Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Zejula (niraparib)

RMP version to be assessed as part of this application	
RMP Version number	11.0
Data lock point for this RMP	11 July 2024: data cut-off for the PASS study 3000- 04-001/GSK213705 final study report
Date of final sign off	25 March 2025

Rationale for submitting an updated RMP

- This updated RMP 11.0 incorporates updates from EU RMP version 9.1 into approved version 10.0.
- RMP version 9.1 incorporated updates from approved EU RMP version 8.0 into version 9.0.
    - RMP version 8.0 was submitted by GSK to remove the category 3 additional pharmacovigilance activity PASS 3000-04-002 / GSK214708 from the niraparib EU RMP. This removal was based on a comprehensive feasibility assessment that revealed the primary objective of the study could not be met due to lack of published data and the secondary objective of study could not be met due to the limited number of events in the indicated population
    - RMP version 9.0 was submitted as part of the post-authorisation measure (PAM) Specific Obligation to submit the final analysis for OS from the post-authorisation efficacy study (PAES) PR-30-5017-C (PRIMA). Safety data analysis was also conducted. Based on the fulfillment of the PAM, PR-30-5017-C (PRIMA) was proposed to be removed from PART IV and Annex 5.

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in the present EU-RMP**
Part II	SI	• Updated epidemiology information with more up to date references
Part II	SII	• Editorial update to clarify data cut-off date for human use data
Part II	SIV.1	• Exclusion criteria in pivotal trials - patients with known active hepatic disease – updated missing information to 'no'
Part II	SV.1	• Added tablet formulationmarketed authorization status • Updated Post-authorisation exposure from PBRER #10
Part II	SVII.2	• Format update - added table with RMP version number for safety concern changes since initial EU RMP • Simplified the rationale for the reclassification of MDS/AML from a potential risk to an important identified risk
Part II	SVII.3	• Updated risk of MDS/AML and other SPMwith incidence rate from PASS 3000-04-001/GSK 213705 CSR • Proposal to remove PASS 3000-04-001/GSK 213705 as additional PV for Important Identified Risk MDS and AML and for Important Potential Risk of SPM other than MDS and AML as PASS completed Q4 2024 • Updated post-marketing experience DLP date for important identified and potential risks • Editorial change to Important Potential Risk of SPM other than MDS and AML that SPM is a potential risk for olaparib and rucaparib per their respective RMPs • Removed Study 3000-04-002 / GSK214708 as additional pharmacovigilance activity for Important Identified Risk MDS and AML and for Important Potential Risk of SPM other than MDS and AML • Editorial update to clarify data cut-off date for human use data • Updated the incidence rate of MDS/AML with the data from the OS analysis of the PR-30-5017-C PRIMA study

Part III.2	Not applicable	• Proposal to remove PASS protocol 3000-04- 001/GSK 213705 as additional PV study • Removed Study 3000-04-002 / GSK214708
Part III.3	Not applicable	• Proposal to remove PASS protocol 3000-04-001/GSK213705 as additional PV study • Removed Study 3000-04-002 / GSK214708
Part IV	Not applicable	• Proposal to remove study information of PR-30-5017-C PRIMA as PAES
Part V	V1.1, V.3	• Removed Study 3000-04-002 / GSK214708 as additional pharmacovigilance activity for Important Identified Risk MDS and AML and for Important Potential Risk of SPM other than MDS and AML
Part VI	IIB, II.C.2	• Update Summary of Risk Management Plan with above updates
Annexes	Annex 2	• Updated Table 1 to 'None' and indicated 3000-04-001: GSK 213705 as completed in Table 2 • Removed Study 3000-04-002 / GSK214708 as additional pharmacovigilance study.
Annexes	Annex 3	• Included new protocol version 9 for 3000-04-001: GSK213705 • Removed Study 3000-04-002 / GSK214708 as additional pharmacovigilance study.
Annexes	Annex 5	• Proposal to remove protocol PR-30-5017-C PRIMA

Other RMP versions under evaluation		
RMP Version number	**Submitted on**	**Procedure number**
None		

Details of the currently approved RMP		
Version number	Approved with procedure	Date of approval (opinion date)
10.0	EMEA/H/C/004249/II/0058	13 Mar 2025
QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV	
QPPV Signature	Electronic signature on file	

Abbreviations

1LM	first-line maintenance
2LM+	second-line maintenance or beyond
ADP	adenosine diphosphate
ADR	adverse drug reaction
AML	acute myeloid leukaemia
ATC	Anatomical-Therapeutic-Chemical classification
BRCA	breast cancer gene
BRCAmut	breast cancer gene mutation
CHO-K1	chinese hamster ovary K1
CI	confidence interval
Cmax	maximum serumconcentration
CNS	central nervous system
CSR	clinical study report
CVD	cardiovascular disease
DAT	dopamine transporter
DLP	data lock point
DNA	deoxyribonucleic acid
EAP	expanded access programmes
EAR	excess absolute risk (excess cancers per 10,000 person-years)
ECG	electrocardiogram
ECIS	European Cancer Information System
eCTD	electronic common technical document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
ESRD	end stage renal disease
EU	European Union
EU-28	28 EU Member States
gBRCAmut	germline breast cancer gene mutation
GLP	Good Laboratory Practice
hERG	human Ether a Go-go Related Gene
HLT	high level term
HRD	homologous recombination deficiency
IC50	half maximal inhibitory concentration
IL	interleukin
INN	international nonproprietary name
IST	investigator sponsored trials
MAA	marketing authorisation application
MAH	marketing authorisation holder
MDCK	Madin-Darby Canine Kidney
MDS	myelodysplastic syndrome
MedDRA	medical dictionary for regulatory activities
NA	not applicable
NACT	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NET	norepinephrine transporter
NICE	National Institute for Health and Care Excellence
NOAEL	no observed adverse effect level
O/E	ratio of observed to expected cancers

OS	overall survival
PARP	poly (ADP-ribose) polymerase
PARPi	poly (ADP-ribose) polymerase inhibitor
PAES	post-authorisation efficacy study
PASS	post-authorisation safety study
PBRER	periodic benefit-risk evaluation report
PFS	progression-free survival
PL	package leaflet
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PV	pharmacovigilance
QD	once daily
QPPV	Qualified Person for Pharmacovigilance
QT	QT interval
QTc	corrected QT interval
QTcF	corrected QT interval using Fridericia'sformula
ΔQTcF	QTcF mean change frombaseline
RMP	Risk Management Plan
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SPM	Second Primary Malignancies
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States
UV	ultraviolet
VTE	vascular thromboembolic event

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Zejula

Trademarks not owned by the GlaxoSmithKline group of companies
Abraxane
Avastin
Carboplatin
Lynparza
Rubraca

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Niraparib
Pharmacotherapeutic group(s) (ATC Code)	Other antineoplastic agents L01XK02
Marketing Authorisation Holder/ Applicant	GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland
Medicinal products to which this RMP refers	Zejula 100 mg hard capsules Zejula 100 mg film-coated tablets
Invented name(s) in the European Economic Area (EEA)	Zejula
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Niraparib (formerly MK-4827) is an orally available, potent, highly selective poly (adenosine diphosphate (ADP)-ribose) polymerase (PARP)1 and PARP2 inhibitor. Niraparib co-crystallized with the human PARP1 catalytic domain and was shown to inhibit PARP1 and PARP2 activity in vitro with a 50% maximum inhibitory concentration (IC_{50}) of 3.8 and 2.1 nM, respectively.
	Summary of mode of action Niraparib demonstrated 25- to 200-fold increased selectivity against cancer cell lines that were engineered to be homologous recombination-deficient (HRD) via breast cancer gene 1 (BRCA1) or breast cancer 2 (BRCA2) silencing, or that carried BRCA1 or

	BRCA2 mutations, as compared to their wild-type counterparts. Treatment of xenograft bearing mice at clinically relevant doses resulted in tumour regression in BRCA and ataxia telangiectasia mutated tumour models. At these dose levels, 90% PARP inhibition was observed in tumours for up to 24 hours after a single dose and was greater and more durable than PARP inhibition in the corresponding peripheral blood mononuclear cells, where inhibition levels were 50% or less by 24 hours post dose.
	Important information about its composition Niraparib drug substance is a crystalline tosylate monohydrate salt. This salt form is non-hygroscopic and is off-white to pale brown in colour. It is formulated as a dry blend of niraparib and lactose lubricated with magnesium stearate.
Reference to the Product Information	Please refer to the summary of product characteristics (SmPC) (section 1.3.1 of the eCTD).
Indications in the EEA	**Current** Zejula is indicated as monotherapy for the maintenance treatment of adult 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. Zejula is indicated as monotherapy for the 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.
	Proposed (if applicable):

Dosage in the EEA	**Current (if applicable):** *Recurrent ovarian cancer maintenance treatment* The dose is three 100 mg hard capsules once daily, equivalent to a total daily dose of 300 mg. The dose is three 100 mg tablets once daily, equivalent to a total daily dose of 300 mg. *First-line ovarian cancer maintenance treatment* The recommended starting dose of Zejula is 200mg (two 100-mg capsules), taken once daily. However, for those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL, the recommended starting dose of Zejula is 300 mg (three 100-mg capsules), taken oncedaily. The recommended starting dose of Zejula is 200 mg (two 100-mg tablets), taken once daily. However, for those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL, the recommended starting dose of Zejula is 300 mg (three 100-mg tablets), taken once daily.
	Proposed (if applicable):
Pharmaceutical form(s) and strengths	Current (if applicable): Capsule for oral use Each hard capsule contains niraparib tosylate monohydrate equivalent to 100 mg niraparib. Tablet for oral use Each film-coated tablet contains niraparib tosylate monohydrate equivalent to 100 mg niraparib.
	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Indication

Approved Indication: Monotherapy for the maintenance treatment of adult 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.

Approved Indication: Monotherapy for the 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.

Incidence and prevalence

Incidence:

Ovarian cancer is the 8th most common cancer in women worldwide (18th most common cancer overall); estimated 324,603 new cases diagnosed in 2022 and 206,956 deaths [Ferlay, 2024].

In Europe, the age-standardised (to the World standard population) incidence rate of ovarian cancer in 2022 was 9.3 per 100,000 (estimated 69,472 incident cases) and there were an estimated 46,232 deaths from ovarian cancer in 2022 [Ferlay, 2024].

In the United States (US), the age-standardised (to the World standard population) incidence rate of ovarian cancer in 2022 was 7.3 per 100,000 in the US (estimated 21,179 incident cases) and there were an estimated 13,273 deaths from ovarian cancer in 2022 [Ferlay, 2024

Incidence data retrieved from European Cancer Information System (ECIS) for the EEA-30 (28 EU Member States (EU-28) plus Iceland and Norway) for 2018 estimated a total of 45,134 new cases of ovarian cancer [ECIS, 2019]. The combined population of EU-28 plus Norway and Iceland in 2018 was 518,023,294 persons [EUROSTAT, 2019]. For this population, 45,134 cases of newly diagnosed ovarian cancer corresponds to a crude incidence rate (both sexes) of 8.71/100,000 population. Crude incidence rate for primary fallopian tube cancer and primary peritoneal cancer was 0.27/100,000 and 0.34/100,000, respectively. Thus, the total crude incidence for these conditions is 9.32/100,000 (Data on file).

Epithelial ovarian cancer occurs in more than 90% of cases, with less than 10% originating from germ cells, sex cords, or ovarian stroma cells [Torre, 2018, ESGO-ESMO-ESP; 2024]. Approximately 75–80% of epithelial ovarian cases are of the serous (high-grade or low-grade) histological type [Webb, 2024].

Prevalence:

Worldwide, there were an estimated 929,996 women alive within five years of an ovarian cancer diagnosis (5-year prevalence) in 2022; and 208,930 in Europe [Ferlay, 2024].

Estimated point prevalence for ovarian cancer was calculated as follows: P = 0.932 x 5= 4.66/ 10,000. For a population of 519,205,271 in the EEA in 2019 [EUROSTAT, 2019] this corresponds to 241,950 patients with ovarian cancer (Date on file).

SI.1.1 Demographics of the population in the authorised indication and risk factors for the disease:

Ovarian cancer incidence is strongly related to age, with the highest incidence rates being in older females. In women of ages <65 years, the age-standardised incidence rates in 2022 were estimated at 7.0 per 100,000 in Europe and 5.5 per 100,000 in the US. In contrast, the age-standardised incidence rates for women ages ≥65 years were 39.9 per 100,000 in Europe and 31.8 per 100,000 in the US [Ferlay, 2024].

The age-standardised incidence rates of ovarian cancer (2013-2017) in England for Whites were 22.28 per 100,000, in Asians 16.10 per 100,000 and in Blacks 14.69 per 100,000 [Delon, 2022].

Age-standardised incidence rates of ovarian cancer (per 100,000) in the US in 2021 by race were 10.0 for Non-Hispanic Whites, 8.9 for Non-Hispanic Blacks, 10.8 for Non-Hispanic American Indian/Alaska Natives, 9.2 for Non-Hispanic Asian/Pacific Islanders, and 9.7 for Hispanics [U.S. Cancer Statistics Working Group, 2024].

Risk factors for the disease:

There are several demographic, clinical and genetic factors associated with increased risk of ovarian cancer, and which may vary by histology [Jones, 2017; Mavadddat, 2013; Beral, 2015; Norquist, 2016; Tsilidis, 2011; Cibula, 2011; Sieh, 2013; Wentzensen, 2016; Kuchenbaecker, 2017; Lheureux, 2019; Webb, 2024].

- Older age (>35 years) at first pregnancy and first birth
- Nulliparity; 31% decreased risk with having at least one child
- Ashkenazi Jewish descent
- Postmenopausal hormone therapy; 36% increased risk with having everused postmenopausal hormone therapy
- History of pelvic inflammatory disease
- History of endometriosis (35% increased risk)
- Family history of breast or ovarian cancer; 48% increased risk with first-degreefamily history of ovarian cancer
- Presence BRCA1 and BRCA2 mutations; 44% cumulative risk for BRCA1 and17% cumulative risk for BRCA2
- Lynch syndrome
- No historical or current use of oral contraceptives; 16% decreased risk with having ever used oral contraceptives

- Not breastfeeding
- Not undergoing procedures such as tubal ligation and oophorectomy; 18% decreased risk with having ever had tubal ligation

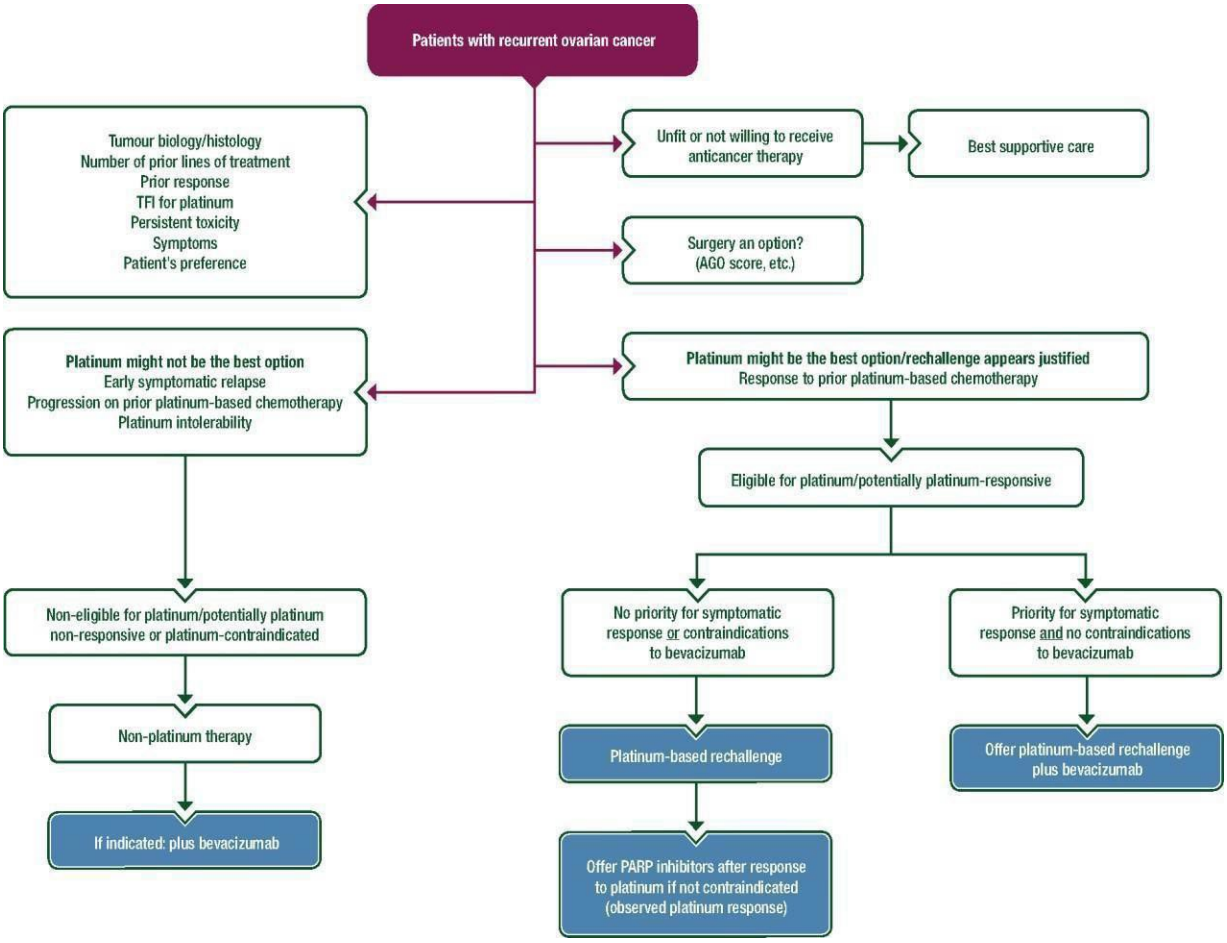
SI.1.2 The main existing treatment options

The paradigm for first-line treatment of newly diagnosed ovarian cancer includes a combination of surgery and chemotherapy: either primary debulking surgery followed by adjuvant chemotherapy or neoadjuvant chemotherapy (NACT) with subsequent interval debulking surgery followed by additional chemotherapy [EMR Database, 2019; Liu, 2017; Vergote, 2010; Nicklin, 2017; Meyer, 2016]. The preferred standard of care chemotherapy regimen is carboplatin and paclitaxel [Ozols, 2003; du Bois, 2005].

