17 September 2020
EMA/531223/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zejula

International non-proprietary name: niraparib

Procedure No. EMEA/H/C/004249/II/0019

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALB	albumin
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
AUCss	area under the concentration-time curve at steady state
BICR	blinded independent central review
BRCA	breast cancer susceptibility gene
BRCAmut	mutation in the BRCA gene
BRCAwt	wild type BRCA gene
CA-125	cancer antigen 125
Cave	Average concentration
CL/F	Apparent clearance
Cmax	Maximum concentration
Cmin	Minimum concentration
CBC	complete blood count
CI	confidence interval
COPD	Chronic obstructive pulmonary disease
CR	complete response
CRCL	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D1	duration of zero-order drug release
DCO	Data cut-off
ECG	electrocardiogram
EDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
EQ-5D-5L	European Quality of Life Scale, 5-Dimensions
ETA	inter-individual random effect
FDA	Food and Drug Administration (US)
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy – Ovarian Symptom Index
Frel	Relative bioavailability
FSD	Fixed starting dose
gBRCAmut	germline BRCA mutation
GCIG	Gynecologic Cancer Intergroup
HR	hazard ratio
HRD	homologous recombination deficiency
HR-deficient	homologous recombination deficient status determined by the clinical trial assay developed by Myriad Genetics, Inc.; also referenced in text as HRDpos=positive test result
HR-not determined	homologous recombination status was not determined by the clinical trial assay developed by Myriad Genetics, Inc.; also referenced in text as HRDnd=not determined test result
HR-proficient	homologous recombination proficient status determined by the clinical trial assay developed by Myriad Genetics, Inc.; also referenced in text as HRDneg=negative test result
HUI	health utility index
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Review Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISD	Individualised starting dose
ITT	intent-to-treat (population)
Ka	First-order absorption rate constant
KM	Kaplan-Meier
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures

MRI	magnetic resonance imaging
NACT	neoadjuvant chemotherapy
NCI	National Cancer Institute
NCRCL	body surface area-normalised creatinine clearance
NONMEM	nonlinear mixed-effects modelling software
OFV	objective function value
OS	overall survival
PARP	poly(adenosine diphosphate-ribose) polymerase
pcVPC	Prediction-corrected visual predictive check
PD	progressive disease
PDS	primary debulking surgery
PET	positron emission tomography
PEY	person exposure years
PFS	progression-free survival
PFS2	progression-free survival 2
PK	pharmacokinetic(s)
PP	per protocol
PROs	patient-reported outcomes
PT	preferred term
QD	once daily
QoL	quality of life
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAF	Safety Population
SAP	statistical analysis plan
SD	stable disease
SMQ	Standardized MedDRA Query
SOC	System Organ Class
StD	standard deviation
TEAE	treatment-emergent adverse event
TFST	time to first subsequent treatment
ULN	upper limit of normal

VAS	visual analog scale
Vc/F	apparent central volume of distribution
Vp2/F	apparent second peripheral volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline (Ireland) Limited submitted to the European Medicines Agency on 10 February 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy for Zejula in monotherapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The MAH is also taking the opportunity to make minor corrections throughout the PI. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted to add the new indication, bring it in line with the RMP template Rev. 2.0.1 and update due dates for category 3 studies.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Zejula, was designated as an orphan medicinal product EU/3/10/760 on 04 August 2010. Zejula was designated as an orphan medicinal product in the following indication: treatment of ovarian cancer.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0313/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0313/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The applicant received the following Protocol Assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 October 2014	EMEA/H/SA/2605/1/FU/1/2014/PA/II	*Dr Pierre Demolis and Dr Bertil Jonsson*

The Protocol Assistance pertained to clinical aspects.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bjorg Bolstad Co-Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	10 February 2020
Start of procedure:	29 February 2020
CHMP Rapporteur Assessment Report	30 April 2020
CHMP Co-Rapporteur Assessment Report	4 May 2020
PRAC Rapporteur Assessment Report	4 May 2020
PRAC members comments	6 May 2020
Updated PRAC Rapporteur Assessment Report	8 May 2020
PRAC Outcome	14 May 2020
CHMP members comments	18 May 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 May 2020
Request for supplementary information (RSI)	28 May 2020
CHMP Rapporteur Assessment Report	18 August 2020
PRAC Rapporteur Assessment Report	21 August 2020
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	03 Sep 2020
CHMP members comments	07 Sep 2020
Updated CHMP Rapporteur Assessment Report	10 Sept 2020

Timetable	Actual dates
CHMP opinion:	17 September 2020
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Zejula in comparison with existing therapies (Appendix 1)	17 September 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The applied indication was for Zejula in monotherapy for the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

Epidemiology

Ovarian cancer is the fifth overall cause of cancer death in women, representing 5% of all cancer deaths. It is also the deadliest of gynaecologic cancers in 2014, 14,270 women in the United States (US) and 18,303 in the European Union (EU) died from ovarian cancer.

Across Europe, the estimated age standardised rate of newly diagnosed ovarian cancer cases in 2020 is 15.5/100,000 and the mortality is 10.3/100,000 (ECIS 2020).

Biologic features

Epithelial ovarian cancer represents the majority of malignant ovarian neoplasm (about 90%) (Chan JK et al 2006; Jelovac D et al. 2011). The World Health Organization (WHO) classification of surface epithelial ovarian tumours includes six major histotypes - serous, mucinous, endometrioid, clear cell, transitional cell and epithelial-stromal. The serous subtype of ovarian carcinoma accounts for approximately 60-80% of ovarian cancer cases and is the most aggressive type of ovarian cancer. Grade is an additional prognostic determinant and a number of grading systems currently exist which are derived from reviewing the following tumour characteristics: architectural features, mitotic counts and nuclear atypia (ESMO Clinical Practice Guidelines, 2013). Low grade (grade 1, well differentiated) serous ovarian carcinoma is considered a distinct type of disease compared with high grade (grade 2 and 3 – moderately and poorly differentiated) serous carcinoma based on a number of clinical and molecular features, thus forming a 2 tier classification of low and high grade disease widely accepted and used in clinical practice (Levanon et al 2008; Vang et al 2009).

Breast cancer genes (BRCA) 1 and 2 are tumour suppressors that play a role in DNA repair: a deleterious mutation in BRCA leads to an inability to repair DNA via the homologous recombination pathway. Approximately 15%-22% of ovarian cancer patients have germline or somatic BRCA mutations (Alsop et

al. 2012, Cancer Genome Atlas Research N 2011, Hennessy et al. 2010, Pal et al. 2010, Pennington et al. 2014).

Recent research shows that homologous recombination deficiency can also be induced by other genes involved in DNA damage repair or by genetic alterations such as DNA methylation that lead to genomic instability. Approximately 41% to 50% of newly diagnosed ovarian carcinomas are estimated to exhibit homologous recombination deficiency (Elvin et al. 2017, Moschetta et al. 2016) which is also a phenotype that predicts improved rate of responses to platinum-based therapy and PARP inhibitors relative to tumours that are homologous recombination proficient (Kaufman et al. 2015).

Clinical presentation, diagnosis and stage/prognosis

Ovarian cancer is often asymptomatic in the early stages and is, therefore, first detected in advanced stages, when prognosis is poor. For women who do experience symptoms in the early stages, ovarian cancer is sometimes misdiagnosed because the majority of symptoms are nonspecific. These symptoms may overlap those of gastrointestinal and other diseases, and as a result, many patients may be treated incorrectly for months or years.

The advanced stage at which ovarian cancer is generally detected is reflected in the 5-year survival rates; 46% across all stages and 29% for advanced stages (Siegel et al 2017).

Management

The paradigm for first-line treatment of newly diagnosed ovarian cancer includes a combination of surgery and chemotherapy: either primary debulking surgery (PDS) followed by adjuvant chemotherapy or neoadjuvant chemotherapy (NACT) with subsequent interval debulking surgery (IDS) followed by additional chemotherapy. Worldwide, the use of NACT is increasing in patients with large volume Stage IIIC/IV disease, such that 45-60% of these patients will receive NACT (Epi Flatiron Database EMR Database 2019, Liu *et al.* 2017, Vergote *et al.* 2010, Monitor IHGO 2019, Nicklin *et al.* 2017). The preferred standard of care chemotherapy regimen is carboplatin and paclitaxel, based upon an improved toxicity profile and comparable efficacy when compared to cisplatin and paclitaxel (Ozol *et al.* 2003, duBois *et al.* 2005).

Bevacizumab is an additional option for first line treatment. The addition of bevacizumab to every-3-week paclitaxel and carboplatin, followed by continuation of maintenance for up to 15 cycles with bevacizumab improved PFS over placebo in the Phase 3 GOG 218 study (PFS hazard ratio [HR] 0.62) and in the high-risk population subgroup, as defined by Stage and residual disease, in the open-label Phase 3 ICON 7 study (PFS HR 0.68) (Burger *et al.* 2003, Perren *et al.* 2011). However, bevacizumab provided no overall survival benefit in the Intent-to-Treat (ITT) population in either study.

Olaparib, a PARP inhibitor, was approved for use as a maintenance treatment in patients with ovarian cancer and a mutation in the breast cancer susceptibility gene (BRCAmut) following complete response (CR) or partial response (PR) to first line platinum based chemotherapy based on an improvement in PFS over placebo (HR 0.30; [OS data is not yet available]) in study SOLO-1 (see SmPC Lynparza).

Data were recently reported from the Phase 3 PAOLA trial, which assessed the combination of bevacizumab plus olaparib versus bevacizumab in the ovarian cancer front line setting. Clinical benefit of the combination was observed in patients with homologous recombination deficiency (HR 0.33) but not in the remaining population (HR 0.92) (Ray-Coquard *et al*., paper presented at European Society for Medical Oncology 2019).

Observation, or "watch and wait" after response to first line therapy is included in the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology, and American Society of

Clinical Oncology guidelines and is the approach currently taken for the majority (>75%) of patients with advanced ovarian cancer (Epi Flatiron Database EMR Database 2019, Liu *et al.* 2017, Colombo *et al.* 2019).

Despite high response rates to first line standard-of-care platinum-based chemotherapy, 85% of patients with advanced ovarian cancer will experience disease recurrence and ultimately die of the disease. Prolonging the benefit of first line platinum is currently the best chance these patients have to avoid recurrence and potentially improve survival outcomes. Development of new therapies is essential to address the unmet medical need and improve the overall outlook for patients with this lethal cancer (Lorusso *et al.* 2012).

2.1.2. About the product

Niraparib is an orally available, highly selective poly(adenosine diphosphate-ribose) polymerase (PARP) -1 and -2 inhibitor exhibiting potent anti-tumour activity through the direct inhibition of PARP.

To date, niraparib has been approved in 37 countries for use in patients with ovarian cancer.

Zejula (niraparib) was approved on 16 November 2017 by the European Commission with the following indication: "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". The basis for this indication was the phase III study named NOVA. NOVA was a double-blind, 2:1 randomized, placebo-controlled, multicenter, global clinical trial designed to evaluate the efficacy and safety of niraparib as maintenance treatment for patients with platinum-sensitive, recurrent, ovarian, fallopian tube, or primary peritoneal cancer who had received at least 2 platinum-based regimens and were in response (CR or PR) following completion of last platinum-based chemotherapy. Platinum-sensitive was defined by complete response (CR) or partial response (PR) for more than 6 months to their penultimate (next to last) platinum-based therapy. The recommended posology in this indication is three 100 mg hard capsules once daily, equivalent to a total daily dose of 300 mg. Dose reductions may be implemented based on adverse reactions. The recommended dose reductions are first from three hard capsules daily (300 mg) to two hard capsules daily (200 mg). If further dose reduction is needed, a second dose reduction from two hard capsules daily (200 mg) to one capsule daily (100 mg) may be implemented (see SmPC section 4.2).

The SmPC also includes a statement that a starting dose of 200 mg for patients weighing less than 58 kg may be considered.

The MAH was encouraged to further investigate alternative dosing strategies to reduce adverse events for niraparib while still maintaining clinical efficacy.

In the present Type II Variation, the MAH is seeking authorisation to extend the indication to first-line treatment: "for the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy."

This is based on data from a Phase 3 trial called PRIMA, a double-blind, multicenter, randomised, placebo-controlled 2:1 (niraparib:placebo) study in subjects with ovarian, fallopian tube, or primary peritoneal cancer, collectively referred to as ovarian cancer.

With this application, the MAH seeks approval for a starting dose of 200 mg for the first-line ovarian cancer maintenance treatment. However, for patients weighing ≥77 kg and having baseline platelet count ≥150,000/µL, the recommended starting dose of Zejula is 300 mg.

The final recommended indication for Zejula as monotherapy is 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.

In first line ovarian maintenance treatment, the recommended starting dose of Zejula is 200 mg (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 once daily.

It is recommended that treatment should be continued until disease progression or toxicity.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

A full environmental risk assessment (Phase I and Phase II Tier A and Tier B) has been completed for niraparib tosylate (initiated as part of the initial MAA procedure and completed in 2019). The $PEC_{SURFACE\ WATER}$ was refined based on the prevalence of ovarian cancer, thus the proposed extended indication to include patients who are in response following completion of first-line platinum-based chemotherapy will not lead to altered $PEC_{SURFACE\ WATER}$. No further assessment is therefore considered required.

It can be concluded that niraparib is unlikely to represent as risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of niraparib.

Considering the above data, niraparib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Pivotal clinical study (PRIMA)

Study ID	No. of Centers (Location)	Study Status Type of Report	Total Enroll-ment (Planned/ Actual[a])	Design / Control	Route and Regimen	Indication	No. of Patients by Treatment (Entered/ Treated)	Median Treatment Duration (cycles, days, or months)	Location of Study Report
PR-30-5017-C PRIMA	~250 (global)	Ongoing, enrolling; closed to enrollment Full CSR (Dec 2019)	620/733	Double- blind, randomized, placebo-controlled (2:1 niraparib:placebo)	Niraparib: 300 mg QD PO in continuous 28-day cycles Niraparib: 200 mg QD PO in continuous 21-day cycles (for patients with a baseline actual body weight of <77 kg **and/or** screening platelet count of <150,000/µL), 300 mg QD PO in continuous 21-day cycles (for patients with a baseline actual body weight of ≥77 kg **and** screening platelet count of ≥150,000/µL)	Stage III or IV OC	733/728	Not available	Module 5.3.5.1

2.3.2. Pharmacokinetics

An overview of the clinical studies referred to in the Clinical pharmacology section is shown in Table 2.

Table 2. Clinical studies and designs referred to in the Clinical pharmacology section.

Study Number, Type	Study Design, N	Drug Dose and Regimen	PK Sampling
STUDY NEWLY ADDED TO THE POPULATION PK ANALYSIS			
PR-30-5017-C (PRIMA) Phase 3 study of niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy	Randomized (2:1 niraparib:placebo), double-blind, placebo-controlled trial N = 620 planned	QD (niraparib or matching placebo) in 28-day cycles FSD subgroup: 300 mg ISD subgroup: - 300 mg if baseline body weight ≥ 77 kg and baseline platelet count ≥150,000 µL	All patients Cycle 1 Day 1 and Cycle 2 Day 1: predose and 2 h postdose Cycle 4 Day 1 and Cycle 8 Day 1: predose EOT if patient discontinues before Cycle 8 Day 1

		- 200 mg QD if baseline body weight <77 kg or baseline platelet count <150,000 µL	
STUDIES INCLUDED IN THE PREVIOUS POPULATION PK ANALYSIS			
PN001 Phase 1 dose escalation and confirmation in patients with advanced solid tumors or hematologic malignancies	Multicenter, open-label, dose escalation nonrandomized, and confirmation study N = 104	Part A: 30, 40, 60, 80, 110, 150, 210, 290, 300, and 400 mg continuous QD for the first 21 days in Cycle 1, followed by a 7-day treatment holiday prior to starting Cycle 2 for the dose escalation component. QD continuously in 21-day cycles from Cycle 2 onward. Part B: 300 mg QD continuously for 21-day cycles with no treatment holidays. Part D: 300 mg QD continuously for 28-day cycles with no treatment holidays.	Part A: Cycle 1 Day 1: predose, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after first dose Cycle 1 Days 2, 3, 5, 8, and 12: predose only Cycle 1 Day 21: predose, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 h postdose Part B: Cycle 1 Day 1: predose, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after first dose Cycle 1 Days 2, 3, 5, 8, 12, and 21: predose only Cycle 2 Day 1: predose; 1, 1.5, 2, 3, 4, 6, 8, and 12 h postdose Part D: Cycle 1 Day 1: predose and 3 h postdose Cycle 1 Day 15: 8 h postdose Cycle 2 Day 1: predose and 3 h postdose
PR-30-5011-C (NOVA) Phase 3 maintenance trial of niraparib versus placebo in patients with platinum-sensitive ovarian cancer	Main study: randomized double-blind placebo-controlled, N = 553 (372 niraparib, 181 placebo)	Main study: 300 mg QD or matching placebo (2:1) in 28-day cycles	Main study: Cycle 1 Day 1 and Cycle 2 Day 1: predose and 2 h postdose Cycle 4 Day 1 and Cycle 8 Day 1: predose only;

Study Number, Type	Study Design, N	Drug Dose and Regimen	PK Sampling
	Food effect substudy: open-label crossover single-dose study, N = 17 QTc substudy: open-label, N = 36[a]	Food effect substudy: 300 mg single doses on food effect Days 1 and 8, followed by 300 mg QD in 28-day cycles beginning on Cycle 1 Day 1 (~2 weeks after start of substudy) QTc substudy: 300 mg QD in 28-day cycles	US subset: predose, 1, 1.5, 2, 3, 4, 6, and 8 h postdose Food effect substudy: Days 1 and 8: predose and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h postdose QTc substudy: Cycle 1 Day 1: predose, 1, 1.5, 2, 3, 4, 6, and 8 h postdose
PR-30-5020-C (QUADRA) Phase 2, open-label, single-arm study to evaluate the safety and efficacy of niraparib in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 3 or more previous chemotherapy regimens	Open label, N = 463	300 mg QD	All patients Cycle 1 Day 1 and Cycle 2 Day 1: predose and 2 h postdose Cycle 4 Day 1 and Cycle 8 Day 1: predose only ECG subset (N = 14) predose and at 1, 1.5, 2, 3, 4, 6, and 8 h postdose on Cycle 1 Day 1

ECG = electrocardiogram; EOT = end of treatment; FSD = fixed starting dose; ISD = individualized starting dose; N = number of patients; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; US = United States; QTc = corrected QT interval.

Introduction

The clinical pharmacokinetics of niraparib have previously been investigated in three clinical studies: **PN001**, **NOVA** and **NOVA-food-effect** sub-study (Table 2). These studies were performed to support the initial marketing application for the use of niraparib 300 mg once daily in platinum-sensitive recurrent ovarian cancer who are in response to second-line or greater platinum-based chemotherapy.

Table 3 summarised the key PK characteristics of niraparib established in previous procedures (see also Zejula EPAR and SmPC).

Table 3. Brief overview of key PK characteristics of niraparib.

Absorption	• Absolute bioavailability: ~73% • Tmax 2.5-4 hours • Not significantly affected by concomitant food
Distribution	• 83% protein bound in human plasma (mostly to albumin) • Extensive tissue distribution (Vd/F of 1,074 L) • Active transport: Substrate of P-gp and BCRP

Elimination	• Primarily through the hepatobiliary and renal routes.
	• Radioactive drug recovery over 21 days (total recovery 86.2%):
	  ○ Urine: 47.5% (primarily as metabolites)
	  ○ Faeces 38.8% (primarily as unchanged drug)
	• Apparent clearance (CL/F): 16.2 L/h
	• T1/2 = 48-51 hours

Metabolism	• Primary metabolic pathway: Carboxylesterase-catalysed amide hydrolysis to a major inactive metabolite, M1 • Secondary metabolic pathways: UDP-glucuronosyltransferase-mediated glucuronidation • Minor pathway of oxidative metabolism: CYP1A1/2 and CYP3A4/5 with minor contribution from CYP2D6
Dose proportionality	• Established from 30 to 400 mg. • Accumulation ratios after 21 days of dosing: 1.99-4.22 for AUC_{0-24}

Pharmacokinetic variability	• Between subjects: Moderate (CV 38.7% in CL/F) • Within subjects: Not studied
Sources of variability	• None identified

During the initial MAA review, it was noted that the majority of patients in the pivotal study (NOVA) had dose reductions due to adverse events. After 4 months and onwards, ~25% received 300 mg, ~45% received 200 mg and ~30% received 100 mg daily.

To support the current application to extend the indication to patients with platinum-sensitive ovarian cancer in response to first-line therapy, the results of a Phase 3 randomised, placebo-controlled study ("PRIMA study") have been submitted. The PRIMA study was initiated with a starting dose of 300 mg QD for all patients. At the time of implementation of Protocol Amendment 2 (protocol dated 16 November 2017), 317 patients (65%) had been enrolled with this starting dose. Then, due to a high frequency of dose interruptions and dose reductions with this starting dose and in order to improve the safety profile of niraparib, a dosing algorithm (termed "individualised starting dose [ISD]" by the MAH, see Table 4) previously applied (variation EMEA/H/004249/II/0006, withdrawn) was implemented for the remaining 170 patients (35%) who were randomized to active treatment.

The ISD regimen was derived from retrospective, exploratory statistical multivariable analysis of the NOVA data to investigate predictors of Grade 3 thrombocytopenia. Baseline body weight and platelet counts were identified as predictors of adverse events that required dose modification in patients treated with niraparib at 300 mg QD based on a classification tree analysis. Patients with body weight <77 kg or platelet counts <150,000/µL at baseline had higher rates of Grade 3 thrombocytopenia (35% versus 12%) and were more likely to require dose modification to 200 mg within the first two months of treatment with only 17% of patients with these baseline characteristics remaining on 300 mg by Month 4. On this basis, it was proposed to test a lower starting dose (200 mg daily) in this subgroup, while the remaining patients should still start on 300 mg daily.

The PRIMA study was not originally designed for testing multiple dose levels and was not powered for statistically testing of the efficacy at the lower dose (see clinical efficacy).

Table 4. Starting dose algorithm proposed in the current application ("ISD")

Patient characteristics	Starting dose	% of target population[a]	Patients studied in PRIMA, n[b]
Body weight < 77 kg **or** baseline platelet count <150,000/µL	200 mg daily	75-80%	122
Body weight ≥ 77 kg **and** baseline platelet count ≥150,000/µL	300 mg daily	20-25%	34

[a] based on subject characteristics in NOVA and PRIMA trials.

[b] After protocol Amendment 2. The number of patients is lower than the actually enrolled number because of incorrect dosing in some subjects.

No new dedicated clinical pharmacology studies have been submitted to support the current application. Additional PK data were sparsely collected from patients in PRIMA. These PK data were used to update a previously established population PK (popPK) model and re-investigate covariates impacting the PK of niraparib.

Methods

- **Analytical methods in PRIMA trial**

The analysis of patient samples from study PR-30-5017-C (PRIMA) of niraparib in human (K_3EDTA) plasma have been performed by an LC-MS/MS method (report KB-0226-RB-CS). The validation reports included a validation report of long-time stability, KB-0179-RB-CL.

The main validation KB-0167-RB-CV was performed pre-study and included all important parameters according to the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** Committee for Medicinal Products for Human Use (CHMP). The objective was to develop and validate an analytical method for quantification of Niraparib and M1 in human plasma (K3EDTA) using D7-Niraparib and D7-M1 as the respective internal standards.

- **Pharmacokinetic data analysis**

All PK data in the PRIMA trial have been analysed using popPK modelling. No non-compartmental analyses have been performed.

- **Evaluation and Qualification of models**

PopPK modelling

Previous models

- Model #1. A two-compartment model with first-order absorption and linear elimination with **no identified covariate effects**, was submitted to support the initial MAA. Data were available from two studies: **PN001** and **NOVA.**
- Model #2. A refined modelling report (**TES-PKER-NIRAPARIB-648**) was submitted to support the type II variation to alter the posology in the currently approved indication (which was eventually withdrawn). Data were available from two studies: **PN001** and **NOVA**, i.e. the same data set as Model #1. The final model was a two-compartment model with linear elimination and a constant (zero-order) rate of drug release into the absorption compartment preceded by an absorption lag time, with the released drug absorbed into the central compartment at a first-order rate. The following covariate effects were identified: increase in duration of zero-order drug release in **fed/unknown prandial state**, increase in apparent clearance (CL/F) and apparent peripheral volume of distribution (Vp/F) with increasing **albumin**, and decrease in relative bioavailability with increasing **body weight**. The covariate effects had only a minor impact on exposure (<20%). Overall, the model was considered to describe the data adequately, although the biological plausibility of body weight influencing bioavailability was questioned.
- Model #3. A refined model was developed based on the above data added to the data from the **QUADRA** study (n=455). This model was not submitted in any prior procedure and was provided upon request with this application (report reference **TESA-PMX-NIRAPARIB-893**). The final model was a 3-compartment model with linear elimination and a constant rate of drug release into the absorption compartment preceded by a lag time, and first-order absorption. The same covariate effects as for Model #2 were identified (**prandial state, albumin, body weight**) in addition to decreasing CL/F with increasing **age**.

Models in current application

- Model #4. The initial submission included a full modelling report (report reference **TESA-PMX-NIRAPARIB-1391,** dated 02 December 2019) for a model updated with data from the PRIMA study. This model is described in detail below and is termed the preliminary final model.

- Model #5. In the response to the concerns raised on Model #4, the MAH provided a slightly refined model (using the same data set as Model #4) which was termed the new final model. This model is described in the final section below.

First updated model for the current application (Model #4)

Objectives

To update the existing popPK model for niraparib (i.e. Model #3), including the assessment of the sources of PK variability, using data from the PRIMA study.

Estimation method

Concentration-time data of niraparib were fitted using nonlinear mixed-effects modelling software (NONMEM, version 7.3.0)). All PK analyses were performed using the first-order conditional estimation method with interaction (FOCE-INTER) with the ADVAN12 subroutine. R version 3.5.3 was used for exposure response modelling.

Data

The previous data set was updated with data from the PRIMA study (the pivotal study supporting the current application). Once assembled, analysis-ready datasets underwent a formal quality control review by an analyst other than the data programmer. The quality control review included exploratory plots of the constructed data to identify potential errors.

The study designs of the available PK data are shown below (Figure 1) and in Table 2.

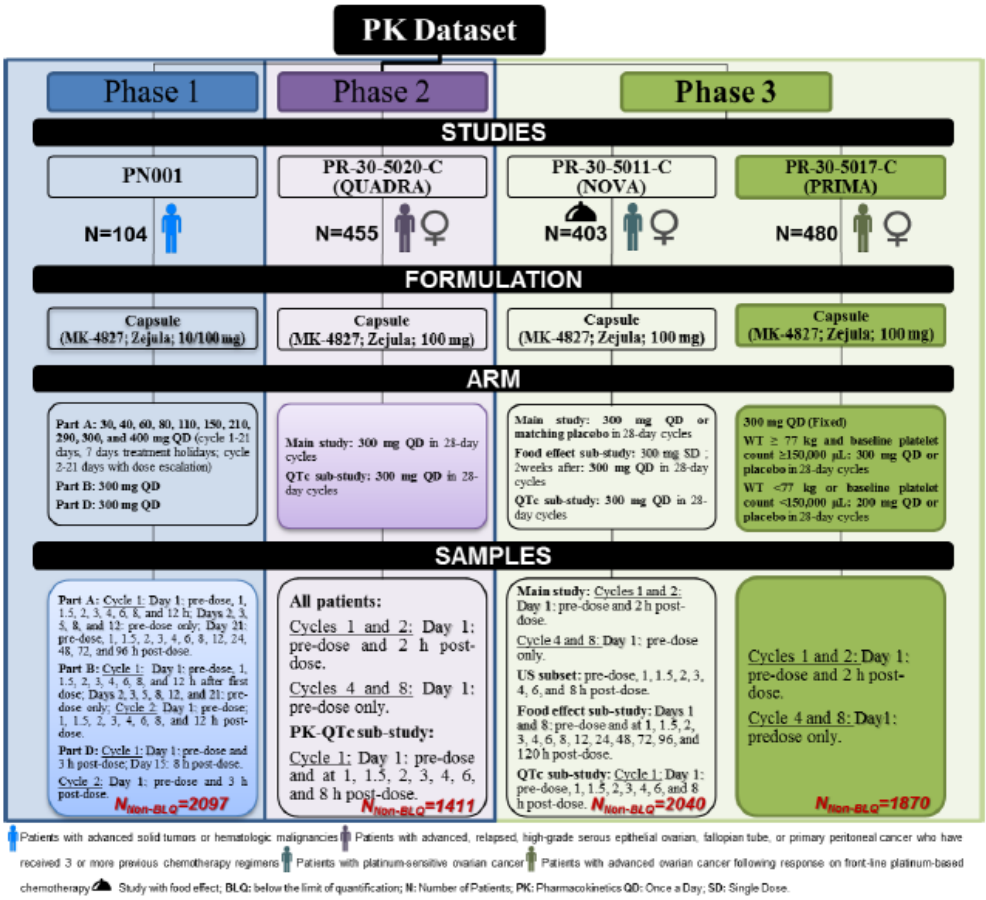


Figure 1. Overview of PK data for popPK analysis. Source: PopPK report, Figure 16.

Sparse pharmacokinetic data were collected for all patients in the PRIMA trial (n=480). The raw PK data available in PRIMA are shown in Figure 2, stratified by starting dose. Two-hour concentration data by starting dose group are shown in Figure 3.

