinical trial (other than TESARO/GSK sponsored or supported niraparib trial please see exclusions below), regardless of whether the patient is receiving niraparib at the time of enrollment.
4. Patient must be able and agree to sign a consent form.

Exclusion criteria

Patients who fulfil ANY of the following criteria will be excluded from the study:

1. Patient is receiving niraparib for use that is not according to the approved EU SmPC.
2. Patient is receiving or received Zejula in the past as part of TESARO or GSK clinical trial, where there are still participating in active follow-up to reduce the risk of double reporting of safety events.
3. Patients enrolled into a GSK Investigator Supported Study or Supported Collaborative Study.

Secondary Data Cohort

This cohort will comprise of 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 with similar characteristics to the primary data collection cohort, selected from either an electronic medical records (non-claims) European electronic healthcare database. These patients would have been eligible for treatment with niraparib but did not receive such treatment. To ensure that the secondary data cohort fully reflects the primary data collection cohort, 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. The characteristics will include the age at enrolment, weight, history of cancer, prior anticancer chemo- and radiotherapy received, history of autoimmune diseases, history of thrombocytopenia, platelet transfusion, anemia, renal and hepatic insufficiency, neutropenia, and treatment history to identify patients who were treated with any PARP inhibitor. The patients will be followed from the date of completion of the first-line or second-line chemotherapy (index date) up to 5 years or loss to follow-up, death or initiation of a PARP inhibitor. Demographic, medical and treatment information prior to the index date will be used to define the baseline characteristics of the patients. Data during the following up period from the index date will be used to identify study outcomes (i.e., MDS/AML and SPMs) and to describe chemotherapy treatment in order to censor any patients who initiate PARP inhibitors during the follow-up period.

Inclusion criteria

Patients will be eligible for enrolment into this cohort if they fulfill ALL of the following criteria at the time of enrollment (i.e. index date) into the study:

1. Patients must be female patients and aged at least 18 years at the index date
2. Patients who had a diagnosis of
   a. high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy OR,
   b. relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer OR

Patients received platinum-based chemotherapy as first or second line therapy

Exclusion criterion

- Patients who were exposed to any PARP inhibitor in the baseline period.

8.2.2. Data Collection

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 until 1 of the following events, whichever comes first: patient death, loss to follow-up, 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 enrollment into the study.

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. **Complete blood count (CBC) abnormalities:** Elevated MCV is associated with early stages of MDS[39] and can be evaluated by conducting a CBC with leukocyte differentials.

To determine whether the occurrence of MDS/AML and SPMs is associated with niraparib treatment and not with other potential risk factors, 3 types of data will be collected in the primary data cohort:

1) Data for variables that are critical and moderate risk factors for MDS/AML and SPMs as described in Section 8.2.3
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 8.2.3.
3) Data to confirm use the of niraparib according to EU SmPC guidelines.

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

Primary Data Collection

For the primary data cohort, data will be collected at 2 different time periods as follows:

1) Baseline data (at initiation of niraparib treatment)
2) Follow-up data (collection will occur quarterly during a maximum 5-year clinical follow-up of the patient after enrollment into the study).

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.

The participating physicians will document the measures in a web-based documentation sheet (eCRF) that has been develop for this noninterventional study. The schedule of data collection for all study variables is provided in Table 6.

8.2.3. Study Variables

Baseline data for the primary data cohort will include the following:

- Tumor diagnosis (histological type, grade, FIGO stage, primary location)
- Age at diagnosis (derived from year of birth until date of diagnosis)
- Age at study entry (derived from year of birth until date of enrollment)
    - Height
    - Weight within 3 months of study enrollment (initiation of niraparib)
    - If available: germline and/or somatic breast cancer susceptibility gene (*BRCA*) status
    - If available: Homologous recombination deficiency (HRD) 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
    - CBC (the latest before initiation of niraparib)
    - MCV (the latest before initiation of niraparib)
    - 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 inhibitors (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)
- CBC