Bevacizumab is an option for first line treatment. In addition, NACT is increasingly being used in patients with bulky disease who might otherwise be considered as candidates for bevacizumab [Tewari, 2019]. In the EU, bevacizumab usage in first-line treatment is limited due to safety concerns, and data are lacking on its use in the growing number of patients who receive NACT [Moore, 2018]. Observation, or "watch and wait" after response to first line therapy is included in the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines and is the approach taken for the majority (>75%) of patients with advanced ovarian cancer [EMR Database, 2019; Liu, 2017; Colombo, 2019].

Olaparib, a PARP inhibitor, is approved for first-line maintenance in patients with mutations in the breast cancer susceptibility gene (breast cancer gene mutation [BRCAmut]) [Olaparib SmPC].

The following recurrent ovarian cancer treatment algorithm is based on recommendations from ESMO 2017 guidelines:



Source : Columbo et al., 2019

Main risks associated with commonly utilised treatments for advanced ovarian cancer include the following:

Treatment	**Main treatment-related risks**
Carboplatin [Carboplatin SmPC]	• Myelosuppression • Allergic reactions • Renal toxicity • Haematologic toxicity, haemolytic-uraemic syndrome • Neurologic toxicity • Reversible Posterior Leukoencephalopathy Syndrome

Paclitaxel [Paclitaxel SmPC]	• Hypersensitivity • Haematologic toxicity • Neurologic toxicity • Sepsis • Pneumonitis • Use in hepatic impairment • Cardiotoxicity • Gastrointestinal toxicity
Bevacizumab [Bevacizumab SmPC]	• Gastrointestinal perforations and fistulae • Non-gastrointestinal fistulae • Wound healing complications • Hypertension • Posterior Reversible Encephalopathy Syndrome • Proteinuria • Arterial thromboembolism • Venous thromboembolism • Haemorrhage • Aneurysms and artery dissections • Congestive heart failure • Neutropenia and infections • Infusion reactions • Osteonecrosis of the jaw • Eye disorders
PARP inhibitors: Olaparib, rucaparib, niraparib [Olaparib SmPC; Rucaparib SmPC; Niraparib SmPC]	• Haematological toxicity • Myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) • Embryofoetal toxicity • Pneumonitis (olaparib) • Photosensitivity (rucaparib) • Gastrointestinal toxicity (rucaparib) • Bone marrow suppression • Cardiovascular effects (niraparib, rucaparib)

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Ovarian cancer, when diagnosed at later stages, remains an incurable disease, and treatment aims to prolong the time to disease progression and reduce disease-related symptoms. In Europe, there were an estimated 46,232 deaths from ovarian cancer in 2022 [Ferlay, 2024]. Only 36.3% of women with ovarian cancer live for 5 years after diagnosis in Europe [Sant, 2015]. Low survival rates in ovarian cancer patients are attributed to late-stage diagnosis; an estimated two-thirds of patients in Europe have advanced disease at diagnosis [Oberaigner, 2012; Gaitskell, 2022]. Even

upon complete remission with first-line chemotherapy, ovarian epithelial cancer recurs in over 50% of women [Vargas, 2014]. Age, tumour stage and grade, genetic mutations, and residual tumour are well- established prognostic factors for the survival of patients with epithelial ovarian cancer [Jayson, 2014; Sarkar, 2024, Andreou, 2023; Lheureux, 2019].

SI.1.4 Important co-morbidities

The presence of co-morbidities in ovarian cancer patients influence treatment decisions and tolerance of standard of care therapies, limiting the potential impact of treatment [Jorgensen, 2012]. Co-morbidities are prevalent in ovarian cancer patients, partially attributable to the age distribution of disease [Maas, 2005; O'Malley, 2003; Chia, 2013]. Background rates of important co-morbidities in ovarian cancer patients are as follows:

Cardiovascular disease (CVD)	▪ CVD was the most prevalent (30%) co-morbidity among newly diagnosed patients ≥70 years old; prevalence was 10% among patients <70 years old (The Netherlands) [Maas, 2005] ▪ CVD was reported among 49% newly diagnosed patients (US) [Shinn,2013] ▪ CVD was the most prevalent(47.5%) comorbidity in recurrent patients (Germany) [Woopen, 2015] ▪ CVD and thromboembolic events were reported among 11.9% and 8.3% of advanced patients, respectively (Sweden) [Stalber, 2014] ▪ Incidence of venous thromboembolism was 10%-27% (Ireland, US) [Abu Saadeh, 2013; Greco, 2017] ▪ Incidence of deep venous thrombosis and pulmonary embolism was 10.8% and 7.2%, respectively (US) [Bakhru, 2013]
Metabolic syndromes	▪ Type II diabetes and hypertension were reported among 11.2% and 30.5% patients, respectively (US) [Bakhru, 2011] ▪ 15.4% newly diagnosed patients had diabetes and 42.7% had chronic hypertension (Israel) [Bar, 2016] ▪ Diabetes and hypertension were reported in 18% and 42% newlydiagnosed patients, respectively (The Netherlands) [Maas, 2005] ▪ Type I and II diabetes was prevalent in 2.7% newlydiagnosed patients (Denmark) [Grann, 2013] ▪ Diabetes was prevalent in 6.9% recurrent patients (Germany) [Woopen,2015] ▪ Prevalence of diabetes and hypertension was reported as 5.1% and 11.2%, respectively, in advanced patients (Sweden) [Stalberg,2014]
Cerebrovascular disease	▪ History of stroke or transient ischaemic attack was prevalent in 4% patients (US) [Bakhru, 2011] ▪ Cerebrovascular disease was reported in 5.8% newly diagnosedpatients (Denmark) [Grann, 2013]

Respiratory disease	▪ Pulmonary diseases other than asthma was prevalent among 4.8% patients [Bakhru, 2011] ▪ Chronic obstructive pulmonary disease was reported among 5.3%-13% in newly diagnosed patients (Denmark, The Netherlands) [Grann, 2013] ▪ Comorbid disease in the respiratory system was prevalent in 7.4% recurrent patients (Germany) [Mahner, 2012]
Gastrointestinal disease	▪ Peptic ulcer disease was prevalent in 2.9% newly diagnosed patients (Denmark) [Grann, 2013] ▪ Comorbid disease in the lower and upper gastrointestinal tract was prevalent in 9% and 4.9% recurrent patients, respectively (Germany) [Mahner,2012].
Other cancers	▪ Any cancer was the most prevalent comorbidity in 7.9% newly diagnosed patients (Denmark) [Grann, 2013]. ▪ Prevalence of MDS and AML was 0.2% and 0.1%, respectively (US) [Shenolikar, 2018].
Musculoskeletal diseases	▪ Comorbid disease in the musculoskeletal system was prevalent in 14.8% recurrent patients (Germany) [Mahner, 2012].
Mental health	▪ Comorbid psychiatric conditions were observed in 2.5% recurrentpatients (Germany) [Mahner, 2012]. ▪ Depression was reported in 15%-39% advanced patients, based on various measures (France) [Rhondali, 2015].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including: **Key issues identified from acute or repeat-dose toxicity studies** Results from repeat-dose oral toxicity studies up to 3 months in rats and dogs indicate that the bone marrow and the testes are the target organs of niraparib in both species. These target organ toxicities were observed at exposure levels below those observed in patients at the therapeutic dose of 300 mg. ▪ Bone marrow suppression affects cells of both white and red lineages. It is often heralded by early decreases in reticulocytes, followed by adverse decreases of circulating white and red cells. In rats, infections and septicaemia are considered to have resulted from the depletion of leukocytes (mainly neutrophils).	The adverse non-clinical findings are considered to reflect the exaggerated pharmacology of niraparib. They are monitorable, dose-related, and reproducible across studies and species. All findings were found to be reversible in both species and anticipated to be the same for humans. Clinical data as of 17 May 2019 integrated analysis of PRIMA and NOVA studies: In the NOVA study, 62.1%, 52% and 30.8% of the patients treated with niraparib experienced thrombocytopenia, anaemia and neutropenia events compared to 5%, 6.7%, and 6.1% in the placebo group, respectively. 11.2%, 4.1% and 1.4% of the thrombocytopenia, anaemia and neutropenia events were serious in the niraparib-treated patients compared to 0% in the placebo group. In the PRIMA study, 73%, 71.7% and 46% of the patients dosed with a fixed dose of 300 mg niraparib experienced thrombocytopenia, anaemia and neutropenia events, respectively; 53.8%, 50.3% and 35.5% of the patients dosed with individualised dose of niraparib experienced thrombocytopenia, anaemia and neutropenia events, compared to 4.9%, 17.6%, and 7.8% in the placebo group, respectively. 21.3%, 4.1% and 2.2% of the thrombocytopenia, anaemia and neutropenia events were serious in the fixed-dose of 300 mg niraparib-treated patients compared to 0% in the placebo group; 7.1%, 8.3% and 2.4% of the patients dosed with individualised dose of niraparib experienced thrombocytopenia, anaemia and neutropenia events compared to 0% in the placebo group.
▪ The effect on the spermatogenic epithelium was characterised by a decreased amount of spermatogenic epithelium in dogs andtesticular	Effects on spermatogenesis are not relevant for the indicated population of women with ovarian cancer. The decreased spermatogenesis was largely reversible within 4 weeks of cessation of dosing

germ cell depletion in rats. Extension of dosing from 1 month to 3 months did not lower the no observed adverse effect level (NOAEL) in either species. In a 3-month study, NOAEL for dogs was 4.5 mg/kg/day in 3-month study and NOAEL for rats was 10 mg/kg/day.	and thus, it is not considered to pose an important safety risk for patients.
Reproductive/developmental toxicity ▪ No fertility toxicity studies were conducted.	There are no clinical data on fertility.
▪ In the general toxicity studies, as described above, reversible findings were observed on spermatogenesis, there were no adverse findings caused by niraparib in the female reproductive tract.	Based on its mechanism of action, niraparib is expected to lead to embryo-foetal development toxicity.
▪ No embryo-foetal developmental toxicity studies were performed. In mice, PARP1 and PARP2 double knock-out mutant embryos are not viable and die around the onset of gastrulation, demonstrating that the expression of both PARP1 and PARP2 is essential during early embryogenesis [Menissier de Murcia, 2003]	Niraparib should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy because of the potential embryo-foetal developmentaltoxicity.
Genotoxicity ▪ Niraparib was negative in microbialmutagenesis assays (Ames test) and is not considered mutagenic.	The clastogenicity of niraparib is consistent with its ability to inhibit deoxyribonucleic acid (DNA) repair [Bailey, 1999; Simbulan-Rosenthal, 1999] and observations from other members of this class.
▪ Niraparib was genotoxic in in vitro and in vivo mammalian systems and is considered to be clastogenic.	
Carcinogenicity No carcinogenicity studies were performed for niraparib.	A potential risk for drug related malignancies cannot be excluded. MDS/AML has been identified as a risk associated with niraparib treatment and has been reported in clinical trials and from the postmarketing setting, from both spontaneous sources and postmarketing surveillance programs. In the NOVA study, 5 patients treated with niraparib experienced second primary malignancies (SPM) other than MDS and AML compared to one in the placebo group. In the PRIMA study there were 4 cases of malignancies other than MDS/AML in the fixed dose and none in the individualised dose compared to 3 cases in the placebogroup.

General Safety pharmacology: **Cardiovascular system, including potential effect on the QT interval (QT)** **Cardiovascular system** ▪ Niraparib inhibited human ether a go-go related gene (hERG) potassium current with an IC_{50} value of 15 µM (4800 ng/mL, unbound) in a Good Laboratory Practice (GLP) assay, similar to an IC_{50} of 10 µM observed in the previous non-GLP assay. The IC_{50} of 4800 ng/mL is approximately 20 times the maximum serum concentration (C_{max}) of 238 ng/mL* (unbound) observed in patients (300 mg/day). ▪ In a GLP cardiovascular safety pharmacology study using a Latin square crossover design, dogs (4/sex/group) received single doses of niraparib at 0, 3, 6, or 15 mg/kg via oral gavage. Transient and slight increases in blood pressure (systolic, diastolic and mean arterial pressures) were noted within 7 hours post dose at 15 mg/kg in male and female dogs. These effects were consistent with those observed in a non-GLP cardiovascular study. In that study, 3 anaesthetised, vagotomised male dogs received 3 consecutive ascending doses of niraparib (1, 3, and 10 mg/kg) over 30-minute intravenous infusion periods. Niraparib had no effect on QT/corrected QT interval (QTc) up to and including the highest dose of 10 mg/kg. At that dose, the peak average plasma concentration measured during infusion in dogs was 15.3 ± 1.1 µM (4896 ng/mL total bound and unbound). Peak average plasma concentrations (total bound and unbound) measured during infusion of the 1, and 3 mg/kg doses were 1.2 µM (384 ng/mL) and 3.9 µM (1248 ng/mL) at the 1 and 3 mg/kg dose levels, respectively. Niraparib increased the heart rate in a dose-dependent fashion (+5%, +9%, and +17%). A dose-independent increase (+16% to +21%) in mean arterial pressure was observed from 1 mg/kg. **Central Nervous system (CNS)** In the initial in vitro screening assays, niraparib showed binding to the dopamine transporter (DAT) with IC_{50} of < 5 µM (PD011). In the subsequent in vitro assays (PD012), niraparib inhibited the uptake of dopamine and norepinephrine with IC_{50} values of 24 and 130 nM in	No effects were observed on QTc at plasma levels at up to 4896 ng/mL (or 832 ng/mL unbound) in the anaesthetised, vagotomised male dogs. These results are consistent with results from the human QTc substudy (PR-30-5011C1). In 58 patients who underwent intensive electrocardiogram (ECG) monitoring, no exposure-related positive trends were observed in mean QTcF (QTc using Fridericia's formula) or mean changes from baseline (ΔQTcF) versus time since dosing. More importantly, no statistically significant relationship between ΔQTcF and niraparib plasma concentration was observed (estimated slope: 0.0049, 95% confidence interval: -0.0020, 0.0117). There were no clinically relevant changes in other ECG parameters or abnormal ECG findings attributable to the administration of niraparib. Although maximum increases from baseline in systolic and diastolic blood pressure did not reveal substantial differences between the niraparib and placebo arms, the mean and median greatest increases on treatment were higher for niraparib. In the NOVA study, 23.2% of the patients treated with niraparib experienced hypertension compared to 5.6% in the placebo group. There was only one serious event of hypertension in the niraparib group. In the PRIMA study, 18.7% of the patients dosed with a fixed dose of 300 mg niraparib experienced hypertension; 16.6% of the patients dosed with individualised dose of niraparib experienced hypertension, compared to 7% in the placebo group. There was only one serious event of hypertension in the fixed-dose niraparib group. The clinical relevance of these findings is not known.

human Chinese hamster ovary (CHO)-K1 cells expressing DAT and in human Madin-Darby canine kidney (MDCK) cells expressing norepinephrine transporter (NET), respectively. Data from studies in mice indicated that niraparib does not result in behavioral or neurochemical effects consistent with enhanced dopamine availability in the CNS, nor does it occupy the dopamine reuptake transporter at plasma levels which have been shown to cause anti-tumour activity. Similarly, in a CNS safety pharmacology study, niraparib had no effect on neurological function, including general behaviour, neural reflexes, or spontaneous activity during the 24-hour post-dose period.	
Other toxicity-related information or data (as applicable) **Phototoxicity** Niraparib absorbs in the ultraviolet (UV) spectrum 193-311 nm. In an in vitro screening assay using BALB/c 3T3 mouse fibroblasts, UV light increased the cytotoxicity caused by niraparib. However, based on the inhibitory action of niraparib on DNA repair, the increase of cytotoxicity is most likely due to the inability of the cell to repair the DNA damage caused by UV light. The results from an in vivo phototoxicity study using Long Evans pigmented rats showed no evidence of cutaneous or ocular phototoxicity after a three-day oral administration of niraparib at doses as high as 100 mg/kg/day, demonstrating that niraparib does not have phototoxicity.	Nonclinical data do not indicate the phototoxicity potential of niraparib. Current clinical evidence from the phase 3 NOVA study (PR-30-5011-C) has identified photosensitivity reactions in 8.7% patients treated with niraparib, compared to 0.6% in the placebo group. In the PRIMA study, the person exposure years-adjusted rate for photosensitivity was 0.07 and 0.01 for niraparib and placebo, respectively.

* Based on the previously submitted information in Table 2 of Module 2.7.2 Summary of Clinical Pharmacology Studies submitted to the initial marketing authorisation application (MAA) (electronic common technical document (eCTD) 0000), a steady-state C_{max} value of 4367.55 nM was observed in cancer patients treated with 300 mg niraparib (Part A, Final Intensive). Given a molecular weight of 320.4 Dalton for niraparib (free base) and a protein binding of 83% (17% unbound drug), the unbound niraparib concentration was 238 ng/mL (4367.55 x 0.001 x 320.4 x 0.17).

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Cumulative subject exposure in completed and ongoing studies per treatment arm (niraparib, comparators and placebo) through 26 March 2021 are broken down by demographic variables and presented in Table 2 and Table 3.

Table 2 Cumulative Number of Subjects from Ongoing and Completed GSK-Sponsored Interventional Studies (Safety Population)[1]

	Number of Subjects	
Treatment	**Ongoing**	**Completed**
Niraparib	2064†	180
Placebo	423	0
Comparator*	88	0
Blinded Study**	1423	
Total	3998	180

[1] Data as of 26 March 2021
Studies Included: 3000-01-004(TABLET), PR-30-5010-C(BRAVO), PR-30-5011-C(NOVA), PR-30-5011-QTc(NOVA-QTC), PR-30-5011-FE(NOVA-FE), PR-30-5015-C(ADME), PR-30-5020-C(QUADRA), PR-30-5017-C(PRIMA), 3000-02-001(JASPER), 3000-01-002(IOLITE), 3000-01-003(HEPATIC), 3000-02-004(OVARIO), 3000-01-005(NEOADJUVANT), 3000-PN162-01-001(TOPACIO), MK-4827(PN001), 3000-02-005(OPAL), 3000-02-006(MOONSTONE), 3000-03-005 (FIRST), 213406 (SCOOP) and 213400 (ZEAL-1L).
*Comparator Includes PR-30-5010-C (BRAVO)Physician's choice and 3000-01-002 (IOLITE) Dostarlimab + Carboplatin + Paclitaxel + Bevacizumab + Pemetrexed + Cobolimab treatments.
**3000-03-005 (FIRST) and 213400 (ZEAL-1L) are blinded during the creation of this report
Completed Studies: PR-30-5011-QTc(NOVA-QTC), PR-30-5011-FE(NOVA-FE), PR-30-5015-C(ADME), MK-4827(PN001) and 3000-01-005(NEOADJUVANT).
†Additional 12 subjects have been exposed to niraparib liquid formulation in ongoing taste study 213405.