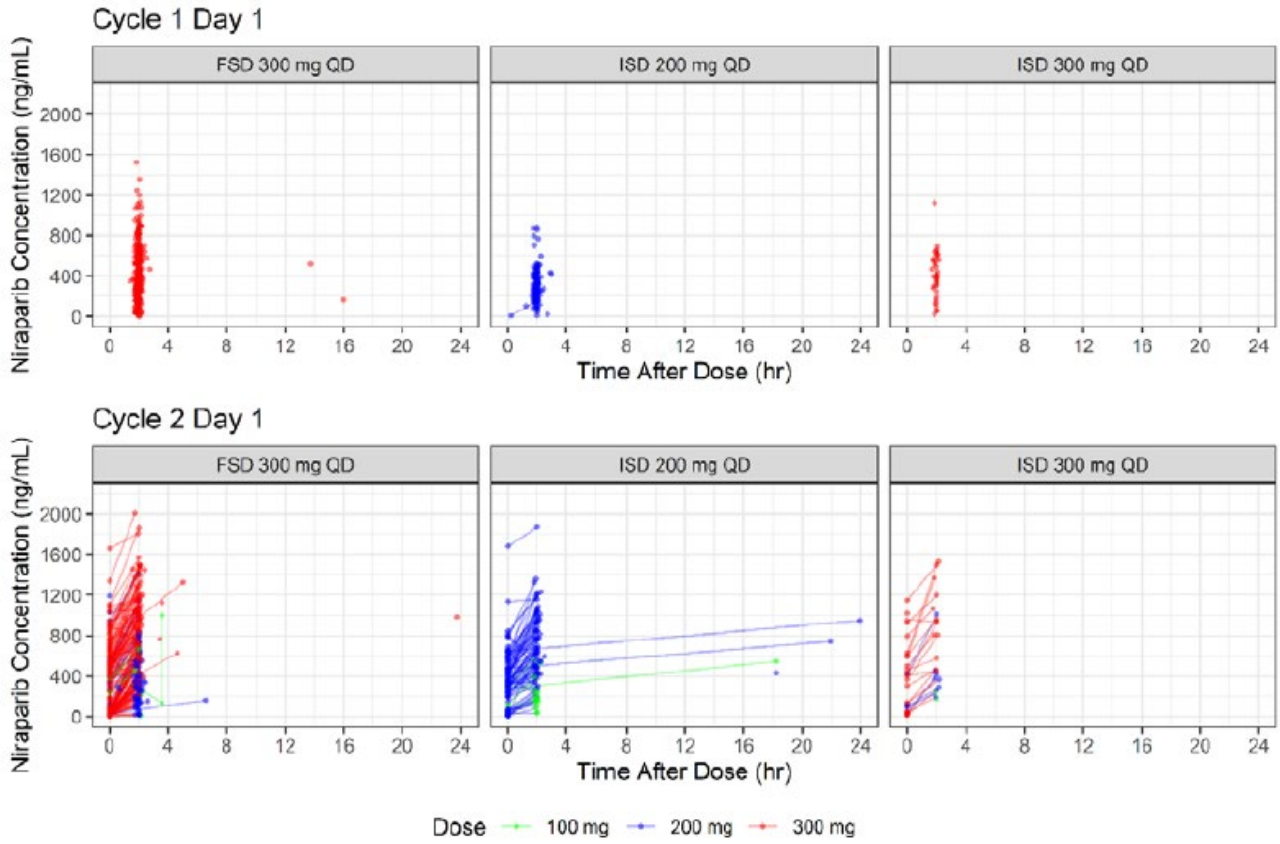


Figure 2. Niraparib concentration time profiles in PRIMA.

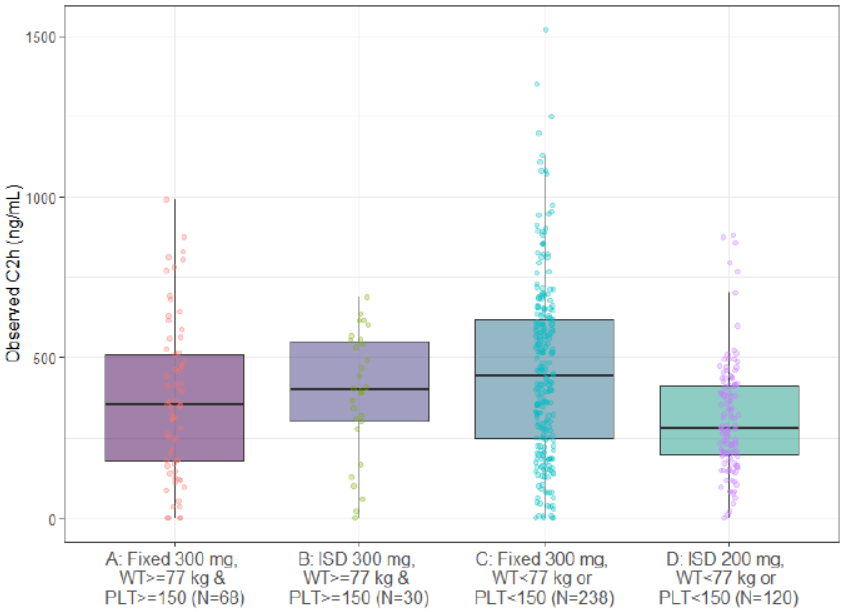


Figure 3. Observed C2h by weight/platelet level groups – Cycle 1 Day 1.

Data exclusion prior to modelling

In the full analysis dataset, there were a total of 8973 concentration records. Table 5 shows the number of concentration samples excluded from the analysis and the reasons for exclusion.

Table 5. Summary of excluded concentration samples

Reason for Removal	Number (%) of Records
Samples prior to the first dose of niraparib	1432 (16%)
Missing/uncertain dosing times	4 (0.04%)
Missing time only	9 (0.1%)
Missing date only	2 (0.02%)
Missing date and time	36 (0.4%)
Total Number of Exclusions	**1483 (16.5%)**

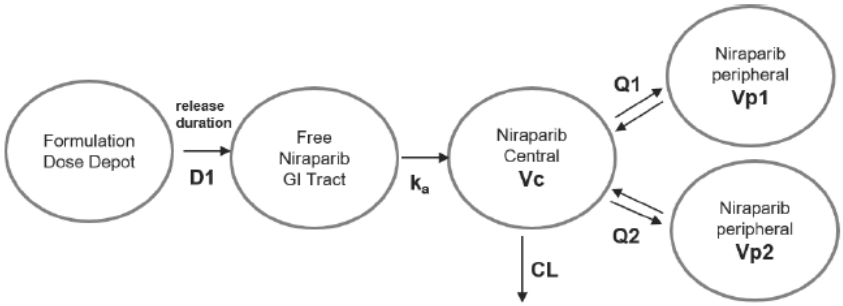
In addition, concentration samples below quantification limit (BQL) (72 samples, <1% of total data set) were discarded. The final population PK analysis dataset consisted of 7418 quantifiable niraparib concentration measurements in 1442 subjects. Of these 1915 concentrations [26%] and 480 patients [33%] were from the **PRIMA** study.

Outlier handling

When the below base model structure was fit to all of the data, 41 (0.6 %) of the 7418 observations had |CWRES| >4 and were excluded from further analysis. Thus, the base model was developed from 7377 quantifiable plasma niraparib concentrations. The final population PK model was re-run using the entire dataset.

Structural model

During development of the previous model (Model #3), prior to availability of the PRIMA data, a 3-compartment model with linear elimination and a constant rate of drug release into the absorption compartment preceded by a time lag, with the drug released from the dosage form absorbed into the central compartment at a first-order rate (Figure 4) was selected as the final structural model. Briefly, this model provided a superior fit compared with the previous two-compartment model (Model #1 and #2), as evidenced by an OFV reduction of 157.6 units and an improvement in the CWRES versus time diagnostic plot (Figure 5). This model structure was adopted in the current analysis. Alternative absorption models were not considered because the PRIMA data primarily included only sparse sampling.



CL = clearance; D1 = duration of zero-order drug release; GI = gastrointestinal; K_a = first-order absorption rate constant; PK= pharmacokinetic; Q1 = first inter-compartmental clearance; Q2 = second inter-compartmental clearance; Vc = central volume of distribution; Vp1 = first peripheral volume of distribution; Vp2 = second peripheral volume of distribution.

Figure 4. Schematic structural model. Source: PopPK report, Figure 17.

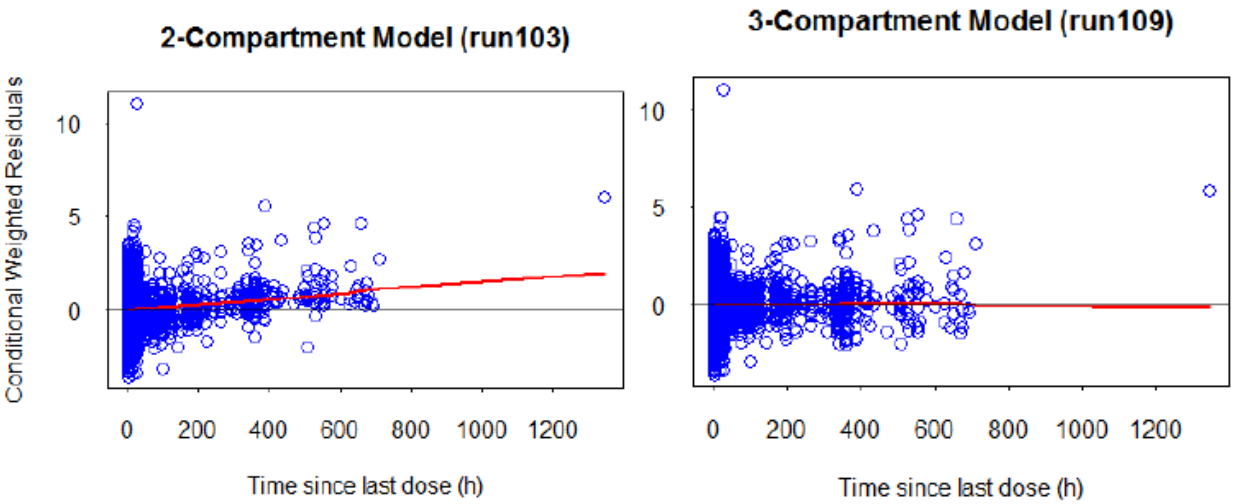


Figure 5. Comparison of goodness-of-fit: 2- versus 3-compartment model. Source: Model #3 report (tesa-pmx-niraparib-893).

The inter-individual random effects on model parameters were modelled assuming a log-normal distribution. In the final model, BSV was included on CL/F, Ka, D1 (duration of zero-order release), bioavailability (Frel), and Vp2/F. The residual variability was best described using separate additive error components by study on log-transformed data.

In the final base model, fixed-effect parameter estimates were also very similar to those from the previously developed base model (Table 6). All the parameters were precisely estimated, with relative standard errors (RSEs) less than 20%. The base model showed an adequate fit to the data (Figure 6, VPCs not provided).

Table 6. Typical Values for the Population PK Base Model of Niraparib. Source: PopPK report Table 17.

PK Parameters	Previous Model (PN001/NOVA/QUADRA)	Current Model (PN001/NOVA/QUADRA/PRIMA)			
	Estimate	Estimate	RSE%	BSV (%)	Shrinkage (%)
CL/F (L/h)	16.0	16.3	1.36	24.10	41.4
Vc/F (L)	369	388	2.10	0 FIX	N/A
Q1/F (L/h)	1.05	1.39	6.96	0 FIX	N/A
Vp1/F (L)	220	312	4.39	0 FIX	N/A
Q2/F (L/h)	83.1	77.7	4.23	0 FIX	N/A
Vp2/F (L)	573	608	6.76	115	51.9
Ka (1/h)	0.826	0.848	4.55	71.0	54.1
D1 (h)	0.379	0.441	8.82	260	45.4
Tlag (h)	0.445	0.472	1.01	0 FIX	N/A
Frel (-)	1 FIX	1 FIX		33.6	31.3
Residual error SD PN001 [ln(ng/mL)][b]	0.207[a]	0.214	0.678	-	-
Residual error SD NOVA [ln(ng/mL)] [b]	0.324 [a]	0.396	0.783	-	-
Residual error SD QUADRA [ln(ng/mL)] [b]	0.348 [a]	0.373	1.47	-	-
Residual error SD PRIMA [ln(ng/mL)] [b]	-	0.459	1.34	-	-

[a] Proportional residual error CV reported for previously developed model.
[b] An additive residual error model on log-transformed concentrations was used for the current model.
BSV % was calculated as sqrt(exp(OMEGA) - 1) × 100%.
BSV = between-subject variability; CL/F = apparent central clearance; D1 = duration of zero-order release; Frel = relative bioavailability; Ka = first-order absorption rate constant; N/A = not applicable; ; Q1/F = apparent first inter-compartmental clearance; Q2/F = apparent second inter-compartmental clearance; res. = residual; RSE = relative standard error; Tlag = lag time; Vc/F = apparent central volume of distribution; Vp1/F = apparent first peripheral volume of distribution; Vp2/F = apparent second peripheral volume of distribution.

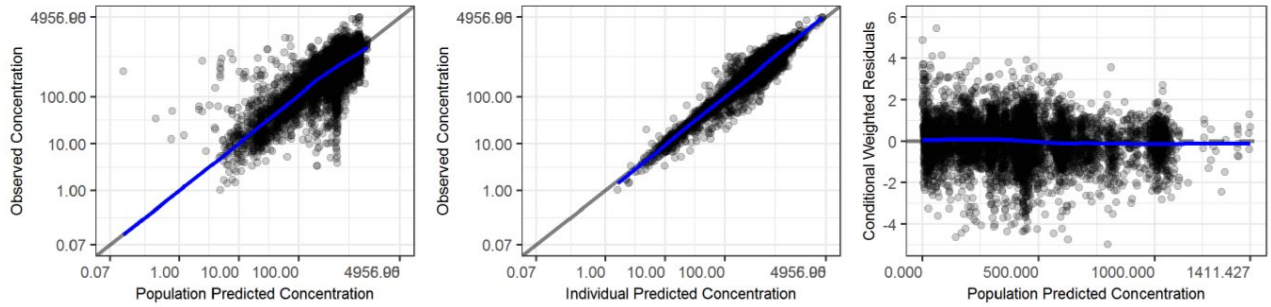


Figure 6. Base model goodness-of-fit plots

Covariates – data and methodology

Baseline characteristics for patients in the analysis dataset are summarized in Table 7. The vast majority (97.9%) were female and had ovarian cancer (96.1%). Most patients were White (88.0%). The pooled mean body weight was 70.8 kg (range 36-147 kg) and the mean age was 62 years (range 29-91 years).

For missing continuous covariates, the median value was imputed. For missing categorical values, the most common category was imputed. If more than 10% of patients had missing values for a covariate, that covariate was excluded from the analysis.

Table 7 Baseline characteristics of patients in the PK analysis dataset (continuous covariates left and categorical covariates right). Source: PopPK report, Table 4 and 5.

Covariate	PN001 (n = 104)	QUADRA (n = 455)	NOVA (n = 403)	PRIMA (n = 480)	Overall (n = 1442)
Age (years)					
Mean (CV%)	58.3 (16.0%)	64.2 (14.5%)	60.3 (15.6%)	61.1 (17.7%)	61.7 (16.3%)
Median [Min, Max]	59.0 [35.0, 75.0]	64.0 [29.0, 91.0]	61.0[33.0, 83.0]	62.0 [32.0, 85.0]	62.5 [29.0, 91.0]
ALB (g/dL)					
Mean (CV%)	3.59 (12.5%)	3.81 (13.2%)	4.08 (10.7%)	4.15 (9.61%)	3.98 (12.1%)
Median [Min, Max]	3.60 [2.30, 4.60]	3.90 [2.30, 6.60]	4.10 [1.70, 5.20]	4.20 [2.84, 5.40]	4.00 [1.70, 6.60]
Missing	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)	3 (0.2%)
ALP (IU/L)					
Mean (CV%)	122 (116%)	101 (86.9%)	89.0 (53.6%)	86.2 (46.8%)	94.3 (76.2%)
Median [Min, Max]	85.0 [41.0, 1330]	83.0 [28.0, 1230]	82.0 [28.0, 785]	76.5 [0.860, 317]	81.0 [0.860, 1330]
ALT (IU/L)					
Mean (CV%)	20.4 (45.0%)	23.3 (72.4%)	24.3 (50.8%)	23.7 (202%)	23.5 (128%)
Median [Min, Max]	18.0 [7.00, 57.0]	19.0 [3.00, 173]	21.0 [6.00, 97.0]	19.0 [0.270, 1030]	19.0 [0.270, 1030]
AST (IU/L)					
Mean (CV%)	26.9 (48.5%)	26.8 (55.6%)	25.2 (40.4%)	26.1 (298%)	26.1 (176%)
Median [Min, Max]	24.0 [9.00, 85.0]	23.0 [10.0, 121]	23.0 [10.0, 109]	21.0 [0.360, 1710]	22.0 [0.360, 1710]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)
BILI (µmol/L)					
Mean (CV%)	8.71 (69.2%)	7.46 (45.6%)	7.36 (52.6%)	7.29 (52.7%)	7.46 (52.6%)
Median [Min, Max]	8.00 [1.71, 58.0]	6.84 [1.71, 22.2]	6.84 [0.580, 22.2]	6.84 [0.342, 28.0]	6.84 [0.342, 58.0]
Missing	5 (4.8%)	0 (0%)	1 (0.2%)	0 (0%)	6 (0.4%)
BMI (kg/m^2)					
Mean (CV%)	28.1 (23.0%)	27.4 (23.9%)	26.9 (28.2%)	26.2 (19.2%)	26.9 (23.9%)
Median [Min, Max]	27.3 [16.5, 53.0]	26.2 [13.8, 51.5]	25.6 [17.2, 94.9]	25.3 [16.7, 46.0]	25.8 [13.8, 94.9]
Missing	0 (0%)	16 (3.5%)	0 (0%)	0 (0%)	16 (1.1%)
CRCL (mL/min)					
Mean (CV%)	97.1 (33.0%)	79.7 (39.1%)	86.3 (32.7%)	87.4 (33.7%)	85.4 (35.4%)
Median [Min, Max]	95.3 [36.8, 236]	73.5 [27.6, 205]	82.4 [36.4, 196]	83.3 [32.2, 209]	81.4 [27.6, 236]
PLT ($10^9/L$)					
Mean (CV%)	249 (29.2%)	253 (36.5%)	234 (35.4%)	243 (32.1%)	244 (34.4%)
Median [Min, Max]	235 [137, 506]	232 [104, 607]	215 [85.0, 648]	235 [100, 662]	228 [85.0, 662]
Weight (kg)					
Mean (CV%)	77.4 (24.2%)	72.3 (25.2%)	70.1 (23.0%)	68.6 (20.6%)	70.8 (23.4%)
Median [Min, Max]	75.8 [43.5, 135]	70.1 [36.3, 147]	67.0 [43.4, 130]	66.0 [38.0, 116]	68.0 [36.3, 147]

ALB = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; BMI = body mass index; CRCL = creatinine clearance; CV = coefficient of variation; Max = maximum; Min = minimum; N = number of subjects, PK = pharmacokinetic; PLT = platelet count.

Covariate	n (%)				
	PN001 (n = 104)	QUADRA (n = 455)	NOVA (n = 403)	PRIMA (n = 480)	Overall (n = 1442)
Gender					
Female	73 (70.2%)	455 (100%)	403 (100%)	480 (100%)	1411 (97.9%)
Male	31 (29.8%)	0 (0%)	0 (0%)	0 (0%)	31 (2.1%)
Race					
White	99 (95.2%)	387 (85.1%)	351 (87.1%)	432 (90.0%)	1269 (88.0%)
Black or African American	2 (1.9%)	19 (4.2%)	9 (2.2%)	8 (1.7%)	38 (2.6%)
Asian	1 (1.0%)	16 (3.5%)	11 (2.7%)	14 (2.9%)	42 (2.9%)
American Indian/Alaskan Native	0 (0%)	1 (0.2%)	2 (0.5%)	1 (0.2%)	4 (0.3%)
Native Hawaiian or Other	0 (0%)	0 (0%)	1 (0.2%)	1 (0.2%)	2 (0.1%)
Unknown	2 (1.9%)	32 (7.0%)	29 (7.2%)	24 (5.0%)	87 (6.0%)
HRD Status					
Negative	0 (0%)	193 (42.4%)	106 (26.3%)	166 (34.6%)	465 (32.2%)
Positive	0 (0%)	218 (47.9%)	230 (57.1%)	243 (50.6%)	691 (47.9%)
Unknown	104 (100%)	44 (9.7%)	67 (16.6%)	71 (14.8%)	286 (19.8%)
Cancer Diagnosis					
Ovarian/fallopian/peritoneal	48 (46.2%)	455 (100%)	403 (100%)	480 (100%)	1386 (96.1%)
Prostate	23 (22.1%)	0 (0%)	0 (0%)	0 (0%)	23 (1.6%)
Breast	13 (12.5%)	0 (0%)	0 (0%)	0 (0%)	13 (0.9%)
Other	20 (19.2%)	0 (0%)	0 (0%)	0 (0%)	20 (1.4%)
Baseline ECOG Performance Status					
0: Fully active	42 (40.4%)	262 (57.6%)	279 (69.2%)	332 (69.2%)	915 (63.5%)
1: Restricted	57 (54.8%)	193 (42.4%)	124 (30.8%)	148 (30.8%)	522 (36.2%)
2: Only self-care	5 (4.8%)	0 (0%)	0 (0%)	0 (0%)	5 (0.3%)

ECOG = Eastern Cooperative Oncology Group; HRD = homolog recombination deficiency; n = number of patients; PK = pharmacokinetic.

The covariates considered for the population PK analysis are presented in Table 8.

Table 8. Baseline covariates to be evaluated in the population PK model.

Covariate	Parameters	Rationale
Body weight	Clearances, volumes of distribution, bioavailability	Clinical interest; disposition may be body size-dependent; identified as covariate on bioavailability in previous model
Sex	Clearance, volumes of Distribution, absorption	Clinical interest
Age	Clearance, central volume of distribution	Clinical interest; identified as covariate on clearance in previous model
Race	Clearance, central volume of distribution	Clinical interest
Cancer type	Clearance	Clinical interest
Prandial state	Absorption parameters, bioavailability	Clinical interest; food known to delay absorption
Creatinine clearance	Clearance	Clinical interest
Liver function tests (AST, ALT, ALP, BILI)	Clearance	Clinical interest; known hepatic elimination of niraparib
Albumin	Clearance, volumes of distribution	Clinical interest; albumin identified as covariate on clearance and volume distribution in previous models
ECOG performance status	Clearance	Clinical interest
HRD status	Clearance	Clinical interest
BRCA status	Clearance	Clinical interest
Baseline platelet count	Clearance	Clinical interest; baseline platelet count is used in determination of starting dose

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; BRCA = breast cancer susceptibility gene; ECOG = Eastern Cooperative Oncology Group; HRD = homologous recombination deficiency; PK = pharmacokinetic.
Creatinine clearance was estimated using Cockcroft-Gault formula.

Sources of variability in niraparib PK were investigated using a **full model approach** (as opposed to stepwise addition and elimination of covariates). A subset of covariate-parameter relationships from Table 8 to be included in the full model were selected based on knowledge from previous analyses, clinical interest (defined as covariates for which there is a reasonable hypothesis of an effect on PK, and those which are frequently and commonly identified as covariates in pop-PK models) or statistically significant relationships in ETA versus covariate plots (in case shrinkage was <30% according to the modelling analysis plan).

Table 9 summarises the covariates selected to be included in the *Full model*. After addition of these covariates, the OFV was decreased by 597 units compared to the base model. Covariates with small estimated effects were then removed.

Table 9. Covariates tested in full model

Parameter	Covariate (functional form tested)	Selected for full model based on	Retained in final model
Apparent clearance (CL/F)	Age (power)	Identified in previous analysis (Model #3) and significant in ETA-covariate plot	Yes
	ALB (power)		Yes
	Weight (power)	Clinical interest	Yes
	HRD status		No. Small estimated effect (8%-fold change)
	BSA-normalised creatinine clearance (NCRCL) (power)	Statistically significant correlation in ETA-covariate plot	Yes
	Alkaline phosphatase (power)		No. Small estimated effect (power exponent -0.02)
	Baseline platelet count (power)		No. Small estimated effect (power exponent -0.09)
Vc/F	Weight (power)	Clinical interest	Yes
Frel	Weight (power)	Identified in previous analysis (Model #3) and significant in ETA-covariate plot	Yes
D1	Prandial state	Identified in previous analysis (Model #3) and significant in ETA-covariate plot	Yes

CL/F: Apparent oral clearance. Vc/F: Apparent central volume of distribution. Frel: Relative bioavailability. D1: Duration of zero-order drug release into absorption compartment. ALB: Albumin. HRD: Homologous recombination deficiency.

As a final step, the full covariate model was reduced using a backward elimination procedure, using the likelihood ratio test to evaluate the significance of removing covariate effects from the population model based on a statistical significance level of 0.005 (Joerger 2012). According to the modelling analysis plan, covariate-parameter relationships that when removed resulted in an increase in OFV corresponding to p>0.005 were to be removed from the model unless retained for reasons of scientific or clinical interest. The results are shown in Table 10. All covariates shown in the table were retained, despite some being associated with a p-value above 0.005.

Table 10. Summary of backward covariate elimination

Model	OFV	ΔOFV	p-value
Full model	-3974.211	N/A	N/A
Without age on CL/F	-3968.646	5.565	0.0183
Without albumin on CL/F	-3936.57	37.641	8.5×10^{-10}
Without NCRCL on CL/F	-3950.609	23.602	1.18×10^{-6}
Without weight on CL/F	-3967.854	6.357	0.0117
Without weight on Frel	-3965.406	8.805	0.00300
Without weight on Vc/F	-3967.551	6.66	0.00986
Without high-fat meal on D1	-3536.263	437.948	3.03×10^{-97}
Without unknown prandial state on D1	-3969.13	5.081	0.0242

The p-values were calculated based on one degree of freedom using the likelihood ratio test.
ΔOFV = increase in OFV from final model in population PK report; CL/F = apparent clearance; D1 = duration of zero-order absorption; Frel = relative bioavailability; N/A = not applicable; NCRCL = body surface area-normalized creatinine clearance; OFV = objective function value; Vc/F = apparent central volume of distribution.
Source: \Analysis\Development\ema-analysis\analyses\q10\d\Backward_covariate_analysis_summary.xlsx

The inclusion of covariate effects decreased the BSV coefficient of variation (CV) for CL/F, Frel, and Vc/F by less than 5% and D1 by 16% when compared to the base model. The covariates NCRCL and body weight were moderately correlated (r=0.34, p<0.001).

Preliminary final model evaluation

Parameter estimates for the preliminary final population PK model, including bootstrap results for runs that converged successfully (303 out of 700) and a comparison between the current preliminary final model and Model #3 are provided in Table 11. In general, the parameter estimates for the current model and the previous Model #3 were consistent. Parameters were precisely estimated except the effects of body weight on CL/F, Vc/F and Frel (standard errors>82%).

Table 11. Parameter Estimates for the preliminary Final Population PK Model (Model #4).

PK Parameters	Current Model (Full 3) (BSV %)	Bootstrap Median - [95th CI]	Previously Developed Model Without the Prima Study (BSV %)
CL/F (L/h)	**16.5 (23.5)** × (Age/62.5 years)$^{-0.211}$ × (ALBBL/4 g/dL)$^{0.503}$ × (WTBL/70 kg)$^{-0.0818}$ ×(NCRCL/80.6 mL/min/m^2)$^{0.214}$	16.5 [16.0, 16.9] -0.181 [-0.351,-0.0123] 0.498 [0.302, 0.680] -0.101 [-0.544, 0.174] 0.225 [0.128, 0.314]	**16.1 (28.3)** × (Age/63 years)$^{-0.348}$ × (ALBBL/4 g/dL)$^{0.644}$
Vc/F (L)	**429** × (WTBL/70)$^{0.308}$	419 [378, 454] 0.239 [-0.354, 0.653]	**365**
Q1/F (L/h)	**1.36**	1.38 [1.04, 1.77]	**1.06**
Vp1/F (L)	**312**	317 [274, 364]	**226**
Q2/F (L/h)	**66.4**	69.6 [60.9, 82.3]	**80.3**
Vp2/F (L)	**579 (117)**	582 [513, 661]	**564 (44.1)**
Ka (1/h)	**1.03 (72.1)**	1.03 [0.848, 1.22]	**0.849 (61.7)**
D1 (h)	**0.274 (244)** × 13.6 if high fat meal × 0.911 if unkn. prandial state	0.257 [0.0801, 0.358] 14.9 [7.94, 34.1] 0.859 [-0.172, 2.04]	**0.197 (151)** × 16.1 if high fat meal × 2.04 if unkn. prandial state
Tlag (h)	**0.472**	0.478 [0.397, 0.618]	**0.425**
Frel (-)	**1 (30.3)** × (WTBL/70)$^{-0.171}$	-0.210 [-0.667, 0.113]	**1 (35.0)** × (1 - 0.0155*(WTBL - 60) + 0.138) If WTBL <= 60kg × (1 - 0.00300*(WTBL – 68.9)) If WTBL > 60kg
Res. error SD PN001	0.214	0.214 [0.194, 0.234]	0.207 [a]
Res. error SD NOVA	0.331	0.329 [0.301, 0.360]	0.300 [a]
Res. error SD QUADRA	0.379	0.379 [0.337, 0.428]	0.340 [a]
Res. error SD PRIMA	0.459	0.455 [0.422, 0.493]	-

[a] Proportional residual error CV reported for previously developed model.
An additive residual error model on log-transformed concentrations was used for the current model.
BSV % was calculated as sqrt(exp(OMEGA) - 1) × 100%.
There were 41 (0.6%) observations with |CWRES| >4 in the base model and were excluded from the final model.

ALBBL = baseline albumin; BSV = between-subject variability; CL/F = apparent central clearance; CV = coefficient of variation; D1 = duration of zero-order drug release; Frel = relative bioavailability; Ka = first-order absorption rate constant; N/A = not applicable; PK = pharmacokinetic; NCRCL = body surface area-normalized creatinine clearance; Q1/F = apparent first inter-compartmental clearance; Q2/F = apparent second inter-compartmental clearance; res. = residual; RSE = relative standard error; SD = standard deviation; Tlag = lag time; unkn. = unknown; Vc/F = apparent central volume of distribution; Vp1/F = apparent first peripheral volume of distribution; Vp2/F = apparent second peripheral volume of distribution; WTBL = baseline body weight.

Goodness-of-fit plots and prediction-corrected visual predictive checks (pcVPCs) are shown in Figure 7 and Figure 8, respectively.