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

Table 6 Schedule of Data Collection for the Primary Data Cohort

Data Collection and study assessments	Patient Baseline Assessment Day 0	Interval Data Collections Quarterly Every 3 months (+/-) 10 working days	Unscheduled Intervals During Observation Period (up to 5 years from start date of niraparib)	Lost to follow up	End of Study Period	Notes
Informed consent form (ICF)	X					
Inclusion and exclusion criteria check	X					
Year of birth	X					
Weight	X	X				At baseline or within last 3 months.
Height	X					
Family Cancer History	X					
BRCA/HRD status	X					
Auto-immune history	X					
Ovarian cancer diagnosis	X					
Other cancer diagnosis	X	X		X	X	
Cancer treatment	X	X		X	X	
Radiotherapy Treatment	X	X		X	X	
Risk Factors	X			X	X	
Complete blood cell counts	X			X	X	
Myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) and other secondary primary malignancies (SPM) Summary at Enrollment	X	X	X	X	X	Refer to protocol section 10.0 for reporting timeframes
Adverse Events (AE) reporting	X	X	X	X	X	Refer to protocol section 10.0 for reporting timeframes

Data Collection and study assessments	Patient Baseline Assessment Day 0	Interval Data Collections Quarterly Every 3 months (+/-) 10 working days	Unscheduled Intervals During Observation Period (up to 5 years from start date of niraparib)	Lost to follow up	End of Study Period	Notes
Pregnancy Reporting and Outcomes	X	X	X	X	X	Refer to protocol section 10.0 for reporting timeframes
COVID-19 infection assessment			X			

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

8.2.4. Secondary Data Collection

Similar data will be collected for the secondary data cohort (listed in Section 8.2.3), and will include critical and moderate factors associated with the risk for development for the AML, DMS and SPMs. At a minimum, the following information will be collected during the follow-up period: age at diagnosis, weight, history of any other cancers, any chemotherapy treatment during the baseline and follow-up period, and the study outcomes (MDS, AML and SPMs).

8.3. Data Sources

8.3.1. Primary Data Collection

This primary data collection will include patients who have received or are receiving niraparib through the EAP), in a clinical trial (other than TESARO/GSK sponsored or supported niraparib trial, GSK investigator sponsored studies or supported collaborative studies), and patients treated post-approval in routine clinical practice. Data will be collected from electronic medical records of patients enrolled into the study. The data will be entered by the staff at each clinical site into a web-based, password-protected documentation system (eCRF).

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 loss to follow-up or the patient's death, whichever occurs first.

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 anticipated overall average follow-up of 2.5 years.

Secondary Data Collection

An electronic medical record (non-claims) European Healthcare database will be used for the retrospective analysis. The database will be selected based on the following factors:

- The population coverage at a national level to maximize the representativeness of the study results
- Availability of patient longitudinal data to define:
    - The diagnosis of advanced/recurrent ovarian cancer
    - Describe the demographic characteristics
    - Describe the clinical history of the study population (i.e., age at study enrolment, weight, history of cancer, prior anticancer chemo- and radiotherapy received, history of autoimmune diseases, history of thrombocytopenia, platelet transfusion, anemia, renal and hepatic insufficiency, neutropenia, and treatment history to identify patients who were treated with any PARP inhibitor, and if available ovarian cancer BRCA and HRD biomarker status),
    - Identify patients who develop the safety events of interest (i.e., AML, MDS and SPMs

- Sufficient follow-up time similar to the primary data collection cohort to identify the safety events of interest.

A feasibility assessment will be conducted select the most appropriate database for the analysis.

8.4. Study Size

The mean duration of follow-up among 372 ITT patients randomized into the NOVA study niraparib arms was 26.9 months (as of 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. Data from a clinical trial that evaluated survival in patients treated with olaparib maintenance therapy suggest that with maximum 5-years follow-up from treatment initiation it is possible to achieve an average of approximately 2.5 years of follow-up per patient.[11] This is consistent with the data collected from the NOVA study (as of the data cutoff of 03/26/2018) 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 losing patients to follow-up in a non-interventional study within a real world setting, this study plans 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.