Table 3 Cumulative Subject Exposure to Niraparib Monotherapy in Completed GSK Sponsored Interventional Studies by Age, Sex and Racial Group[1]

Characteristics	Number of Subjects
Total	180
Age (years)	
≤18	0
19 – 64	128
65 – 84	52
≥85	0
Unknown	0
Sex	
Male	31
Female	149
Racial Group[2]	
White	166

Black	7
Asian	3
Other	2
Unknown	2

[1]Data as of 26 March 2021

Studies Included: PR-30-5011-QTc(NOVA-QTC PR-30-5011-FE(NOVA-FE), PR-30-5015-C(ADME), MK-4827(PN001) and 3000-01-005(NEOADJUVANT).

[2]White, ashkenazi jewish descendant=white, black or African American=black, american indian or alaska native, native hawaiian or other pacific islander, other=other, asian=asian, unknown, not reported, missing=unknown.

Exposure in pivotal studies NOVA and PRIMA

Table 4 Duration of exposure in pivotal studies NOVA and PRIMA

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Parameter	All (N=244)	All (N=484)	Fixed[a] (N=315)	Individualised[b] (N=169)	All (N=179)	Fixed[a] (N=367)	All (N=423)	Fixed[a] (N=682)
Duration of Exposure								
<1 month	3 (1.2)	34 (7.0)	22 (7.0)	12 (7.1)	2 (1.1)	27 (7.4)	5 (1.2)	49 (7.2)
1 to <3 months	35 (14.3)	59 (12.2)	37 (11.7)	22 (13.0)	32 (17.9)	42 (11.4)	67 (15.8)	79 (11.6)
3 to <6 months	47 (19.3)	67 (13.8)	39 (12.4)	28 (16.6)	75 (41.9)	77 (21.0)	122 (28.8)	116 (17.0)
>=6 months	159 (65.2)	324 (66.9)	217 (68.9)	107 (63.3)	70 (39.1)	221 (60.2)	229 (54.1)	438 (64.2)
Person Time (Months) for Duration of Exposure								
<1 month	1.6	19.4	12.7	6.7	1.1	13.5	2.7	26.2
1 to <3 months	81.6	139.3	85.3	54.0	69.9	90.2	151.5	175.5
3 to <6 months	222.0	307.0	177.2	129.8	327.6	348.3	549.7	525.4
>=6 months	2020.2	4543.1	3275.3	1267.9	1167.5	5020.6	3187.7	8295.9
Total Person Time (Months)	2325.4	5008.8	3550.4	1458.4	1566.1	5472.5	3891.5	9022.9

[a] Fixed = A starting dose of 300 mg daily regardless of body weight and platelet count.

[b] Individualised = A starting dose of 200 or 300mg daily depending on body weight and platelet count.

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Table 5 Exposure by age, gender, race and ethnicity in pivotal studies NOVA and PRIMA

		PRIMA				NOVA		Pooled	
		Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Parameter	Statistic	All (N=244)	All (N=484)	Individualised[b] (N=169)	Fixed[a] (N=315)	All (N=179)	Fixed[a] (N=367)	All (N=423)	Fixed[a] (N=682)
Age	n	244	484	169	315	179	367	423	682
	Mean (SD)	61.3 (10.42)	61.1 (10.81)	62.0 (9.80)	60.6 (11.30)	59.8 (9.64)	60.2 (9.63)	60.7 (10.11)	60.4 (10.43)
	SEM	0.67	0.49	0.75	0.64	0.72	0.50	0.49	0.40
	Median	62.0	62.0	63.0	62.0	60.0	61.0	61.0	61.0
	Min, Max	33, 88	32, 85	39, 85	32, 83	34, 82	33, 84	33, 88	32, 84
Age Category									
18 to 64	n (%)	145 (59.4)	294 (60.7)	100 (59.2)	194 (61.6)	117 (65.4)	238 (64.9)	262 (61.9)	432 (63.3)
65 to < 75	n (%)	77 (31.6)	136 (28.1)	52 (30.8)	84 (26.7)	54 (30.2)	106 (28.9)	131 (31.0)	190 (27.9)
>= 65	n (%)	99 (40.6)	190 (39.3)	69 (40.8)	121 (38.4)	62 (34.6)	129 (35.1)	161 (38.1)	250 (36.7)
>= 75	n (%)	22 (9.0)	54 (11.2)	17 (10.1)	37 (11.7)	8 (4.5)	23 (6.3)	30 (7.1)	60 (8.8)

		PRIMA				NOVA		Pooled	
		Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Parameter	Statistic	All (N=244)	All (N=484)	Individualised[b] (N=169)	Fixed[a] (N=315)	All (N=179)	Fixed[a] (N=367)	All (N=423)	Fixed[a] (N=682)
Race									
White	n (%)	218 (89.3)	434 (89.7)	150 (88.8)	284 (90.2)	155 (86.6)	321 (87.5)	373 (88.2)	605 (88.7)
Black or African American	n (%)	2 (0.8)	9 (1.9)	2 (1.2)	7 (2.2)	2 (1.1)	5 (1.4)	4 (0.9)	12 (1.8)
Asian	n (%)	11 (4.5)	14 (2.9)	6 (3.6)	8 (2.5)	6 (3.4)	11 (3.0)	17 (4.0)	19 (2.8)
American Indian or Alaska Native	n (%)	0	1 (0.2)	0	1 (0.3)	0	1 (0.3)	0	2 (0.3)
Native Hawaiian or other Pacific Islander	n (%)	0	1 (0.2)	0	1 (0.3)	0	0	0	1 (0.1)
Other	n (%)	0	0	0	0	0	0	0	0
Unknown	n (%)	1 (0.4)	6 (1.2)	3 (1.8)	3 (1.0)	16 (8.9)	29 (7.9)	17 (4.0)	32 (4.7)
Not Reported	n (%)	12 (4.9)	19 (3.9)	8 (4.7)	11 (3.5)	0	0	12 (2.8)	11 (1.6)
Missing	n	0	0	0	0	0	0	0	0
Ethnicity									
Hispanic or Latino	n (%)	9 (3.7)	28 (5.8)	12 (7.1)	16 (5.1)	6 (3.4)	17 (4.6)	15 (3.5)	33 (4.8)
Not Hispanic or Latino	n (%)	222 (91.0)	429 (88.6)	144 (85.2)	285 (90.5)	154 (86.0)	318 (86.6)	376 (88.9)	603 (88.4)
Unknown	n (%)	9 (3.7)	17 (3.5)	3 (1.8)	14 (4.4)	2 (1.1)	3 (0.8)	11 (2.6)	17 (2.5)
Not Reported	n (%)	4 (1.6)	10 (2.1)	10 (5.9)	0	17 (9.5)	29 (7.9)	21 (5.0)	29 (4.3)
Missing	n	0	0	0	0	0	0	0	0

[a] Fixed = A starting dose of 300 mg daily regardless of body weight and platelet count.

[b] Individualised = A starting dose of 200 or 300mg daily depending on body weight and platelet count.

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PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies withinthe development programme

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Known hypersensitivity to the components of niraparib (NOVA, PRIMA)	To minimise risk to patients.	No	Contraindication; thus, use in this population in the post-marketing period is not anticipated.
Diagnosis, detection, or treatment of invasive cancer other than ovarian cancer ≤ 2 years prior to randomisation (except basal or squamous cell carcinoma of the skin that has been definitively treated) (NOVA)	To avoid confounding evaluation of safety and efficacy.	No	MDS/AML and other malignancies were considered important potential risks at study start.
Immunocompromised patients (NOVA)	To avoid confounding evaluation of safety and efficacy.	No	This exclusion criterion was specific to the clinical study assessment of efficacy, and it is not relevant to the post-marketing setting; all patients with advanced platinum sensitive recurrent ovarian cancer are immunocompromised to a certain degree.
Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include,but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major	To avoid confounding evaluation of safety and efficacy due to study treatment and reduce occurrence of complications of other treatments.	No	Use of niraparib in these patients is very unlikely, because use of niraparib can be postponed until thecondition is successfully treated or patients are medically controlled and stabilised.

seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent (NOVA)			
Patients with known active hepatic disease (i.e. hepatitis B or C) (NOVA)	To avoid confounding evaluation of safety and efficacy due to study treatment and reduce occurrence of complications of other treatments.	No	Niraparib has been studied in moderate hepatic impaired patients and label was updated accordingly with study results.
Patients with a baseline QT prolongation > 470 milliseconds (NOVA)	To avoid confounding evaluation of safety as QTc prolongation was observed in patients during the Phase 1 study PN001, although the association with niraparib was unclear.	No	The relationship between niraparib plasma concentration and change from baseline in the QTcF interval was explored and no exposure-related positive trends were observed in mean QTcF or mean changes from baseline (ΔQTcF) versus time since dosing. More importantly, no statistically significant relationship between ΔQTcF and niraparib plasma concentration was observed. There were no clinically relevant changes in other ECG parameters or abnormal ECG findings attributable to the administration of niraparib. Use in this population is not predicted to be associated with additional risks of clinical significance.
Patients are receiving concomitant medications that prolong QTc and are unable to discontinue use for the duration of the study (NOVA)	QTc analysis in NOVA was performed to determine if there was an effect of niraparib on QTc prolongation and	No	Use in this population is not predicted to be associated with additional risks of clinical significance.

	thus restrictions for drugs known to prolong the QT interval were included.		
Patient has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer (PRIMA)	To avoid confounding the evaluation of efficacy outcomes	No	Use in this population is unlikely as treatment benefit is not known in this population.
Patients with Stage III ovarian cancer who have had complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery (PRIMA)	To avoid confounding the evaluation of efficacy outcomes	No	Use in this population is likely as treatment benefit is expected in this population.
Patient has undergone more than 2 debulking surgeries for the study disease (PRIMA)	To avoid confounding the evaluation of efficacy outcomes	No	Use in this population is not predicted to be associated with additional risks of clinical significance.
Patient is to receive bevacizumab as maintenance treatment. Patients who have received bevacizumab with their first-line platinum based therapy but are unable to receive bevacizumab as maintenance therapy due to adverse events or any other reason are not excluded from study as long as the last dose of bevacizumab was received ≥ 28 days prior to signing the main informed consent form (PRIMA)	To avoid confounding the evaluation of efficacy and safety outcomes	No	Use in this population is not predicted to be associated with additional risks of clinical significance.
Patient has had any known ≥Grade 3 anaemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted>4 weeks (PRIMA)	Potential impact on the efficacy and safety evaluation of the treatment	No	Haematological toxicity (thrombocytopenia, anaemia, neutropenia) is considered an important identified risk.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	2,165 patients were exposed over the whole clinical trial programme.	Adverse drug reaction (ADRs) with a frequency greater than 1 in 721 could be detected if there were no background incidences.
Due to prolonged exposure	A total of 438 patients completed 6 months of treatment with niraparib (see Table 4).	Maintenance therapy with niraparib for a prolonged time is likely in some patients with improved survival. However, the long-term safety information of niraparib is limited. The mean overall treatment duration with niraparib was 13.2 months with maximum overall treatment duration of 61 and 29 months in the NOVA and PRIMA studies, respectively.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 6 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: Patients with severe hepatic impairment	Patients with severe hepatic impairment were not included in the clinical development programme. The patients in the phase 1 and 3 studies included approximately 146 patients with hepatic impairment (based on serum albumin level), including 35 mild and 111 moderate impaired patients.
Patients with severe renal impairment	Patients with severe renal impairment were not included in the clinical development programme.

	The patients in the phase 1 and 3 studies included approximately 302 patients with renal impairment (based on creatinine clearance), including 221 mild and 81 moderate impaired patients.
Patients with cardiovascular impairment	88 out of 372 (23.7%) and 162 out of 484 (33.3%) of the patients took concomitant cardiovascular medications in NOVA and PRIMA, respectively and were exposed to niraparib.
Patients with disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	605 (88.7%) of patients exposed to niraparib were White.
Subpopulations carrying relevant genetic mutation	

			PRIMA			NOVA		Pooled	
		Placebo		**Niraparib**		**Placebo**	**Niraparib**	**Placebo**	**Niraparib**
Parameter	Statistic	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
HRD status									
HRD positive	n (%)	125 (51.2)	245 (50.6)	86 (50.9)	159 (50.5)	121 (67.6)	242 (65.9)	246 (58.2)	401 (58.8)
BRCA mutation	n (%)	70 (28.7)	152 (31.4)	53 (31.4)	99 (31.4	77 (43.0)	171 (46.6)	147 (34.8)	270 (39.6)
non-BRCA mutation and HRD positive	n (%)	55 (22.5)	93 (19.2)	33 (19.5)	60 (19.0	44 (24.6)	71 (19.3)	99 (23.4)	131 (19.2)
HRD negative	n (%)	79 (32.4)	168 (34.7)	61 (36.1)	107 (34.0)	42 (23.5)	92 (25.1)	121 (28.6)	199 (29.2)
HRD not determined	n (%)	40 (16.4)	71 (14.7)	22 (13.0)	49 (15.6	16 (8.9)	33 (9.0)	56 (13.2)	82 (12.0)

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Niraparib 100 mg hard capsule, for oral use, was first authorised for marketing in the US on 27 March 2017 and in the EU on 16 November 2017. Niraparib is also approved in tablet pharmaceutical form in all EEA countries, the US, Japan, UK, and additional countries.

SV.1.1 Method used to calculate exposure

The algorithm used to derive post-approval exposure data utilising sales figures sourced from IQVIA is total number of capsules or tablets/(2 x 365).

SV.1.2 Exposure

The cumulative worldwide exposure of niraparib is 73,980 patient-years as of 26 March 2024.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Given the pharmacological class of niraparib and the absence of psychotropic effects, there is no expected potential for drug abuse and the potential for misuse for illegal purposes is low.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMPsubmission

Table 7 Summary of the safety concerns from Initial RMP v0.4 11 September 2017

Summary of safety concerns	
Important identified risks	Haematological toxicity (thrombocytopenia, anaemia, neutropenia) Hypertension
Important potential risks	MDS and AML SPM other than MDS and AML Embryo-foetal toxicity Pneumonitis
Missing information	Exposure in patients with severe renal impairment and end stage renal disease (ESRD) Exposure in patients with severe hepatic impairment

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

There are none.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk #1: Haematological toxicity (thrombocytopenia, anaemia, neutropenia)

During the clinical study NOVA (clinical study report (CSR) PR-30-5011-C), a total of 225 of 367 patients (61%) treated with niraparib experienced thrombocytopenic events. In comparison, of the patients receiving placebo, only 6% experienced thrombocytopenic events. A total of 184 patients (50 %) experienced anaemia events (anaemia and haemoglobin decreased) and a total of 111 patients (30%) experienced neutropenia events (neutropenia, neutrophil count decreased, and febrile neutropenia).

Risk Benefit Impact

The incidence of thrombocytopenic events decreased over treatment time, indicating that the toxicity was manageable. Thrombocytopenia, anaemia and neutropenia were more common in patients with lower baseline counts or a prior history. If patients were monitored and managed by careful dose reduction, and in some cases transfusions, then the toxicity was predominantly reversible.

Important Identified Risk #2: Hypertension

Hypertension was experienced in 71 of 367 patients receiving niraparib (19%) (CSR PR-30-5011-C). Of these, two patients experienced hypertensive crisis. Grade 3 hypertension was experienced by 32 of 367 patients (9%) and of these 47% had a prior medical history of hypertension. In comparison, only 8 of 179 patients receiving placebo (5%) experienced hypertension and of these 2% were Grade 3 or 4.

Risk-Benefit impact

Hypertension is asymptomatic. In addition to hypertensive crisis, further complications of hypertension include serious cardiovascular disease. Health care professionals are warned about the risk of hypertension including hypertensive crisis within the SmPC. Blood pressure should be monitored throughout treatment. Risk factors including lifestyle, age and family history should be taken into consideration. Although, white patients experienced more events of hypertension at any grade (21%) compared to non-whites (11%), there was no difference in incidence for Grade 3 or 4 across race. Furthermore, patients who had received more than 2 lines of prior platinum therapy were more likely to experience hypertension at any grade (26%) than patients who had received only 2 lines (16%).

Important Potential Risk #1: MDS and AML

MDS is a pre-cancerous abnormality of the bone marrow. MDS can progress to AML, a cancer of the blood and bone marrow, resulting in anaemia, infection, or easy bleeding. Both MDS and AML are serious conditions, which can result in death. Remission is less likely in AML following myelodysplasia or previous cytotoxic chemotherapy. Treatment related MDS/AML is a rare complication of cytotoxic chemotherapy. Accurate incidence data of MDS /AML is poorly captured in cancer patient registries. In the NOVA study, the incidence of MDS/AML was similar in the niraparib arm (5 of 367 patients, 1.4%) and the placebo arm (2 of 179 patients, 1.1%). In total, 9 cases of MDS/AML were reported across all studies included as of DLP of 20 June 2016.

Risk-benefit impact

The potential mechanism of MDS/AML is not known, and as such is not preventable in this treatment population. More general risk factors include age, previous cancer treatments, genetic factors and environmental toxins.

Important Potential Risk #2: SPM other than MDS and AML

Three patients out of a total of 854 patients treated with niraparib have reported SPM other than MDS/AML, which has a cumulative incidence of 0.4%. The types of SPM reported in these three patients are undifferentiated sarcoma, intestinal carcinoma, and lymphocytic leukaemia.

One patient out of 181 patients in the placebo group of NOVA study also reported a SPM event (breast cancer), which has a cumulative incidence of 0.6%.

Risk-benefit impact

Due to the rarity of occurrence of SPM other than MDS/AML in human clinical development studies, there is insufficient evidence to confirm a causal association with niraparib treatment in humans. In general, people with BRCA mutations have an increased risk of getting cancer at an early age, developing breast cancer in both breasts, or developing more than one type of cancer in their lifetime. The benefit of niraparib as an effective treatment for a life-threatening condition like ovarian cancer outweighs the important potential risk of SPM other than MDS/AML thathas yet to be confirmed.

Important Potential Risk #3: Embryo-foetal toxicity

No cases were reported during the clinical development programme (NOVA study).

Risk-benefit impact

There is insufficient evidence to confirm a causal association with niraparib treatment. The SmPC states that niraparib should not be used during pregnancy. Thus, the benefit of niraparib as an effective treatment for a life-threatening condition like ovarian cancer outweighs the potential risk of embryofoetal toxicity.