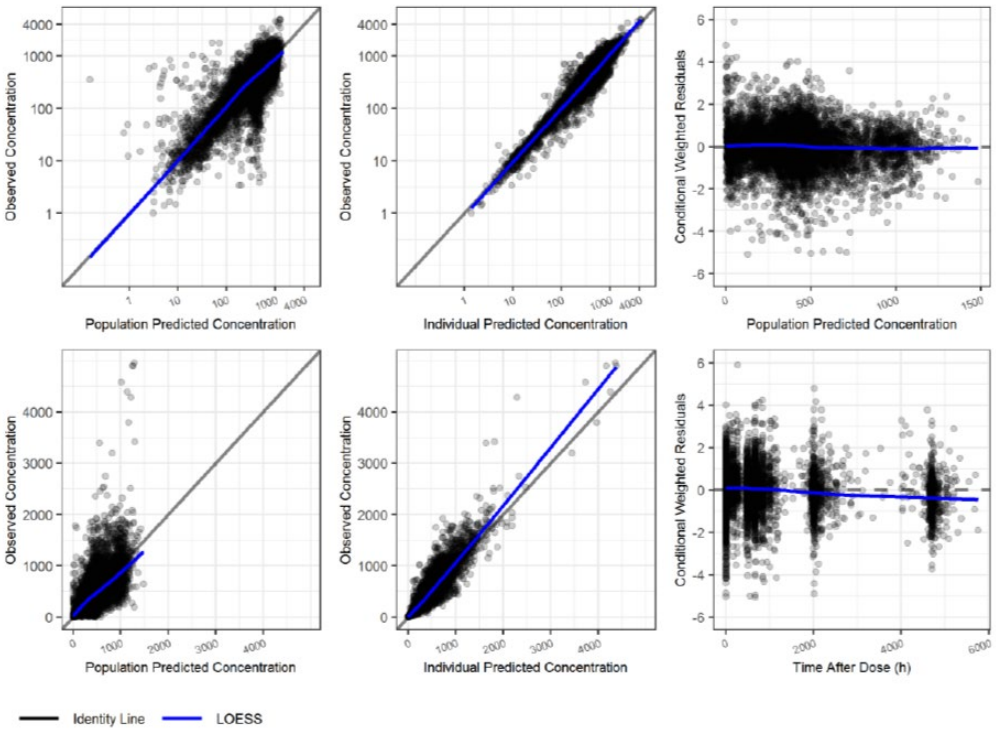


Figure 7. Goodness-of-Fit Plots for the preliminary Final Population PK Model (Model #4).
Source: PopPK report Figure 5. The observed versus predicted plots are shown in the log scale on the top row and in the linear scale in the bottom row. Black points represent individual data points. Black lines represent the line of unity for observation versus prediction plots, y = 0 for the conditional weighted residual plots. Blue lines represent LOESS smooth regression lines. LOESS = local regression; PK = pharmacokinetic.

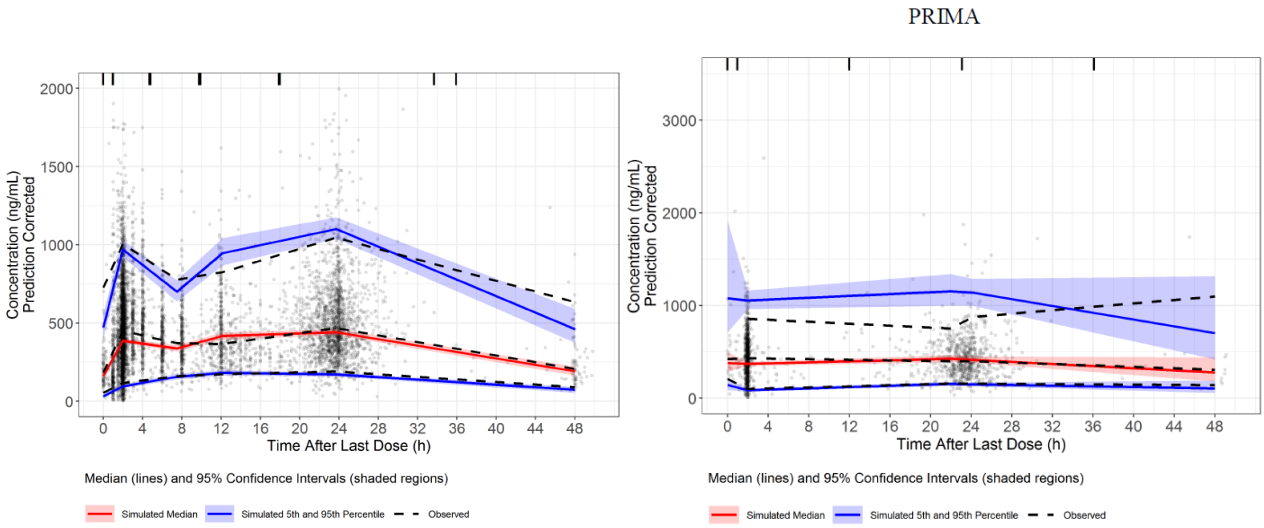


Figure 8. Prediction-corrected VPCs for the preliminary final population PK model (Model #4) – overall (left) and in PRIMA (right)

Black points represent observed concentrations. Dashed lines represent the 5th, 50th, and 95th percentiles of the observations. The red shaded region represents the 95% CIs of the medians of the simulations. The blue shaded regions represent the 95% CIs of the 5th and 95th percentiles of the simulations. CI = confidence interval; PK = pharmacokinetic; VPC = visual predictive check.

Model refinement: New final model (Model #5)

Due to concerns raised regarding the estimated impact of body weight (see discussion on clinical pharmacology), the preliminary final model was refined.

Initially, the effect of body weight on bioavailability (F) was removed (OFV increased by 3.5 points, p=0.06). Fixing the exponents to allometric values (0.75 for CL/F, 1 for Vc/F) increased the OFV substantially (+168 points), and only estimated exponents were further tested. Then, removing body weight on CL/F increased the OFV by 0.27 points (p=0.61), while removing body weight on Vc/F increased the OFV by 37 points (p<0.001). The effect of body weight on CL/F was not significant and therefore removed. Finally, a model without body weight increased the OFV by 39 points, and an effect of body weight solely on Vc/F was retained. This model was selected as the new final model.

The new final model achieved a successful covariance step and a condition number of 458, indicating that the model was stable.

Except from the weight exponent on Vc/F estimated to 0.47, modestly higher than the previous estimate of 0.31, the remaining estimates were similar to those of the previous model (Model #4). Parameter estimates are presented in Table 12 and pcVPCs in Figure 9 and Figure 10. The prediction-corrected VPCs demonstrated good predictive performance for the PRIMA study over time and across the range of weight in the analysis dataset.

The inter-individual variability in bioavailability was estimated to a coefficient of variation (CV) of 31%. The apparent volume of distribution (Vd/F) was 1,311 L (based on a 70 kg patient) in cancer patients (CV 116%), indicating extensive tissue distribution of niraparib. The apparent total clearance (CL/F) of niraparib was 16.5 L/h in cancer patients (CV 23.4%).

Table 12. Parameter estimates for the new, final model (Model #5)

Parameter	Fixed Effects		BSV CV%		Shrinkage
	Estimate	RSE%	Estimate	RSE%	
CL/F (L/h)	16.5	1.4%	23.4%	7.1%	39.9%
Vc/F (L)	424	2.2%	0 FIX	N/A	N/A
Q1/F (L/h)	1.37	6.1%	0 FIX	N/A	N/A
Vp1/F (L)	312	4.0%	0 FIX	N/A	N/A
Ka (1/h)	1.04	5.2%	72.8%	10.6%	56.4%
D1, fasted (h)	0.235	34.9%	225%	8.1%	43.5%
Tlag (h)	0.473	2.3%			
Frel (-)	1 FIX	N/A	30.9%	6.5%	31.5%
Q2/F (L/h)	68.3	2.5%	0 FIX	N/A	N/A
Vp2/F (L)	575	7.1%	116%	8.5%	51.5%
CL/F ~ age exponent	-0.184	36.1%			
CL/F ~ albumin exponent	0.500	17.4%			
CL/F ~ NCRCL exponent	0.230	18.4%			
Vc/F ~ weight exponent	0.470	11.9%			
D1 ~ fed fractional change	15.2	22.1%			
D1 ~ unknown prandial state fractional change	1.39	59.7%			
Proportional res. variability CV PN001	0.214	0.8%			
Proportional res. variability CV NOVA	0.330	1.0%			
Proportional res. variability CV QUADRA	0.380	1.5%			
Proportional res. variability CV PRIMA	0.456	1.3%			

ALB = albumin; BSV = between-subject variability; CL/F = apparent clearance; CV = coefficient of variation; D1 = duration of zero-order drug release; Frel = relative bioavailability; Ka = first-order absorption rate constant; NCRCL = body surface area-normalized creatinine clearance; Q1/F = apparent first inter-compartmental clearance; Q2/F = apparent second inter-compartmental clearance; Res. = residual; RSE = relative standard error; Tlag = lag time; Vc/F = apparent central volume; Vp1/F = apparent first peripheral volume of distribution; Vp2/F = apparent second peripheral volume of distribution; WT = weight; NCRCL = body surface area-normalized creatinine clearance.
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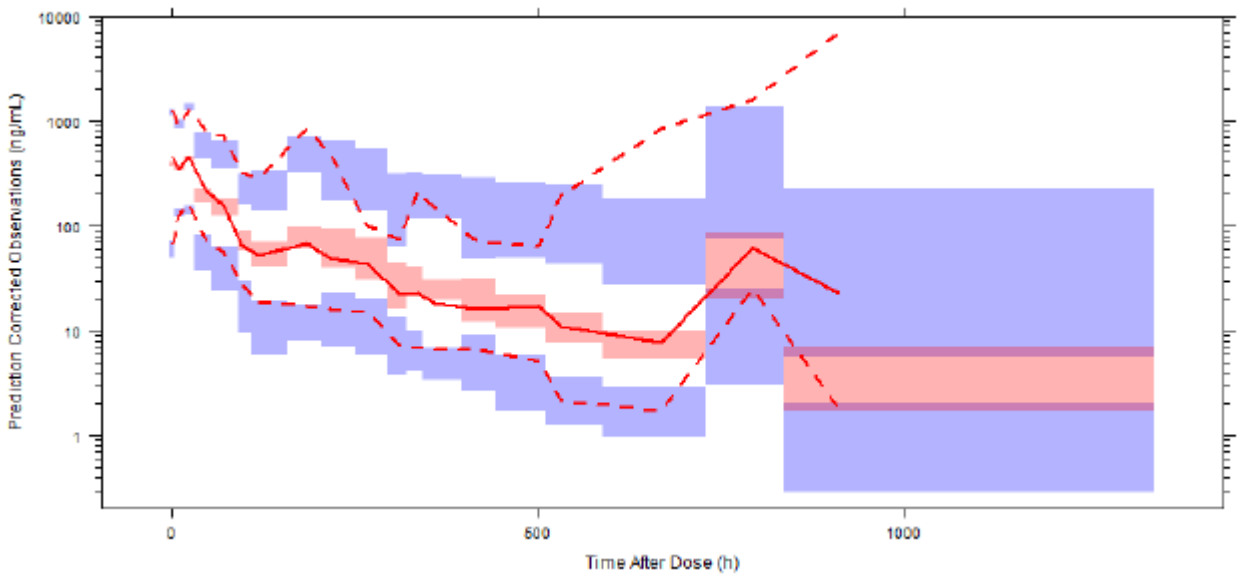


Figure 9. Prediction-corrected VPCs for the new final population PK model

Observed concentrations are not shown. Solid line represents the median of the observed data. Dashed lines represent the 5th and 95th percentiles of the observations. The red shaded region represents the 95% CIs of the medians of the

simulations. The blue shaded regions represent the 95% CIs of the 5th and 95th percentiles of the simulations. CI = confidence interval; PK = pharmacokinetic; VPC = visual predictive check.

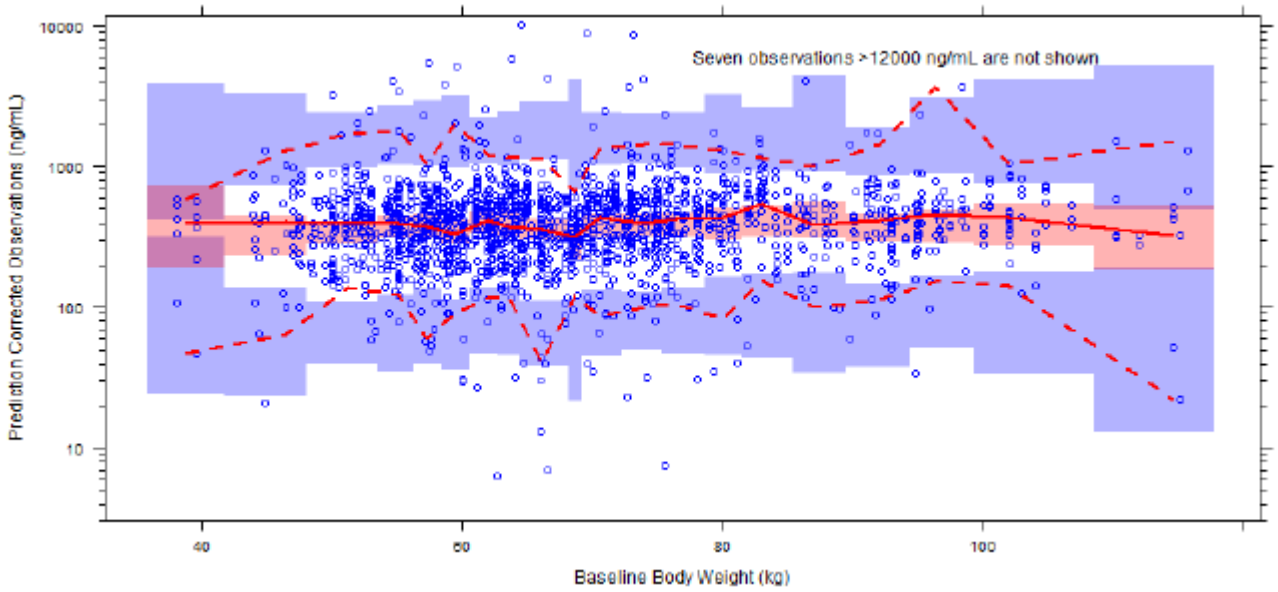


Figure 10. Prediction-corrected VPCs for the new final population PK model – body weight on x-axis.

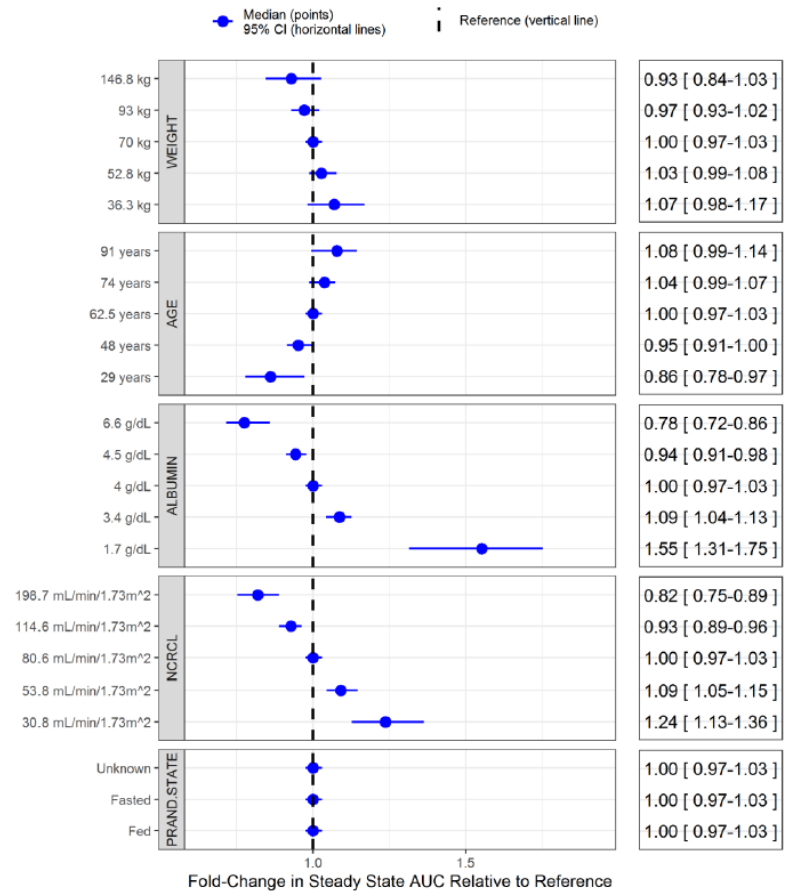
Open circles represent observed concentrations. Otherwise, figure interpretation as in Figure 9

Pharmacokinetics in target population

Sparse PK data were presented from the target population studied in the PRIMA study (see discussion on clinical pharmacology)

Special populations

In the updated population PK models, body weight, age, albumin, BSA-standardised creatinine clearance and prandial state were identified as covariates influencing niraparib PK. Figure 11 shows a forest plot of the estimated effect of covariates on niraparib exposure (steady state AUC) over the range of covariate values represented in the data set, using Model #4.



For all covariate scenarios, all other covariates were maintained at values for the reference patient (weight 70 kg, age 62.5 years, ALB 4 g/dL, NCRCL 80.6 mL/min/1.73 m^2, and administered niraparib in the fasted state; median 300 mg QD typical steady-state AUC from bootstrap estimates = 18198 ng·h/mL).
Numbers in the right panel represent median [95% CI] values.
ALB = albumin; AUC = area under the concentration-time curve; CI = confidence interval;
NCRCL = body surface area-normalized creatinine clearance; QD = once daily.

Figure 11. Forest plot of covariate effects on niraparib AUCss using Model #4 (preliminary model). Source: PopPK report, Figure 7. Note that the updated Model (#5) did not predict a change in AUCss with different body weights.

- **Impaired renal function**

No dedicated study to investigate the impact of impaired renal function on niraparib pharmacokinetics has been performed.

The updated population PK data set included patients with a median CRCL of 81 (range 28-236) mL/min. There were 232 patients (16.1%) with moderate renal impairment (CRCL 30-59 mL/min). Twenty-six patients (1.8%) had BSA-standardised CRCL (NCRCL) <40 mL/min/1.73 m^2.

There was a tendency to a relationship between BSA-normalised CRCL and CL/F in the ETA plot (Figure 12) and BSA-normalised CRCL was included on CL/F in the final model as a power function with an estimated exponent of 0.23.

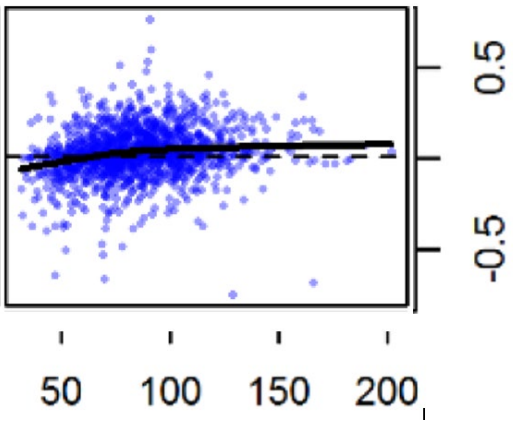


Figure 12. BSA-normalised CRCL (mL/min/1.73m^2) (x-axis) vs. individually estimated ETA for clearance (y-axis) using the popPK base model. Pearsons r=0.19 (p<0.001). Shrinkage in ETA CL: 41%.

Decreasing exposures of niraparib were predicted with increasing NCRCL, giving AUC ratios ranging from 0.82 at the maximum of 198.7 mL/min/1.73 m2 to 1.24-fold at the minimum of 30.8 mL/min/1.73 m^2 than the reference value.

- **Impaired hepatic function**

No dedicated study to investigate the impact of impaired hepatic function on niraparib pharmacokinetics has been performed.

The following liver function tests were considered as covariates on CL/F by assessing them in covariate-ETA plots: AST, ALT, ALP and bilirubin. ALP was also tested in the model but was not significant (p>0.005).

- **Gender**

Of the 1442 subjects in the population PK data set, 41 (2%) were males. Gender was not tested as a covariate in the full model.

- **Race**

In the data, there were 88 % White subjects, 6% unknown subjects and <3% Black or Asian subjects. The effect of race was considered in exploratory plots (shown in Figure 13 for clearance) but was not evaluated by including race in the model.

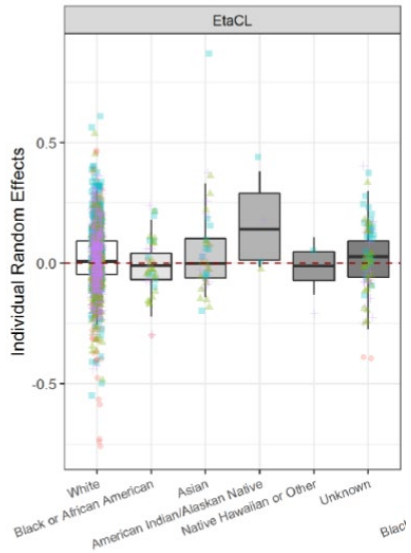


Figure 13. Relationship Between Race and Individual Random Effects for CL using the base model. Shrinkage: 41%.

- **Weight**

Figure 14 shows the relationships between body weight (x-axis) and etas for CL/F, V2p/F and F (y-axes, respectively), using the base model prior to covariate inclusion.

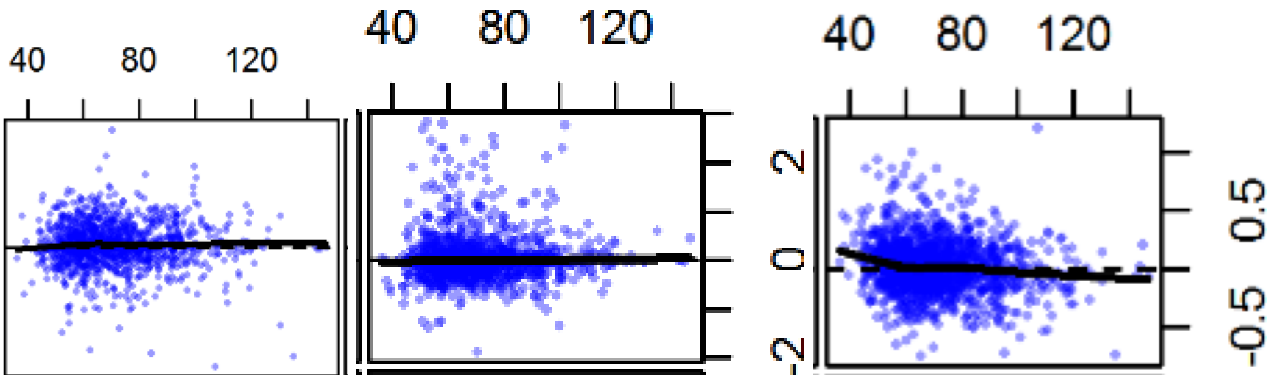


Figure 14. Left: Relationship between baseline body weight and eta for apparent clearance (CL/F) and their individual distributions in the population PK analysis base model.

Shrinkage for eta CL was 41%. Center: Relationship between weight and eta for apparent second peripheral volume of distribution (V2/F). Shrinkage for eta V2 was 52%. Right: Relationship between weight and eta for bioavailability, shrinkage 31%. Source: PopPK report, Appendix 1.

The final model (Model #5) did not identify a significant relationship between body weight and CL/F or F, while a significant effect was identified on Vc/F.

- **Elderly**

The effect of age on niraparib PK was evaluated in the population PK analysis. Figure 15 shows the distribution of age in the data set (~30-90 years) and the exploratory relationship between age and

individually estimated clearance values. Age was included in the model as a covariate on CL/F (p=0.02, Table 10). According to the MAH, the extent of change in exposure with increasing age is minor.

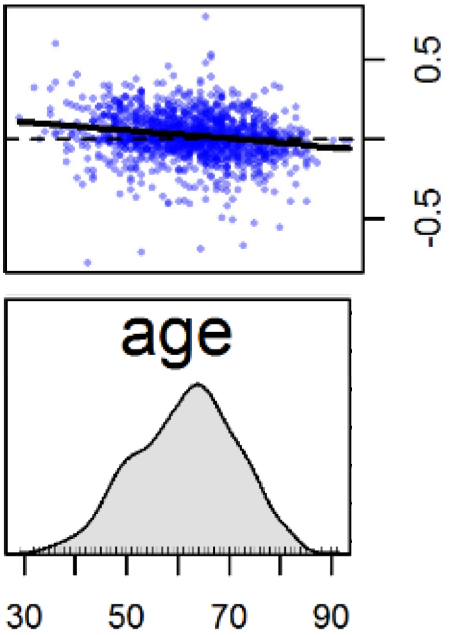


Figure 15. Top: Relationship between age and individual random effects for CL using the base model (r=-0.20, p<0.001). Bottom: Distribution of age in the popPK data set. Shrinkage in ETA CL: 41%.

- **Albumin**

According to the updated popPK analysis, decreasing albumin was associated with increasing clearance.

2.3.3. Pharmacodynamics

Mechanism of action

No new studies were submitted.

Niraparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role in DNA repair. *In vitro* studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death. Increased niraparib-induced cytotoxicity was observed in tumour cell lines with or without deficiencies in the BReast CAncer (*BRCA)* 1 and 2 tumour suppressor genes. In orthotopic high-grade serous ovarian cancer patient-derived xenograft tumours (PDX) grown in mice, niraparib has been shown to reduce tumour growth in *BRCA* 1 and 2 mutant, *BRCA* wild-type but homologous recombination (HR) deficient, and in tumours that are *BRCA* wild-type and without detectable HR deficiency (see SmPC section 5.1).

Primary and secondary pharmacology

No new primary or secondary PD studies were submitted in support of the current application.

Exposure-response relationships

Efficacy

Efficacy at the two dose levels tested (200 mg vs. 300 mg) is described and discussed in section "*Clinical efficacy"*. This section describes the exposure-efficacy relationship.

Data

A total of 480 PRIMA study patients randomised to niraparib treatment were available for exposure-response analyses. The original analyses used the 17 May 2019 data cut date. The analyses presented below used the efficacy dataset updated to include 6 months of additional data (data cut date: 17 Nov 2019) provided during the procedure.

Summary statistics for covariates by exposure quartiles are provided for the total PRIMA population in Table 13.

Table 13. Categorical (left) and continuous (right) covariate summary by AUCss quartile – total PRIMA population

Covariate	Category	[6.5,13.1] (N = 120)	(13.1,16.1] (N = 120)	(16.1,19.2] (N = 120)	(19.2,59.1] (N = 120)
BRCA status	Mutant	49 (40.8%)	44 (36.7%)	25 (20.8%)	32 (26.7%)
	Unknown	1 (0.8%)	8 (6.7%)	13 (10.8%)	3 (2.5%)
	Wild-type	70 (58.3%)	68 (56.7%)	82 (68.3%)	85 (70.8%)
Best response to pt therapy	Complete response	79 (65.8%)	78 (65%)	84 (70%)	82 (68.3%)
	Partial Response	41 (34.2%)	42 (35%)	36 (30%)	38 (31.7%)
ECOG Status	0	91 (75.8%)	86 (71.7%)	78 (65%)	77 (64.2%)
	1	29 (24.2%)	34 (28.3%)	42 (35%)	43 (35.8%)
Dose Group	A: FSD 300 mg, WT≥77 kg & PLT≥150	9 (7.5%)	15 (12.5%)	25 (20.8%)	21 (17.5%)
	B: ISD 300 mg, WT≥77 kg & PLT≥150	3 (2.5%)	7 (5.8%)	9 (7.5%)	14 (11.7%)
	C: FSD 300 mg, WT<77 kg or PLT<150	42 (35%)	57 (47.5%)	68 (56.7%)	75 (62.5%)
	D: ISD 200 mg, WT<77 kg or PLT<150	64 (53.3%)	38 (31.7%)	14 (11.7%)	6 (5%)
	Incorrect ISD assignment	2 (1.7%)	3 (2.5%)	4 (3.3%)	4 (3.3%)
HRD status	Negative	34 (28.3%)	34 (28.3%)	41 (34.2%)	57 (47.5%)
	Positive	73 (60.8%)	67 (55.8%)	55 (45.8%)	48 (40%)
	Unknown	13 (10.8%)	19 (15.8%)	24 (20%)	15 (12.5%)
Neoadj. Chemo.	No	43 (35.8%)	43 (35.8%)	38 (31.7%)	34 (28.3%)
	Yes	77 (64.2%)	77 (64.2%)	82 (68.3%)	86 (71.7%)
Race	American Indian or Alaska Native	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)
	Asian	7 (5.8%)	3 (2.5%)	2 (1.7%)	2 (1.7%)
	Black or African American	2 (1.7%)	0 (0%)	2 (1.7%)	4 (3.3%)
	Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)
	Not Reported	7 (5.8%)	1 (0.8%)	5 (4.2%)	5 (4.2%)
	Unknown	0 (0%)	0 (0%)	3 (2.5%)	3 (2.5%)
	White	103 (85.8%)	116 (96.7%)	108 (90%)	105 (87.5%)
Starting Dose	200 mg	65 (54.2%)	40 (33.3%)	14 (11.7%)	6 (5%)
	300 mg	55 (45.8%)	80 (66.7%)	106 (88.3%)	114 (95%)

Summary statistics are presented as number (%) of subjects.
AUCss = steady-state area under the concentration-time curve based on the starting dose; BRCA = breast cancer susceptibility gene; ECOG = Eastern Cooperative Oncology Group; FSD = fixed starting dose; HRD = homologous recombination deficiency; ISD = individualized starting dose; N = number of subjects; Neoadj. Chemo. = neoadjuvant chemotherapy; PLT = baseline platelet count; pt = platinum; WT = baseline weight.