The sample size was not revised following the addition to the study population patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. It is anticipated that the exposure to Niraparib will be similar in the two populations based on the data from the NOVA and PRIMA clinical studies.

Table 7 below provides the 95% CIs for different numbers of observed events of MDS/AML during this follow-up period.

Table 7 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

8.5. Data Management

Primary Data Collection

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 8.7.1 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.

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 biannually 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 and/or site visits 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 safety database (see also Section 10). Analysis will be performed using SAS statistical software v9.4 or later, unless otherwise noted.

Secondary Data Collection

Data that will be used for the retrospective analysis will be anonymized. No potentially identifying information will be included in the data that will be used for the data analysis. The data management process will include ensuring storage of the data in a secure location with limited access, only to study personnel. The extraction of the analysis database will be based on the coding system used in the database. The final code list will be created and reviewed prior to extracting the analytical database. Data cleaning and processing will be performed by experienced data analysts prior to statistical analysis,

8.6. Data Analysis

Details of the statistical analyses presented below will be provided in the study's 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 tumour 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 8.2.3). 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.

The primary analysis will also be stratified by the indication used niraparib treatment i.e., by the following cohorts:

- advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
- platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy

If sufficient data is available, secondary analyses will be conducted, stratifying the study population by HRD and BRCA status.

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.

8.7. Quality Control

To ensure compliance with all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 8.7.8 for more details regarding the audit process.

8.7.1. 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 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.

8.7.2. 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.

8.7.3. 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.

Study documents will be archived by participating investigator sites and GSK for a minimum of 10 years following the finalization of a study report.

8.7.4. Regulatory Guidelines

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

8.7.5. 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 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; 1 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.

8.7.6. 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.

8.7.7. Study Monitoring

A site management plan has been established to include scheduled monitoring calls biannually 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 and/or site visits where data collection presents persistent problems. A risk-based monitoring approach will be followed and adapted as required in consultation with the Clinical Research Organisation overseeing the implementation of the plan.

Travel limitations, quarantine and shutdowns caused by the COVID –19 pandemic may lead to difficulties in the implementation of agreed monitoring activities. This will be kept under review until normal activities can commence.

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.

8.7.8. 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.

8.7.9. 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.

8.8. 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.

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. The retrospective cohort will be selected ensuring that the characteristics of the secondary data cohort are similar to the primary cohort. However, there is a probability that there may be outstanding unmeasured differences in the characteristics of the two cohorts.

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 of MDS/AML and up to 3 events of 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 events, 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 analysis than for the primary data analysis 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 Section 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 and 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.

8.9. 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. 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.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Definitions

10.1.1. Adverse Event

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. For a marketed Medicinal Product this can also include those related to a deficiency occurring with a medical device. GSK defines a Medical Device Incident as any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health and a Serious Adverse Device Effect (SADE).

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.

10.1.2. Adverse Drug Reaction

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

10.1.3. 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**

* Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an 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, result in death, or require hospitalization but may jeopardize the patient or

require intervention to prevent 1 of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, 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.

10.1.4. 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.

10.1.5. 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:** The 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, or 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 10.5.2.
- **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 must be assessed by the Investigator for severity* according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0, 27 November 2017, 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 v5.0 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 SAE criteria in Section 10.1.3. For example, a mild degree of gastrointestinal bleeding requiring a hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

10.2.2. Relationship to the Study Product

The Investigator must provide a causality assessment regarding the relationship of the event with the niraparib treatment prescribed 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. 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, 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 AEs, serious and non-serious, regardless of the source of identification (eg, physical examination, laboratory assessment, electrocardiogram, reported by patient), will be collected and recorded in the eCRF for each patient from the signing of the ICF for this study through 30 days after the last dose of niraparib or patient’s death for any cause, whichever comes first. However, if there is reasonable belief that an SAE that occurred after the 30 days window is related to study drug, it will be reported to the safety database.