Important Potential Risk #4: Pneumonitis

In the NOVA study pneumonitis was reported in 3 patients overall, 2 in the niraparib arm and 1 in the placebo arm.

Risk-benefit impact

Due to the rarity of occurrence of pneumonitis in human clinical development studies, there is insufficient evidence to confirm a causal association with niraparib treatment in humans. The benefit of niraparib as an effective treatment for a life-threatening condition like ovarian cancer outweighs the important potential risk of pneumonitis that has yet to be confirmed.

Missing Information #1: Exposure in patients with severe renal impairment and ESRD

There is no formal study of niraparib in patients with renal impairment. However, based on population pharmacokinetics (PK) analysis from pooled Phase 1, 2, and 3 studies (PN001, PR-30-5011-C, PR-30-5020-C, and PR-30-5017-C), body surface-normalized creatinine clearance in the range of 31 to 199 mL/min had no clinically relevant impact on the PK of niraparib.

Risk-benefit impact

The potential benefits as demonstrated with the efficacy may outweigh the risk of use in patients with severe renal impairment and ESRD but sufficient data is not available to make a definitive statement. The SmPC states that there are no data in patients with severe renal impairment or ESRD undergoing haemodialysis and thus caution should be exercised in these patients.

Missing Information #2: Exposure in patients with severe hepatic impairment

There is no formal study of niraparib in patients with severe hepatic impairment. However, based on population PK analysis from pooled Phase 1, 2, and 3 studies (PN001, PR-30-5011-C, PR-30-5020-C, and PR-30-5017-C), serum albumin in the range of 3.4 to 6.6 g/dL had no clinically relevant impact on the PK of niraparib. For the minimum albumin level of 1.7 g/dL, a 1.55-fold higher AUC (95% CI = 1.31, 1.75) was estimated relative to the reference (i.e. 4 g/dL).

Risk-benefit impact

The potential benefits as demonstrated with the efficacy may outweigh the risk of use in patients with severe hepatic impairment but sufficient data is not available to make a definitive statement. The SmPC states that there are no data in patients with severe hepatic impairment and thus caution should be exercised in these patients.

SVII.2 New safety concerns and reclassification with a submission of in updated RMP

The table below summarizes the changes to the list of safety concerns since the initial EU-RMP.

Table 8 Summary of changes to the list of safety concerns

EU-RMP version number	Changes to the list of safety concerns
1.1	Addition of important potential risk of embolic and thrombotic events.
3.0	Included important identified risk of 'neutropenic infections and neutropenic sepsis'.
5.0	The important identified risks of 'Haematological toxicity (thrombocytopenia, anaemia)' and 'Neutropenic infections and neutropenic sepsis' (a risk derived from PBRER#2), were combined and renamed 'Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infections and neutropenic sepsis).
5.0	The CHMP Rapporteur is of opinion, that the inclusion of 'Embryo-foetal toxicity', Pneumonitis' and 'Embolic and thrombotic events' in the safety specification as important potential risks and 'Exposure in patients with severe renal impairment and ESRD' and 'Exposure in patients with severe hepatic impairment' as missing information is not supported. The benefit- risk balance of these safety issues in the indicated populations will continue to be monitored and discussed in aggregate periodic reports; however, routine pharmacovigilance and routine risk minimisation measures are considered sufficient to manage these risks. Therefore, in line with the risk definitions and safety specifications of GVP V, Rev 2, these were removed from the list of safety concerns.
6.0	MDS/AML previously classified as an important potential risk was reclassified as an important identified risk based on an increase in the number of reports of MDS/AML for niraparib, primarily from clinical trials. MDS/AML has also been reported from the postmarketing setting from both spontaneous sources and postmarketing surveillance programs.

SVII.3 Details of important identified risks, important potentialrisks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

The data from PRIMA and NOVA studies are based on integrated analysis of data cut-off of 17 May 2019 unless otherwise noted.

Important Identified Risk: Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infections and neutropenic sepsis)

Potential mechanism(s):	PARP1 trapping onto the chromatin by PARP inhibitors drives cytotoxicity in healthy bone marrow [Hopkins, 2019]. Another possible mechanism is through the dysregulation of interleukin (IL)-12 and IL-23 in antigen presenting cells [Zhao, 2017].
Evidence source(s) and strength of evidence:	**Non-clinical**: Toxicology studies in rats and dogs showed haematologic adverse events, including decreased red cell mass, decreased leukocyte counts in the peripheral blood, decreased circulating platelets, and hypocellularity in the bone marrow. **Clinical**: In the NOVA study, 62.1%, 52% and 30.8% of the patients treated with niraparib experienced thrombocytopenia, anaemia and neutropenia events compared to 5%, 6.7%, and 6.1% in the placebo group, respectively. 11.2%, 4.1% and 1.4% of the thrombocytopenia, anaemia and neutropenia events were serious in the niraparib-treated patients compared to 0% in the placebo group. In the PRIMA study, 73%, 71.7% and 46% of the patients dosed with a fixed dose of 300 mg niraparib experienced thrombocytopenia, anaemia and neutropenia events, respectively; 53.8%, 50.3% and 35.5% of the patients dosed with individualised dose of niraparib experienced thrombocytopenia, anaemia and neutropenia events, compared to 4.9%, 17.6%, and 7.8% in the placebo group, respectively. 21.3%, 4.1% and 2.2% of the thrombocytopenia, anaemia and neutropenia events were serious in the fixed-dose of 300 mg niraparib-treated patients compared to 0% in the placebo group; 7.1%, 8.3% and 2.4% of the patients dosed with individualised dose of niraparib experienced thrombocytopenia, anaemia and neutropenia events compared to 0% in the placebo group. **Class-effect**: Haematological toxicities are known risks of other PARP inhibitors like olaparib and rucaparib [Olaparib SmPC; Rucaparib SmPC]
	Post-marketing experience (PBRER evaluation of clinical and post-marketing data): Cumulatively, up to DLP of 26 Mar 2024, a review of the haematological toxicities cases indicate that they are consistent with the known safety profile of niraparib.

Characterisation of the risk:

Frequency

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Preferred Term	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
Thrombocytopenia Event	12 (4.9)	321 (66.3)	91 (53.8)	230 (73.0)	9 (5.0)	228 (62.1)	21 (5.0)	458 (67.2)
Thrombocytopenia	9 (3.7)	222 (45.9)	57 (33.7)	165 (52.4)	6 (3.4)	171 (46.6)	15 (3.5)	336 (49.3)
Platelet count decreased	3 (1.2)	133 (27.5)	38 (22.5)	95 (30.2)	3 (1.7)	78 (21.3)	6 (1.4)	173 (25.4)
Anaemia Event	43 (17.6)	311 (64.3)	85 (50.3)	226 (71.7)	12 (6.7)	191 (52.0)	55 (13.0)	417 (61.1)
Anaemia	43 (17.6)	307 (63.4)	84 (49.7)	223 (70.8)	12 (6.7)	184 (50.1)	55 (13.0)	407 (59.7)
Haemoglobin decreased	0	5 (1.0)	1 (0.6)	4 (1.3)	0	7 (1.9)	0	11 (1.6)
Red blood cell count decreased	0	4 (0.8)	1 (0.6)	3 (1.0)	0	0	0	3 (0.4)
Anaemia macrocytic	0	1 (0.2)	0	1 (0.3)	0	0	0	1 (0.1)
Haematocrit decreased	0	2 (0.4)	1 (0.6)	1 (0.3)	0	0	0	1 (0.1)
Leukopenia Event	32 (13.1)	241 (49.8)	75 (44.4)	166 (52.7)	22 (12.3)	134 (36.5)	54 (12.8)	300 (44.0)
Neutropenia	16 (6.6)	128 (26.4)	41 (24.3)	87 (27.6)	6 (3.4)	66 (18.0)	22 (5.2)	153 (22.4)
Neutrophil count decreased	5 (2.0)	82 (16.9)	21 (12.4)	61 (19.4)	5 (2.8)	53 (14.4)	10 (2.4)	114 (16.7)
White blood cell count decreased	8 (3.3)	74 (15.3)	23 (13.6)	51 (16.2)	5 (2.8)	42 (11.4)	13 (3.1)	93 (13.6)
Leukopenia	13 (5.3)	57 (11.8)	20 (11.8)	37 (11.7)	9 (5.0)	28 (7.6)	22 (5.2)	65 (9.5)
Lymphocyte count decreased	3 (1.2)	25 (5.2)	9 (5.3)	16 (5.1)	2 (1.1)	8 (2.2)	5 (1.2)	24 (3.5)
Lymphopenia	0	12 (2.5)	2 (1.2)	10 (3.2)	3 (1.7)	6 (1.6)	3 (0.7)	16 (2.3)
Febrile neutropenia	0	4 (0.8)	1 (0.6)	3 (1.0)	0	2 (0.5)	0	5 (0.7)
Monocyte count decreased	0	2 (0.4)	1 (0.6)	1 (0.3)	0	1 (0.3)	0	2 (0.3)
Eosinophil count decreased	0	1 (0.2)	1 (0.6)	0	0	0	0	0
Neutropenic sepsis	0	1 (0.2)	1 (0.6)	0	0	0	0	0
Neutropenia Event	19 (7.8)	205 (42.4)	60 (35.5)	145 (46.0)	11 (6.1)	113 (30.8)	30 (7.1)	258 (37.8)
Neutropenia	16 (6.6)	128 (26.4)	41 (24.3)	87 (27.6)	6 (3.4)	66 (18.0)	22 (5.2)	153 (22.4)
Neutrophil count decreased	5 (2.0)	82 (16.9)	21 (12.4)	61 (19.4)	5 (2.8)	53 (14.4)	10 (2.4)	114 (16.7)
Febrile neutropenia	0	4 (0.8)	1 (0.6)	3 (1.0)	0	2 (0.5)	0	5 (0.7)
Neutropenic sepsis	0	1 (0.2)	1 (0.6)	0	0	0	0	0
Pancytopenia Event	0	2 (0.4)	0	2 (0.6)	0	8 (2.2)	0	10 (1.5)
MDS	0	1 (0.2)	0	1 (0.3)	0	5 (1.4)	0	6 (0.9)
Pancytopenia	0	1 (0.2)	0	1 (0.3)	0	3 (0.8)	0	4 (0.6)

Seriousness and outcomes

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Serious adverse event (SAEs)	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
Thrombocytopenia Event	0	79 (16.3)	12 (7.1)	67 (21.3)	0	41 (11.2)	0	108 (15.8)
Thrombocytopenia	0	59 (12.2)	7 (4.1)	52 (16.5)	0	40 (10.9)	0	92 (13.5)
Platelet count decreased	0	20 (4.1)	5 (3.0)	15 (4.8)	0	1 (0.3)	0	16 (2.3)
Anaemia Event	0	27 (5.6)	14 (8.3)	13 (4.1)	0	15 (4.1)	0	28 (4.1)
Anaemia	0	27 (5.6)	14 (8.3)	13 (4.1)	0	15 (4.1)	0	28 (4.1)
Leukopenia Event	0	11 (2.3)	4 (2.4)	7 (2.2)	0	5 (1.4)	0	12 (1.8)
Neutropenia	0	6 (1.2)	2 (1.2)	4 (1.3)	0	2 (0.5)	0	6 (0.9)
Febrile neutropenia	0	3 (0.6)	1 (0.6)	2 (0.6)	0	2 (0.5)	0	4 (0.6)
Neutrophil count decreased	0	1 (0.2)	0	1 (0.3)	0	1 (0.3)	0	2 (0.3)
Neutropenic sepsis	0	1 (0.2)	1 (0.6)	0	0	0	0	0
Neutropenia Event	0	11 (2.3)	4 (2.4)	7 (2.2)	0	5 (1.4)	0	12 (1.8)
Neutropenia	0	6 (1.2)	2 (1.2)	4 (1.3)	0	2 (0.5)	0	6 (0.9)
Febrile neutropenia	0	3 (0.6)	1 (0.6)	2 (0.6)	0	2 (0.5)	0	4 (0.6)
Neutrophil count decreased	0	1 (0.2)	0	1 (0.3)	0	1 (0.3)	0	2 (0.3)
Neutropenic sepsis	0	1 (0.2)	1 (0.6)	0	0	0	0	0
Pancytopenia Event	0	2 (0.4)	0	2 (0.6)	0	7 (1.9)	0	9 (1.3)
MDS	0	1 (0.2)	0	1 (0.3)	0	4 (1.1)	0	5 (0.7)
Pancytopenia	0	1 (0.2)	0	1 (0.3)	0	3 (0.8)	0	4 (0.6)

Outcomes

	Placebo (n=423)					Niraparib Fixed Dose (n=682)				
		Outcome					Outcome			
Preferred Term	SAE	SAE Recovered /Resolved	SAE Recovered/ Resolved With Sequelae	SAE Did Not Recovered /Resolved	Fatal	SAE	SAE Recovered /Resolved	SAE Recovered/ Resolved With Sequelae	SAE Did Not Recovered /Resolved	Fatal
Thrombocytopenia Event										
Thrombocytopenia	0	0	0	0	0	130	113 (86.9)	17 (13.1)	0	0
Platelet Count Decreased	0	0	0	0	0	20	19 (95.0)	1 (5.0)	0	0
Anaemia Event										
Anaemia	0	0	0	0	0	33	31 (93.9)	2 (6.1)	0	0
Leukopenia Event										
Neutropenia	0	0	0	0	0	6	6 (100.0)	0	0	0
Febrile Neutropenia	0	0	0	0	0	4	3 (75.0)	0	1 (25.0)	0
Neutrophil Count Decreased	0	0	0	0	0	2	2 (100.0)	0	0	0
Neutropenia Event										
Neutropenia	0	0	0	0	0	6	6 (100.0)	0	0	0
Febrile Neutropenia	0	0	0	0	0	4	3 (75.0)	0	1 (25.0)	0
Neutrophil Count Decreased	0	0	0	0	0	2	2 (100.0)	0	0	0
Pancytopenia Event										
MDS	0	0	0	0	0	5	1 (20.0)	0	4 (80.0)	0
Pancytopenia	0	0	0	0	0	5	5 (100.0)	0	0	0

	PRIMA Individualised dose									
	Placebo (n=86)					Niraparib Fixed Dose (n=169)				
		Outcome					Outcome			
Preferred Term	SAE	SAE Recovered /Resolved	SAE Recovered/ Resolved With Sequelae	SAE Did Not Recovered /Resolved	Fatal	SAE	SAE Recovered /Resolved	SAE Recovered/ Resolved With Sequelae	SAE Did Not Recovered /Resolved	Fatal
Thrombocytopenia Event										
Thrombocytopenia	0	0	0	0	0	8	4 (50.0)	4 (50.0)	0	0
Platelet Count Decreased	0	0	0	0	0	6	6 (100.0)	0	0	0
Anaemia Event										
Anaemia	0	0	0	0	0	14	11 (78.6)	3 (21.4)	0	0
Leukopenia Event										
Neutropenia	0	0	0	0	0	2	2 (100.0)	0	0	0
Febrile Neutropenia	0	0	0	0	0	1	1 (100.0)	0	0	0
Neutropenic sepsis	0	0	0	0	0	1	1 (100.0)	0	0	0

Neutropenia Event										
Neutropenia	0	0	0	0	0	2	2 (100.0)	0	0	0
Febrile Neutropenia	0	0	0	0	0	1	1 (100.0	0	0	0
Neutropenic sepsis	0	0	0	0	0	1	1 (100.0)	0	0	0

Severity

	PRIMA				NOVA		Pooled	
Grade ≥ 3	**Placebo**	**Niraparib**			**Placebo**	**Niraparib**	**Placebo**	**Niraparib**
Preferred Term	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
Thrombocytopenia Event	1 (0.4)	188 (38.8)	36 (21.3)	152 (48.3)	1 (0.6)	128 (34.9)	2 (0.5)	280 (41.1)
Thrombocytopenia	1 (0.4)	139 (28.7)	25 (14.8)	114 (36.2)	1 (0.6)	106 (28.9)	2 (0.5)	220 (32.3)
Platelet count decreased	0	63 (13.0)	12 (7.1)	51 (16.2)	0	29 (7.9)	0	80 (11.7)
Anaemia Event	4 (1.6)	150 (31.0)	38 (22.5)	112 (35.6)	0	98 (26.7)	4 (0.9)	210 (30.8)
Anaemia	4 (1.6)	150 (31.0)	38 (22.5)	112 (35.6)	0	96 (26.2)	4 (0.9)	208 (30.5)
Haemoglobin decreased	0	0	0	0	0	2 (0.5)	0	2 (0.3)
Haematocrit decreased	0	1 (0.2)	0	1 (0.3)	0	0	0	1 (0.1)
Red blood cell count decreased	0	1 (0.2)	0	1 (0.3)	0	0	0	1 (0.1)
Leukopenia Event	4 (1.6)	105 (21.7)	27 (16.0)	78 (24.8)	4 (2.2)	83 (22.6)	8 (1.9)	161 (23.6)
Neutropenia	3 (1.2)	62 (12.8)	16 (9.5)	46 (14.6)	1 (0.6)	43 (11.7)	4 (0.9)	89 (13.0)
Neutrophil count decreased	0	37 (7.6)	9 (5.3)	28 (8.9)	2 (1.1)	35 (9.5)	2 (0.5)	63 (9.2)
Leukopenia	0	10 (2.1)	3 (1.8)	7 (2.2)	0	10 (2.7)	0	17 (2.5)
White blood cell count decreased	0	12 (2.5)	5 (3.0)	7 (2.2)	0	10 (2.7)	0	17 (2.5)
Lymphocyte count decreased	1 (0.4)	3 (0.6)	1 (0.6)	2 (0.6)	0	6 (1.6)	1 (0.2)	8 (1.2)
Febrile neutropenia	0	4 (0.8)	1 (0.6)	3 (1.0)	0	2 (0.5)	0	5 (0.7)
Lymphopenia	0	0	0	0	1 (0.6)	1 (0.3)	1 (0.2)	1 (0.1)
Neutropenic sepsis	0	1 (0.2)	1 (0.6)	0	0	0	0	0
Neutropenia Event	3 (1.2)	100 (20.7)	25 (14.8)	75 (23.8)	3 (1.7)	76 (20.7)	6 (1.4)	151 (22.1)
Neutropenia	3 (1.2)	62 (12.8)	16 (9.5)	46 (14.6)	1 (0.6)	43 (11.7)	4 (0.9)	89 (13.0)
Neutrophil count decreased	0	37 (7.6)	9 (5.3)	28 (8.9)	2 (1.1)	35 (9.5)	2 (0.5)	63 (9.2)
Febrile neutropenia	0	4 (0.8)	1 (0.6)	3 (1.0)	0	2 (0.5)	0	5 (0.7)
Neutropenic sepsis	0	1 (0.2)	1 (0.6)	0	0	0	0	0
Pancytopenia Event	0	2 (0.4)	0	2 (0.6)	0	7 (1.9)	0	9 (1.3)
MDS	0	1 (0.2)	0	1 (0.3)	0	4 (1.1)	0	5 (0.7)
Pancytopenia	0	1 (0.2)	0	1 (0.3)	0	3 (0.8)	0	4 (0.6)