Covariate	Statistic	[6.5,13.1] (N = 120)	(13.1,16.1] (N = 120)	(16.1,19.2] (N = 120)	(19.2,59.1] (N = 120)
Age (years)	Mean (SD)	57.5 (10.4)	59.9 (10.9)	61.7 (9.8)	65.3 (10.7)
	Median [Min, Max]	58.5 [32, 83]	62 [34, 82]	63 [36, 83]	66 [38, 85]
AUCss (ug*h/mL)	Mean (SD)	10.8 (1.7)	14.7 (0.8)	17.7 (0.9)	23.1 (4.9)
	Median [Min, Max]	11.1 [6.5, 13]	14.7 [13.1, 16.1]	17.7 [16.1, 19.2]	21.6 [19.3, 59.1]
Duration of Last Pt Treatment (wks)	Mean (SD)	5.2 (1.3)	5.2 (1.4)	5.3 (1.6)	5.4 (1.4)
	Median [Min, Max]	4.9 [3.4, 9.4]	5 [3.3, 10.1]	5.1 [1.2, 10.7]	5.3 [3.3, 10.5]
Pt-free interval (wks)	Mean (SD)	7.9 (2.9)	8.2 (2.9)	8.7 (3.5)	8.7 (3.5)
	Median [Min, Max]	7.9 [0.3, 16.9]	7.7 [2.1, 20.9]	8.4 [2.9, 28]	8.4 [1.6, 24]
Weight (kg)	Mean (SD)	66 (12.1)	66.9 (13.3)	70.5 (15.7)	71 (14.8)
	Median [Min, Max]	64 [39.5, 104]	64.2 [44.4, 115.2]	68 [38, 114.6]	69 [46.4, 115.8]

Exposure-efficacy relationship

- *Efficacy outcome analysed*: Progression-free survival (PFS)
- *Exposure metric*: Individual model-predicted steady-state exposures (AUCss) derived using the individual (post hoc) PK parameter estimates (CL/F and Frel) from the niraparib population PK model.
    - The initial analysis presented by the MAH: **Average concentration (Cave) up to the time of event**, predicted using popPK Model #4 and analysed as a categorical covariate. Cave was approximated by multiplying the individual model-predicted steady-state exposure at the nominal dose of 200 or 300 mg QD by the relative dose intensity up to the time of first event/end of treatment/censoring. These results are not further presented in this report.
    - The updated analysis provided during the procedure: **AUCss associated with first dose,** predicted using popPK Model #5, analysed as a continuous variable and with the updated efficacy data set (data cut date: 17 Nov 2019). These results are presented below.
- *Analysis method*: Exploratory by exposure quartiles and Cox proportional hazards modelling

Evaluation of exposure metric

In order to evaluate the reliability of the individual exposure metrics for exposure-response analysis, shrinkage for the PRIMA dataset was specifically calculated. In the sparsely sampled PK data from the PRIMA study, shrinkage values were high (calculated as described in Karlsson and Savic 2007) with 50% for CL/F and 47% for Frel. In addition, the following analysis was performed: An artificially sparse dataset was created with data from patients in phase 1 study PN001 using only the 2-h samples on Day 1 and the pre-dose and 2-h samples at steady state (i.e. mimicking the PK sampling in PRIMA). *Post hoc* estimates of the PK parameters for these subjects were obtained by using the sparse dataset as the input dataset, setting the initial estimates in the $THETA, $OMEGA, and $SIGMA blocks to the final estimates from the refined model, and setting MAXEVAL to 0. The rich PK samples from these patients were also used to perform a non-compartmental analysis (NCA) in Phoenix WinNonlin (version 8.2) and calculate AUC values. The linear up log down method was used.

Overall, the NCA- and model-derived AUCss were similar for PN001 patients, as shown in Figure 16.

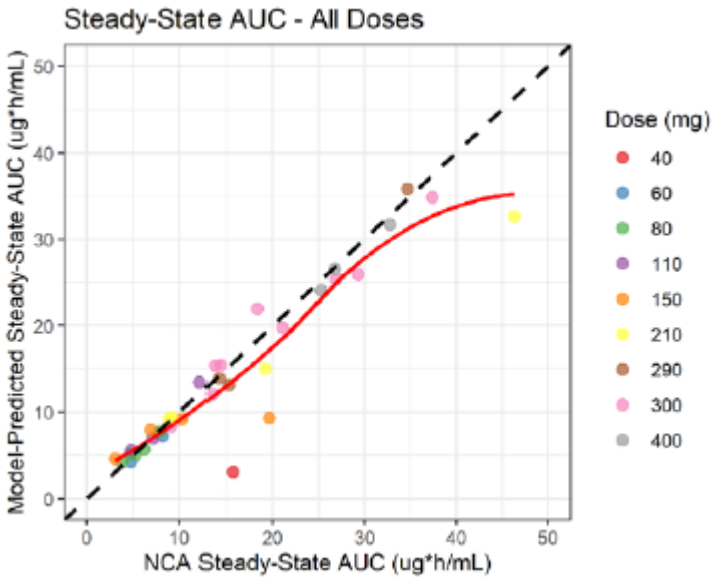
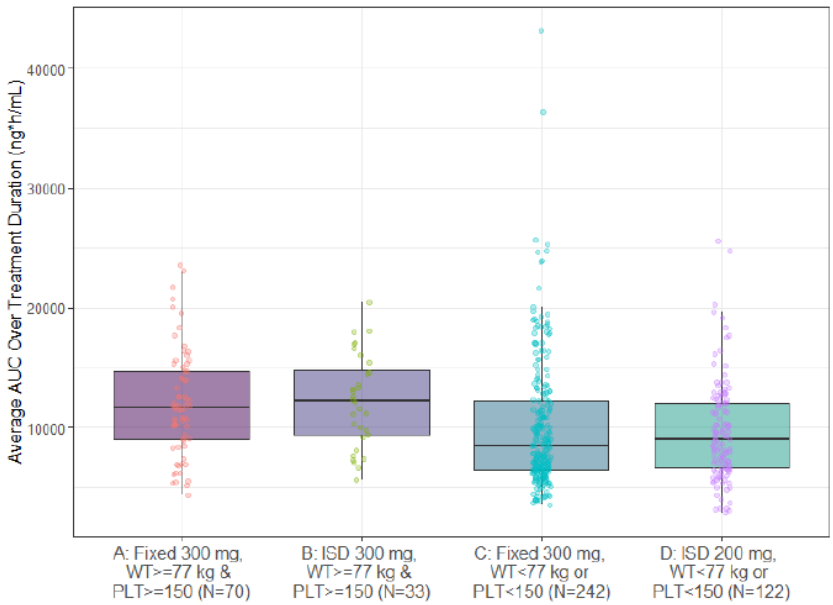


Figure 16. Comparison between NCA-derived and model-predicted steady state AUC in PN001. Source: RSI response document, Figure 34.

Dose reductions and exposure

Although niraparib exposures at the beginning of treatment would be lower in the 200 mg ISD group relative to the 300 mg FSD group due to the lower dose, exposures were comparable over the course of treatment (Figure 17), consistent with a lower rate of dose reduction in the ISD dose groups.



AUC = area under the concentration-time curve; ISD = individualized starting dose; N = number of subjects; PLT = baseline platelet count in $\times 10^3$ µg*h/mL; WT = baseline weight.

Figure 17. Comparison of model-predicted average AUC across dose groups.

Source: RSI response Figure 43. The average AUC over the duration of treatment was calculated for PRIMA subjects using the refined pop-PK model by multiplying the AUCss value associated with the starting dose by the relative dose intensity

Exploratory analysis

Figure 18 shows the relationship between model-predicted steady-state average concentration associated with the starting dose (AUCss quartiles) and PFS. The plot indicates that PFS is similar across exposure quartiles.

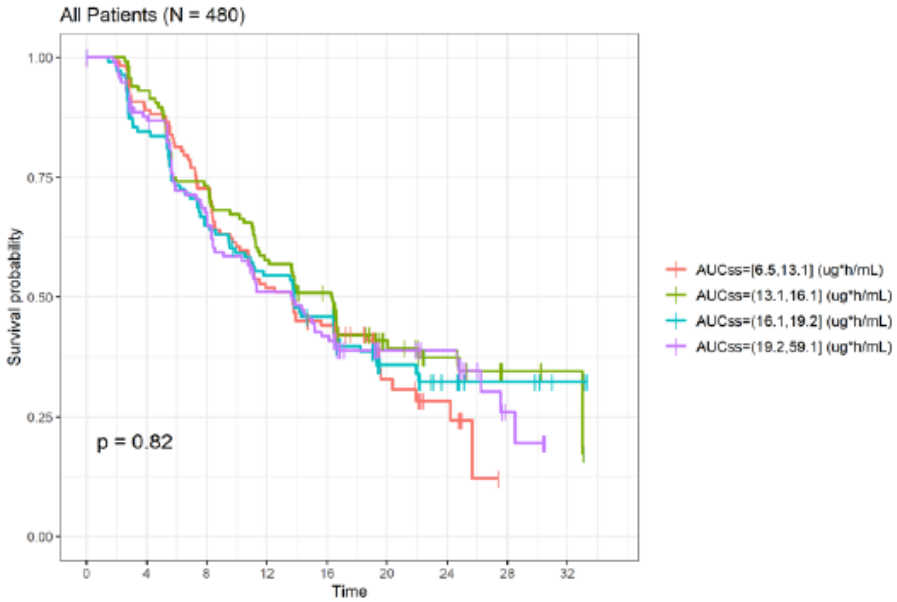
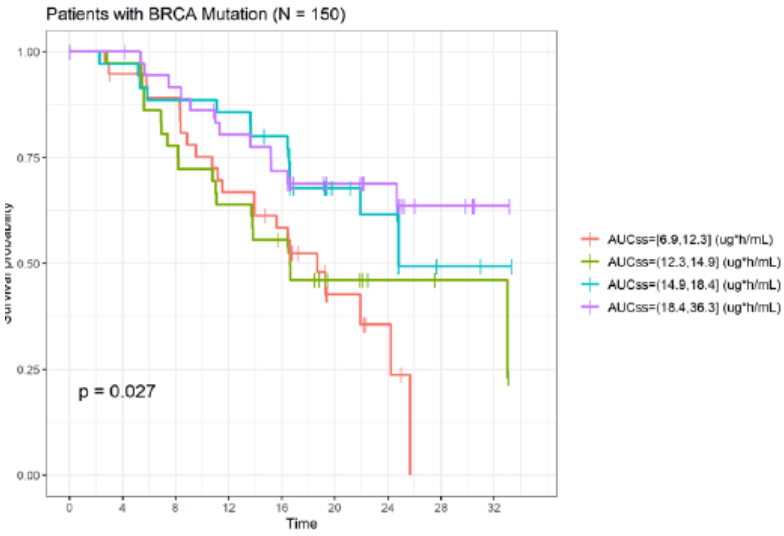


Figure 18. Kaplan-Meier plot by exposure quartile in the total PRIMA population.

AUCss=steady state area under the concentration time curve based on starting dose. P = p value for the log-rank test.

Figure 19 shows the relationship between AUCss quartile and PFS in subgroups according to BRCA status.



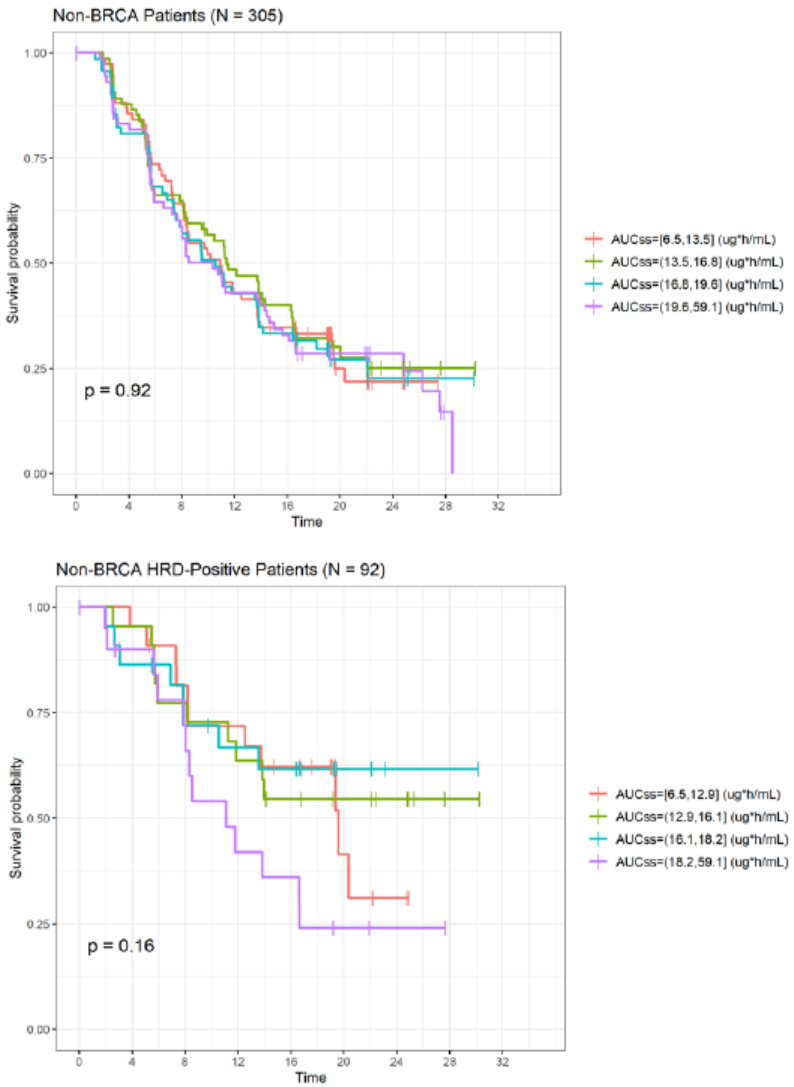


Figure 19. Kaplan-Meier plots by exposure quartiles in BRCA mutated, non-BRCA mutated and non-RCA HRD-positive patients, respectively.

Figure interpretation as in Figure 18.

The survival curves for all the exposure quartiles overlapped in the Kaplan-Meier plots for the non-BRCAmut patients, and the p-values based on the log-rank test indicated no statistically significant exposure-response relationships for PFS in these groups (p ≥0.16). For the BRCAmut population (N = 150), PFS was shorter in the two lower exposure groups compared to the higher exposure groups (p = 0.027). There was no statistically significant difference between the survival curves for BRCAmut population patients who received a starting dose of 200 mg compared to those who received 300 mg (p = 0.57; Figure 18).

Modelling analysis

Methods and results: A Cox proportional hazards model was used to model the exposure-response relationship between niraparib exposure and PFS. HRD status was the only covariate investigated in the updated analysis. A backward deletion step was performed for a model with AUCss and HRD status. The increase in -2×loglikelihood was statistically significant when the effect of HRD status was removed (p < 0.0001), but not when AUCss was removed (p =0.1804). However, AUCss was retained in the model in order to investigate the potential exposure-response relationship. The estimated hazard ratios (HR) and 95% CI are shown in Table 14.

The HR (95% CI) for median simulated AUCss of **200 mg** (11.8 µg*h/mL) vs. **300 mg** (17.5 µg*h/mL) is predicted to be 1.10 (0.943, 1.26), with a 95% CI including the null effect.

Table 14. Model-estimated hazard ratios for the PFS exposure-response model.

Parameter	HR	95% CI	p-value
AUCss	0.983	0.958 - 1.01	0.1854
HRD positive	0.350	0.269 - 0.454	<0.0001
HRD status unknown	0.787	0.567 - 1.09	0.1545

AUCss = steady-state area under the concentration-time curve based on starting dose in µg*h/mL; CI = confidence interval; HR = hazard ratio; HRD = homologous recombinant deficiency status.

Model evaluation: The model was evaluated using Schoenfeld tests and Martingale residuals vs. covariates.

Additional analysis in BRCAmut population

As presented in the exploratory analyses above, the Kaplan-Meier plots for the BRCAmut population (N = 150) stratified by AUCss quartiles suggested an exposure-response relationship for PFS. Therefore, the exposure-response relationship in the BRCAmut population was also investigated using a Cox proportional hazards model with AUCss as the only explanatory variable used in the model. The estimated HR (95% CI; p-value) for AUCss was 0.911 (0.858 - 0.967; p = 0.0021), indicating a statistically significant exposure-response relationship, with higher exposures associated with improved PFS in the BRCAmut population.

Safety

Exposure-safety relationship

The results of the initial analysis below are not presented.

- *Data:* Patients from PRIMA study (n=480), data cut date: 17 May 2019
- *Safety end points*: Any grade and grade 3 or higher (Gr3+) **thrombocytopenia, anaemia, neutropenia, hypertension,** and **fatigue** occurring at any point during the study, treated as binary variables.
- *Exposure metric*: Individual model-predicted steady-state exposures (Cave, Cmax and Cmin) derived using the individual (post hoc) PK parameter estimates (CL/F and Frel) from the niraparib preliminary population PK model (Model #4), calculated as the average exposure up to the time of event/end of treatment/censoring.
- *Analysis method*: Exploratory by quartiles and univariate logistic regression modelling
- *Covariates tested:* None

The updated analysis is presented below:

- *Data:* Patients from PRIMA study, prior to protocol amendment (n=312, i.e. excluding patients dosed by presumed thrombocytopenia risk), data cut date: 17 Nov 2019, and patients from previous NOVA study (n=361)
- *Safety end point*: Grade 3 or higher (Gr3+) **thrombocytopenia** occurring at any point during the study, treated as a binary variable.

- *Exposure metric*: Individual model-predicted steady-state exposures (AUCss) associated with the first dose, derived using the individual (post hoc) PK parameter estimates (CL/F and Frel) from the niraparib refined population PK model.
- *Analysis method*: Univariate (exploratory) and multivariate logistic regression modelling
- *Covariates tested:* Body weight, baseline platelet count, age, ECOG status

Exposure-thrombocytopenia model

Summary statistics for the frequency of Grade 3+ thrombocytopenia and baseline characteristics are provided in Table 15. Grade 3+ thrombocytopenia was more frequent in PRIMA (48.4%) compared to NOVA (33.8%), and AUCss were slightly lower in NOVA. The remaining evaluated baseline characteristics had similar distributions in both studies.

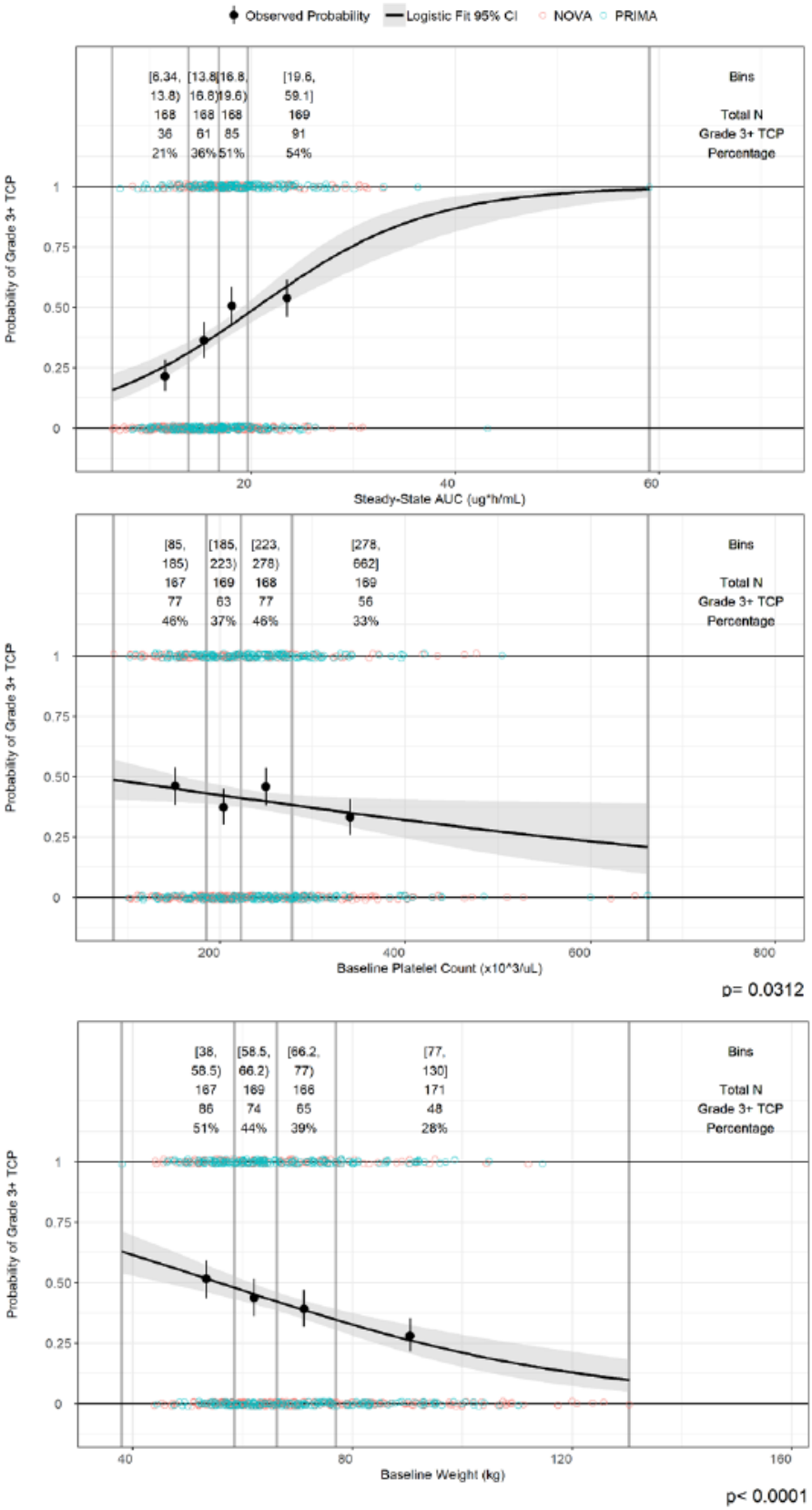
Table 15. Grade 3+ thrombocytopenia and baseline characteristics summary for patients included in the safety exposure-response analysis. Source: RSI response document, Table 26.

Covariate	Statistic	NOVA (N = 361)	PRIMA (N = 312)	Overall (N = 673)
Grade 3+ TCP				
No	n (%)	239 (66.2%)	161 (51.6%)	400 (59.4%)
Yes	n (%)	122 (33.8%)	151 (48.4%)	273 (40.6%)
ECOG Status				
0	n (%)	252 (69.8%)	219 (70.2%)	471 (70%)
1	n (%)	107 (29.6%)	93 (29.8%)	200 (29.7%)
Missing	n (%)	2 (0.6%)	0 (0%)	2 (0.3%)
Age (years)	Mean (SD) Median [Min, Max]	60.2 (9.54) 61 [33, 83]	60.6 (11.3) 61.5 [32, 83]	60.4 (10.4) 61 [32, 83]
AUCss (µg*h/mL)	Mean (SD) Median [Min, Max]	16.6 (4.78) 16.3 [6.34, 32.9]	17.7 (5.27) 17.2 [7.08, 59.1]	17.1 (5.04) 16.8 [6.34, 59.1]
Baseline Platelet Count ($\times 10^3$/µL)	Mean (SD) Median [Min, Max]	233 (82.2) 215 [85, 648]	241 (76.3) 236 [101, 662]	237 (79.6) 223 [85, 662]
Weight (kg)	Mean (SD) Median [Min, Max]	69.9 (16.1) 66.5 [43.9, 130]	68.8 (14) 65.9 [38, 115]	69.4 (15.2) 66.2 [38, 130]

AUCss = steady-state area under the concentration-time curve based on starting dose; ECOG = Eastern Cooperative Oncology Group; Grade 3+ = grade 3 or higher; Min = minimum; Max = maximum; n = number of subjects in category; N = total number of subjects; SD = standard deviation; TCP = thrombocytopenia.

Univariate analyses

Exploratory univariate logistic regression plots with AUCss, weight, and baseline platelet count (PLT) indicated that the probability of Grade 3+ thrombocytopenia increased with increasing niraparib exposure and decreased with increasing weight and PLT (Figure 20). The effect of PLT appeared to be less pronounced than the effects of exposure and weight.



AUC = area under the concentration-time curve; AUCss = steady-state area under the concentration-time curve based on starting dose; Grade 3+ = grade 3 or higher; N = number of subjects: p = p-value of logistic regression model slope; TCP = thrombocytopenia.

Figure 20. Univariate relationships between AUCss (top), baseline platelet count (middle), and baseline weight (bottom) and the probability of grade 3 or higher thrombocytopenia.

The independent variables were divided into 4 equally sized rank-ordered groups. Black points and error bars represent the observed proportions and 95% CIs for each exposure group (plotted at the mean exposure within each exposure group), respectively. The black curve represents the prediction of the univariate logistic regression model, and the gray shaded region represents the 95% CI of the prediction. Percentages in the upper part of the graph represent the fraction of patients in the exposure group arising from each dose group. Source: RSI response, Figure 40.

Multivariate analysis

A full model was run with the following explanatory variables: AUCss, weight, PLT and age (all continuous), and ECOG performance status (serving as a surrogate for comorbidities) as a categorical covariate. Backward deletion was then performed, using an increase in AIC of any amount as the criterion for deletion. During backward deletion, age and ECOG performance status dropped out of the model. The model arising from this step was considered the final exposure-response model for Grade 3+ thrombocytopenia and included AUCss, weight, and PLT as explanatory variables. The final model equation was:

$$\log(p/(1-p)) = 0.317 + 0.122 \times AUCss - 0.0304 \times WT - 0.00302 \times PLT$$

where AUCss is in μg*h/mL, WT is in kg, and PLT is in $\times 10^3/\mu L$.

Parameter estimates and odds ratios for the final model are presented in Table 16. The coefficients for AUCss, weight, PLT were statistically significant ($p \leq 0.0062$). The model predicts that the probability of Grade 3+ thrombocytopenia increases with increasing AUCss, decreasing weight, and decreasing PLT, consistent with the exploratory plots.

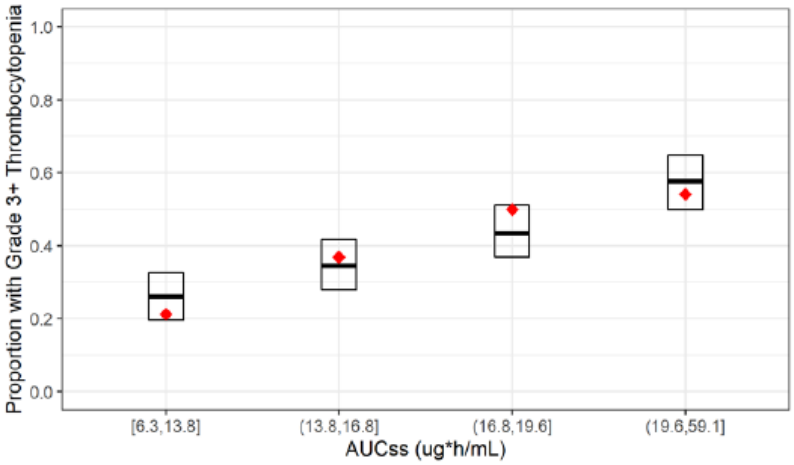
Table 16. Parameter Estimates for the Final Model for Grade 3+ Thrombocytopenia. Source: RSI response Table 27.

Coefficient	Units	Estimate	RSE	p-value	Odds Ratio (95% CI)
Intercept		0.317	181.8%	0.5825	
AUCss	1/(μg*h/mL)	0.122	15.5%	<0.0001	1.13 (1.09, 1.17)
WT	1/kg	-0.0304	20.0%	<0.0001	0.97 (0.958, 0.981)
PLT	$1/(10^3/\mu L)$	-0.00302	36.5%	0.0062	0.997 (0.995, 0.999)

AUCss = steady-state area under the concentration-time curve based on starting dose; CI = confidence interval; RSE = relative standard error; PLT = baseline platelet count; WT = baseline weight.

Model evaluation

Figure 21 shows a VPC for the logistic regression model using 1000 replicates of the patients in the analysis datasets, plotted against AUCss. It demonstrates good agreement between the observed and simulated proportions. VPCs for weight and PLT indicated an adequate fit of the model to the overall data.



The red diamonds represent the observed proportion of patients with Grade 3+ thrombocytopenia. The boxes bound the 2.5th and 97.5th percentiles (95% PI) of the simulated proportions, and the crossbars within the boxes represent the median of the simulated proportions.
AUCss = steady-state area under the concentration-time curve based on starting dose; PI = prediction interval; VPC = visual predictive check.

Figure 21. VPC of the final grade 3+ thrombocytopenia model plotted against AUCss quartiles. Source: RSI response, Figure 42.

Model predictions of benefit of dose reduction

The final model was used to predict the probability of Grade 3+ thrombocytopenia for different dosing regimens and patient groups to investigate the potential benefit of the individualized starting dose: i.e. reducing the starting dose from 300 mg to 200 mg for patients with low WT (WT <77 kg) and/or low PLT (<150,000/μL). For the predictions, the median simulated AUCss were used as estimates of 200 mg and 300 mg exposures (11.8 and 17.5 ug*h/mL, respectively). The median WT and PLT values among PRIMA patients in the respective weight and platelet groups were used as representative values (with low WT and low PLT defined as above and high WT and high PLT defined as WT ≥77 kg and PLT ≥150,000/μL, respectively). The probability predictions are tabulated in Table 17.

In every case, equivalent WT and PLT patient groups had substantially lower predicted probability of Grade 3+ thrombocytopenia for the 200 mg starting dose compared to 300 mg. Patients with low WT or low PLT (Groups A1 to A3) receiving the 300 mg dose were predicted to have a probability ranging from 35.9% to 53.9%. When these patients receive the lower starting dose of 200 mg, the probability of Grade 3+ thrombocytopenia was predicted to decrease (probabilities ranging from 21.9% to 36.9%), with 95% CIs that did not overlap or overlapped minimally. Therefore, lowering the starting dose to 200 mg for subjects with low WT or low PLT was predicted to reduce the incidence of Grade 3+ thrombocytopenia.

Table 17. Predictions of the probability of Grade 3+ thrombocytopenia for various covariate values and dosing strategies. Source: First RSI response, Table 28.

Scenario (Starting Dose; Patient Group)	AUCss (µg*h/mL)	WT (kg)	PLT (×10³/µL)	Probability (%) (95% CI)
200 mg; A1: Low WT + High PLT	11.8	62.0	241.0	29.8 (24.2, 35.4)
300 mg; A1: Low WT + High PLT	17.5	62.0	241.0	45.8 (41.4, 50.3)
200 mg; A2: High WT + Low PLT	11.8	86.3	133.5	21.9 (15.2, 28.6)
300 mg; A2: High WT + Low PLT	17.5	86.3	133.5	35.9 (28.1, 43.7)
200 mg; A3: Low WT + Low PLT	11.8	62.0	133.5	36.9 (29.1, 44.7)
300 mg; A3: Low WT + Low PLT	17.5	62.0	133.5	53.9 (46.9, 61.0)
300 mg; B: High WT + High PLT	17.5	86.3	241.0	28.8 (23.2, 34.5)

AUCss = steady-state area under the concentration-time curve based on starting dose; CI = confidence interval; PLT = baseline platelet count; WT = baseline weight.

2.3.4. Discussion on clinical pharmacology

Niraparib is currently approved as maintenance treatment of adult patients with platinum-sensitive recurrent ovarian cancer who are in response to second-line or greater platinum-based chemotherapy. The applied indication is for patients with the same diagnoses, but as first-line maintenance treatment.