Exceptions to the reporting requirements detailed above are as follows:

- MDS/AML and SPM as the study endpoint should be collected and reported to the Sponsor from first dose of niraparib until death or loss to follow-up, whichever comes first.
- Embryo fetal toxicity should be reported as outlined in Section 10.5.1.

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.

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 or 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.

The safety database will collect narratives for SAEs and ADRs, including all events of MDS/AML and SPM. It is the responsibility of the Investigator to provide case narrative in the dedicated eCRF field.

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.

10.4. Reporting to Sponsor

The Investigator must report all SAEs (related and nonrelated) including follow-up information to the Sponsor's safety database through the eCRF-generated Safety Form within 24 hours of becoming aware of the initial event or follow-up information. Further, non-serious ADRs should be reported to the Sponsor within five (5) days of awareness of the quarterly interval data collections through the Safety Form

It is the responsibility of the Investigator to review source documentation, describe pertinent information, and then print and sign the Safety Form before sending to the contact information below. 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 Safety Form or query the Sponsor to confirm the reporting route.

After receipt of the Safety Form, 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 ADR reporting should be performed by the treating physicians per regulations.

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

- Email: OAX37649@gsk.com or Fax: +44(0) 208754 7822

10.5. Sponsor Submission and Distribution of Adverse Drug Reactions

Per regulatory requirements, if an event is assessed as an adverse drug reaction (ADR) (serious or non-serious), it is the responsibility of the Sponsor, and not of the Investigator, to report the ADR to Regulatory Authorities according to applicable regulations.

If any ADRs are observed related to **any other products of the Sponsor**, the Investigator should report the ADRs to the Sponsor's safety database within 24 hours. If any ADRs are observed related to drug product(s) not related to the Sponsor, the Investigator should report

the ADRs to the appropriate marketing authorisation application of the product(s) or Health Authority per local regulations.

All AEs and SAEs including all MDS/AML and SPM events and embryo fetal toxicity, collected through primary data collection will be reported through the study interim safety analyses as well as in the final study report to the competent authority of each country where the study is being conducted. The study progress will be reported through the product periodic safety update reports.

10.5.1. Pregnancy

The Investigator must report all pregnancies that occur from the signing of the ICF up to 180 days after last dose of niraparib treatment using the Initial Pregnancy Notification Report Form and forward it to the Sponsor (or designee) within 24 hours of first awareness of the pregnancy. The details of the pregnancy outcomes or other associated event (eg, elective abortion) must be reported to the Sponsor using the Pregnancy Outcome Report Form.

Pregnancy is not an AE and therefore does not need to be reported as an AE 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 awareness—even if the patient was withdrawn from the study or the study has finished.

Pregnancy is not considered an SAE unless there is an associated serious outcome that must be recorded on the Pregnancy Outcome Report Form, and reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor within 24 hours in accordance with the procedure for reporting SAEs.

10.5.2. Special Situations

All occurrences of abuse, misuse, medication error, overdose, accidental, or occupational exposure with the study product must be reported through the Special Situation Report Form provided by the Sponsor regardless of whether an AE or SAE has occurred. The form must 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.

10.5.3. Covid-19 Infection Assessment

A COVID-19 infection assessment form should be completed for ALL cases of COVID-19 cases identified during the study.

COVID 19 cases should be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines

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 8.6, of variables collected as described in Section 8 and other eventual adverse reactions collected during the study and reported in the safety database.

TESARO (A GSK company) retains the right to publish the results from this study.

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ANNEX 1. 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 GVPs)

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, 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				
1.1.1 Start of data collection[1]	☒	☐	☐	5
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)	☒	☐	☐	5 and 8
1.1.5 Registration in the EU PAS register	☒	☐	☐	5 and 8
1.1.6 Final report of study results.	☒	☐	☐	5 and 8

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

[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**
.3.2 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
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

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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
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

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
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))	☐	☒	☐	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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? 12.1.2 Information bias?	☒	☐	☐	8.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	8.9
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: PPD

Date:

Signature: _____