Post-marketing experience (PBRER evaluation of clinical and post-marketing data)

Period	Medical dictionary for regulatory activities (MedDRA) terms	No. of cases (sources)	No. of serious cases	No. of events	No. of serious events
27 September 17 to 26 March 18	Broad standardised MedDRA queries (SMQ): Haematopoietic cytopenias	1,676 (1,387 solicited sources, 147 spontaneous, 142 clinical trials)	40%	Not available	Not available

27 March 2018 to 26 September 2018	Broad SMQ: Haematopoietic cytopenias	1,803 (1,676 clinical studies, 127 spontaneous)	39.1%	Not available	Not available
27 September 2018 to 26 March 2019	Broad SMQ Haematopoietic cytopenias	587 (446 Clinical studies, 141 spontaneous)	361	959	379
27-Mar-2019 to 26-Sep-2019	SMQ Haematopoietic cytopenias (broad)	468 (312 post-marketing surveillance, 117 spontaneous, and 39 clinical trial.	321	1442	614
	SMQ Agranulocytosis (narrow) and High level term (HLT) Sepsis, bacteraemia, viraemia, fungemia & HLT Sepsis, bacteraemia, viraemia, fungemia	13 (8 Clinical trial, 3 Spontaneous, and 2 Post-marketing surveillance)	13	15	15
27-Sep-2019 to 26-Mar-2020	SMQ Haematopoietic cytopenias (broad)	456 (261 post-marketing surveillance, 159 spontaneous, and 36 clinical trial).	275	813	238
	SMQ Agranulocytosis (narrow) and High level term (HLT) Sepsis, bacteraemia, viraemia, fungemia & HLT Sepsis, bacteremia, viraemia, fungemia	25 (10 Spontaneous, 8 Clinical trial, and 7 Post-marketing surveillance)	25	31	29
27-Mar-2020 to 26-Sep-2020	SMQ Haematopoietic cytopenias (broad)	788 (461 spontaneous, 274 post-marketing surveillance, and 53 clinical trial)	Not available	852	236
	SMQ Agranulocytosis (narrow) and High level term (HLT) Sepsis, bacteraemia, viraemia, fungemia & HLT Sepsis, bacteraemia, viraemia, fungemia	30 (14 Spontaneous, 9 Clinical trial, and 7 Post-marketing surveillance)	Not available	32	30
27-Sep-2020 to 26-Mar-2021	SMQ Haematopoietic cytopenias (broad)	1,794 (1,002 spontaneous, 673post-marketing surveillance, and 119 clinical trial).	Not available	2,573	694
	SMQ Agranulocytosis (narrow) and High level term (HLT) Sepsis, bacteraemia, viraemia, fungemia & HLT Sepsis, bacteraemia, viraemia, fungemia	71 (33 Clinical trial, 24 Spontaneous, and 14 Post-marketing surveillance)	Not available	73	73

Reversibility

The incidence of thrombocytopenic type events decreased over treatment time. If patients were monitored and managed by careful dose reduction, and in some cases

	transfusions, the toxicity was predominantly reversible. The incidence of neutropenia of patients discontinuing treatment due to infection was low. If patients were monitored and managed by careful dose reduction, and in some cases transfusions, the toxicity was predominantly reversible. *Long-term outcomes* Thrombocytopenia events generally occurred early during niraparib treatment (during Cycle 1) with the incidence decreasing over time; as the number of patients discontinuing treatment due to this event was low, this decrease in incidence is consistent with the toxicity being manageable by dose interruption and dose reduction based on individual patient tolerability. Most events were transient with Grade 3/4 thrombocytopenia resolving within approximately 10 days following interruption of treatment. Most neutropenia events were transient with Grade 3/4 resolving within approximately 10 days following interruption of treatment. *Impact on quality of life* Thrombocytopenia: Symptoms of thrombocytopenia include easy or excessive bruising (purpura), superficial bleeding into the skin that appears as a rash of pinpoint-sized reddish-purple spots (petechiae), prolonged bleeding from cuts, bleeding from gums or nose, and blood in urine or stools. Of note, Grade 3 petechiae and haematoma was only observed in one patient in NOVA. Thrombocytopenia may require platelet transfusion if dose interruption or reduction or niraparib is insufficient to control thrombocytopenia. However, once niraparib dose is modified based on individual patient tolerability, niraparib treatment may continue without further need for additional platelet transfusions. Anaemia: General symptoms of anaemia include fatigue and loss of energy, unusually rapid heartbeat (particularly with exercise), shortness of breath and headache (particularly with exercise), difficulty concentrating, dizziness, pale skin, leg cramps and insomnia. Anaemia may require red blood cell transfusion, if dose interruption or reduction or niraparib is insufficient to control anaemia. Neutropenia: Infections are more likely with neutropenia. Symptoms include fever (100.5°F or higher), chills or sweating, sore throat, sores in the mouth, or a toothache, abdominal pain, anal pain, and pain or burning upon urinating. Neutropenia may be managed by dose interruption or reduction until toxicity reverts to baseline.
Risk factors and risk groups:	Thrombocytopenia: The incidence of on-treatment thrombocytopenia was more common among patients with lower baseline platelet counts (<150,000/µL) with 13 (93%) of 14 patients developing thrombocytopenia compared to those patients with higher baseline levels (<150,000/µL), although the incidence in this group was also high (211 of 352 patients, 60%). Patients with any prior history of thrombocytopenia also had a higher risk (121 of 172 patients, 70%) compared to those without a prior history (104 of 195 patients, 53%). There were no clinically meaningful differences in the overall incidence of any grade thrombocytopenia events based on age or number of prior platinum therapies. Thrombocytopenia events were more commonly reported in the niraparib arm among

	patients who were non-white (72%) compared to white patients (60%) and among patients with lower baseline weight (<67 kg; 67%) compared to those with higher weight (≥67 kg; 56%). Niraparib-treated patients who had a prior history of myelosuppression reported thrombocytopenia events at a higher incidence (64%) than those without a history of myelosuppression (50%). Thrombocytopenia events were also more common among niraparib-treated patients with ovarian cancer (62%) and fallopian tube cancer (67%) compared to those with primary peritoneal cancer (48%). The incidence of Grade 3/4 thrombocytopenia events was higher among niraparib-treated patients who received 2 prior platinum therapies (37%) compared to those who had received >2 prior therapies (26%) and among patients with lower baseline weight (<67 kg, 38%) compared to those with higher weight (≥67 kg, 28%). There was no effect of age, race, cancer subtype, or history of myelosuppression on the incidence of Grade 3/4 thrombocytopenia events. Thrombocytopenia events were more common in niraparib-treated patients who had a germline breast cancer gene mutation (g*BRCA*mut) (97 of 136 patients, 71%) compared to patients who did not (non-g*BRCA*mut; 128 of 231 patients, 55%). Analysis conducted by the Sponsor identified two clinical variables, body weight (<77 kg) and platelet count (<150,000/µL) associated with high-grade (i.e. grade 3-4 thrombocytopenia); patients with baseline body weight < 77 kg or baseline platelet count <150,000/µL platelets showed higher incidence of grade 3 or 4 thrombocytopenia during the first cycle of niraparib than patients with weight ≥77 kg and platelet count ≥150,000/µL. For patients who weigh less than 77 kg (170 lbs) or have baseline platelet count <150,000/µL, the recommended starting dose of ZEJULA is 200 mg (two 100 mg capsules or tablets) taken orally once daily. For all others, the recommended starting dose is 300 mg (three 100 mg capsules or tablets). If patients were monitored and managed by careful dose reduction, and in some cases transfusions, then the toxicity was generally reversible. The PRIMA study adopted the modified starting dose and this study safety analyses indicated that reducing the starting dose to 200 mg in these patients could reduce the incidence of grade 3 or 4 thrombocytopenia without compromising the efficacy of Zejula. <u>Anaemia</u>: The incidence of on-treatment anaemia was more common among patients with lower baseline haemoglobin concentration (<10 g/dL) with 18 (82%) of 22 patients developing anaemia compared to those patients with higher baseline levels (≥12 g/dL), although the incidence in this group was also high (63 of 154 patients, 41%). Patients with any prior history of anaemia also had a somewhat higher risk (126 of 236 patients, 53%) compared to those without a prior history (58 of 131 patients, 44%). There was no considerable difference in the incidence of anaemia events or Grade 3/4 anaemia events based on age, race, number of prior platinum therapies, or prior myelosuppression. Anaemia events were more common among niraparib-treated patients with lower baseline weight (<67 kg; 57%) compared to those with higher

	weight (≥67 kg; 43%) and in patients with ovarian cancer (52%) compared to those with fallopian tube cancer (41%) or primary peritoneal cancer (42%). The incidence of Grade 3 or 4 anaemia events was also higher among niraparib-treated patients with ovarian cancer (27%) compared to those with fallopian tube cancer (15%) or primary peritoneal cancer (16%). The incidence of Grade 3/4 anaemia events was higher among niraparib-treated patients in the g*BRCA*mut cohort (33%) compared to the non-g*BRCA*mut cohort (21%). Neutropenia: The incidence of on-treatment neutropenia was most common among patients with a prior history of Grade 4 neutropenia (20 of 36 patients, 56%) and was also more common among patients with any prior history of neutropenia (75 of 206 patients, 36%) compared to those without a prior history (36 of 161 patients, 22%). There was no considerable difference in the incidence of neutropenia events regardless of grade or for Grade 3/4 neutropenia events based on age, race, number of prior platinum therapies or cancer subtype. Patients with lower baseline weight (<67 kg) had a higher incidence of neutropenia events (38%) compared to those with higher weight (≥67 kg; 22%); similarly, patients who had a prior history of myelosuppression had a higher incidence (33%) compared to those without a history of myelosuppression (21%). The incidence of Grade 3/4 neutropenia events was higher in patients with lower baseline weight (24%) compared to those with higher weight (16%); the incidence of Grade 3/4 events was 21% for patients with a history of myelosuppression and 15% for those without a reported history. Overall, neutropenia events were reported at similar incidences among niraparib-treated patients in the g*BRCA*mut cohort (42 of 136 patients, 31%) compared to patients in the non-g*BRCA*mut cohort (69 of 231 patients, 30%). The incidence of Grade 3/4 neutropenia events was similar among niraparib-treated patients in the g*BRCA*mut cohort (21%) and in the non-g*BRCA*mut cohort (19%).
Preventability:	Section 4.2 of the SmPC states that haematologic adverse reactions have been observed during the treatment with Zejula especially during the initial phase of the treatment. It is therefore recommended to monitor complete blood counts weekly during the first month of treatment and modify the dose as needed. After the first month, it is recommended to monitor complete blood counts monthly and periodically after this time. Based on individual laboratory values, weekly monitoring for the second month may be warranted. Thrombocytopenia: At first occurrence of thrombocytopenia treatment with niraparib should be withheld for a maximum of 28 days and blood counts should be monitored weekly until platelet counts return to ≥ 100,000/µL. Treatment should be resumed at same or reduced dose based on clinical evaluation. If platelet count is < 75,000/µL at any time, treatment should be resumed at a reduced dose. At second occurrence of thrombocytopenia treatment with niraparib should be withheld for a maximum of 28 days and blood counts should be monitored weekly until platelet counts return to ≥ 100,000/µL. Treatment should be resumed at a reduced dose and discontinued if the platelet count has not returned to acceptable levels within 28 days of the dose

	interruption period, or if the patient has already undergone dose reduction to 100 mg once daily (QD). For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors for bleeding such as co administration of anticoagulation or antiplatelet medicinal products, interrupting these substances should be considered and/or transfusion at a higher platelet count. Treatment should be resumed at a reduced dose. Anaemia: Treatment with niraparib should be withheld for a maximum of 28 days and blood counts should be monitored weekly until haemoglobin returns to ≥ 9 g/dL. Treatment should be resumed at a reduced dose and discontinued if the haemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD. Neutropenia: Treatment with niraparib should be withheld for a maximum of 28 days and blood counts should be monitored weekly until neutrophil counts return to ≥ 1,500/µL. Treatment should be resumed at a reduced dose and discontinued if the neutrophils have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD. Section 4.4 of the SmPC states that if a patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, Zejula should be discontinued. Testing complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time is recommended to monitor for clinically significant changes in any haematologic parameter during treatment. Due to the risk of thrombocytopenia, anticoagulants and medicinal products known to reduce the thrombocyte count should be used with caution.
Impact on the risk-benefit balance of the product:	Haematological toxicity may have a significant impact on the patient requiring medical care, hospitalisation or be life-threatening in serious cases. Routine pharmacovigilance activities will further characterise the risk of haematological toxicity with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical study data. Advice on how to minimise the risk of haematological toxicity is disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive.
Public health impact:	Due to the small number of patients affected by the indication, the public health impact is considered minimal.

Important Identified Risk: Hypertension

Potential mechanism(s):

There is no proposed mechanism for hypertension relating to niraparib.
Primary hypertension results from a complex interaction of genes and environmental factors. In most people with established hypertension, increased resistance to blood flow (total peripheral resistance) accounts for the high pressure while cardiac output remains normal. Most evidence implicates either disturbances in the kidneys' salt and water handling and/or abnormalities of the sympathetic nervous system. These mechanisms are not mutually exclusive, and it is likely that both contribute to some extent in most cases of primary hypertension. It has also been suggested that endothelial dysfunction and vascular inflammation may also contribute to increased peripheral resistance and vascular damage in hypertension [Oparil, 2003].

Evidence source(s) and strength of evidence:

Clinical: In the NOVA study, 23.2% of the patients treated with niraparib experienced hypertension compared to 5.6% in the placebo group. There was only one serious event of hypertension in the niraparib group.
In the PRIMA study, 18.7% of the patients dosed with a fixed dose of 300 mg niraparib experienced hypertension; 16.6% of the patients dosed with individualised dose of niraparib experienced hypertension, compared to 7% in the placebo group. There was only one serious event of hypertension in the fixed-dose niraparib group.
Post-marketing experience (PBRER evaluation of clinical and post-marketing data): Serial reviews of hypertension cases over time, up to DLP of 26 Mar 2024, indicate that they are consistent with the known safety profile of niraparib.

Characterisation of the risk

Frequency

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Preferred Term	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
Hypertension Event	17 (7.0)	87 (18.0)	28 (16.6)	59 (18.7)	10 (5.6)	85 (23.2)	27 (6.4)	144 (21.1)
Hypertension	17 (7.0)	82 (16.9)	27 (16.0)	55 (17.5)	9 (5.0)	83 (22.6)	26 (6.1)	138 (20.2)
Blood pressure increased	0	5 (1.0)	1 (0.6)	4 (1.3)	1 (0.6)	1 (0.3)	1 (0.2)	5 (0.7)
Hypertensive crisis	0	0	0	0	0	2 (0.5)	0	2 (0.3)
Blood pressure fluctuation	0	1 (0.2)	0	1 (0.3)	0	0	0	1 (0.1)

Seriousness and outcomes

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
SAEs	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
Hypertension Event	0	1 (0.2)	0	1 (0.3)	0	1 (0.3)	0	2 (0.3)
Hypertension	0	1 (0.2)	0	1 (0.3)	0	0	0	1 (0.1)
Hypertensive crisis	0	0	0	0	0	1 (0.3)	0	1 (0.1)

Outcomes

	Placebo (n=423)					Niraparib Fixed Dose (n=682)				
		Outcome					Outcome			
Preferred Term	SAE	SAE Recovered /Resolved	SAE Recovered/ Resolved With Sequelae	SAE Did Not Recovered /Resolved	Fatal	SAE	SAE Recovered /Resolved	SAE Recovered/ Resolved With Sequelae	SAE Did Not Recovered /Resolved	Fatal
Hypertension Event										
Hypertension	0	0	0	0	0	1	1 (100.0)	0	0	0
Hypertensive Crisis	0	0	0	0	0	1	1 (100.0)	0	0	0

Severity

	PRIMA				NOVA		Pooled	
Grade ≥ 3	**Placebo**	**Niraparib**			**Placebo**	**Niraparib**	**Placebo**	**Niraparib**
Preferred Term	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
Hypertension Event	3 (1.2)	30 (6.2)	9 (5.3)	21 (6.7)	4 (2.2)	36 (9.8)	7 (1.7)	57 (8.4)
Hypertension	3 (1.2)	29 (6.0)	9 (5.3)	20 (6.3)	4 (2.2)	34 (9.3)	7 (1.7)	54 (7.9)
Hypertensive crisis	0	0	0	0	0	2 (0.5)	0	2 (0.3)
Blood pressure increased	0	1 (0.2)	0	1 (0.3)	0	0	0	1 (0.1)

Post-marketing experience (PBRER evaluation of clinical and post-marketing data)

Period	MedDRA terms	No. of cases (sources)	No. of serious cases	No. of events	No. of serious events
27 September 17 to 26 March 18	SMQ: Hypertension	621 (581 solicited, 38 spontaneous, 2 clinical trials)	Not available	Not available	Not available
27 March 2018 to 26 September 2018	Broad SMQ Hypertension	232	124	742	327
27 September 2018 to 26 March 2019	Narrow SMQ Hypertension	520	320	530	372
27-Mar-2019 to 26-Sep-2019	SMQ Hypertension (narrow)	190	Not available	199	29
27-Sep-2019 to 26-Mar-2020	SMQ Hypertension (narrow)	173 (128 Post-marketing surveillance, 42 Spontaneous, and 3 Clinical trial)	59	173	16
27-Mar-2020 to 26-Sep-2020	SMQ Hypertension (narrow)	441 (248 Spontaneous, 190 Post-marketing surveillance, and 3 Clinical trial)	Not available	525	8
27-Sep-2020 to 26-Mar-2021	SMQ Hypertension (narrow)	961 (529 Spontaneous, 426 Post-marketing surveillance, and 6 Clinical trial)	Not available	1013	50

	Reversibility Medication can normalise blood pressure. Changes in lifestyle risk factors, for example reducing salt intake, smoking cessation and reducing alcohol consumption can all improve increased blood pressure values. *Long-term outcomes* The long-term outcome of niraparib patients with hypertension is currently not known. In the general population, hypertension is asymptomatic and treatable. However, if left untreated can progress to serious complications including long term co-morbidities and in some cases events with fatal outcomes. *Impact on quality of life* Generally, hypertension is asymptomatic. Complications of hypertension include heart failure, coronary artery disease, stroke, renal disease, and peripheral arterial disease.
Risk factors and risk groups	There are multiple risk factors for hypertension in the general population including: Lifestyle factors (excess salt intake, excess body weight, smoking, alcohol), renal disease, endocrine disease, and family history. The incidence rates of treatment-emergent adverse events (TEAEs) of hypertension regardless of grade and of Grade 3 hypertension were similar in patients <65 years and those ≥65 years who received niraparib. Patients in the niraparib arm who are White were more likely to have hypertension of any grade reported as a TEAE(21%) compared to non-whites (11%); the incidence of Grade 3 hypertension was similar across race. Patients in the niraparib arm who had received more than 2 lines of prior platinum therapy were more likely to experience hypertension of any grade (26%) and Grade 3 hypertension (13%) compared to those who had received only 2 prior lines (16% and 6%, respectively). There were no substantial differences in the incidence of hypertension across cancer subtype.
Preventability	Healthcare professionals are warned about the risk of hypertension, including hypertensive crisis, in section 4.4 of the SmPC. Pre-existing hypertension should be adequately controlled before starting Zejula treatment. Blood pressure should be monitored at least weekly for the first two months, monitored monthly afterwards for the first year and periodically thereafter during treatment with Zejula. Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the Zejula dose, if necessary. Zejula should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy. In addition, healthy and balanced diet, smoking abstention, regular physical exercise and a reduction in alcohol, caffeine and sodium intake are advised by National Institute for Health and Care Excellence (NICE) guideline, CG127.
Impact on the risk-benefit balance of the product:	Hypertension may have serious outcomes in severe cases. Routine pharmacovigilance activities will further characterise the risk of hypertension with respect to number of reports, seriousness, outcome, and risk factors and

	whether experience in the post marketing setting is consistent with the information already known for this risk from clinical study data. Advice on how to minimise the risk of hypertension is disseminated through routine risk minimisation measures (i.e., blood pressure monitoring and treatment with hypertensive medications) to ensure that the benefit-risk for the product remains positive.
Public health impact:	Due to the small number of patients affected by the indication, the public health impact is considered minimal.