The currently approved starting dose for niraparib monotherapy is 300 mg for all patients, taken orally once daily. In the registrational study NOVA, doses were reduced over the first 3 cycles based on individual tolerance, and this reduced the incidence and severity TEAEs in patients enabling them to continue on a sustained maintenance treatment. At Cycle 12, of the 163 patients remaining on niraparib treatment in the NOVA study, only 37 patients (23%) remained on a daily dose of 300 mg with the remaining patients at either 200 mg (n=65, 40%) or 100 mg (n=61, 37%). Dose reduction reduced Grade 3/4 thrombocytopenia from 36% during Month 1 to <1% after Month 3. It was therefore suggested that a lower dose may improve the benefit-risk balance of niraparib, emphasising that the treatment is maintenance treatment and that reducing the adverse event burden is of high importance. A variation application was submitted in 2019 (EMEA/H/004249/II/0006, variation withdrawn) in order to change the posology in the currently approved indication. Retrospective, exploratory statistical multivariable analysis of the NOVA data was used to investigate predictors of Grade 3 thrombocytopenia. Low body weight and low baseline platelet count were identified as predictors of thrombocytopenia, which is one of the most frequent adverse events, and an alternative dosing algorithm based on these factors was proposed. The proposed dosing algorithm implied that ~75% of the target population will receive a lower starting dose (200 mg QD), while the remaining patients will still receive 300 mg (if they fulfil both the criteria of a body weight ≥77 kg and a normal baseline platelet count [≥150,000/µL]). This posology change, however, was not considered acceptable by the CHMP because there was no prospective data to confirm maintained efficacy at this alternative dose. Furthermore, the proposed dosing algorithm was questioned because body weight and platelet count did not influence the PK or PD of niraparib. The MAH was encouraged to also consider other dosing strategies using more recognised and comprehensive pharmacometrics methodology.

In the present application, the MAH has prospectively tested the dosing algorithm described above, without further refining it. Exposure-response analyses have been proposed as supplementary evidence of maintained efficacy at the 200 mg starting dose.

The application encompasses an updated population PK model based on a large data set from multiple studies, including the sparsely collected PK data from the PRIMA study, in addition to exposure-response modelling for efficacy and safety end points.

Analytical methods used in PRIMA study are considered acceptable. With regards to the PopPK modelling, standard and adequate methodology was used.

A three-compartment model with linear elimination and a constant rate of drug release into the absorption compartment preceded by a time lag and first-order absorption was used to describe the data.

The base model parameter estimates were similar to those of a previously established base model, indicating that the PK in the current indication is similar to the PK in previous indications. Inter-occasion variability has not been estimated. The shrinkage in all parameters was high (>30% for all parameters, 41.4% for CL/F). This is expected based on the very sparse PK sampling in the majority of patients. Due to high shrinkage, the individually predicted parameters are not considered reliable and not appropriate for Empirical Bayes Estimate (EBE)-based diagnostics (e.g. covariate vs. ETA plots).

In final model (Model #5) the following covariates were identified: age, albumin and BSA-normalised creatinine clearance on apparent clearance, and body weight on volume of distribution. Prandial state was included as a covariate on the duration of drug release prior to absorption. None of the covariates were deemed to impact on exposure to an extent that would warrant dose adjustment in any special population. The popPK model adequately and reliably described the data as judged by a range of standard model diagnostic techniques, including prediction-corrected visual predictive checks. For completeness, the MAH is recommended to update the modelling report with the most recent results and also include a backward elimination procedure for the final covariate selection, a procedure to determine the parameter uncertainty for the refined model parameter estimates (e.g. bootstrap), and an updated forest plot for the impact of covariates at the covariate ranges. The report should also be updated with the most recent exposure-response modelling results (recommendation). The MAH informed that an updated population PK and exposure-response report will be submitted when available, estimated to occur by 30 September 2021.

Regarding special populations, clinical studies investigating the impact of renal impairment on niraparib PK have not been submitted. The effect of renal impairment was studied in the population pharmacokinetic analyses using creatinine clearance as a marker for renal function. In contrast to previous popPK analyses, creatinine clearance was identified as a covariate in the updated modelling. Patients with mild (creatinine clearance 60-90 ml/min) and moderate (30-60 mL/min) renal impairment had mildly reduced niraparib clearance compared to individuals with normal renal function (7-17% higher exposure in mild and 17-38% higher exposure in moderate renal impairment). However, the difference in exposure is not considered to warrant dose adjustment for patients with reduced renal function. This is reflected in section 5.2. of the SmPC.

There is no formal study of niraparib in subjects with hepatic impairment. Hepatic impairment has not been identified as a covariate in previous modelling exercises of niraparib and was not tested in the modelling performed for this application.

With regards to gender, it cannot be expected to identify a potential underlying effect of gender on niraparib PK considering the small number of male subjects in the data set (2%). The effect of gender is therefore unknown. Considering the target population, this is acceptable.

There is insufficient data across races to conclude on the impact of race on niraparib pharmacokinetics. According to the box plots of etaCL in the limited number of subjects of other races, there is no tendency towards a race-related difference. However, this plot is limited by high shrinkage. Therefore, it is concluded that the effect of race on niraparib PK is unknown and the SmPC has been updated accordingly.

The updated popPK modelling identified a significant relationship between age and niraparib CL/F. Increasing age was found to decrease niraparib clearance (after accounting for the impact of renal function). The average exposure in a 91-year old patient was predicted to be 23% higher than in a 30-year old patient. Age was not tested as a covariate on volume of distribution in the model. Based on these results, it is not considered warranted to suggest posology changes based on age. However, section 5.2 of the SmPC has been updated with the new results.

The effect of albumin on plasma-based CL/F was consistent with that niraparib is moderately protein bound (83%) in plasma, mainly to albumin. It is not expected that differences in albumin leads to differences in unbound niraparib exposure. Therefore, the model-predicted changes according to changes in serum albumin are not expected to be clinically relevant and do not warrant dose adjustment.

As mentioned above, the estimated impact of body weight is of special interest because the proposed dose regimen implies the use of different doses for patients below and above 77 kg (and also according to platelet count). Increasing weight was found to increase niraparib volume of distribution in the population pharmacokinetic analysis. No impact of weight was identified on niraparib clearance or overall exposure. No difference in exposure (AUCss) across the body weight range for fixed dose administration is predicted, and with the proposed posology, exposure is predicted to be 50% higher in patients with body weight ≥77 kg (and normal platelet count). There is no clear reason for targeting different exposures in these subgroups and dose adjustment according to body weight is not warranted from a pharmacokinetic point of view. The proposed dosing algorithm therefore does not seem justified from a clinical pharmacology viewpoint.

Exposure-response relationship

Summary statistics for covariates by exposure quartiles were provided for the total PRIMA population. The distribution of covariates across each AUCss quartile was mostly similar. The patients in the highest exposure quartile tended to be older, which is in line with decreasing niraparib CL/F with increasing age. Notably, BRCA status and HRD status was not evenly distributed, with ~28% HRD negative subjects in the two lower exposure quartiles vs. 48% in the highest exposure quartile. As HRD status is highly predictive of clinical outcomes, this uneven distribution would confound the results. The exposure-response results were therefore also presented in subgroups according to BRCA/HRD status in addition to the analysis on the overall population.

The MAH initially primarily explored the relationship between exposure quartiles based on average concentration (Cave) up to the time of progression/death or censoring and PFS (data not shown). However, this exposure metric is not considered appropriate because of a high frequency of dose reductions in the PRIMA study (~80%). Conceptually, patients with short PFS due to early death or disease progression will be less likely to have a dose reduction (and therefore tend to have a high Cave in the analysis), while patients with long PFS are more likely to have a dose reduction during the course of the study, and therefore tend to have lower Cave values. Updated analyses using exposure associated with the first dose were therefore provided and led to the following overall conclusions:

- In the overall population and in the non-BRCA patients, there is no tendency of an exposure-response relationship across the exposure range tested. However, the absence of a relationship in the overall population could be confounded by uneven distribution of BRCA/HRD status across the AUCss range (Table 13).

- In the BRCA mutated population specifically, which represents a subgroup of 31% of the overall population, the Kaplan-Meier plot indicated an apparent exposure-response relationship, and modelling identified AUCss as a significant predictor of PFS. The model-estimated HR between average predicted exposures at 200 mg vs. 300 mg. was 0.49. This indicates that in this subpopulation, an exposure-response relationship could be present over the relevant dose range. However, these results are

contrasting the results of the dose-efficacy analyses, in which similar efficacy for the two starting doses was seen in the HRD positive patients, but not in the HRD negative patients (See Clinical efficacy section). The MAH provided no explanation to these conflicting results.

Taken together, it is considered that the refined analyses provide some reassurance that there are likely no major differences in treatment effects at the two dose levels under comparison. However, there are still limitations in the input data, including extensive parameter shrinkage (50% in CL/F and F) due to very sparse PK sampling in the PRIMA study leading to potentially inaccurate exposure predictions, narrow exposure range due to the use of only two dose starting dose levels (with the majority at 300 mg) in the data set used for analysis, and frequent dose adjustments during the study which further narrows the actually studied exposure range. Moreover, there are conflicting results between the various dose- and exposure-based sub-analyses performed. Therefore, the results should be interpreted with caution, and although some reassurance could be derived from these analyses, they provide only limited supplementary evidence for maintained efficacy at 200 mg.

The refined exposure-safety model predicted approximately 15 percentage points reduction in the risk of Grade 3+ thrombocytopenia when reducing the starting dose from 300 mg to 200 mg, which is considered a clinically meaningful reduction. The modelling also identified body weight and baseline platelet count as independent and significant predictors of Grade 3+ thrombocytopenia, which is the MAH's rationale for dosing by these factors despite not being determinants of AUCss. It should be noted that the dosing algorithm is purely data-driven and lacks pharmacological or biological rationale. It also showed poor performance in terms of identifying patients who will tolerate the 300 mg dose, as most of the patients meeting the criteria of receiving the 300 mg starting dose required a dose reduction. If adequate treatment effect at the exposure associated with 200 mg could be firmly concluded, there would be no clear pharmacological reason not to allow *all* patients to benefit from the lower starting dose, independently of their body weight and platelet count. However, with the remaining efficacy uncertainties at 200 mg (see clinical efficacy section), it could be argued that the presumed thrombocytopenia risk (as predicted by body weight and platelet count) should determine whether the benefits of reducing the starting dose outweighs the risk of potential efficacy loss. Still, the specific threshold values of 77 kg and 150,000/µL for discriminating between starting doses has not been well justified, and there is no convincing scientific basis for selecting these exact values. The dosing strategy could probably be further optimized, for example by dosing based on HRD or BRCA mutation status. It is biologically plausible that drug sensitivity may be higher in HRD positive subjects, and dose requirement to achieve adequate efficacy may thereby be lower in these patients. This, however, was not pursued as there is currently no available test for HRD status in the EU (see Clinical efficacy section).

Despite its limited pharmacological basis, the proposed posology is considered acceptable as it seems to be the best option among the posology strategies that have been prospectively tested.

2.3.5. Conclusions on clinical pharmacology

The systemic exposure (AUCss) of niraparib is influenced by prandial state, age and renal function, while body weight has no impact on AUCss. The pharmacokinetics of niraparib does not support dosing by any of the studied patient characteristics, including the body weight and platelet count criteria included in the proposed posology.

The risk of Grade 3+ thrombocytopenia is reduced when lowering the starting dose from 300 mg to 200 mg. The risk is also reduced with increasing body weight or increasing baseline platelet count. This provides some rationale for differentiating the starting dose by these factors as long as efficacy is not confidently established at the 200 mg starting dose. However, the scientific basis for selecting the exact threshold values of 77 kg and 150,000/uL, respectively, is limited.

The exposure-response analyses for efficacy indicated a flat relationship across the exposures associated with 200 mg to 300 mg. These results are uncertain due to limitations in the exposure input data and provide only limited supportive evidence of maintained efficacy at the 200 mg starting dose (see also discussion on clinical efficacy).

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No clinical dose response studies have been submitted in relation to the present application.

2.4.2. Main study(ies)

Study PR-30-5017-C (PRIMA)

PRIMA study is a double-blind, multicentre, randomised, placebo-controlled 2:1 (niraparib:placebo) study in patients with ovarian, fallopian tube, or primary peritoneal cancer, collectively referred to as ovarian cancer. To be eligible for the study, participants must have achieved a complete or partial response to front-line platinum-based regimen. Subjects who had received primary debulking surgery (PDS), intraperitoneal chemotherapy (IHEC), or neoadjuvant chemotherapy (NACT) were eligible.

A schema over the study design is provided in the figure below.

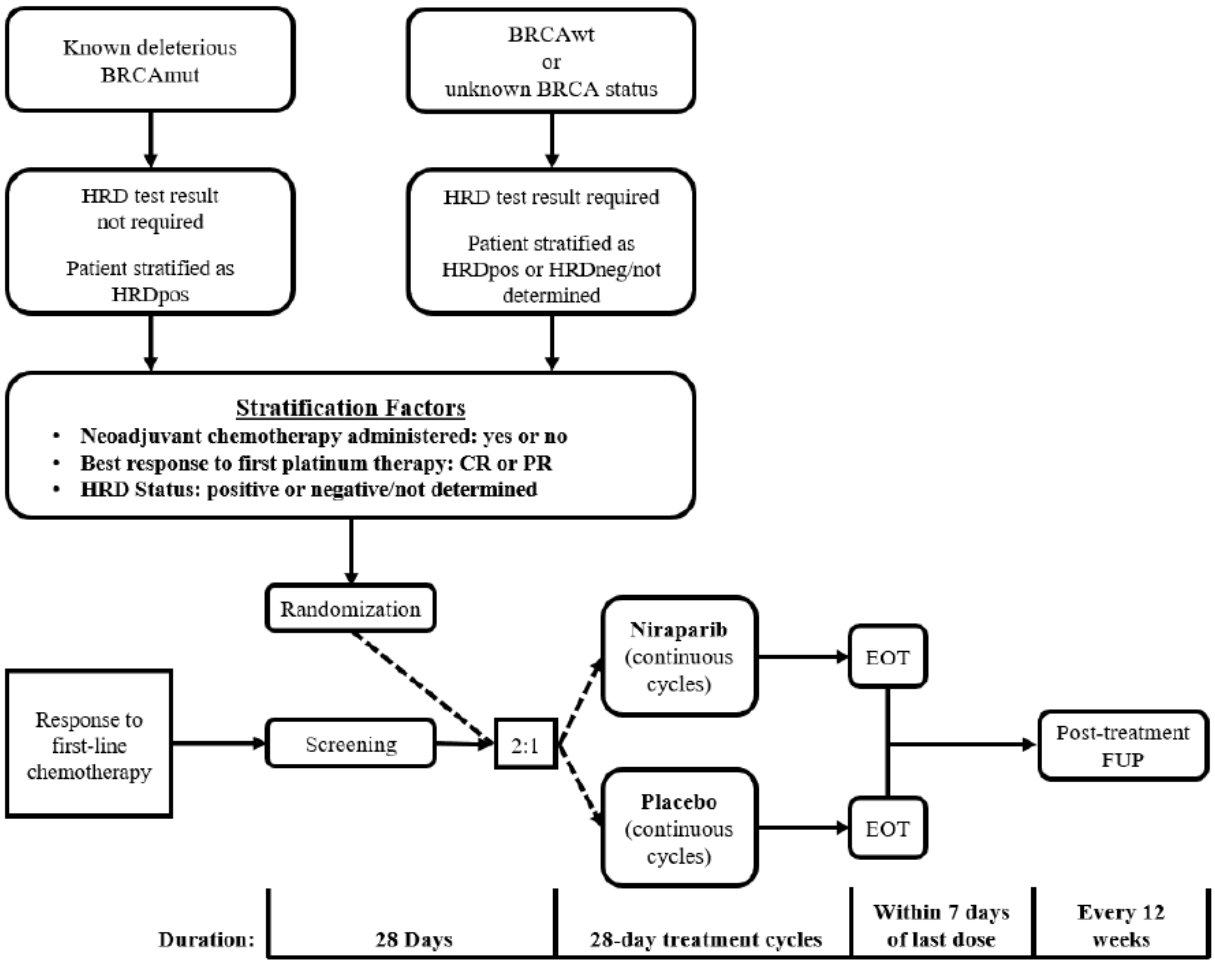


Figure 22. Study schema

Abbreviations: BRCA=breast cancer susceptibility gene; EOT=end of treatment; HRD= homologous recombination deficiency; HRDneg=homologous recombination deficiency test negative (HR-proficient tumor tumors); HRDpos=homologous recombination deficiency test positive (HR-deficient tumors).
Note 1: Per Protocol Amendment 2, the starting dose of study treatment was based upon the subject's baseline body weight or baseline platelet count. Subjects with a baseline body weight ≥77 kg and baseline platelet count ≥150,000/µL were to receive 300 mg; subjects with a baseline body weight <77 kg or baseline platelet count <150,000/µL were to receive 200 mg.
Note 2: Treatment was continuous (in 28-day cycles) until subject discontinued. Post-treatment follow-up was continuous (every 12 weeks) until subject discontinued study.

All subjects must have received at least 6 and no more than 9 cycles of frontline or neoadjuvant/adjuvant platinum-based therapy (including at least 2 post-operative cycles of platinum-based therapy after interval debulking surgery), with a physician-assessed response of CR or PR after at least 3 cycles of therapy.

Subjects who were randomised to placebo were not allowed to cross over to the niraparib arm at any time during the study.

Methods

Study participants

The study was initiated at 220 sites globally and the following countries participated:

United States (67 sites), Spain (19 sites), Germany (16 sites), Russian Federation (15 sites), Ukraine (12 sites), Belgium (11 sites), Canada, Italy, and United Kingdom (10 sites each), France (9 sites), Israel (7 sites), Czech Republic and Poland (5 sites each), Denmark, Finland, Hungary, Ireland, and Switzerland (4 sites each), Norway and Sweden (2 sites each).

The inclusion and exclusion criteria for the PRIMA study are listed below:

Inclusion criteria
1. Subjects were female ≥18 years of age, able to understand the study procedures and agree to participate in the study by providing written informed consent;
2. Histological and staging criteria: a. Subjects had histologically diagnosed high-grade serous or endometrioid, or high-grade predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer that was Stage III or IV according to International Federation of Gynecology and Obstetrics (FIGO) criteria. Note: Subjects who had received neoadjuvant chemotherapy may have been included in the study if post-chemotherapy tumour grade was not evaluable.
3. Surgical criteria: a. Subjects with inoperable Stage III and IV disease were eligible; b. All Stage IV subjects with operable disease were eligible; c. Subjects with Stage III or IV disease treated with neoadjuvant chemotherapy and interval debulking surgery were eligible; d. Subjects with Stage III disease who had visible residual disease after primary debulking surgery were eligible.
4. Chemotherapy criteria: a. Subjects who received intraperitoneal chemotherapy were eligible; b. Subjects had ≥6 and ≤9 cycles of platinum-based therapy; c. Subjects had ≥2 post-operative cycles of platinum-based therapy following interval debulking surgery; d. Subjects had physician assessed CR or PR after ≥3 cycles of therapy; e. Subjects had either CA-125 in the normal range or CA-125 decrease by more than 90% during their front-line therapy that was stable for at least 7 days (i.e., no increase >15% from nadir).
5. Subjects were randomized within 12 weeks of the first day of the last cycle of chemotherapy.

6. Subjects agreed to undergo central tumour homologous recombination deficiency testing. a. The central homologous recombination deficiency test result was required for randomisation as it was a stratification factor. Subjects with documented gBRCA1 or gBRCA2 mutation or sBRCA1/2 mutation by local testing were allowed to have been randomised prior to the receipt of the clinical trial assay test results. However, all these subjects also submitted tissue for the homologous recombination deficiency test for confirmation. b. A tumour sample may have been submitted for homologous recombination deficiency testing prior to the screening period if it appeared the subject was likely to meet other eligibility requirements. Subjects were not required to have repeat homologous recombination deficiency testing if the result was "not determined" (e.g., due to insufficient tumour specimen). c. Subjects with known homologous recombination deficiency test results from any commercially available sources including Myriad Genetics were allowed to participate in the study; however, they were required to submit a tumour sample for central homologous recombination deficiency testing. The results of the central homologous recombination deficiency testing must have been available prior to randomisation and used for stratification.
7. Subjects of childbearing potential had a negative serum or urine pregnancy test (beta human chorionic gonadotropin [hCG]) within 7 days prior to receiving the first dose of study treatment.
8. Subjects were postmenopausal, free from menses for >1 year, surgically sterilized, or willing to use adequate contraception to prevent pregnancy or must have agreed to abstain from activities that could result in pregnancy throughout the study, starting with enrolment through 180 days after the last dose of study treatment.
9. Subjects had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Subjects had adequate organ function, defined as follows: a. Absolute neutrophil count ≥1,500/μL; b. Platelets ≥100,000/μL; c. Hemoglobin ≥10 g/dL; d. Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation; e. Total bilirubin ≤1.5 × ULN; f. Aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN unless liver metastases are present, in which case they must be ≤5 × ULN. Note: complete blood count [CBC] test should be obtained without transfusion or receipt of stimulating factors within 2 weeks before obtaining screening blood sample)
11. Subjects agreed to complete PROs during study and then at 4, 8, 12, and 24 weeks after end of treatment (EOT), regardless of subsequent treatment;
12. Subjects had formalin-fixed, paraffin-embedded tumor samples available from the primary cancer or agree to undergo fresh biopsy prior to study treatment initiation;
13. Subjects were able to take oral medications.

Exclusion criteria

1. Subject had mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer;
2. Subjects with Stage III disease who had complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery;
3. Subject had undergone more than two debulking surgeries;
4. Subject was pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and for up to 180 days after the last dose of study treatment;
5. Subject had a known hypersensitivity to the components of niraparib or its excipients;
6. Subject was simultaneously enrolled in any clinical trial of niraparib or any other investigational therapy;
7. Subject had received prior treatment with a known PARP inhibitor or had participated in a study where any treatment arm included administration of a known PARP inhibitor;
8. Subject was to receive bevacizumab as maintenance treatment. Subjects who had received bevacizumab with their first-line platinum-based therapy but were unable to receive bevacizumab as maintenance therapy due to AEs or for any other reason were not excluded from study as long as the last dose of bevacizumab was received ≥28 days prior to signing the main informed consent form;
9. Subject had investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever was longer, prior to the first scheduled day of dosing in this study;
10. Subject had any known ≥Grade 3 anaemia, neutropenia, or thrombocytopenia due to prior chemotherapy that persisted >4 weeks;
11. Subject had any known history or current diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML);
12. Subject had undergone major surgery (per Investigator judgment) within 3 weeks of starting the study or subject had not recovered from any effects of any major surgery;
13. Subject had drainage of ascites within 4 weeks prior to enrolment;
14. Subject had undergone palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment;
15. Subject had a condition (such as transfusion dependent anaemia or thrombocytopenia), therapy, or laboratory abnormality that could have confounded the study results or interfere with the subject's participation for the full duration of the study treatment, including: a. Subject received a transfusion (platelets or red blood cells) within 2 weeks of the first dose of study treatment; b. Subject received colony-stimulating factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 2 weeks prior to the first dose of study treatment.
16. Subject planned to donate blood during the study or within 90 days after the last dose of study treatment.
17. Subject had been diagnosed and/or treated for invasive cancer less than 5 years prior to study enrolment. Note: Subjects with definitively treated uterine cervical or urinary tract carcinoma in situ, non-melanomatous skin cancer or ductal carcinoma in situ of the breast were not excluded

18. Subject had known brain or leptomeningeal metastases that were untreated or uncontrolled (i.e., new or worsening symptom or signs, or unstable steroid requirements); Note: A scan to confirm the absence of brain metastases was not required. Subjects with spinal cord compression may have been be considered if they had received definitive treatment for this and demonstrate evidence of clinically stable disease for 28 days.
19. Subject was considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection; Examples include, but were not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
20. Subject was immunocompromised (subjects with splenectomy are allowed).
21. Subject had known active hepatic disease (i.e., hepatitis B or C).
22. Subject had a corrected QT interval (QTc) prolongation >480 milliseconds at screening; Note: If a subject had a prolonged QTc interval and the prolongation was deemed to be due to a pacemaker upon Investigator evaluation (i.e., the subject otherwise had no cardiac abnormalities), then the subject may have been eligible to participate in the study following discussion with the Medical Monitor.

Testing of HRD status

Testing for HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis. For all potentially eligible subjects, a tumour sample was sent for centralized homologous recombination deficiency testing. To facilitate the screening and enrolment process, the samples could be sent in advance of the protocol-defined screening period. The central homologous recombination deficiency test result was required for randomisation as it was a stratification factor. This result had to be available prior to randomisation and used for stratification. Homologous recombination deficiency (HRD) status was determined at screening by tumour samples via the clinical trial assay based on the myChoice homologous recombination deficiency test (Myriad Genetics, Inc.). The test is an integrated genome-based assay for homologous recombination that quantitates genomic instability of the tumour and, in parallel, detects and classifies variants in BRCA1 and BRCA2. Tumours were identified as positive by this test if they harboured deleterious or suspected deleterious mutations in BRCA-1 or -2 or if the combined genomic instability scoring (based on large-scale state transitions [LST], telomeric-allelic imbalance [TAI], and loss of heterozygosity [LOH]) was ≥42. The homologous recombination deficiency score represents a continuum of genomic instability accumulated over time in the tumour.

Tumours with a negative test result had neither of these characteristics (neither BRCAmut nor homologous recombination deficiency score ≥42). If test results were inconclusive or the test was not done, tumours were considered as homologous recombination status not determined.

Treatments

Patients were administered niraparib or placebo (matched in appearance) using 100 mg capsules orally QD during continuous 28-day cycles in a double-blind fashion. At the time of study initiation (01 December 2016), all subjects received 300 mg as the starting dose. On 16 November 2017, the protocol was amended to change the starting dose of study treatment to either 300 mg or 200 mg based upon the subject's baseline body weight and/or baseline platelet count, see table below.

Table 18. Recommended initial starting dose

Baseline Criteria	Starting Dose
≥77 kg **and** ≥150,000/µL	300 mg (3 × 100 mg capsules) or placebo (3 capsules) daily
<77 kg **or** <150,000/µL	200 mg (2 × 100 mg capsules) or placebo (2 capsules) daily

Source: PR-30-5017-C Protocol

Study treatment was dispensed to subjects on Cycle 1/Day 1 and every cycle (28 days) thereafter until the subject discontinued study treatment. The first dose was administered at the site.

Dose modification

At the Investigator's discretion, dose interruption and/or reduction could have been implemented at any time for any grade toxicity considered intolerable by the subject. Treatment was required to be interrupted for any non-hematologic AE that was Grade 3 or 4 per the NCI-CTCAE (v4.03) that the Investigator considered to be related to administration of study treatment. If Grade 3 or 4 non-hematologic toxicity was appropriately resolved to baseline or Grade 1 or less within 28 days of interruption, the subject was allowed to restart study treatment but with a dose level reduction if prophylaxis was not considered feasible. If the event recurred at a similar or worse grade, treatment was interrupted again; upon event resolution, a further dose reduction was required.

For subjects whose starting dose was 3 capsules daily (300 mg/day), dose reductions to 2 capsules daily (200 mg/day) and subsequently to 1 capsule daily (100 mg/day) were allowed. No further dose reduction was allowed without discussion with the Medical Monitor. For subjects whose starting dose was 2 capsules (200 mg/day), dose reduction to 1 capsule once daily (100 mg/day) was allowed. No further dose reduction was allowed without discussion with the Medical Monitor.

Additional dose modifications of study treatment were not based upon changes in the subject's body weight during study participation. For subjects whose initial starting dose was 2 capsules (200 mg/day), escalation to 3 capsules once daily was permitted if no treatment interruption or discontinuation was required during the first 2 cycles of therapy. For any dose modification, the number of capsules administered were modified accordingly.

If the toxicity requiring dose interruption had not resolved completely or to CTCAE Grade 1 during the maximum 4-week (28-day) dose interruption period, and/or the subject had already undergone the maximum number of dose reductions, the subject was required to permanently discontinue study treatment.

The dose interruption/modification criteria for hematologic parameters was based on blood counts.

If the hematologic toxicity did not recover to specified levels within 4 weeks (28 days) of the dose interruption period, and/or the subject had already undergone the maximum number of dose reductions, the subject was required to permanently discontinue study treatment.

If dose interruption or modification was required at any point on study because of hematologic toxicity, weekly blood draws for complete blood count (CBC) were monitored until the AE resolved. To ensure safety of the new dose, weekly blood draws for CBC were also required for an additional 4 weeks after the AE resolved to the specified levels, after which monitoring every 4 weeks may have been resumed.

Any subject requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support was required to undergo a dose reduction upon recovery if study treatment was resumed.

If a subject was diagnosed with MDS/AML (confirmed by a hematologist) or secondary cancer (new malignancies other than MDS/AML) while on study, the subject was required to permanently discontinue study treatment.

If a subject had major surgery while on treatment, up to 28 days of study treatment interruption was allowed. Once the dose of study treatment was reduced, any re-escalation was discussed with the Medical Monitor.

No other anticancer therapy was permitted during the course of the study treatment for any subject. Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment) was allowed for pre-existing small areas of painful metastases that could not be managed with local or systemic analgesics, as long as no evidence of disease progression was present. Prophylactic cytokines (granulocyte colony-stimulating factor) were not administered in the first cycle of the study but may have been administered in subsequent cycles according to local guidelines.

Objectives

Primary objective

The primary objective of this study was to evaluate the efficacy of niraparib versus placebo as maintenance treatment, as measured by PFS, in subjects with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) with a CR or PR following front-line platinum-based chemotherapy treatment.

Secondary objectives

1. To evaluate additional measures of clinical benefit for niraparib versus placebo as maintenance treatment, such as OS (key secondary endpoint), patient-reported outcomes (PROs), outcomes for next anticancer therapy following study treatment, time to first subsequent therapy (TFST), time to progression on the next anticancer therapy (PFS2) and time to CA-125 progression;

2. To evaluate the safety and tolerability of niraparib versus placebo.

Outcomes/endpoints

Primary efficacy endpoint	
Progression-free survival (PFS)	Defined as the time from treatment randomisation to the earlier date of assessment of progression (by blinded central review) or death by any cause in the absence of progression, whichever occurs first. PFS as determined by BICR based on RECIST (version 1.1).
Secondary efficacy endpoints	
Overall survival (OS) (key secondary)	The time from the date of randomization to the date of death by any cause.
Patient-reported outcome (PRO)	• FOSI: Validated, 8-item measure of symptom response to treatment for ovarian cancer • EQ-5D-5L: Validated general preference-based health related QOL instrument in oncology, as well as other conditions, and is intended to compliment other QOL instruments

	• EORTC-QLQ-C30: validated, 30-item, health-related QoL instrument developed to assess health outcomes from a wide variety of interventions on a common scale • EORTC-QLQ-OV28: assesses ovarian cancer subjects' abdominal/ gastrointestinal symptoms, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning
Time to first subsequent therapy (TFST)	The time from the date of randomisation to the date of the first subsequent anticancer therapy or death, whichever occurs first
Outcomes for the next anticancer therapy following study treatment	Data on the next anticancer therapy following study treatment was collected in the eCRF: name of drug (and/or class), start and stop date, progression date, best response and dose-limiting toxicities.
Progression-free survival – 2 (PFS2)	The time from the date of randomisation to the date of disease progression on the next anticancer therapy following study treatment or death due to any cause, whichever occurs first
Time to CA-125 progression	The time from the date of randomisation to the date of CA-125 progression as specified by GCIG criteria (i.e., an increase in CA-125 relative to the normal range or the on-study nadir value depending on baseline and on-study levels)

The exploratory endpoints were as follows:

- Population PK and estimate PK parameters for niraparib and its major metabolite;
- Biomarkers of PARP inhibitor sensitivity (e.g., DNA repair pathways);
- Homologous recombination deficiency status and platinum sensitivity in ovarian cancer subjects who had an initial response to front-line platinum therapy.

Schedule of events

Visits were scheduled weekly during the first cycle and then on Day 1 (every 4 weeks +/- 3 days) for each subsequent cycle.

Radiologic determination of disease progression

Determination of response to treatment/progression of disease by central blinded review was based on imaging assessments according to RECIST v1.1.

Clinical determination of disease progression

Clinical disease progression might have been determined if 1 of the following 2 criteria were met:

1. CA-125 progression according to Gynecologic Cancer Intergroup (GCIG)-criteria AND additional diagnostic tests (e.g., histology/cytology, ultrasound techniques, endoscopy, PET) may identify new lesions or determine existing lesions qualify for unequivocal PD;

2. CA-125 progression according to GCIG criteria AND definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes, such as:

a. intractable cancer-related pain;

b. malignant bowel obstruction/worsening dysfunction; or

c. unequivocal symptomatic worsening of ascites or pleural effusion.

An elevation in CA-125 without accompanying radiological changes or clinical symptoms/signs consistent with PD were not considered disease progression.

Central disease response assessment

Blinded independent central review (BICR) was established to assess study imaging and available clinical data to determine overall tumour assessment for each patient at each time point for the primary analysis of PFS. BICR consisted of a primary radiologic assessment (conducted by two independent radiologists) for all patients followed by review by an independent oncologist on cases for which progression based on RECIST 1.1 criteria had not been confirmed during the radiologic assessment. In the event that the primary radiologic assessments did not agree, a third radiologist was to adjudicate by selecting one of the radiology review assessments in its entirety. Radiographic assessments were conducted according to RECIST v1.1 tumour assessment via CT or MRI scan of the abdomen/pelvis and other areas as clinically indicated. Assessments were conducted at screening, then every 12 weeks (± 7 days) from Cycle 1/Day 1 visit until progression was confirmed by BICR. CA-125 evaluations were required at the end of every cycle (4 weeks ±3 days) until PD was centrally confirmed.

Cycle timing was not modified/delayed for treatment interruptions and tumour assessment continued according to the established schedule, regardless of whether study treatment was interrupted. If a subject discontinued treatment for a reason other than PD or death, withdrawal of consent, or loss to follow up, scans and CA 125 testing were expected to continue at the specified intervals until disease progression was confirmed or until the start of subsequent anticancer treatment. All subjects were followed off treatment every 12 weeks for assessment of next anticancer therapy, evaluation of any subsequent malignancies and for survival status.

Determination of the date of PD was made by central blinded review as outlined in the table below.

Table 19. Determination of disease progression date

BICR		Investigator	Date of Progressive Disease
Radiology	Oncology		
PD	PD	PD	Earliest date of BICR and Investigator
PD	Non-PD	PD	BICR (Radiology)
PD	PD	Non-PD	BICR (Radiology)
PD	Non-PD	Non-PD	BICR (Radiology)
Non-PD	PD	PD	Earliest date of BICR and Investigator
Non-PD	PD	Non-PD	Non-PD
Non-PD	Non-PD	PD	Non-PD

Abbreviations: BICR=Blinded Independent Central Review; PD=progressive disease.

PRO data were collected every 8 weeks (± 7 days) for 56 weeks beginning on Cycle 1/Day 1, then every 12 weeks (± 7 days) while on study treatment. During the follow-up period; PRO assessments occurred at 4, 8, 12 and 24 weeks (± 1 week for each time point) regardless of the status of subsequent treatment.

Sample size

The sample size calculations were based on PFS in the HRDpos group and an event-based analysis. Assuming a median PFS of 21 months for the HRDpos placebo group, a hazard ratio (HR) of 0.5, 90% power, one-sided alpha of 0.025, and a 2:1 randomisation ratio, it was calculated that 99 PFS events were needed. Further assuming that 50% randomised patients were HRDpos it was calculated that 620 patients (310 HRDpos) would be needed to enrol to complete the study in 44 months.

The final analysis of PFS for HRDpos and ITT population was to be performed sequentially after approximately 99 HRDpos PFS events are reached. The PFS analysis in the ITT population was to include all PFS events observed at the time of the final analysis. Assuming a median PFS of 14 months for all placebo patients, a total of approximately 270 PFS events were expected for the final analysis of PFS in the ITT population. This was expected to provide at least 90% power to detect a true HR of 0.65.

Type-I error control at a one-sided alpha of 0.025 was achieved by employing hierarchical testing of first the primary endpoint, PFS in the HRDpos population, followed sequentially by the same test in the entire ITT population, then by OS in the ITT population, and finally OS in the HRDpos population. The analysis of OS was to include an interim analysis of OS at the time of the final PFS analysis and a final analysis of OS when approximately 440 deaths have occurred in the ITT population (60% data maturity). A Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundaries was used to determine the significance levels for interim and final OS analyses. The final analysis of OS is expected to occur approximately 70 months after first patient randomized.

Randomisation

Eligible patients were randomised to treatment with niraparib or placebo in a 2:1 (niraparib:placebo) ratio using an interactive web response system. In the Original Protocol, patients had to be HRDpos and were randomised by one stratification factor: best response to platinum therapy (CR or PR). Since Protocol Amendment 1, patients were randomised by three stratification factors: best response to platinum therapy (CR or PR), administration of neoadjuvant therapy (Yes or No), and HRD status (HRDpos or HRDneg/HRDnd).

Blinding (masking)

The patient, Investigator, study staff, and the Sponsor study team and its representatives were blinded to the patients' tumor HRD status and identity of the assigned treatment from the time of randomization until database lock. If an individual's role on the trial requires information about HRD status or treatment assignment (e.g., an individual is involved in emergency un-blinding or entry of HRD status for stratification), procedures were in place to ensure all other personnel remained blinded.

Statistical methods

Analysis populations

The Intent-to-Treat (ITT) population was defined as all patients randomised into the study and was the primary analysis population for the efficacy analysis. For this analysis, patients were analysed as randomised. Patients who were incorrectly stratified during randomisation will be analysed and presented under the stratum assigned during randomisation.

The Per-protocol (PP) population was defined as all patients randomised and treated in the study who do not have protocol deviations that could significantly impact the interpretation of efficacy results. Patients

were analysed according to the treatment they actually received. Patients who were incorrectly stratified during randomisation was analysed and presented under the correct stratum based on the clinical database.

The Safety (SAF) population was defined as all patients who receive at least 1 dose of study drug. Patients were analysed as treated. Patients receiving treatment from more than one treatment arm will be accounted for based on their first study treatment.

Primary endpoint analysis

The primary endpoint, PFS by Blinded Independent Central Review (BICR), was tested hierarchically first in the HRDpos population and then in the ITT population by a stratified log-rank test at a one-sided 0.025 alpha level. The stratification factors were the ones used at randomization; administration of neoadjuvant chemotherapy (yes or no) and best response to platinum therapy (CR or PR), for the HRDpos population test. For the test in the ITT population, HRD status (HRDpos or HRDneg/HRDnd) was an additional stratification factor. The hazard ratio with 2-sided 95% CI was estimated using a stratified Cox proportional hazards model with the above-described stratification factors.

Censoring of PFS events was done for patients without baseline or with no evaluable post-baseline radiological assessments, patients who did not progress or die, patients who started subsequent anti-cancer therapy, and patients who progressed or died after two or more missed radiological assessments.

Sensitivity analyses for PFS included using Investigator assessed progression instead of BICR data, not censoring patients starting new anti-cancer therapy or progressing after two missed assessments, using stratification factors from eCRF instead of from randomization, using the mid-point between progression time and previous assessment for unscheduled assessments, using only BICR radiology data, analysing in the per-protocol population, considering new anti-cancer therapy as an event, and not stratifying for neoadjuvant chemotherapy.

The following subgroup analyses were performed on the BICR data in HRDpos and ITT population:

- Age categories [<65 or ≥65]
- Race [White or non-White]
- ECOG performance status [0 or 1]
- Stage of disease at initial diagnosis [III or IV]
- Primary tumour site [ovarian, primary peritoneal, fallopian tube]
- Neoadjuvant chemotherapy [yes or no], according to randomization
- Best response to first platinum regimen [CR or PR], according to randomization
- Neoadjuvant chemotherapy [yes or no], according to eCRF
- Best response to first platinum regimen [CR or PR], according to eCRF
- Baseline CA-125 level [≤ULN or >ULN]
- Region [North America or Rest of World]
- Starting dose subgroup [Fixed Starting Dose or Individualized Starting Dose]

- tBRCA status [tBRCAmut, tBRCAwt] (ITT population)
- HRD status [tBRCAmut, (non-tBRCAmut and HRDpos), HRDneg, HRDnd] (ITT population)

Key secondary efficacy analysis

If a statistically significant PFS treatment difference was observed in the ITT population, the sequential testing was to continue for OS endpoint first in the ITT population and then in HRDpos population. The analysis of OS was to include an interim analysis of OS at the time of the final analysis of PFS and a final analysis of OS when approximately 440 deaths have occurred in the ITT population (60% data maturity). A Lan-DeMets alpha-spending function with the O'BrienFleming stopping boundaries was to be used to determine the significance levels for interim and final analyses based on the observed fraction of OS events [8]. The final analysis of OS is expected to occur approximately 70 months after first patient randomized. To detect a statistically significant OS treatment difference at 1-sided 0.025 Type I error, the analysis of OS with 440 events will have at least 80% power if the true HR is 0.75 or less in the ITT population. Although this study was not powered for OS analysis in HRDpos population, about one third of deaths in the ITT population were estimated to be HRDpos patients at the time of final analysis of OS, thus the analysis of OS with 150 HRDpos events will have at least 70% power if the true HR is 0.65 or less in HRDpos population.

The following subgroup analyses were to be performed for OS:

- Neoadjuvant chemotherapy [yes or no], according to the eCRF
- Best response to first platinum regimen [CR or PR], according to the eCRF
- Region [North America or Rest of World]
- Starting dose subgroup [Fixed Starting Dose or Individualized Starting Dose]

Results

Participant flow

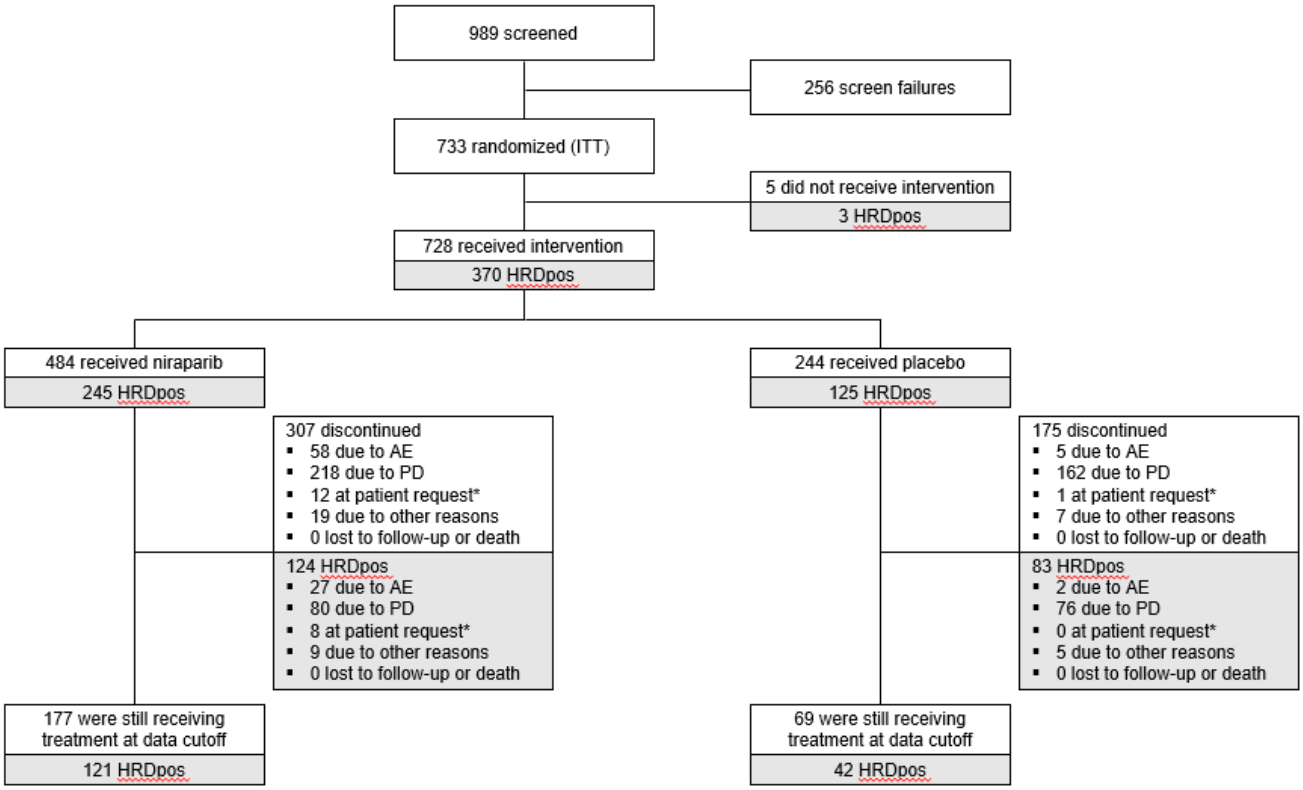


Figure 23. Patient disposition flowchart

Table 20. Summary of subject disposition in the PRIMA study (all enrolled subjects) (17 May 2019)

Population Disposition	HRDpos		Overall	
	Niraparib n (%)	Placebo n (%)	Niraparib n (%)	Placebo n (%)
Randomized	247	126	487	246
Randomized but not treated	2	1	3	2
Safety population[a]	245 (100)	125 (100)	484 (100)	244 (100)
Treatment ongoing at time of data cutoff	121 (49.4)	42 (33.6)	177 (36.6)	69 (28.3)
Discontinued from treatment	124 (50.6)	83 (66.4)	307 (63.4)	175 (71.7)
Adverse event	27 (11.0)	2 (1.6)	58 (12.0)	5 (2.0)
Disease progression	80 (32.7)	76 (60.8)	218 (45.0)	162 (66.4)
Severe non-compliance	0	0	1 (0.2)	0
Death	0	0	0	0
Platelet count not reverted within 28 days of dose interruption	0	0	0	0
Subject withdrew consent	8 (3.3)	0	12 (2.5)	1 (0.4)
Other	9 (3.7)	5 (4.0)	18 (3.7)	7 (2.9)
Discontinued from study	36 (14.7)	20 (16.0)	90 (18.6)	55 (22.5)
Withdrawal of consent	17 (6.9)	7 (5.6)	36 (7.4)	18 (7.4)
Lost to follow-up	1 (0.4)	1 (0.8)	1 (0.2)	1 (0.4)
Death	16 (6.5)	9 (7.2)	48 (9.9)	30 (12.3)
Sponsor decision to terminate study	0	0	1 (0.2)	0
Other	2 (0.8)	3 (2.4)	4 (0.8)	6 (2.5)
Number of Deaths	16 (6.5)	10 (8.0)[b]	48 (9.9)	31 (12.7)[b]
On treatment	0	0	0	0
During follow-up	16 (6.5)	10 (8.0)[b]	48 (9.9)	31 (12.7)[b]

Abbreviations: HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors.
Source: Table 14.1.1A
[a] Percentages were based on safety population.
[b] As permitted by regulation, survival data were collected for 1 subject after study discontinuation.

A total of 989 subjects were screened, and of these 733 subjects were randomised into the PRIMA trial and constituted the ITT population. There were 256 screening failures. Data were missing for 22/256 (~ 9%) patients. Most screening failures were due to the patient not meeting the clinical or laboratory inclusion criteria. Of the 234 patients for whom data were available, the majority of patients (62/234; 26%) failed due to lack of "having either CA-125 in the normal range or CA-125 decreased by more than 90% during their frontline therapy that was stable for more than 7 days".

Fixed and individualised starting dose groups

As per Protocol Amendment 2, analyses summarised by starting dose group for subjects with homologous recombination deficient tumours and all randomised subjects (Overall population) were included. The table below summarises the disposition of subjects with homologous recombination deficient tumours (HRDpos) and Overall by fixed and individualised dose.

Table 21. Summary of subject disposition by fixed and individualised starting dose subgroups (all enrolled subjects)

Population Disposition	Fixed				Individualized			
	HRDpos		Overall		HRDpos		Overall	
	Niraparib n (%)	Placebo n (%)	Niraparib n (%)	Placebo n (%)	Niraparib n (%)	Placebo n (%)	Niraparib n (%)	Placebo n (%)
Randomized	160	83	317	158	87	43	170	88
Randomized but not treated	1	0	2	0	1	1	1	2
Safety population[a]	159 (100)	83 (100)	315 (100)	158 (100)	86 (100)	42 (100)	169 (100)	86 (100)
Treatment ongoing at time of data cutoff	74 (46.5)	24 (28.9)	111 (35.2)	42 (26.6)	47 (54.7)	18 (42.9)	66 (39.1)	27 (31.4)
Discontinued from treatment	85 (53.5)	59 (71.1)	204 (64.8)	116 (73.4)	39 (45.3)	24 (57.1)	103 (60.9)	59 (68.6)
Adverse event	17 (10.7)	2 (2.4)	35 (11.1)	3 (1.9)	10 (11.6)	0	23 (13.6)	2 (2.3)
Disease progression	56 (35.2)	54 (65.1)	144 (45.7)	109 (69.0)	24 (27.9)	22 (52.4)	74 (43.8)	53 (61.6)
Severe non-compliance	0	0	1 (0.3)	0	0	0	0	0
Death	0	0	0	0	0	0	0	0
Platelet count not reverted within 28 days of dose	0	0	0	0	0	0	0	0
Subject withdrew consent	6 (3.8)	0	10 (3.2)	0	2 (2.3)	0	2 (1.2)	1 (1.2)
Other	6 (3.8)	3 (3.6)	14 (4.4)	4 (2.5)	3 (3.5)	2 (4.8)	4 (2.4)	3 (3.5)
Discontinued from study	29 (18.2)	19 (22.9)	68 (21.6)	38 (24.1)	7 (8.1)	1 (2.4)	22 (13.0)	17 (19.8)
Withdrawal of consent	12 (7.5)	7 (8.4)	30 (9.5)	12 (7.6)	5 (5.8)	0	6 (3.6)	6 (7.0)
Lost to follow-up	0	1 (1.2)	0	1 (0.6)	1 (1.2)	0	1 (0.6)	0
Death	15 (9.4)	8 (9.6)[b]	33 (10.5)	20 (12.7)[b]	1 (1.2)	1 (2.4)	15 (8.9)	10 (11.6)
Sponsor decision to terminate study	0	0	1 (0.3)	0	0	0	0	0
Other	2 (1.3)	3 (3.6)	4 (1.3)	5 (3.2)	0	0	0	1 (1.2)
Number of deaths	15 (9.4)	9 (10.8)[b]	33 (10.5)	21 (13.3)[b]	1 (1.2)	1 (2.4)	15 (8.9)	10 (11.6)
On treatment	0	0	0	0	0	0	0	0
During follow-up	15 (9.4)	9 (10.8)[b]	33 (10.5)	21 (13.3)[b]	1 (1.2)	1 (2.4)	15 (8.9)	10 (11.6)

Source: Table 14.1.1B
Abbreviations: HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors.
[a] Percentages were based on safety population.
[b] As permitted by regulation, survival data were collected for 1 subject after study discontinuation.

A total of 473 subjects (315 niraparib, 158 placebo) received the 300 mg starting dose (nominated "fixed starting dose") prior to the change of dosing strategy (Amendment 2 of the protocol), while 255 subjects (169 niraparib, 86 placebo) received the individualised dosing scheme (of note, this number encompasses both patients receiving 200 mg and those receiving 300 mg as their individualised starting dose and regardless of baseline bodyweight and platelet count and all of these patients will therefore not have been dosed in accordance with the algorithm recommended by the MAH).

Of the 315 niraparib patients who received the fixed dose of 300 mg, it was shown that it was only 72 patients (~23%) who fulfilled the requirements of the high body weight and high platelet count algorithm while 243 patients (~77%) had either too low weight or too low platelet counts (and in accordance with the amended dosing strategy should have been given 200 mg). The proportion in the placebo groups was nearly the same (~74% and ~27%, respectively).

There was a total of 238 patients (156 in the niraparib group and 82 in the placebo group) who received either 200 mg or 300 mg in accordance with the algorithm of body weight and platelet count (nominated "individualised starting dose"). Of these 238 patients, it was 122/156 in the niraparib group (i.e., 78%) vs. 61/82 in the placebo group (i.e., 74%) who specifically received the applied 200 mg starting dose in line with the algorithm.

Recruitment

Date first subject enrolled: 03 August 2016.

Last subject treatment visit: enrolment is complete (June 2018) with treatment ongoing.

Data cut-off for primary data analysis described in the clinical study report is 17 May 2019.

Database lock was 3 July 2019.

Conduct of the study

Protocol amendments

The original protocol (final: 26 October 2015) was amended during the study for clarification and changes in analyses. The key revisions based on the protocol amendments are outlined in the table below.

Table 22. Protocol amendment history for Study PR-30-5017-C

Amendment	Date Amendment Final	Key Changes and Rationale
1	01 December 2016	• Expanded inclusion criteria to include all patients with Stage III or IV ovarian cancer following front-line platinum- based chemotherapy treatment and not limit to subjects of HR-deficient status. • Outcomes for next anticancer therapy following study treatment and time to first subsequent therapy were added as secondary endpoints. • The relationship between HRD status and platinum sensitivity in ovarian cancer subjects who have initial response to front-line platinum therapy was added as an exploratory objective. • Stratification factors were revised to add administration of neoadjuvant chemotherapy (yes or no) and HRD status to CR/PR. • MDS and AML were added as adverse events of special interest. • Inclusion criteria were revised to indicate high-grade and predominantly serous or endometrioid ovarian cancers, to provide more specific guidance on the surgical and chemotherapy criteria. • Exclusion criteria were revised to provide more specific guidance.
2	16 November 2017	• Revision of the dosing scheme to include a fixed dose option and an individualized dose option based on a subject weight and or platelet count. • The sample size was revised from 330 expected subjects to 468 expected subjects based on a reduced median PFS. • Secondary cancers (new malignancies other than MDS/AML), pneumonitis, and embryo-fetal toxicity were added as adverse events of special interest. • Rules for dose modifications were clarified based on the new fixed and individualized starting dose structure.
3	12 February 2018	• The sample size was revised from 468 expected subjects to 620 expected subjects based on longer median PFS expected for patients with g*BRCA* mutations.

Changes in the planned analyses

The following were the changes between the protocol-defined statistical analyses and the final SAP:

- The Patient Reported Outcome neuropathy questionnaire evaluation was removed in Protocol Amendment 1.
- Based on the Protocol Amendment 1 expanded inclusion criteria to include all subjects with Stage III or IV ovarian cancer following front-line platinum-based chemotherapy treatment and not limit to subjects of homologous recombination deficiency status, the SAP specified analysis populations were clarified to include a homologous recombination deficient population consisting of subjects from the pre-specified ITT population who had a tumor homologous recombination deficiency test status of positive by the clinical trial assay. Full disposition, efficacy, and safety analyses were performed.
- Full efficacy and safety analyses by starting dose subgroups.

The following were the changes between analyses defined in the SAP and those presented in this report:

- The protocol and SAP defined exploratory objective to explore the relationship between homologous recombination deficiency (HRD) status and platinum sensitivity in ovarian cancer patients who have initial response to front-line platinum therapy were not analysed because platinum sensitivity status cannot be defined for the study population who were enrolled earlier than 6 months after the first line platinum-based chemotherapy.
- The study protocol specified secondary endpoint analysis of time to CA-125 progression was not performed because the CA-125 progression is part of the clinical evaluation of PFS, the time to CA-125 progression alone has limited clinical interpretation; therefore, it was not analysed.
- The study protocol specified exploratory analysis of estimating PK parameters for niraparib's major metabolite, M1, was not completed. The rationale was that M1 had been confirmed to have no pharmacological activity against PARP along with completed non-clinical safety evaluations that supported its negligible contribution to overall safety and toxicity as compared to parent drug.

Protocol deviations

A summary of significant and important protocol deviations in the overall population is provided in the table below.

Table 23. Summary of significant and important protocol deviations (ITT population)

Protocol Deviation Classification/ Category	Overall	
	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
Subjects with at least 1 significant protocol deviation	4 (0.8)	3 (1.2)
Adverse Event/SAE	0	0
Disallowed Medication	0	1 (0.4)
Documentation	0	0
Inclusion/Exclusion Criteria	0	0

Informed Consent	0	0
IP Administration/Study Treatment	4 (0.8)	2 (0.8)
Randomization	0	0
Study Visit/Procedures	0	0
Withdrawal Criteria	0	0
Subjects with at least 1 important protocol deviation	210 (43.1)	67 (27.2)
Adverse Event/SAE	19 (3.9)	4 (1.6)
Disallowed Medication	0	0
Documentation	2 (0.4)	1 (0.4)
Inclusion/Exclusion Criteria	8 (1.6)	5 (2.0)
Informed Consent	1 (0.2)	1 (0.4)
IP Administration/Study Treatment	68 (14.0)	24 (9.8)
Randomization	28 (5.7)	13 (5.3)
Study Visit/Procedures	128 (26.3)	31 (12.6)
Withdrawal Criteria	2 (0.4)	0

Source: Table 14.1.2
Abbreviations: IP=investigational product; ITT=intent-to-treat; SAE=serious adverse event.

Baseline data

Table 24. Randomisation stratification factors (ITT population)

Parameter	Applied in the Primary Analysis	
	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
Best response to first platinum regimen		
CR	327 (67.1)	165 (67.1)
PR	160 (32.9)	81 (32.9)
Neoadjuvant chemotherapy		
Yes	326 (66.9)	165 (67.1)
No	161 (33.1)	81 (32.9)
Clinical trial assay test status		
Positive	253 (52.0)	129 (52.4)
Negative/Not determined	234 (48.0)	117 (47.6)

Source: Table 14.1.8
Abbreviations: CR=complete response; ITT=intent-to-treat; PR=partial response.

Note: There was a small discrepancy in the randomization stratification from the reported eCRF data: 69% of patients had CR as best response to first platinum regimen based on the reported eCRF data.

Table 25. Subject demographics and baseline characteristics (ITT population)

Parameter	HRDpos		Overall	
	Niraparib (N=247) n (%)	Placebo (N=126) n (%)	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
Age at time of screening				
Median	58.0	58.0	62.0	62.0
Min, Max	32, 83	33, 82	32, 85	33, 88
18 to <65	173 (70.0)	88 (69.8)	297 (61.0)	147 (59.8)
65 to <75	49 (19.8)	32 (25.4)	136 (27.9)	77 (31.3)
≥65	74 (30.0)	38 (30.2)	190 (39.0)	99 (40.2)
≥75	25 (10.1)	6 (4.8)	54 (11.1)	22 (8.9)
Reproductive Status				
Childbearing potential	1 (0.4)	0	2 (0.4)	0
Non-childbearing potential	246 (99.6)	126 (100)	485 (99.6)	246 (100)
Race				
White	218 (88.3)	108 (85.7)	436 (89.5)	219 (89.0)
Black	5 (2.0)	1 (0.8)	10 (2.1)	2 (0.8)
Asian	10 (4.0)	8 (6.3)	14 (2.9)	11 (4.5)
American Indian or Alaska Native	1 (0.4)	0	1 (0.2)	0
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.2)	0
Unknown	5 (2.0)	0	6 (1.2)	1 (0.4)
Not reported	7 (2.8)	9 (7.1)	19 (3.9)	13 (5.3)
Ethnicity				
Hispanic or Latino	18 (7.3)	5 (4.0)	28 (5.7)	10 (4.1)
Not Hispanic or Latino	220 (89.1)	114 (90.5)	432 (88.7)	223 (90.7)
Unknown	6 (2.4)	5 (4.0)	17 (3.5)	9 (3.7)
Not reported	3 (1.2)	2 (1.6)	10 (2.1)	4 (1.6)
Weight (kg)				
Median	65.30	65.10	66.00	65.55
Min, Max	38.0, 137.0	38.5, 136.5	38.0, 137.0	37.8, 146.5

ECOG PS				
0	182 (73.7)	97 (77.0)	337 (69.2)	174 (70.7)
1	65 (26.3)	29 (23.0)	150 (30.8)	72 (29.3)
Geographic Region, n (%)				
US and Canada	ND	ND	218 (44.8)	115 (46.7)
Eastern Europe	ND	ND	61 (12.5)	27 (11.0)
Western Europe	ND	ND	192 (39.4)	96 (39.0)

Source: Table 14.1.3A, Table 14.1.5A, and Table 14.1.11.

Abbreviations: ECOG=Eastern Cooperative Oncology Group; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; Max=maximum; Min=minimum; ND=not determined; PS=performance score; US=United States.