Important Identified Risk: MDS and AML

Potential mechanism(s):	The mechanism(s) contributing to or driving the occurrence of secondary malignancies have not been identified. It is possible that DNA-repair deficiencies resulting from PARP inhibition and/or BRCA mutations may be involved; however, patients with ovarian cancer have typically been pretreated with cytotoxic chemotherapy which makes it difficult to determine the causality of secondary malignancies.
Evidence source(s) and strength of evidence:	**Clinical**: In the niraparib clinical development program as of 26 Mar 2021, the overall cumulative incidence of MDS/AML unadjusted for duration of follow-up, was comparable between the pooled niraparib treatment group and placebo group (1.0% vs. 0.9%). The total number of cases were 23 in niraparib arm and 4 in placebo arm in GSK sponsored and unblinded clinical trials. In PR-30-5011-C NOVA study (median follow up time of 5.6 years, data cut-off of 01 October 2020) where patients with recurrent ovarian cancer were pre-exposed to 2 or more lines of platinum-based chemotherapies, the subject incidence of MDS/AML was higher in niraparib arm (3.5%) than that in the placebo arm (1.7%). The exposure adjusted event rate was also higher among the niraparib treated patients compared to placebo, 0.0117 and 0.0055 events per patient follow-up year, respectively. The incidences in NOVA are similar to the MDS/AML 3-year cumulative incidences of 3.5% among PARPi treated patients and 2.1% among controls reported in a meta-analysis of randomized trials of PARPi (Nitecki et al, 2021). In the g*BRCA*mut and non-g*BRCA*mut cohorts, the incidence of MDS/AML was 6.6% and 1.7%in patients receiving niraparib and 3.1% and 0.9% in patients receiving placebo, respectively. In PR-30-5017-C PRIMA (median follow up time of 6.2 years, data cut-off of 08 April 2024) where patients with advanced ovarian cancer were pre-exposed to 1 line of platinum-based chemotherapies, the incidence of MDS/AML was 2.3% in patients receiving niraparib and 1.6% in patients receiving placebo. The incidence rate per patient follow-up year of MDS/AML was 0.0062 in the niraparib arm and 0.0046 in the placebo arm.

	In PASS study 3000-04-001/GSK 213705, as of the database lock date of 11 July 2024, 1762.6 patient-years were accumulated (322.9 patient-years accumulated in 1LM patients and 1439.6 patient-years accumulated in 2LM+ patients, median duration of niraparib treatment was 11.0 months in the 1LM cohort and 10.4 months in the 2LM+ cohort). There was a total of 9 (1.2%) patients with MDS/AML events observed with a corresponding MDS/AML incidence rate of 0.51 (95% CI: 0.23, 0.97) per 100 patient-years. Two patients had two events, for a total of 11 MDS/AML events. All events occurred in the 2LM+ population (incidence rate 0.62 [95% CI: 0.29, 1.18] per 100 patient-years). **Class-effect**: MDS and AML are known risks of other PARP inhibitors like olaparib and rucaparib [Olaparib SmPC; Rucaparib SmPC] **Post-marketing experience (PBRER evaluation of clinical and post-marketing data)**: Cumulatively, up to 26 Mar 2024, MDS/AML has been reported from the postmarketing setting, from both spontaneous sources and postmarketing surveillance programs. Disproportional analyses showed relative higher reporting of MDS/AML associated with the use of niraparib in the GSK global safety database, FAERS database and EudraVigilance database.

Characterisation of the risk

Data as of 17 May 2019 integrated analysis of PRIMA and NOVA studies

Frequency

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Preferred Term	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
MDS/AML Event	0	1 (0.2)	0	1 (0.3)	0	8 (2.2)	0	9 (1.3)
MDS	0	1 (0.2)	0	1 (0.3)	0	5 (1.4)	0	6 (0.9)
AML	0	0	0	0	0	5 (1.4)	0	5 (0.7)

Seriousness and outcomes

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
SAEs	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
MDS/AML Event	0	1 (0.2)	0	1 (0.3)	0	7 (1.9)	0	8 (1.2)
MDS	0	1 (0.2)	0	1 (0.3)	0	4 (1.1)	0	5 (0.7)
AML	0	0	0	0	0	5 (1.4)	0	5 (0.7)

Outcomes

	Placebo (n=423)					Niraparib Fixed Dose (n=682)				
		Outcome					Outcome			
Preferred Term	SAE	SAE Recovered /Resolved	SAE Recovered/ Resolved With Sequelae	SAE Did Not Recovered /Resolved	Fatal	SAE	SAE Recovered /Resolved	SAE Recovered/ Resolved With Sequelae	SAE Did Not Recovered /Resolved	Fatal
MDS/AML Event										
MDS	0	0	0	0	0	5	1 (20.0)	0	4 (80.0)	0
AML	0	0	0	0	0	5	0	0	2 (40.0)	2 (40.0)

everity

	PRIMA				NOVA		Pooled	
Grade ≥ 3	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Preferred Term	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
MDS/AML Event	0	1 (0.2)	0	1 (0.3)	0	7 (1.9)	0	8 (1.2)
MDS	0	1 (0.2)	0	1 (0.3)	0	4 (1.1)	0	5 (0.7)
AML	0	0	0	0	0	5 (1.4)	0	5 (0.7)

Post-marketing experience (PBRER evaluation of clinical and post-marketing data)

Period	MedDRA terms	No. of cases (sources)
27 September 17 to 26 March 18	SMQ: MDS and HLT: Leukaemias acute myeloid	3 MDS, 1AML
27 March 2018 to 26 September 2018	SMQ: MDS and HLT: Leukaemias acute myeloid	4 MDS, 3 AML
27 September 2018 to 26 March 2019	Broad SMQ MDS and HLT Leukaemias acute myeloid	4 MDS, 5 AML

	<table><tr><td>27-Mar-2019 to 26-Sep-2019</td><td>SMQ MDS (broad) and HLT Leukaemias acute myeloid</td><td>6 MDS, 2 AML and 1 MDS and AML (1 Post-marketing surveillance, 2 Clinical trial, and 6 Spontaneous)</td></tr><tr><td>27-Sep-2019 to 26-Mar-2020</td><td>SMQ MDS (broad) and HLT Leukaemias acute myeloid</td><td>4 reported MDS, and 4 reported AML (7 Spontaneous, and 1 Clinical trial).</td></tr><tr><td>27-Mar-2020 to 26-Sep-2020</td><td>SMQ MDS (broad) and HLT Leukaemias acute myeloid</td><td>8 reported MDS, 3 reported AML, and 1 case reported both events (8 Spontaneous, and 4 Post-marketing surveillance).</td></tr><tr><td>27-Sep-2020 to 26-Mar-2021</td><td>SMQ MDS (broad) and HLT Leukaemias acute myeloid</td><td>14 reported MDS and 13 reported AML (11 Post-marketing surveillance, 10 Clinical trial 6 Spontaneous).</td></tr></table> *Reversibility* Reversibility of MDS/AML is unlikely in all patient populations. Remission is less likely in AML following myelodysplasia or previous cytotoxic chemotherapy. *Long-term outcomes* MDS/AML in a patient population already experiencing a primary malignancy is a serious debilitating condition and fatal outcomes have been reported in the niraparib clinical development program. *Impact on quality of life* MDS is a pre-cancerous abnormality of the bone marrow. Symptoms include weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness and blood in urine or stools. MDS can progress to AML, a cancer of the blood and bone marrow, resulting in anaemia, infection, or easy bleeding. Both MDS and AML are serious conditions, which can result in death. Remission is less likely in AML following myelodysplasia or previous cytotoxic chemotherapy.
Risk factors and risk groups	All clinical trial patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in g*BRCA*mut carriers. Some of the patients had a history of previous cancer or of bone marrow suppression. More general risk factors include the following: ▪ Increased age. ▪ Previous cancer therapy including radiotherapy, alkylating agents, epipodophyllotoxins, topoisomerase II inhibitors or colony-stimulating factors used to stimulate marrow function during chemotherapy[Hershman, 2007; Hijiya, 2009]. ▪ Prolonged use of alkylator therapy for other illnesses – e.g. rheumatological disease. ▪ Environmental toxins, especially benzene and other organicsolvents, smoking, petroleum products, fertilisers, semi-metal, stone dustsand

	cereal dusts. Exposure to benzene can produce aplastic anaemia and pancytopenia, which can progress to AML. ▪ Other genetically associated diseases – e.g. Schwachman-Diamond syndrome, Fanconi's anaemia and neurofibromatosis type 1 [ESMO Clinical Practice Guidelines, 2014]. ▪ Antecedent haematological disorders including MDS predispose patients to AML [Catenacci, 2005]. ▪ Genetic risk factors such as p53 or BRCAmutations.
Preventability	MDS/AML is not preventable as such since it is a risk in the treatment population. Section 4.4 of the SmPC contains a warning about the possible occurrence of MDS/AML and that if MDS and/or AML are confirmed while on treatment with Zejula, treatment should be discontinued permanently, and the patient treated appropriately.
Impact on the risk-benefit balance of the product:	MDS and AML are serious conditions that may be fatal. Routine pharmacovigilance activities further characterise the risk of MDS/AML with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical study data. Advice about the risk of MDS/AML is disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive.
Public health impact:	Due to the small number of patients affected by the indication, the public health impact is considered minimal.

Important Potential Risk: SPM other than MDS and AML

Potential mechanisms	Second primary cancers are linked to treatment with DNA-damaging agents, such as platinum-based chemotherapy. The accumulation of DNA damage in some cells could create genomic instability, which could contribute to the development of second primary cancers. PARP inhibitors do not directly cause DNA damage but reduces the ability of cells to repair DNA single strand breaks, leading to the accumulation of un-repaired double strand breaks, especially in the cells that have a deficient homologous recombination pathway, such as cells with BRCAmutation.
Evidence source(s) and strength of evidence:	**Clinical**: In the NOVA study, 5 patients treated with niraparib experienced SPM other than MDS and AML compared to one in the placebo group. In the PRIMA study there were 4 cases of malignancies other than MDS/AML in the fixed dose and none in the individualised dose compared to 3 cases in the placebo group. In PASS study 3000-04-001/GSK 213705 (data cut-off of 11 July 2024), 1762.6 patient-years were accumulated (322.9 patient-years accumulated in 1LM patients and 1439.6 patient-years accumulated in 2LM+ patients). There were a total of 6 (0.8%) patients with 7 SPM events observed. The SPM incidence rate was 0.34 (95% CI: 0.12, 0.74) per 100 patient-years), there was one patient with SPM in the 1LM population (incidence rate 0.31 [95% CI: 0.01, 1.73] per 100 patient-years) and 5 patients in the 2LM+ population (incidence rate 0.35 [95% CI: 0.11, 0.81] per 100 patient-years). The type of new malignancy reported were non-melanoma skin cancer including basal cell carcinoma and squamous cell carcinoma, breast cancer, head and neck cancer and chronic myeloid leukemia. **Class-effect**: SPM other than MDS and AML are potential risks of other PARP inhibitors like olaparib and rucaparib [Olaparib RMP; Rucaparib RMP].

	Post-marketing experience (PBRER evaluation of clinical and post-marketing data): Cumulatively, up to DLP of 26 Mar 2024, the post-marketing data has not provided support for this potential risk for niraparib.
Characterisation of the risk	*Frequency* **PRIMA** / **NOVA** / **Pooled** **Placebo** / **Niraparib** / **Placebo Niraparib** / **Placebo Niraparib** **Preferred Term**: All (N=244) / All (N=484) / Individualised (N=169) / Fixed (N=315) / All (N=179) / Fixed (N=367) / All (N=423) / Fixed (N=682) New malignancies other than MDS/AML: 3 (1.2) / 4 (0.8) / 0 / 4 (1.3) / 1 (0.6) / 5 (1.4) / 4 (0.9) / 9 (1.3) Basal cell carcinoma: 0 / 1 (0.2) / 0 / 1 (0.3) / 0 / 2 (0.5) / 0 / 3 (0.4) Invasive ductal breast carcinoma: 1 (0.4) / 1 (0.2) / 0 / 1 (0.3) / 0 / 0 / 1 (0.2) / 1 (0.1) Squamous cell carcinoma: 1 (0.4) / 0 / 0 / 0 / 0 / 1 (0.3) / 1 (0.2) / 1 (0.1) Intraductal proliferative breast lesion: 0 / 0 / 0 / 0 / 0 / 1 (0.3) / 0 / 1 (0.1) Invasive breast carcinoma: 0 / 1 (0.2) / 0 / 1 (0.3) / 0 / 0 / 0 / 1 (0.1) Squamous cell carcinoma of skin: 0 / 0 / 0 / 0 / 0 / 1 (0.3) / 0 / 1 (0.1) Thyroid cancer: 0 / 1 (0.2) / 0 / 1 (0.3) / 0 / 0 / 0 / 1 (0.1) Undifferentiated sarcoma: 0 / 0 / 0 / 0 / 0 / 1 (0.3) / 0 / 1 (0.1) Breast cancer: 0 / 0 / 0 / 0 / 1 (0.6) / 0 / 1 (0.2) / 0 Papillary thyroid cancer: 1 (0.4) / 0 / 0 / 0 / 0 / 0 / 1 (0.2) / 0 *Seriousness and outcomes* **PRIMA** / **NOVA** / **Pooled** **Placebo** / **Niraparib** / **Placebo Niraparib** / **Placebo** / **Niraparib** **SAEs**: All (N=244) / All (N=484) / Individualised (N=169) / Fixed (N=315) / All (N=179) / Fixed (N=367) / All (N=423) / Fixed (N=682) **New malignancies other than MDS/AML**: 3 (1.2) / 2 (0.4) / 0 / 2 (0.6) / 1 (0.6) / 2 (0.5) / 4 (0.9) / 4 (0.6) Breast cancer: 0 / 0 / 0 / 0 / 1 (0.6) / 0 / 1 (0.2) / 0 Intraductal proliferative breast lesion: 0 / 0 / 0 / 0 / 0 / 1 (0.3) / 0 / 1 (0.1) Invasive ductal breast carcinoma: 1 (0.4) / 1 (0.2) / 0 / 1 (0.3) / 0 / 0 / 1 (0.2) / 1 (0.1) Papillary thyroid cancer: 1 (0.4) / 0 / 0 / 0 / 0 / 0 / 1 (0.2) / 0 Squamous cell carcinoma: 1 (0.4) / 0 / 0 / 0 / 0 / 0 / 1 (0.2) / 0 Thyroid cancer: 0 / 1 (0.2) / 0 / 1 (0.3) / 0 / 0 / 0 / 1 (0.1) Undifferentiated sarcoma: 0 / 0 / 0 / 0 / 0 / 1 (0.3) / 0 / 1 (0.1) Outcomes **Placebo (n=423)** / **Niraparib Fixed Dose (n=682)** **Outcome** / **Outcome** **Preferred Term**: **SAE** / **SAE Recovered /Resolved** / **SAE Recovered/ Resolved With Sequelae** / **SAE Did Not Recovered /Resolved** / **Fatal** / **SAE** / **SAE Recovered /Resolved** / **SAE Recovered/ Resolved With Sequelae** / **SAE Did Not Recovered /Resolved** / **Fatal** New Malignancies Other Than MDS/AML Breast Cancer: 1 / 1 (100.0) / 0 / 0 / 0 / 0 / 0 / 0 / 0 / 0

Intraductal Proliferative Breast Lesion	0	0	0	0	0	1	1 (100.0)	0	0	0
Invasive Ductal Breast Carcinoma	1	0	0	1 (100.0)	0	1	0	0	1 (100.0)	0
Papillary Thyroid Cancer	1	1 (100.0)	0	0	0	0	0	0	0	0
Squamous Cell Carcinoma	1	1 (100.0)	0	0	0	0	0	0	0	0
Thyroid Cancer	0	0	0	0	0	1	1 (100.0)	0	0	0
Undifferentiated Sarcoma	0	0	0	0	0	1	1 (100.0)	0	0	0