Table 26. Baseline disease characteristics (ITT population)

Parameter	HRDpos		Overall	
	Niraparib (N=247) n (%)	Placebo (N=126) n (%)	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
Time from diagnosis to first dose (median in months)	7.680	7.440	7.680	7.740
Primary tumor site				
Ovarian	201 (81.4)	105 (83.3)	388 (79.7)	201 (81.7)
Primary peritoneal	14 (5.7)	8 (6.3)	34 (7.0)	13 (5.3)
Fallopian tube	32 (13.0)	13 (10.3)	65 (13.3)	32 (13.0)
Cancer stage (FIGO) at time of diagnosis				
III, not otherwise specified	7 (2.8)	1 (0.8)	10 (2.1)	4 (1.6)
IIIA	4 (1.6)	1 (0.8)	7 (1.4)	4 (1.6)
IIIB	10 (4.0)	9 (7.1)	16 (3.3)	12 (4.9)
IIIC	140 (56.7)	67 (53.2)	285 (58.5)	138 (56.1)
IV	86 (34.8)	48 (38.1)	169 (34.7)	88 (35.8)
Baseline CA-125 level				
≤ULN	236 (95.5)	120 (95.2)	450 (92.4)	226 (91.9)
>ULN	9 (3.6)	5 (4.0)	34 (7.0)	18 (7.3)
Missing	2 (0.8)	1 (0.8)	3 (0.6)	2 (0.8)
Histological subtype				
Serous	234 (94.7)	116 (92.1)	465 (95.5)	230 (93.5)[a]
Endometrioid	5 (2.0)	6 (4.8)	11 (2.3)	9 (3.7)
Other	8 (3.2)	4 (3.2)	11 (2.3)	6 (2.4)

Source: Table 14.1.4A, Table 14.1.5A, and Table 14.1.13A

Abbreviations: CA-125=cancer antigen 125; FIGO= International Federation of Gynecology and Obstetrics; HRDpos= homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; ULN=upper limit of normal.

[a] One subject with missing histology information but cytology result was reported as serous.

Summary demographics and baseline characteristics by starting dose subgroups for the homologous recombination deficient (HRDpos) and Overall subgroups are presented in the table below.

Table 27. Patient demographics and baseline characteristics – individualised and fixed starting dose subgroups (ITT population)

	HRDpos				Overall			
	Niraparib N(%)		Placebo N(%)		Niraparib N(%)		Placebo N(%)	
Parameter	Fixed N=160	Individualized N=87	Fixed N=83	Individualized N=43	Fixed N=317	Individualized N=170	Fixed N=158	Individualized N=88
Age at time of screening								
Median	57.0	60.0	59.0	56.0	61.0	63.0	62.0	60.5
Min, Max	32, 83	39, 83	34, 81	33, 82	32, 83	39, 85	34, 88	33, 82
ECOG PS								
0	118 (73.8)	64 (73.6)	62 (74.7)	35 (81.4)	223 (70.3)	114 (67.1)	114 (72.2)	60 (68.2)
1	42 (26.3)	23 (26.4)	21 (25.3)	8 (18.6)	94 (29.7)	56 (32.9)	44 (27.8)	28 (31.8)
Cancer stage (FIGO) at time of diagnosis								
III, not otherwise specified	3 (1.9)	4 (4.6)	1 (1.2)	0	5 (1.6)	5 (2.9)	4 (2.5)	0
IIIA	2 (1.3)	2 (2.3)	1 (1.2)	0	3 (0.9)	4 (2.4)	4 (2.5)	0
IIIB	7 (4.4)	3 (3.4)	5 (6.0)	4 (9.3)	10 (3.2)	6 (3.5)	7 (4.4)	5 (5.7)
IIIC	90 (56.3)	50 (57.5)	47 (56.6)	20 (46.5)	186 (58.7)	99 (58.2)	88 (55.7)	50 (56.8)
IV	58 (36.3)	28 (32.2)	29 (34.9)	19 (44.2)	113 (35.6)	56 (32.9)	55 (34.8)	33 (37.5)
Primary tumor site								
Ovarian	132 (82.5)	69 (79.3)	71 (85.5)	34 (79.1)	249 (78.5)	139 (81.8)	130 (82.3)	71 (80.7)
Primary	6 (3.8)	8 (9.2)	5 (6.0)	3 (7.0)	20 (6.3)	14 (8.2)	7 (4.4)	6 (6.8)
peritoneal								
Fallopian tube	22 (13.8)	10 (11.5)	7 (8.4)	6 (14.0)	48 (15.1)	17 (10.0)	21 (13.3)	11 (12.5)
NACT								
Y	98 (61.3)	58 (66.7)	55 (66.3)	25 (58.1)	208 (65.6)	114 (67.1)	114 (72.2)	53 (60.2)
N	62 (38.8)	29 (33.3)	28 (33.7)	18 (41.9)	109 (34.4)	56 (32.9)	44 (27.8)	35 (39.8)
Best Response to 1st line platinum-based chemotherapy								
CR	126 (78.8)	59 (67.8)	62 (74.7)	31 (72.1)	233 (73.5)	104 (61.2)	117 (74.1)	55 (62.5)
PR	34 (21.3)	28 (32.2)	21 (25.3)	12 (27.9)	84 (26.5)	66 (38.8)	41 (25.9)	33 (37.5)

Abbreviations: CA-125=cancer antigen 125; ECOG=Eastern Cooperative Oncology Group; FIGO= International Federation of Gynecology and Obstetrics; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; Max=maximum; Min=minimum; ND=not determined; PS=performance score; ULN=upper limit of normal.; US=United States.
with missing histology information but cytology result was reported as serous.
Source: Table 14.1.3B, Table 14.1.4B, Table 14.1.5B, Table 14.1.9b, Table 14.19d, and and Table 14.1.13B

Tumour grade was determined based either on histological or cytological data provided by the investigator. However, the main amount of data was based on histology. For a total of 26/733 (3.5%) patients in the Overall population (ITT) and for a total of 16/373 (4.3%) patients in the HRDpos population (ITT), the histological data were not assessable. The percentage of patients with no assessable data were quite similar between the niraparib arm and the placebo arm for both the HRDpos (4.0% vs. 4.8%, respectively) and the Overall population (3.3% vs. 4.1%, respectively). Of the patients with assessable histological data, all patients were high-grade in the HRDpos population (ITT), while in the Overall population, there were 2 low-grade patients in the niraparib-arm. These 2 patients belonged to the fixed starting dose group. The MAH sought additional tissue biopsies from the 2 subjects, however, no further data became available.

Table 28. Summary of BRCA status based on homologous recombination deficiency clinical trial assay in the Overall population (ITT population)

Parameter	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
BRCA status		
*BRCA*mut	152 (31.2)	71 (28.9)
*BRCA*1	105 (21.6)	43 (17.5)
*BRCA*2	47 (9.7)	28 (11.4)
*BRCA*wt	310 (63.7)	163 (66.3)
*BRCA*nd	25 (5.1)	12 (4.9)
HRD status		
HRDpos	247 (50.7)	126 (51.2)
tBRCAmut	152 (31.2)	71 (28.9)
non-tBRCAmut and HRDpos	95 (19.5)	55 (22.4)
HRDneg	169 (34.7)	80 (32.5)
HRDnot determined	71 (14.6)	40 (16.3)

Source: Table 14.1.14.1A
Abbreviations: *BRCA*=breast cancer gene; *BRCA*mut=*BRCA* mutation positive; *BRCA*nd=*BRCA* not determined; *BRCA*wt=*BRCA* wild type; HRDneg= homologous recombination deficiency test negative, referring to homologous recombination proficient (HR-proficient) tumors; HRDpos= homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to treat.

Table 29. Prior treatment for ovarian cancer (ITT population)

Parameter	HRDpos		Overall	
	Niraparib (N=247) n (%)	Placebo (N=126) n (%)	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
Number of prior lines of platinum therapy				
1	247 (100)	126 (100)	487 (100)	246 (100)
Surgeries/procedures related to study indication				
Yes	247 (100)	126 (100)	481 (98.8)	245 (99.6)
No	0	0	6 (1.2)	1 (0.4)
Number of surgeries				
1	179 (72.5)	86 (68.3)	339 (69.6)	167 (67.9)
2	62 (25.1)	33 (26.2)	129 (26.5)	68 (27.6)
≥3[a]	6 (2.4)	7 (5.6)	13 (2.7)	10 (4.1)
Radiotherapy prior to enrollment[b]				
Yes	8 (3.2)	3 (2.4)	12 (2.5)	7 (2.8)
No	239 (96.8)	123 (97.6)	475 (97.5)	239 (97.2)
Duration (months) of first line platinum therapy				
Mean (StD)	5.22 (1.461)	5.11 (1.365)	5.25 (1.400)	5.32 (1.475)
Median	5.09	5.04	5.09	5.22
Q1, Q3	4.14, 6.01	3.94, 5.78	4.17, 6.01	4.17, 5.98
Min, Max	1.2, 10.7	3.1, 10.8	1.2, 10.7	3.1, 10.8
Total number of cycles in first line platinum therapy				
6	165 (66.8)	84 (66.7)	333 (68.4)	170 (69.1)
7	24 (9.7)	15 (11.9)	57 (11.7)	31 (12.6)
8	17 (6.9)	8 (6.3)	46 (9.4)	24 (9.8)
9	11 (4.5)	5 (4.0)	21 (4.3)	7 (2.8)
Missing[c]	30 (12.1)	14 (11.1)	30 (6.2)	14 (5.7)
Duration (weeks) from end date of first line platinum therapy to date of randomization				
Mean (StD)	8.70 (3.648)	8.29 (3.763)	8.41 (3.209)	8.22 (3.340)
Median	8.43	7.93	8.00	8.14

Parameter	HRDpos		Overall	
	Niraparib (N=247) n (%)	Placebo (N=126) n (%)	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
Q1, Q3	6.14, 11.00	5.57, 10.86	6.14, 10.57	5.86, 10.86
Min, Max	0.3, 28.0	1.1, 26.1	0.3, 28.0	1.1, 26.1
Prior taxane	240 (97.2)	122 (96.8)	476 (97.7)	237 (96.3)
Prior carboplatin	234 (94.7)	119 (94.4)	469 (96.3)	235 (95.5)
Prior cisplatin	23 (9.3)	16 (12.7)	34 (7.0)	22 (8.9)
Prior doxorubicin	5 (2.0)	1 (0.8)	7 (1.4)	2 (0.8)
Prior gemcitabine	2 (0.8)	2 (1.6)	6 (1.2)	3 (1.2)
Prior bevacizumab	5 (2.0)	0	6 (1.2)	1 (0.4)
Prior cyclophosphamide	4 (1.6)	1 (0.8)	5 (1.0)	3 (1.2)
Prior other	6 (2.4)	1 (0.8)	11 (2.3)	3 (1.2)

Source: Table 14.1.12A and Table 14.1.18A

Abbreviations: HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; Max=maximum; Min=minimum; Q1=first quartile; Q3=third quartile; StD=standard deviation.

[a] Per protocol, ≥3 debulking surgeries were prohibited. The inconsistency is due to all types of surgeries/procedures being recorded/counted instead of only the debulking surgeries. Listing 16.2.4.11 provides details of prior surgeries for each subject.

[b] Prior radiotherapy included treatment for ovarian cancer and/or other indications in subjects' medical history. Listing 16.2.4.12 provides the indication for prior radiotherapy for each subject.

[c] Per original protocol, with only subjects with HR-deficient status were enrolled, the number of cycles was not collected, but was estimated from start and end date of chemotherapy for eligibility review.

Numbers analysed

A total of 733 participants were randomised into the study and included in the ITT population.

Table 30. Analysis datasets (all enrolled patients)

Parameter	HRDpos		All Enrolled Subjects	
	Niraparib n (%)	Placebo n (%)	Niraparib n (%)	Placebo n (%)
Intent-to-treat (ITT) population	247	126	487	246
Safety (SAF) population[a]	245 (100)	125 (100)	484 (100)	244 (100)
Per-protocol (PP) population	243 (99.2)	123 (98.4)	480 (99.2)	241 (98.8)

Source: Table 14.1.1A

Abbreviations: HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors.

[a] Percentages were based on safety population.

Table 31. Summary of patient disposition in HRDpos and overall, by fixed and individualized starting dose subgroup

Parameter	HRDpos	All enrolled subjects

	Niraparib n (%)		Placebo n (%)		Niraparib n (%)		Placebo n (%)	
	Fixed	Individualised	Fixed	Individualised	Fixed	Individualised	Fixed	Individualised
ITT population	160	87	83	43	317	170	158	88
Safety population[a]	159 (100)	86 (100)	83 (100)	42 (100)	315 (100)	169 (100)	158 (100)	86 (100)
PP population	157 (98.7)	86 (100)	81 (97.6)	42 (100)	312 (99.0)	168 (99.4)	155 (98.1)	86 (100)

[a]Percentages were based on safety population

Outcomes and estimation

Primary endpoint

Table 32. Progression-free survival based on BICR (ITT population)

Parameter Statistic	HRDpos		Overall	
	Niraparib (N=247) n (%)	Placebo (N=126) n (%)	Niraparib (N=487) n (%)	Placebo (N=246) n (%)
PFS (months)[a,b]				
75th percentile (95% CI)	NE (NE, NE)	NE (16.8, NE)	NE (22.1, NE)	19.4 (16.6, NE)
Median (95% CI)	21.9 (19.3, NE)	10.4 (8.1,12.1)	13.8 (11.5,14.9)	8.2 (7.3,8.5)
25th percentile (95% CI)	11.1 (8.4,13.6)	5.6 (3.9,6.7)	5.7 (5.6,7.4)	4.5 (2.9,5.4)
Survival distribution function (95% CI)[c]				
6-month	0.86 (0.81,0.90)	0.68 (0.59,0.76)	0.73 (0.69,0.77)	0.60 (0.53,0.66)
12-month	0.72 (0.65,0.77)	0.42 (0.33,0.51)	0.53 (0.48,0.58)	0.35 (0.29,0.42)
18-month	0.59 (0.50,0.66)	0.35 (0.25,0.45)	0.42 (0.36,0.47)	0.28 (0.21,0.35)
24-month	0.47 (0.36,0.58)	0.26 (0.14,0.39)	0.32 (0.25,0.39)	0.23 (0.14,0.32)
30-month	0.47 (0.36,0.58)	0.26 (0.14,0.39)	0.32 (0.25,0.39)	0.23 (0.14,0.32)
Censored observations, n (%)	166 (67.2)	53 (42.1)	255 (52.4)	91 (37.0)
Event rate, n (%)	81 (32.8)	73 (57.9)	232 (47.6)	155 (63.0)
p-value[d]	<0.0001		<0.0001	
Hazard ratio (95% CI)[e]	0.43 (0.310,0.588)		0.62 (0.502,0.755)	

Source: Table 14.2.1.1 and Table 14.2.1.2

Abbreviations: BICR=blinded independent central review; CI=confidence interval; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; NE=not estimable; PFS=progression free survival.

[a] Progression-free survival is defined as the time in months from the date of randomization to progression or death.

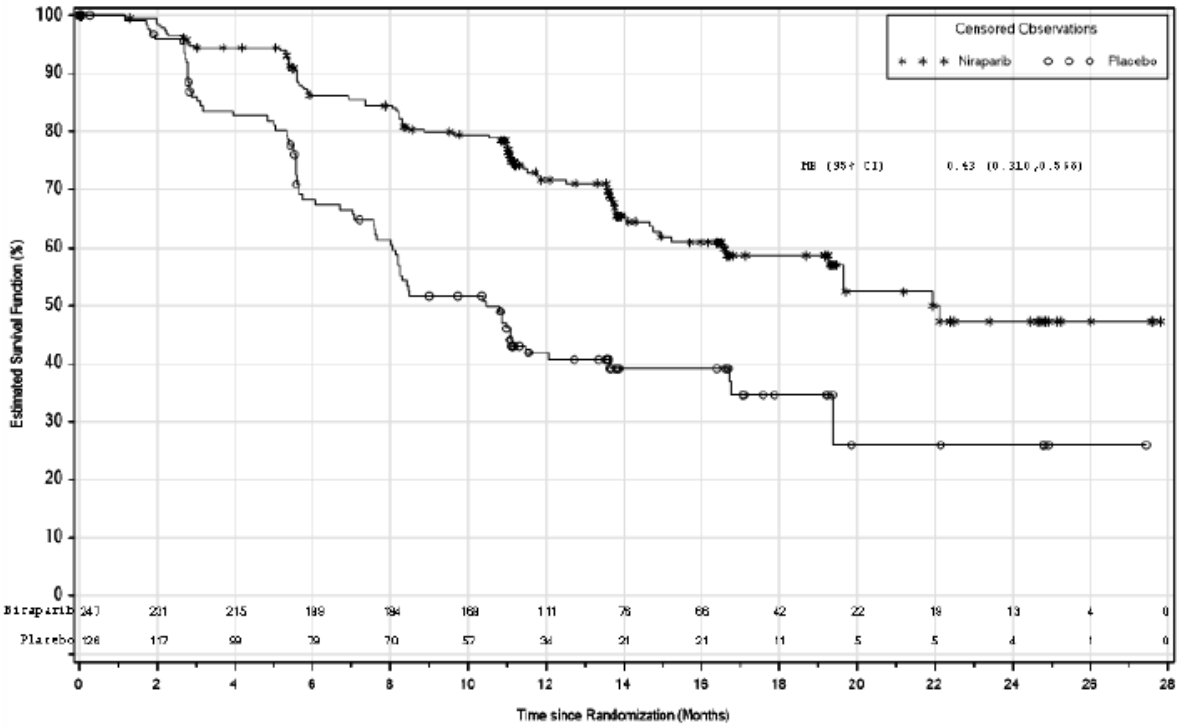
[b] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.

[c] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.

[d] Based on stratified log-rank test using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy and homologous recombination deficiency test status (for overall population only).

[e] Based on stratified Cox proportional hazards model using randomization stratification factors.

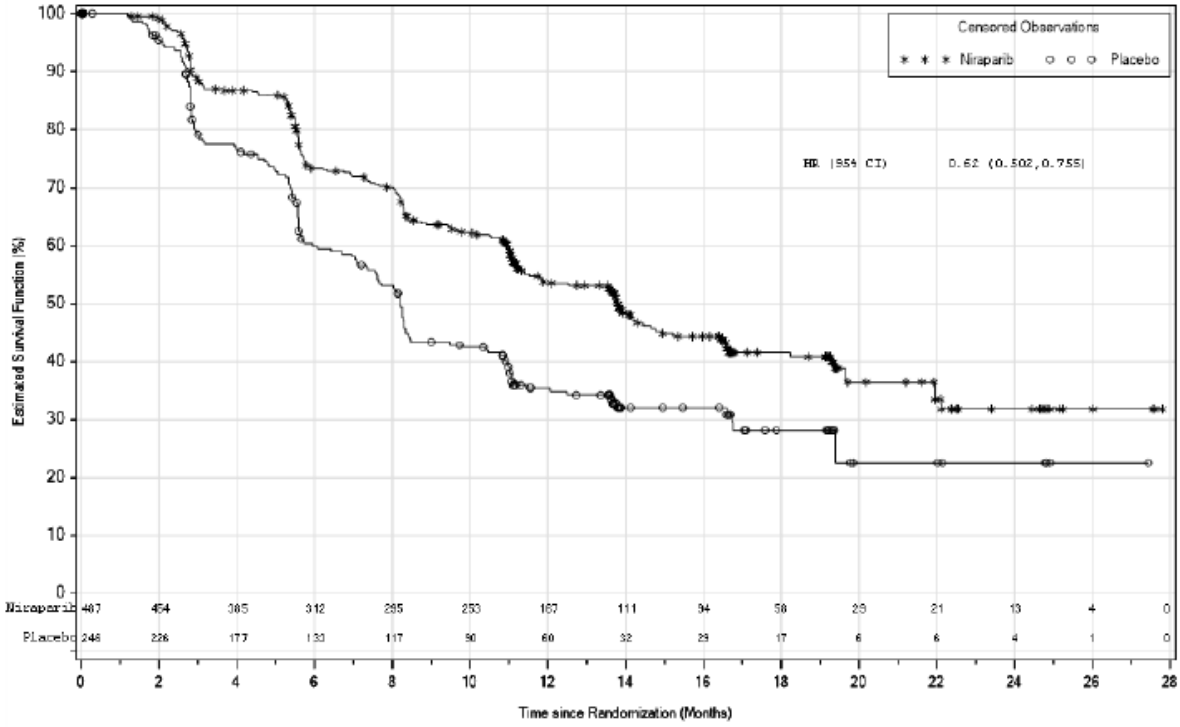
HRDpos population



Source: Figure 14.2.1.1
Abbreviations: BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat.

Figure 24. Kaplan-Meier plot of progression-free survival by BICR assessment in subjects with homologous recombination deficient tumours (ITT population)

Overall population



Source: Figure 14.2.1.2
Abbreviations: BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat.

Figure 25. Kaplan-Meier plot of progression-free survival by BICR assessment in the Overall population (ITT population)

Table 33. Progression-free survival based on BICR assessment by starting dose group (ITT population)

Population Parameter Statistic	Fixed		Individualized	
	Niraparib	Placebo	Niraparib	Placebo
HRDpos				
N	160	83	87	43
PFS (months)[a,b]				
Median (95% CI)	22.1 (19.6, NE)	8.4 (7.6, 13.6)	14.0 (12.5, NE)	10.9 (6.1, NE)
Censored observations, n (%)	103 (64.4)	31 (37.3)	63 (72.4)	22 (51.2)
Event rate, n (%)	57 (35.6)	52 (62.7)	24 (27.6)	21 (48.8)
p-value[c]	<0.0001		0.0019	
Hazard ratio (95% CI)[d]	0.44 (0.298, 0.638)		0.39 (0.215, 0.723)	
Overall				
N	317	158	170	88
PFS (months)[a,b]				
Median (95% CI)	14.7 (13.6, 19.4)	8.2 (7.0, 9.8)	11.4 (9.7, 13.9)	8.2 (5.6, 10.9)
Censored observations, n (%)	167 (52.7)	54 (34.2)	88 (51.8)	37 (42.0)
Event rate, n (%)	150 (47.3)	104 (65.8)	82 (48.2)	51 (58.0)
p-value[c]	<0.0001		0.0389	
Hazard ratio (95% CI)[d]	0.59 (0.457, 0.757)		0.69 (0.481, 0.982)	

Source: CSR PR-30-5017-C Table 14.2.1.10

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CR=complete response; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient tumors; ITT=intent-to-treat; NE=not estimated; PFS=progression-free survival; PR=partial response.

[a] Progression-free survival is defined as the time in months from the date of randomization to progression or death.

[b] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.

[c] Based on stratified log-rank test using randomization stratification factors: administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR), and homologous recombination deficiency test status (for overall ITT population only).

[d] Based on stratified Cox proportional hazards model using randomization stratification factors as above.

Subgroup Fixed starting dose: HRDpos population (cut-off date 17 May 2019)

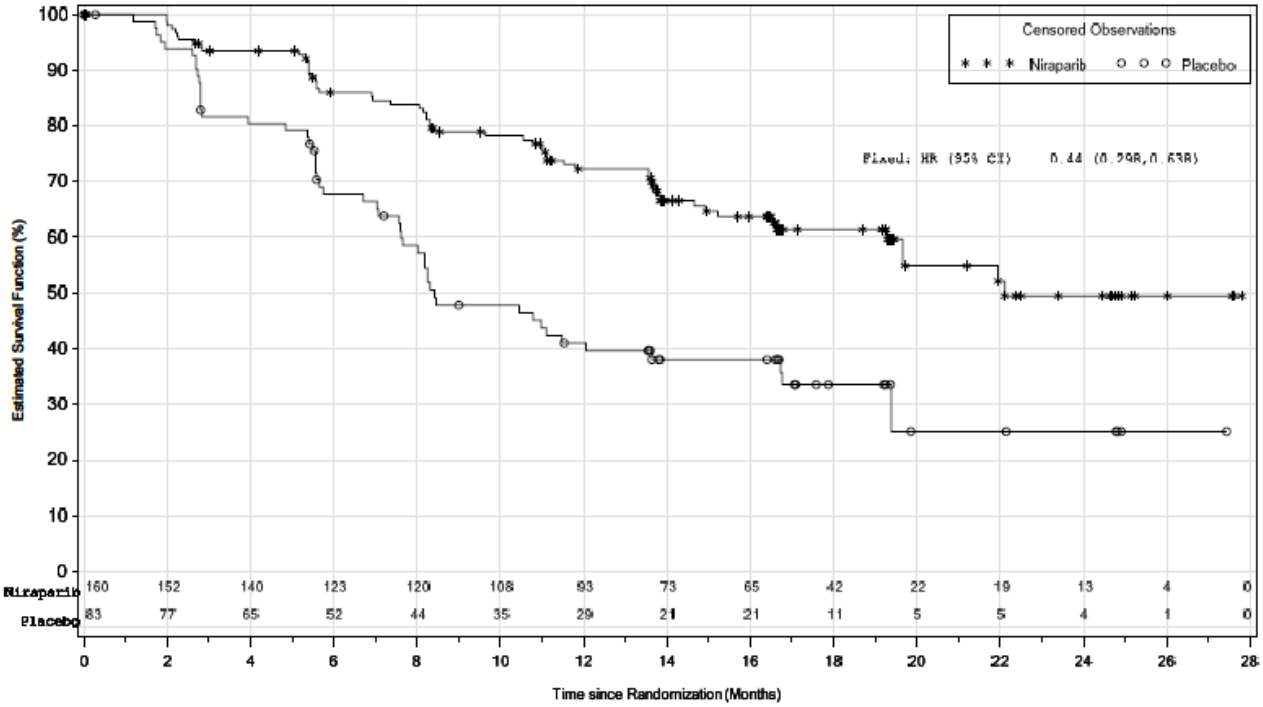


Figure 26. Kaplan-Meier Plot of Progression-Free Survival by BICR in HRDpos and Overall, by Fixed and Individualized Starting Dose Subgroup (ITT Population) – HRDpos population

Subgroup Individualised starting dose: HRDpos population (cut-off date 17 May 2019)

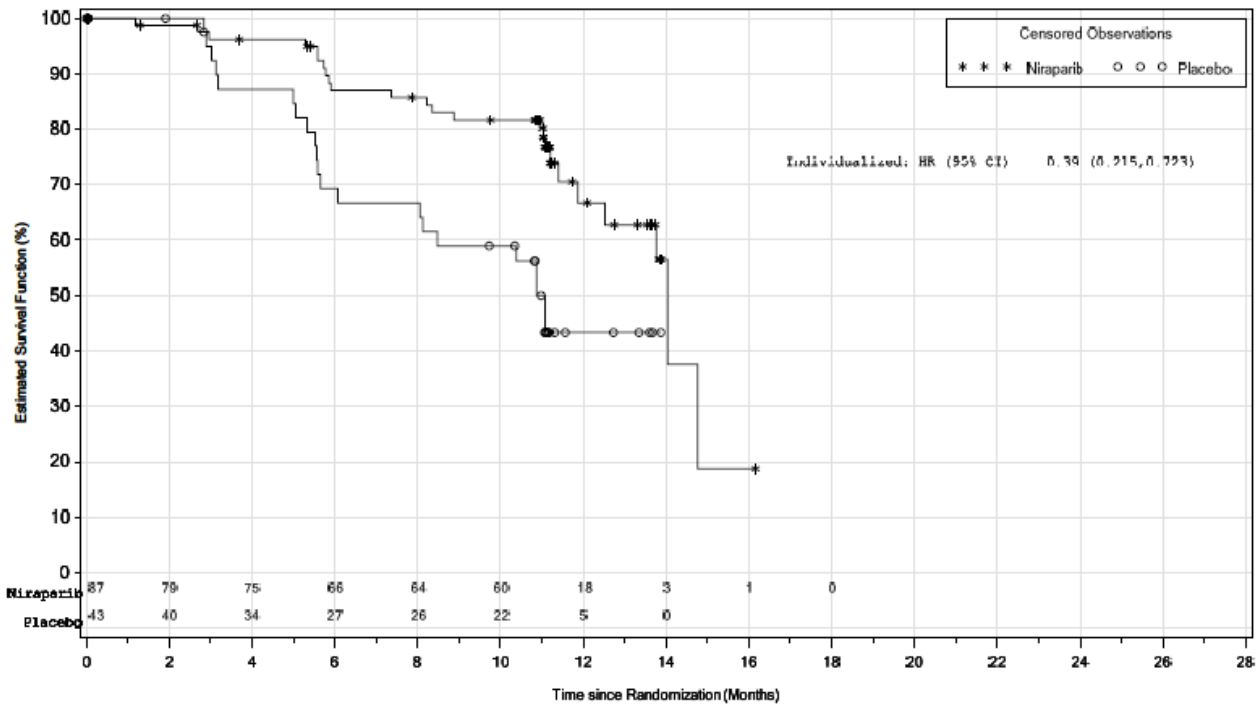


Figure 27. Kaplan-Meier Plot of Progression-Free Survival by BICR in HRDpos and Overall, by Fixed and Individualized Starting Dose Subgroup (ITT Population) – HRDpos population

Subgroup Fixed starting dose: Overall population (cut-off date 17 May 2019)