	PRIMA Individualised dose									
	Placebo (n=86)					Niraparib Fixed Dose (n=169)				
		Outcome					Outcome			
Preferred Term	**SAE**	**SAE Recovered /Resolved**	**SAE Recovered/ Resolved With Sequelae**	**SAE Did Not Recovered /Resolved**	**Fatal**	**SAE**	**SAE Recovered /Resolved**	**SAE Recovered/ Resolved With Sequelae**	**SAE Did Not Recovered /Resolved**	**Fatal**
Invasive Ductal Breast Carcinoma	1	0	0	1 (100.0)	0	0	0	0	0	0
Papillary Thyroid Cancer	1	1 (100.0)	0	0	0	0	0	0	0	0
Squamous Cell Carcinoma	1	1 (100.0)	0	0	0	0	0	0	0	0

Severity

	PRIMA				NOVA		Pooled	
Grade ≥ 3	**Placebo**	**Niraparib**			**Placebo**	**Niraparib**	**Placebo**	**Niraparib**
Preferred Term	All (N=244)	All (N=484)	Individualised (N=169)	Fixed (N=315)	All (N=179)	Fixed (N=367)	All (N=423)	Fixed (N=682)
New malignancies other than MDS/AML	1 (0.4)	1 (0.2)	0	1 (0.3)	1 (0.6)	1 (0.3)	2 (0.5)	2 (0.3)
Breast cancer	0	0	0	0	1 (0.6)	0	1 (0.2)	0
Invasive ductal breast carcinoma	0	1 (0.2)	0	1 (0.3)	0	0	0	1 (0.1)
Papillary thyroid cancer	1 (0.4)	0	0	0	0	0	1 (0.2)	0
Undifferentiated sarcoma	0	0	0	0	0	1 (0.3)	0	1 (0.1)

Post-marketing experience (PBRER evaluation of clinical and post-marketing data)

Period	**MedDRA terms**	**No. of cases (sources)**	**No. of serious cases**	**No. of events**	**No. of serious events**
27 September 17 to 26 March 18	SMQ: Malignant tumours	12 (11 solicited, 1 spontaneous)	Not available	Not available	Not available
27 March 2018 to 26 September 2018	Broad SMQ Malignant tumours	36	Not available	Not available	Not available
27 September 2018 to 26 March 2019	Broad SMQ Malignant tumours	48	Not available	55	Not available

27-Mar-2019 to 26-Sep-2019	SMQ Malignancies (broad)	19 (14 Post-Marketing surveillance, 4 Clinical trials, and 1 Spontaneous)	Not available	Not available	Not available
27-Sep-2019 to 26-Mar-2020	SMQ Malignancies (broad)	16 (11 Post-Marketing surveillance, 7 Spontaneous, and 3 Clinical trial)	Not available	Not available	Not available
27-Mar-2020 to 26-Sep-2020	SMQ Malignancies (broad)	11 (7 Spontaneous, 3 Clinical trial, and 1 Post-marketing surveillance)	Not available	Not available	Not available
27-Sep-2020 to 26-Mar-2021	SMQ Malignancies (broad)	41 (23 Post-Marketing surveillance, 16 Spontaneous, and 2 Clinical trial)	41	44	44

Reversibility
Not reversible.

Long-term outcomes
Secondary malignancy is a serious debilitating condition which could result in a fatal outcome.

Impact on quality of life
SPM could have tremendous impact on the individual patient physically and mentally, just like the original malignancies. Depending upon the nature of the malignancies, the symptoms include weakness, feeling tired, fever, weight loss, and pain. They are serious conditions, which require significant medical attentions and, in many cases, they can result in death.

Risk factors and risk groups:

Prior DNA-damaging chemotherapeutic drugs represents a risk factor for development of new malignancies [Livraghi, 2015].
Curtis et al (2006) reported that excluding female genital sites, overall subsequent cancer risk was higher in blacks (O/E=1.42, excess absolute risk (EAR)=29) than whites (ratio of observed to expected cancers (O/E)=1.16, EAR=14). Women younger than age 50 years at ovarian cancer diagnosis, had a 58% increased risk of new malignancies, whereas risk declined to below unity among patients diagnosed at ages older than 70 years. Most of the overall excess was attributable to significantly increased risks for acute leukaemia, as well as for cancers of the breast, colon, rectum, small intestine, bladder, renal pelvis, eye, and intrahepatic bile ducts [Curtis, 2006].
The risk groups or risk factors for the MDS and AML are also applicable to the other SPM (see risk groups or risk factors for MDS and AML above).

Preventability:

SPM, same as MDS/AML, are not preventable as such since they are risks in the treatment population.

Impact on the risk-benefit

SPM other than MDS and AML are serious conditions that may be fatal.
Routine pharmacovigilance activities further characterise the risk of

balance of the product:	SPM other than MDS and AML with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post marketing setting is consistent with the information already known for this risk from clinical study data.
Public health impact:	Due to the small number of patients affected by the indication, the public health impact is considered minimal.

SVII.3.2 Presentation of the missing information

Not applicable.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 9 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infection and neutropenic sepsis) Hypertension MDS and AML
Important potential risks	SPM other than MDS and AML
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are required:

Specific adverse reaction follow-up questionnaires for MDS/AML, SPM other than MDS and AML:

- MDS and AML (Important Identified Risk): A targeted Questionnaire forMDS/AML cases. The purpose is to keep this topic under regular surveillance and to obtain additional follow-up information when cases occur and to monitor outcomes and trends in incidenceand evaluate risk factors. This questionnaire is appended in Annex 4.

- SPM other than MDS and AML (Important Potential Risk): A targeted Questionnaire for SPM. The purpose is to keep this topic under regular surveillance, monitor outcomes and trends in incidence, and evaluate risk factors. This questionnaire is appended in Annex 4.

Other forms of routine pharmacovigilance activities: None

III.2 Additional pharmacovigilance activities

There are no additional pharmacovigilance activities required for this product.

III.3 Summary Table of additional Pharmacovigilance activities

Table 10 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation under exceptional circumstances				
None				
Category 3- Required additional pharmacovigilance activities				
None				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 12 Description of routine risk minimisation measures by safetyconcern

Safety concern	Routine risk minimisation activities
Important identified risk: Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infection and sepsis)	**Routine risk communication:** **SmPC Sections** • 4.2: Posology and method ofadministration • 4.4: Special warnings and precautions for use • 4.8: Undesirable effects **Package leaflet (PL) Sections** • 2. What you need to know before you take Zejula • 3. How to take Zejula • 4. Possible side effects **Routine risk minimisationactivities recommendingspecific clinical measures to address the risk:** **SmPC Sections** • Guidance in SmPC section 4.2 on dosing interruptions and adjustments in cases of haematologicaltoxicity • Warning in SmPC section 4.4 that haematological toxicity is expected and to use caution with anticoagulation and antiplatelet drugs • Testing blood counts and monitoring is recommended in SmPC section 4.4 **PL Sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding low blood-cell counts. • Section 3 mentions that the recommended starting dose is 200mg and if the patient weigh ≥ 77 kg and have platelet count ≥ 150,000/µL before starting treatment, the recommended starting dose is 300 mg. **Other routine risk minimisation measures beyond the Product Information:** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products
Important identified risk: Hypertension	**Routine risk communication:** **SmPC Sections** • 4.4: Special warnings and precautions for use • 4.8: Undesirable effects

	PL Sections • 2. What you need to know before you take Zejula • 4. Possible side effects **Routine risk minimisationactivities recommending specific clinical measures to address the risk:** **SmPC sections** • Warning in SmPC section 4.4 that hypertension has been reported with niraparib therapy and that blood pressure should bemonitored **PL sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding high blood pressure. **Other routine risk minimisation measures beyond the Product Information:** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products
Important identified risk: MDS and AML	**Routine risk communication:** **SmPC Sections** • 4.2: Posology and method of administration • 4.4: Special warnings and precautions for use • 4.8: Undesirable effects **PL Sections** • 2. What you need to know before you take Zejula **Routine risk minimisationactivities recommendingspecific clinical measures to address the risk:** **PL Sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding MDS/AML. • Section 4. Possible side effects **Other routine risk minimisation measures beyond the Product Information:** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products
Important potential risk: SPM other than MDS and AML	**Routine risk communication:** **SmPC Sections** None proposed **PL Sections** Not applicable

	Routine risk minimisationactivities recommendingspecific clinical measures to address the risk: None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 13 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infection and sepsis)	Routine risk minimisation measures: **SmPC sections** • Guidance in SmPC section 4.2 on dosing interruptions and adjustments in cases of haematological toxicity • Warning in SmPC section 4.4 that haematological toxicity is expected and to use caution with anticoagulation and antiplatelet drugs • Testing blood counts and monitoring is recommended in SmPC section 4.4 • Listed as adverse reactions in SmPC section 4.8 **PL Sections** • Section 2 advises the patient to talk to the practitioner before orwhile	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

	taking Zejula regarding low blood-cell counts. • Section 3 mentions that the recommended starting dose is 200 mg and if the patient weigh ≥ 77 kg and have platelet count ≥ 150,000/µL before starting treatment, the recommended starting dose is 300 mg. • Section 4 lists the haematologic side effects under the very common category. **Prescription status** • Prescription only medicine • Use restricted to physicians experiencedin the use of anticancer medicinal products Additional risk minimisation measures: None	
Important identified risk: Hypertension	Routine risk minimisation measures: **SmPC sections** • Warning in SmPC section 4.4 that hypertension has been reported with niraparib therapy and that blood pressure should be monitored • Listed as an adverse reaction in SmPC section 4.8 **PL sections** • Section 2 advises the patient to talk to the practitioner before orwhile taking Zejula regarding high blood pressure. • Section 4 lists highblood pressure under the very common category.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

	Prescription status • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures: None	
Important identified risk: MDS and AML	Routine risk minimisation measures: **SmPC Sections** • Warning in SmPC section 4.4 of the possible occurrence of MDS/AML and for treatment with niraparib to be discontinued if MDS/AML are confirmed • Listed as adverse reactions in SmPC section 4.8 **PL sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding MDS/AML. • Section 4 lists the MDS/AML side effects under the common category. **Prescription Status** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A targeted questionnaire for MDS/AML cases Additional pharmacovigilance activities: None
Important potential risk: SPM other than MDS and AML	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

	Prescription Status • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures: None	• A targeted questionnaire for SPM other than MDS and AML Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Zejula (Niraparib)

This is a summary of the risk management plan (RMP) for Zejula. The RMP details important risks of Zejula, how these risks can be minimised, and how more information will be obtained about Zejula's risks and uncertainties (missing information).

Zejula's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zejula should be used.

This summary of the RMP for Zejula should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zejula's RMP.

I. The medicine and what it is used for

Zejula is authorised for monotherapy for the maintenance treatment of adult 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 and as monotherapy for the 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 (see SmPC for the full indication). It contains Niraparib as the active substance and it is given by oral route.
Further information about the evaluation of Zejula's benefits can be found in Zejula's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: Zejula | European Medicines Agency (europa.eu).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Zejula, together with measures to minimise such risks and the proposed studies for learning more about Zejula's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g.with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Zejula are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zejula. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infection and sepsis) Hypertension MDS and AML
Important potential risks	SPM other than MDS and AML
Missing information	None

II.B Summary of important risks

The data from PRIMA and NOVA studies are based on integrated analysis of data cut-off of 17 May 2019 unless otherwise noted.

Important identified risk: Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infection and sepsis)

Evidence for linking the risk to the medicine	**Non-clinical**: Toxicology studies in rats and dogs showed haematologic adverse events, including decreased red cell mass, decreased leukocyte counts in the peripheral blood, decreased circulating platelets, and hypocellularity in the bone marrow. **Clinical**: In the NOVA study, 62.1%, 52% and 30.8% of the patients treated with niraparib experienced thrombocytopenia, anaemia and neutropenia events compared to 5%, 6.7%, and 6.1% in the placebo group, respectively. 11.2%, 4.1% and 1.4% of the thrombocytopenia, anaemia and neutropenia events were serious in the niraparib- treated patients compared to 0% in the placebo group. In the PRIMA study, 73%, 71.7% and 46% of the patients dosed with a fixed dose of 300 mg niraparib experienced thrombocytopenia, anaemia and neutropenia events, respectively; 53.8%, 50.3% and 35.5% of the patients dosed with individualised dose of niraparib experienced thrombocytopenia, anaemia and neutropenia events, compared to 4.9%, 17.6%, and 7.8% in the placebo group, respectively. 21.3%, 4.1% and 2.2% of the thrombocytopenia, anaemia and neutropenia events were serious in the fixed-dose of 300 mg niraparib-treated patients compared to 0% in the placebo group; 7.1%, 8.3% and 2.4% of the patients dosed with individualised dose of niraparib experienced thrombocytopenia, anaemia and neutropenia events compared to 0% in the placebo group. **Class-effect**: Haematological toxicities are known risks of other PARP inhibitors like olaparib and rucaparib. **Post-marketing experience (PBRER evaluation of clinical and post-marketing data)**: Cumulatively, up to DLP of 26 Mar 2024, a review of the haematological toxicities cases indicate that they are consistent with the known safety profile of niraparib.

Risk factors and risk groups	Thrombocytopenia: The incidence of on-treatment thrombocytopenia was more common among patients with lower baseline platelet counts (<150,000/µL) with 13 (93%) of 14 patients developing thrombocytopenia compared to those patients with higher baseline levels (<150,000/µL), although the incidence in this group was also high (211 of 352 patients, 60%). Patients with any prior history of thrombocytopenia also had a higher risk (121 of 172 patients, 70%) compared to those without a prior history (104 of 195 patients, 53%). There were no clinically meaningful differences in the overall incidence of any grade thrombocytopenia events based on age or number of prior platinum therapies. Thrombocytopenia events were more commonly reported in the niraparib arm among patients who were non-White (72%) compared to white patients (60%) andamong patients with lower baseline weight (<67 kg; 67%) compared to those with higher weight (≥67 kg; 56%). Niraparib-treated patients who had a prior history of myelosuppression reported thrombocytopenia events at a higher incidence (64%) than those without a history of myelosuppression (50%). Thrombocytopenia events were also more common among niraparib-treated patients with ovarian cancer (62%) and fallopian tube cancer (67%) compared to those with primary peritoneal cancer(48%). The incidence of Grade 3/4 thrombocytopenia events was higher among niraparib-treated patients who received 2 prior platinum therapies (37%) compared to those who had received >2 prior therapies (26%) and among patients with lower baseline weight

	(<67 kg, 38%) compared to those with higher weight (≥67 kg, 28%). There was no effect of age, race, cancer subtype, or history of myelosuppression on the incidence of Grade 3/4 thrombocytopenia events. Thrombocytopenia events were more common in niraparib-treated patients who had a germline breast cancer gene mutation (g*BRCA*mut) (97 of 136 patients, 71%) compared to patients who did not (non-g*BRCA*mut; 128 of 231 patients,55%). Analysis conducted by the Sponsor identified two clinical variables, body weight (<77 kg) and platelet count (<150,000/µL) associated with high-grade (i.e., grade 3-4 thrombocytopenia); patients with baseline body weight < 77 kg or baseline platelet count <150,000/µL platelets showed higher incidence of grade 3 or 4 thrombocytopenia during the first cycle of niraparib than patients with weight ≥77 kg and platelet count ≥150,000/µL. For patients who weigh less than 77 kg (170 lbs) or have baseline platelet count <150,000/µL, the recommended starting dose of ZEJULA is 200 mg (two 100 mg capsules or tablets) taken orally once daily. For all others, the recommended starting dose is 300 mg (three 100 mg capsules or tablets). If patients were monitored and managed by careful dose reduction, and in some cases transfusions, then the toxicity was generally reversible. The PRIMA study adopted the modified starting dose and this study safety analyses indicated that reducing the starting dose to 200 mg in these patients could reduce the incidence of grade 3 or 4 thrombocytopenia without compromising the efficacy of Zejula. <u>Anaemia</u>: The incidence of on-treatment anaemia was more common among patients with lower baseline haemoglobin concentration (<10 g/dL) with 18 (82%) of 22 patients developing anaemia compared to those patients with higher baseline levels (≥12 g/dL), although the incidence in this group was also high (63 of 154 patients, 41%). Patients with any prior history of anaemia also had a somewhat higher risk (126 of 236 patients, 53%) compared to those without a prior history (58 of 131 patients, 44%). There was no considerable difference in the incidence of anaemia events or Grade 3/4 anaemia events based on age, race, numberof prior platinum therapies, or prior myelosuppression. Anaemiaevents were more common among niraparib-treated patients with lower baseline weight (<67 kg; 57%) compared to those with higher weight (≥67 kg; 43%) and in patients with ovarian cancer (52%) compared to those with fallopian tube cancer (41%) or primary peritoneal cancer (42%). The incidence of Grade 3 or 4 anaemia events was also higher among niraparib-treated patients with ovarian cancer (27%) compared to those with fallopian tube cancer (15%) or primary peritoneal cancer (16%). The incidence of Grade 3/4 anaemia events was higher among niraparib-treated patients inthe

	g*BRCA*mut cohort (33%) compared to the non-g*BRCA*mut cohort (21%). Neutropenia: The incidence of on-treatment neutropenia was most common among patients with a prior history of Grade 4 neutropenia (20 of 36 patients, 56%) and was also more common among patients with any prior history of neutropenia (75 of 206 patients, 36%) compared to those without a prior history (36 of 161 patients, 22%). There was no considerable difference in the incidence of neutropenia events regardless of grade or for Grade 3/4neutropenia events based on age, race, number of prior platinum therapies or cancer subtype. Patients with lower baseline weight (<67 kg) had a higher incidence of neutropenia events (38%) compared to those with higher weight (≥67 kg; 22%); similarly, patients who had a prior history of myelosuppression had a higher incidence (33%) compared to those without a history of myelosuppression (21%). Theincidence of Grade 3/4 neutropenia events was higher in patients with lower baseline weight (24%) compared to those with higher weight (16%); the incidence of Grade 3/4 events was 21% for patients with a history of myelosuppression and 15% for those without a reported history. Overall, neutropenia events were reported at similar incidences among niraparib-treated patients in the g*BRCA*mut cohort (42 of 136 patients, 31%) compared to patients inthe non-g*BRCA*mut cohort (69 of 231 patients, 30%). The incidence of Grade 3/4 neutropenia events was similar among niraparib-treated patients in the g*BRCA*mut cohort (21%) and in the non-g*BRCA*mut cohort (19%).
Risk minimisation measures	Routine risk minimisation measures: **SmPC sections** • Guidance in SmPC section 4.2 on dosing interruptionsand adjustments in cases of haematological toxicity • Warning in SmPC section 4.4 that haematological toxicity is expected and to use caution with anticoagulation and antiplatelet drugs • Testing blood counts and monitoring is recommended in SmPC section 4.4 • Listed as adverse reactions in SmPC section 4.8 **PL Sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding low blood-cell counts. • Section 3 mentions that the recommended starting dose is 200 mg and if the patient weigh ≥ 77 kg and have platelet count ≥ 150,000/µL before starting treatment, the recommended starting dose is 300 mg.

	• Section 4 lists the haematologic side effects under thevery common category. **Prescription status** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures: None

Important identified risk: Hypertension	
Evidence for linking the risk to the medicine	**Clinical**: In the NOVA study, 23.2% of the patients treated with niraparib experienced hypertension compared to 5.6% in the placebo group. There was only one serious event of hypertension in the niraparib group. In the PRIMA study, 18.7% of the patients dosed with a fixed doseof 300 mg niraparib experienced hypertension; 16.6% of the patients dosed with individualised dose of niraparib experienced hypertension, compared to 7% in the placebo group. There wasonly one serious event of hypertension in the fixed-dose niraparibgroup. **Post-marketing experience (PBRER evaluation of clinical and post-marketing data)**: Serial reviews of hypertension cases over time, up to DLP of 26 Mar 2024, indicate that they are consistent with the known safety profile of niraparib.
Risk factors and risk groups	There are multiple risk factors for hypertension in the general population including: Lifestyle factors (excess salt intake, excess body weight, smoking, alcohol), renal disease, endocrine disease, and family history. The incidence rates of TEAEs of hypertension regardless of grade and of Grade 3 hypertension were similar in patients <65 years and those ≥65 years who received niraparib. Patients in the niraparib arm who are White were more likely to have hypertension of any grade reported as a TEAE (21%) compared to non-Whites (11%); the incidence of Grade 3 hypertension was similar across race. Patients in the niraparib arm who had received more than 2 lines of prior platinum therapy were more likely to experience hypertension of any grade (26%) and Grade 3 hypertension (13%) compared to those who had received only 2 prior lines (16% and 6%, respectively). There were no substantial differences in the incidence of hypertension across cancer subtype.

Risk minimisation measures	Routine risk minimisation measures: **SmPC sections** • Warning in SmPC section 4.4 that hypertension hasbeen reported with niraparib therapy and that blood pressure should be monitored • Listed as an adverse reaction in SmPC section4.8 **PL sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding high bloodpressure. • Section 4 lists high blood pressure under the very common category. **Prescription status** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures None

Important identified risk: MDS and AML	
Evidence for linking the risk to the medicine	**Clinical**: In the niraparib clinical development program up to the cut-off of 26 Mar 2021, the overall cumulative incidence of MDS/AML unadjusted for duration of follow-up, was comparable between the pooled niraparib treatment group and placebo group (1.0% vs. 0.9%). The total number of cases were, 23 in niraparib arm and 4 in placebo arm in GSK sponsored and unblinded clinical trials. However, in PR-30-5011-C NOVA study (median follow up time of 5.6 years, data cut-off of 01 October 2020) where patients with recurrent ovarian cancer were pre- exposed to 2 or more lines of platinum-based chemotherapies, the subject incidence of MDS/AML was higher in niraparib arm (3.5%) than that in the placebo arm (1.7%). This finding is similar to the corresponding 3-year cumulative incidences of 3.5% and 2.1% of MDS/AML reported in published literature of a meta-analysis of randomized trials of PARPi. The event rate per patient follow-up year was 0.0117 and 0.0055, respectively. In g*BRCA*mut and non- g*BRCA*mut cohorts, the incidence of MDS/AML was 6.6% and 1.7% in patients receiving niraparib and 3.1% and 0.9% in patients receiving placebo, respectively. In PR-30-5017-C PRIMA (median follow up time of 6.2 years, data cut-off of 08 April 2024) where patients with advanced ovarian cancer were pre-exposed to 1 line of platinum-based chemotherapies, the incidence of MDS/AML was 2.3% in patients receiving niraparib and 1.6% in patients receiving placebo. The incidence rate per patient follow-up year of MDS/AML was 0.0062 in

	the niraparib arm and 0.0046 in the placebo arm. In PASS study 3000-04-001/GSK 213705, as of the database lock date of 11 July 2024, 1762.6 patient-years were accumulated (322.9 patient-years accumulated in 1LM patients and 1439.6 patient-years accumulated in 2LM+ patients, median duration of niraparib treatment was 11.0 months in the 1LM cohort and 10.4 months in the 2LM+ cohort). There was a total of 9 (1.2%) patients with MDS/AML events observed with a corresponding MDS/AML incidence rate of 0.51 (95% CI: 0.23, 0.97) per 100 patient-years. Two patients had two events, for a total of 11 MDS/AML events. All events occurred in the 2LM+ population (incidence rate 0.62 [95% CI: 0.29, 1.18] per 100 patient-years). **Class-effect**: MDS and AML are known risks of other PARP inhibitors like olaparib and rucaparib [Olaparib SmPC; Rucaparib SmPC] **Post-marketing experience (PBRER evaluation of clinical and post-marketing data)**: Cumulatively, up to DLP of 26 Mar 2024, MDS/AML has been reported from the postmarketing setting from both spontaneous sources and postmarketing surveillance programs. Disproportional analyses showed relative higher reporting of MDS/AML associated with the use of niraparib in the GSK global safety database, FAERS database and EudraVigilance database.

Risk factors and risk groups	All clinical trial patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in g*BRCA*mut carriers. Some of the patients had a history of previous cancer or of bone marrow suppression. More general risk factors include the following: • Increased age. • Previous cancer therapy including radiotherapy, alkylating agents, epipodophyllotoxins, topoisomerase II inhibitorsor colony- stimulating factors used to stimulate marrow function during chemotherapy [Hershman, 2007; Hijiya, 2009]. • Prolonged use of alkylator therapy for other illnesses – e.g., rheumatological disease. • Environmental toxins, especially benzene and other organic solvents, smoking, petroleum products, fertilisers, semi-metal, stone dusts and cereal dusts. Exposure to benzene can produce aplastic anaemia and pancytopenia, which can progress to AML. • Other genetically associated diseases – e.g., Schwachman-Diamond syndrome, Fanconi's anaemia and neurofibromatosis type 1 [ESMO Clinical Practice Guidelines, 2014]. • Antecedent haematological disorders including MDS predispose patients to AML [Catenacci, 2005]. • Genetic risk factors such as p53 or BRCAmutations

Risk minimisation measures	Routine risk minimisation measures: **SmPC Sections** • Warning in SmPC section 4.4 of the possible occurrenceof MDS/AML and for treatment with niraparib to be discontinued if MDS/AML are confirmed • Listed as adverse reactions in SmPC section 4.8 **PL sections** • Section 2 advises the patient to talk to the practitioner before or while taking Zejula regarding MDS/AML. • Section 4 lists the MDS/AML side effects under the common category. **Prescription Status** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures None

Important potential risk: SPM other than MDS and AML	
Evidence for linking the risk to the medicine	**Clinical**: In the NOVA study, 5 patients treated with niraparib experienced SPM other than MDS and AML compared to one in the placebo group. In the PRIMA study there were 4 cases of malignancies other than MDS/AML in the fixed dose and none in the individualised dose compared to 3 cases in the placebo group. In PASS study 3000-04-001/GSK 213705 (data cut-off of 11 July 2024), 1762.6 patient-years were accumulated (322.9 patient-years accumulated in 1LM patients and 1439.6 patient-years accumulated in 2LM+ patients). There were a total of 6 (0.8%) patients with 7 SPM events observed. The SPM incidence rate was 0.34 (95% CI: 0.12, 0.74) per 100 patient-years), there was one patient with SPM in the 1LM population (incidence rate 0.31 [95% CI: 0.01, 1.73] per 100 patient-years) and 5 patients in the 2LM+ population (incidence rate 0.35 [95% CI: 0.11, 0.81] per 100 patient-years). The type of new malignancy reported were non-melanoma skin cancer including basal cell carcinoma and squamous cell carcinoma, breast cancer, head and neck cancer and chronic myeloid leukemia. **Class-effect**: SPM other than MDS and AML are potential risks of other PARP inhibitors like olaparib and rucaparib [Olaparib RMP; Rucaparib RMP]. **Post-marketing experience (PBRER evaluation of clinical and post-marketing data)**: Cumulatively, up to DLP of 26 Mar 2024, the post-marketing data has not provided support for this potential risk for niraparib.

Risk factors and risk groups	Prior DNA-damaging chemotherapeutic drugs represents a risk factor for development of new malignancies [Livraghi, 2015]. Curtis et al (2006) reported that excluding female genital sites, overall subsequent cancer risk was higher in blacks (O/E=1.42, excess absolute risk (EAR)=29) than whites (ratio of observed to expected cancers (O/E)=1.16, EAR=14). Women younger than age 50 years at ovarian cancer diagnosis, had a 58% increased risk of new malignancies, whereas risk declined to below unity among patients diagnosed at ages older than 70 years. Most of the overall excess was attributable to significantly increased risks for acute leukaemia, as well as for cancers of the breast, colon, rectum, small intestine, bladder, renal pelvis, eye, and intrahepatic bile ducts [Curtis, 2006]. The risk groups or risk factors for the MDS and AML are also applicable to the other SPM (see risk groups or risk factors for MDS and AML above).
Risk minimisation measures	Routine risk minimisation measures: **Prescription Status** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

None

II.C.2 Other studies in post-authorisation development plan

There are no additional pharmacovigilance activities required for this product.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Follow-up forms

1. Targeted Questionnaire for MDS/AML cases

2. Targeted Questionnaire for SPM Other Than MDS/AML

GlaxoSmithKline

ZEJULA® (niraparib)

Myeloid Dysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) Questionnaire

Patient/Subject ID: **DOB/Initials:**	**Sex/Weight: (is patient obese if weight unknown?)**	**GSK Case no:**

Report Information

Date Questionnaire completed: DD/MMM/YYYY	**Report Type:** ☐ Initial ☐ Follow-Up	**MDS or AML:** ☐ MDS ☐ AML	**Diagnosis Date of MDS or AML** DD/MMM/YYYY

Reporter Information

Name and Title of Reporter: Reporter=Person reporting the event, not the person completing the form	**Healthcare Professional (HCP):** ☐Yes ☐No **Qualification:** ☐ Consumer/Other NonHCP ☐Lawyer ☐Pharmacist ☐ Physician ☐Other HCP ☐Sales Rep ☐MSL ☐CNE ☐ Other	
Address:	**Phone #:** **Fax#:**	**Email Address:**

Patient Information

Supply information in compliance with local data privacy laws

Patient ID/Initials:	**Age at time of consent:**	**Gender:** ☐ Female ☐ Male	**Ethnicity:**	**Country of Origin:**

Height: ☐ Centimeters ☐Inches	
Weight at baseline : ☐Kilograms ☐ Pounds	

Question 1: Hematology

Please provide information on hemoglobin, absolute neutrophil count, platelet count, bone marrow blast percentage, WHO or IPSS grading at time of diagnosis and treatment administered.

Myeloid Dysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) Questionnaire

Hematologic Adverse Events

Severity Grades:
Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3) , Life-Threatening (Grade 4), Fatal (Grade 5)

AE #	Hematologic Adverse Event (Verbatim)	Severity Grade (1-5)	Onset Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Ongoing
1.		1 2 3 4 5			☐ Yes ☐ No
2.		1 2 3 4 5			☐ Yes ☐ No
3.		1 2 3 4 5			☐ Yes ☐ No
4.		1 2 3 4 5			☐ Yes ☐ No
5.		1 2 3 4 5			☐ Yes ☐ No
6.		1 2 3 4 5			☐ Yes ☐ No

Question 2: Hematological Medical History

Please provide information and treatment on bone marrow failures (myeloid suppression, anemia, thrombocytopenia, leukopenia, neutropenia) or any associated clinical event and symptom

Diagnosis	Treatment	Onset Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Ongoing
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No

Question 3: Family History

Please provide information regarding the patient's family history

Relationship to patient	Diagnosis	Age	Gender

Question 4: Use of Zejula

Dose	Start Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Duration of treatment

Question 5: Prior Chemotherapy Regimens **Include all prior therapies including alkylating agent /platinum-based regimen**				
Chemotherapy Name	**Indication**	**Start Date** DD/MMM/YYYY	**Stop Date** DD/MMM/YYYY	**Duration of Treatment**

Question 6: Prior Drug Treatment Provide hormonal therapies, prolonged steroid use/abuse, and any prior drug treatment (e.g. lenalidomide, dexrazoxane, prolonged use of alkylator therapy for rheumatological disease, etc.) that is known to cause secondary MDS, AML or other blood disorders				
Drug Name	**Indication**	**Onset Date** DD/MMM/YYYY	**Stop Date** **DD/MMM/YYYY**	**Ongoing**
				☐ Yes ☐No
				☐ Yes ☐No
				☐ Yes ☐No
				☐ Yes ☐No
				☐ Yes ☐No
				☐ Yes ☐No

Question 7: Radiation Oncology Therapy Please provide any prior radiation oncology therapy or repeated radiation exposure		
Therapy Type	**Total Cumulative Radiation Dose Received**	**Date of last treatment prior to study enrollment** DD/MMM/YYYY

Question 8: Environmental Exposure		
Smoking Exposure: ☐ Yes ☐No If yes, specify:	**Benzene Exposure:** ☐ Yes ☐No If yes, specify:	**Organic Solvent Exposure:** ☐ Yes ☐No If yes, specify:

Question 9: Genetic Risk Factors

Please provide information on patient's genetic risk factors including P53, BRAC status, genetically associated diseases, etc.

Question 10: Cytogenetic Profile

Please provide information on cytogenetic profile from bone marrow biopsy and FISH Analysis; if any?

Question 11: Hematologic Profile (After MDS/AML Diagnosis)

Lab/Test Name	Date Performed DD/MMM/YYYY	Test Results	Units	Reference Range

Signature

Signature of person completing the form	Date form completed DD/MMM/YYYY

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

GlaxoSmithKline

ZEJULA® (niraparib)

Second Primary Malignancies (Other Than MDS and AML) Questionnaire[a]

Patient/Subject ID: DOB/Initials:	Sex/Weight: (is patient obese if weight unknown?)	GSK Case no:

Report Information

Date Questionnaire completed: DD/MMM/YYYY	Report Type: ☐ Initial ☐ Follow-Up	Diagnosis:	Diagnosis Date DD/MMM/YYYY

Reporter Information

Name and Title of Reporter: Reporter=Person reporting the event, not the person completing the form	Healthcare Professional (HCP): ☐Yes ☐No Qualification: ☐ Consumer/Other NonHCP ☐Lawyer ☐Pharmacist ☐ Physician ☐Other HCP ☐Sales Rep ☐MSL ☐CNE ☐ Other	
Address:	Phone #: Fax#:	Email Address:

Patient Information

Supply information in compliance with local data privacy laws

Patient ID/Initials:	Age at time of consent:	Gender: ☐ Female ☐ Male	Ethnicity:	Country of Origin:
Height: ☐ Centimeters ☐Inches Weight at baseline : ☐Kilograms ☐ Pounds				

Question 1: Diagnosis

Please provide information on the diagnosis, such as the tumor site, tissue and histological classification, stage and supporting evidences such as lab results, histopathological report, and CT/ultrasonic/MRI images impressions or conclusions.

[a] Please use MDS and AML Questionnaire if the diagnosis is MDS or AML.

Second Primary Malignancies (Other Than MDS and AML) Questionnaire[a]

Question 2: Adverse Events

Please provide information on any adverse events

Severity Grades:
Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3) , Life-Threatening (Grade 4), Fatal (Grade 5)

AE #	Adverse Event (Verbatim)	Severity Grade (1-5)	Onset Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Ongoing
1.		1 2 3 4 5			☐ Yes ☐ No
2.		1 2 3 4 5			☐ Yes ☐ No
3.		1 2 3 4 5			☐ Yes ☐ No
4.		1 2 3 4 5			☐ Yes ☐ No
5.		1 2 3 4 5			☐ Yes ☐ No
6.		1 2 3 4 5			☐ Yes ☐ No

Question 3: Medical History

Please provide information and treatment on medical history and any associated clinical event and symptom

Diagnosis	Treatment	Onset Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Ongoing
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No

Question 4: Family History

Please provide information regarding the patient's family history

Relationship to patient	Diagnosis	Age	Gender

Question 5: Use of Zejula

Dose	Start Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Duration of treatment

[a] Please use MDS and AML Questionnaire if the diagnosis is MDS or AML.

Second Primary Malignancies (Other Than MDS and AML) Questionnaire[a]

Question 6: Prior Chemotherapy Regimens

Include all prior therapies including alkylating agent /platinum-based regimen

Chemotherapy Name	Indication	Start Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Duration of Treatment

Question 7: Prior Drug Treatment

Provide hormonal therapies, prolonged steroid use/abuse, and any prior drug treatment (e.g. lenalidomide, dexrazoxane, prolonged use of alkylator therapcy for rheumatological disease, etc.) that is known to cause second primary malignancies

Drug Name	Indication	Onset Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Ongoing
				☐ Yes ☐No
				☐ Yes ☐No
				☐ Yes ☐No
				☐ Yes ☐No
				☐ Yes ☐No
				☐ Yes ☐No

Question 8: Radiation Oncology Therapy

Please provide any prior radiation oncology therapy or repeated radiation exposure

Therapy Type	Total Cumulative Radiation Dose Received	Date of last treatment prior to study enrollment DD/MMM/YYYY

Question 9: Environmental Exposure & Lifestyle

Smoking Exposure:	Alcohol consumption:	Organic Solvent, Asbestos, Heavy Metals Exposure:
☐ Yes ☐No	☐ Yes ☐No	☐ Yes ☐No
If yes, specify:	If yes, specify:	If yes, specify:

[a] Please use MDS and AML Questionnaire if the diagnosis is MDS or AML.

Second Primary Malignancies (Other Than MDS and AML) Questionnaire[a]

Question 10: Genetic Risk Factors
Please provide information on patient's genetic risk factors including P53, BRAC status, genetically associated diseases, etc.

Question 11: Hematologic Profile
(for second primary malignancies in the blood and bone marrow)

Lab/Test Name	Date Performed DD/MMM/YYYY	Test Results	Units	Reference Range

Signature	
Signature of person completing the form	**Date form completed** DD/MMM/YYYY

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

[a] Please use MDS and AML Questionnaire if the diagnosis is MDS or AML.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IFAPPLICABLE)

Not applicable.