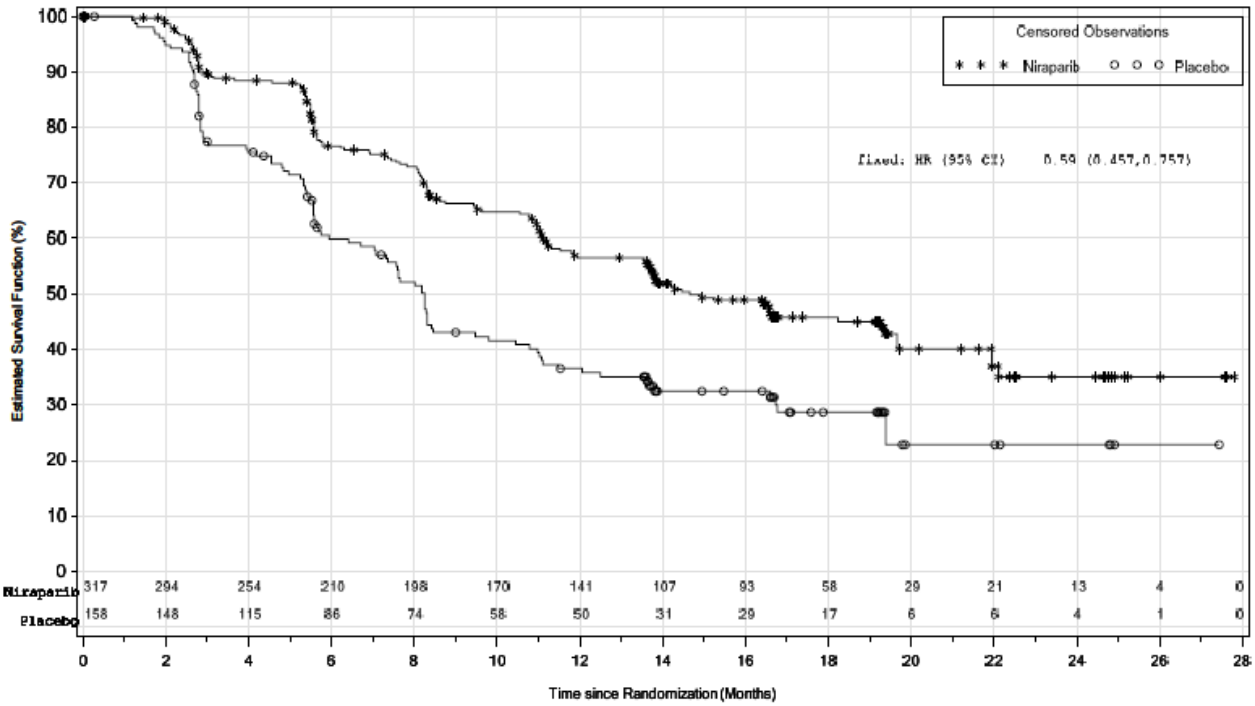


Figure 28. Kaplan-Meier Plot of Progression-Free Survival by BICR in HRDpos and Overall, by Fixed and Individualized Starting Dose Subgroup (ITT Population) – Overall population

Subgroup Individualised starting dose: Overall population (cut-off date 17 May 2019)

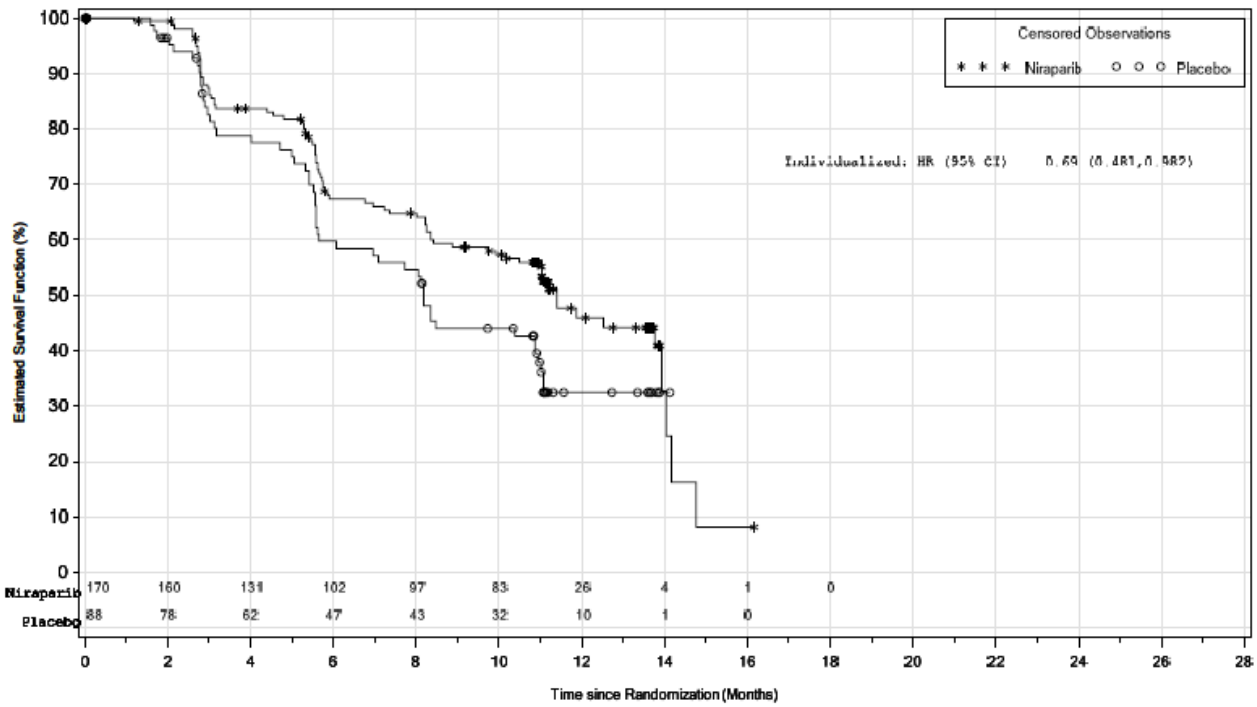


Figure 29. Kaplan-Meier Plot of Progression-Free Survival by BICR in HRDpos and Overall, by Fixed and Individualized Starting Dose Subgroup (ITT Population) – Overall population

Table 34. Kaplan-Meier estimates of PFS follow-up time in HRDpos and overall, by fixed and individualised starting dose subgroup (ITT population)

		HRDpos		Overall	
Parameter	Statistic	Niraparib (N=247)	Placebo (N=126)	Niraparib (N=487)	Placebo (N=246)
Fixed Dose Subgroup					
PFS follow-up time (months) [1] [2]	Median (95% CI)	16.6 (16.4,19.2)	17.1 (13.8,19.3)	16.6 (16.4,16.8)	16.7 (13.8,19.2)
Number of Patients	N	160	83	317	158
Individualized Dose Subgroup					
PFS follow-up time (months) [1] [2]	Median (95% CI)	11.1 (11.1,11.2)	11.1 (11.0,11.6)	11.1 (11.1,11.2)	11.1 (11.0,12.7)
Number of Patients	N	87	43	170	88

[1] PFS follow-up time is estimated by reversing the censoring values in the PFS analysis, such that censored observations are treared as events and PD/deaths are censored using the unstratified model.
[2] Quartile estimates from product limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log-transformation.

Reasons for censoring, including number of patients, for both the HRDpos and the Overall population were provided. This included also the fixed and individualised starting dose groups, in addition to the dosing subgroups C - Fixed Starting Dose subgroup (300 mg starting dose) with BW <77kg or PC <150K/µL and D - Individualised Starting Dose subgroup (200 mg starting dose) with BW <77kg or PC <150K/µL.

The total number of censored patients was, among, the HRDpos patients 166/247 (67.2%) in the niraparib arm and 53/126 (42.1%) patients in the placebo group. For the Overall population, the number of censored patients was 255/487 (52.4%) in the niraparib arm vs. 91/246 (37.0%) in the placebo arm. The most common reason for censoring in both arms in all populations was "last tumour assessment". This comprised patients who had not progressed or died and had not started subsequent anti-cancer therapy and who were censored at the date of the latest evaluable radiological assessment. Censoring due to this reason was more common in the niraparib arm than in the placebo arm (in the ITT population: HRDpos: 132/247, 53.4% vs. 43/126, 34.1% in the placebo arm and in the Overall population: 192/487, 39.4% in the niraparib arm vs. 72/246, 29.3% in the placebo arm). In the niraparib arm, the proportion of patients who were censored due to this reason was a bit higher in the dosing subgroup D (ISD, 200 mg) compared to the dosing subgroup C (FSD, 300 mg) for both the HRDpos patients (59.1% vs. 48.7%, respectively) and the Overall population (41.8% vs. 36.6%, respectively). In the placebo arm, the proportions were lower, however, the same trend as for the niraparib-treated patients was observed. For the Overall and the HRDpos populations, the reason for the PFS events was progression in all patients having an event, apart from one event in the placebo arm in the Overall population which was stated to be death.

Updated analyses fixed starting dose group (FSD) and individualised starting dose group (ISD)

The figure shows a scatter plot between baseline body weight and baseline platelet count for the 156 patients who received the "ISD" in PRIMA, color coded for the actual starting dose.

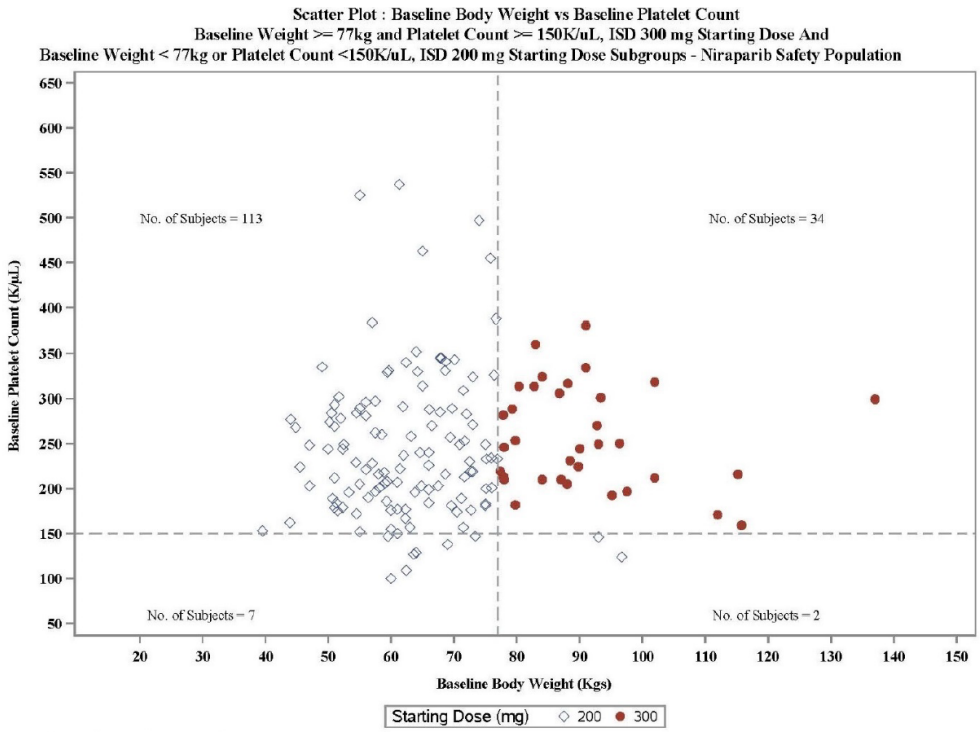


Figure 30. Scatter plot between baseline body weight and baseline platelet count for patients in the individualized starting dose (ISD) subgroup. Source: RSI response document, Figure 30.

The number of subjects with a baseline platelet count <150,000/µL (one of the two proposed discrimination criteria for the starting dose) was low (9 out of 156 patients, 6%) in the PRIMA study. Of the patients who received the 200 mg starting dose, 120 of 122 patients had a body weight below 77 kg. Only two subjects with body weight above 77 kg received the 200 mg starting dose due to a low baseline platelet count.

Table 35. Investigator-assessed follow-up time and event maturity

Median Follow-up Time	**Original (Data cut: 17 May 2019)**	**Updated (Data cut: 17 Nov 2019)**
Overall	14.9 months	19.5 months
FSD	17.1 months	22.4 months
ISD	11.2 months	17.0 months
Inv-PFS Event Maturity		
Overall (n=733)	421 events (57%)	473 events (65%)
FSD (n=475)	281 events (59%)	312 events (66%)
ISD (n=258)	140 events (54%)	161 events (62%)

Source: IR Table 14-2-1-13_sNDA, 14-2-1-13_sNDA6m, 14-2-1-14_sNDA, 14-2-1-14_sNDA6m.
Abbreviations: FSD=fixed starting dose; Inv-PFS=Investigator-assessed PFS; ISD=individualized starting dose; PFS=progression-free survival.

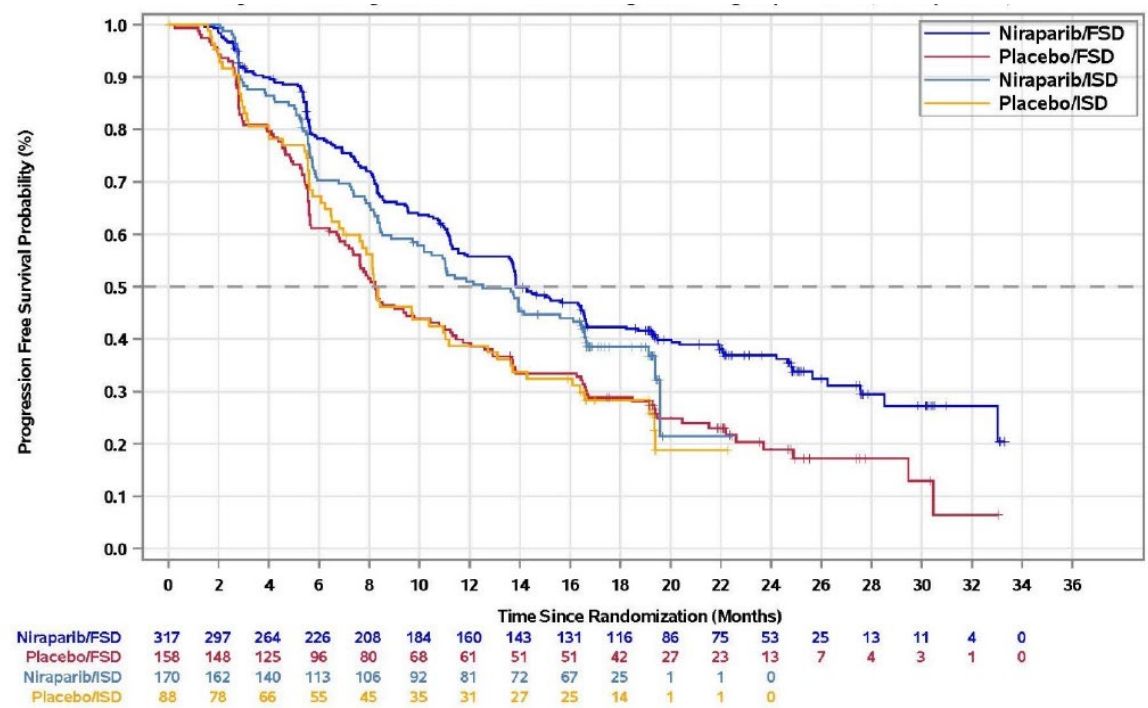
Table 36. Investigator-assessed PFS; subgroups by dosing regimen and HRD biomarker status (original data cut 17 May 2019, updated data cut 17 November 2019)

HR (95% CI) mPFS (NIR vs PBO months)	Overall		HRd		HRp	
	Original Data Cut	Updated Data Cut	Original Data Cut	Updated Data Cut	Original Data Cut	Updated Data Cut
Overall	0.63 (0.51, 0.76) 13.8, 8.2	0.64 (0.53, 0.77) 13.8, 8.2	0.46 (0.34, 0.63) 21.9, 11.2	0.48 (0.36, 0.63) 24.2, 11.2	0.62 (0.45, 0.85) 8.3, 5.4	0.62 (0.46, 0.84) 8.3, 5.4
FSD	0.60 (0.47, 0.77) 13.8, 8.2	0.62 (0.49, 0.78) 13.9, 8.2	0.46 (0.33, 0.66) 24.2, 10.8	0.46 (0.32, 0.64) 24.8, 10.8	0.62 (0.41, 0.93) 10.8, 5.4	0.64 (0.44, 0.95) 10.8, 5.4
ISD	0.68 (0.48, 0.96) 11.4, 8.2	0.68 (0.49, 0.94) 12.5, 8.2	0.45 (0.25, 0.80) 13.9, 11.2	0.54 (0.33, 0.91) 19.4, 12.9	0.59 (0.35, 1.01) 5.9, 5.5	0.56 (0.34, 0.93) 6.6, 5.5

Source: IR Table T_1_sNDA, T_1_sNDA6m, T_2_sNDA, T_2_sNDA6m, T_3_sNDA, T_3_sNDA6m, T_4_sNDA, T_4_sNDA6m, T_5_sNDA, T_5_sNDA6m, T_6_sNDA, T_6_sNDA6m, T_7_sNDA, T_7_sNDA6m, T_8_sNDA, T_8_sNDA6m, T_9_sNDA, T_9_sNDA6m.
Abbreviations: CI=confidence interval; FSD=fixed starting dose; HRd=homologous recombination-deficient; HRp=homologous recombination-proficient; ISD=individualized starting dose; mPFS=median PFS; PFS=progression-free survival.

Updated Kaplan-Meier plots with cut-off date 17 November 2019 (only investigator-assessed PFS data available):

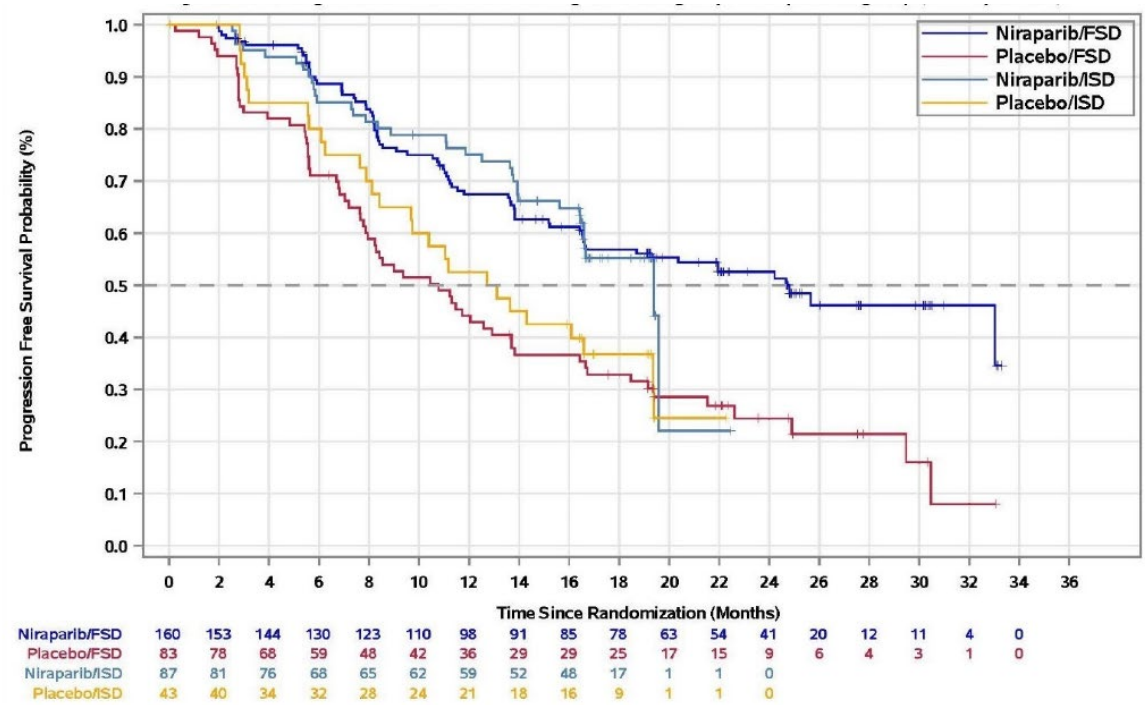
Below follows a presentation of updated 6 months data of Kaplan-Meier plots for the Overall population, HRDpos population and HRDneg population by the starting dose of FSD and ISD in the same graphs.



Source: Figure 14.2.1.22 (data cut date 17 Nov 2019)

Figure 31. Kaplan-Meier plots of progression free survival by Investigator assessment in Overall patient population - fixed starting dose and individualised starting dose (ITT population)

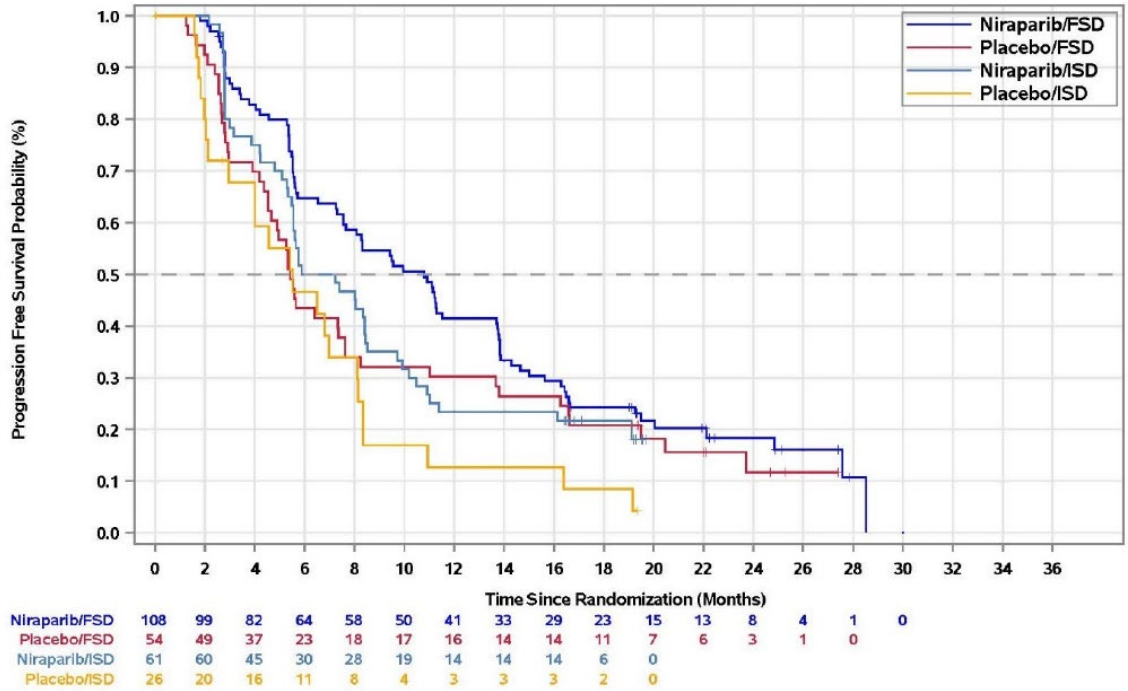
Subgroup Fixed and Individualised starting dose: HRDpos population



Source: Figure 14.2.1.23 (data cut date 17 Nov 2019)

Figure 32. Kaplan-Meier plots of progression free survival by Investigator assessment in HRDpos patient population - fixed starting dose and individualised starting dose (ITT population)

Subgroup Fixed and Individualised starting dose: HRDneg population



Source: Figure 14.2.1.23 (data cut date 17 Nov 2019)

Figure 33. Kaplan-Meier plots of progression free survival by Investigator assessment in HRDneg patient population - fixed starting dose and individualised starting dose (ITT population)

- Sensitivity analysis for the progression-free survival

Table 37. Results of the sensitivity analyses for progression-free survival (ITT population)

Sensitivity Analysis Statistic	HRDpos		Overall	
	Niraparib (N=247)	Placebo (N=126)	Niraparib (N=487)	Placebo (N=246)
Investigator assessment (ITT population)				
Median PFS (months (95% CI)[a,b]	21.9 (16.5, NE)	11.2 (8.4, 13.1)	13.8 (11.3, 14.2)	8.2 (7.6, 9.8)
p-value[c]	<0.0001		<0.0001	
Hazard ratio (95% CI)[d]	0.46 (0.342, 0.626)		0.63 (0.514, 0.763)	
Alternative censoring rules (ITT population)				
Median PFS (months (95% CI)[a,b]	21.0 (16.5, NE)	10.8 (8.1, 12.1)	13.8 (11.4, 14,7)	8.2 (7.3, 8.5)
p-value[c]	<0.0001		<0.0001	
Hazard ratio (95% CI)[d]	0.44 (0.325, 0.608)		0.62 (0.505, 0.758)	
Stratification values from the prior treatment eCRF (ITT population)				
Median PFS (months (95% CI)[a,b]	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)
p-value[c]	<0.0001		<0.0001	
Hazard ratio (95% CI)[d]	0.43 (0.313, 0.594)		0.60 (0.485, 0.731)	
Alternative event times (ITT population)				
Median PFS (months (95% CI)[a,b]	22.1 (18.0, NE)	9.4 (8.1,11.5)	13.8 (11.2, 16.4)	8.2 (6.4, 8.5)
p-value[c]	<0.0001		<0.0001	
Hazard ratio (95% CI)[d]	0.43 (0.310, 0.587)		0.62 (0.506, 0.762)	
BICR radiology data (ITT population)				
Median PFS (months (95% CI)[a,b]	22.1 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.8, 15.2)	8.2 (7.3, 8.5)
p-value[c]	<0.0001		<0.0001	
Hazard ratio (95% CI)[d]	0.42 (0.306, 0.581)		0.61 (0.499, 0.753)	

Stratification values from the prior treatment eCRF (PP population)				
Median PFS (months (95% CI)[a,b]	22.1 (19.3, NE)	10.4 (8.0, 11.5)	13.8 (11.4, 14.9)	8.2 (7.1, 8.4)
p-value[c]	<0.0001		<0.0001	
Hazard ratio (95% CI)[d]	0.42 (0.302, 0.574)		0.60 (0.486, 0.733)	
Subsequent anticancer therapy (ITT population)				
Median PFS (months (95% CI)[a,b]	17.2 (14.9, 21.8)	8.4 (7.7, 11.1)	11.9 (11.1, 13.9)	8.0 (6.7, 8.3)
p-value[c]	<0.0001		<0.0001	
Hazard ratio (95% CI)[d]	0.47 (0.351, 0.633)		0.64 (0.525, 0.774)	
Alternative Randomization Stratification Factors (ITT population)[e]				
Median PFS (months (95% CI)[a,b]	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)
p-value[c]	<0.0001		<0.0001	
Hazard ratio (95% CI)[d]	0.43 (0.312, 0.591)		0.62 (0.503, 0.757)	

Source: Table 14.2.1.3, Table 14.2.1.4, Table 14.2.1.5, Table 14.2.1.6, Table 14.2.1.7, Table 14.2.1.8, Table 14.2.1.11, and Table 14.2.1.12.

Abbreviations: CI=confidence interval; eCRF=electronic case report form; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival; PP=per-protocol.

[a] Progression-free survival is defined as the time in months from the date of randomization to progression or death.

[b] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.

[c] Based on stratified log-rank test using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy, and homologous recombination deficiency test result status (for overall population only).

[d] Based on stratified Cox proportional hazards model using randomization stratification factors.

[e] The analysis on the homologous recombination deficient population used one stratification factor: best response to platinum therapy. The overall analysis used two stratification factors: best response to platinum therapy and homologous recombination deficiency status.

The concordance between BICR and investigator-assessed PFS was high in both the Overall and HRDpos patient populations in both the niraparib (88.8%, 88.2% respectively) and placebo (86.6%, 84.9% respectively) treatment arms. In both the Overall and HRDpos populations, patients were more likely to be considered to have an event by investigator than by BICR in both treatment arms.

Secondary endpoints

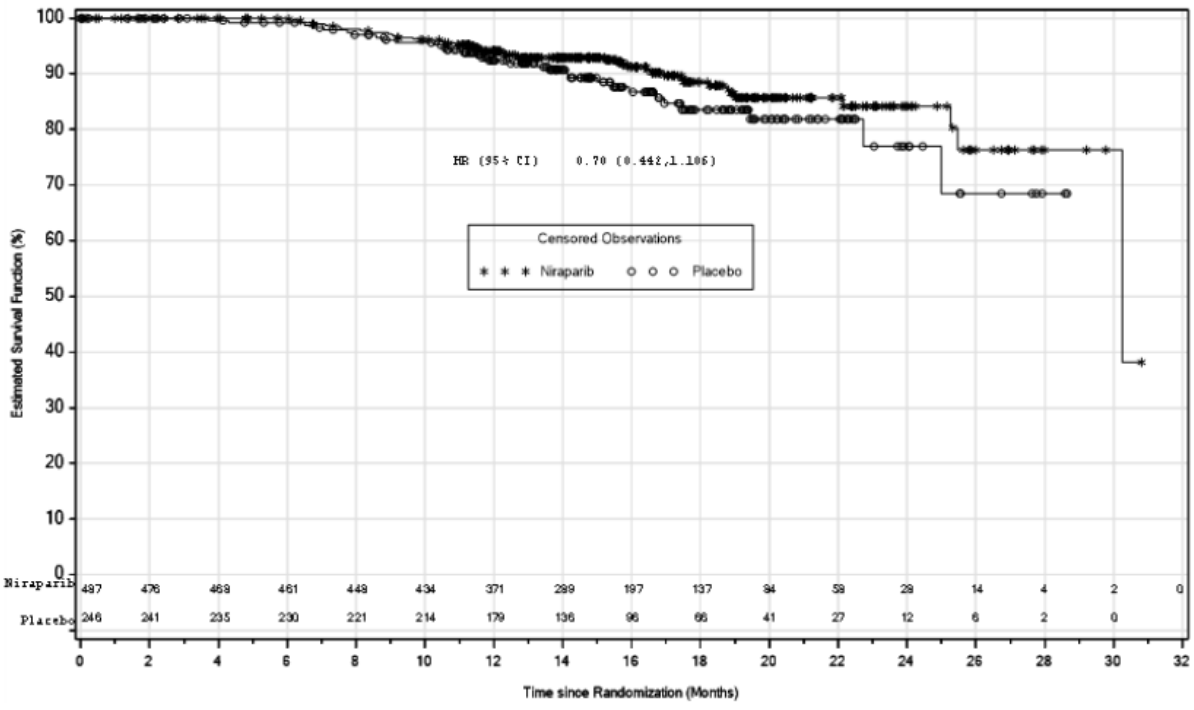
- Key secondary endpoint: Overall survival

At the time of primary PFS analysis, the estimated survival at two years after randomization was 84% for patients receiving Zejula, as compared to 77% for patients receiving placebo in the overall population.

Table 38. Interim analysis of Overall Survival (ITT population)

Parameter Statistic	HRDpos		Overall	
	Niraparib (N=247)	Placebo (N=126)	Niraparib (N=487)	Placebo (N=246)
Time to Death (months)[a,b]				
75th percentile (95% CI)	NE (30.3, NE)	NE (NE, NE)	NE (30.3, NE)	NE (NE, NE)
Median (95% CI)	30.3 (30.3, NE)	NE (25.0, NE)	30.3 (30.3, NE)	NE (25.0, NE)
25th percentile (95% CI)	30.3 (25.3, NE)	NE (22.7, NE)	30.3 (25.3, NE)	25.0 (19.4, NE)
Censored observations, n (%)	231 (93.5)	116 (92.1)	439 (90.1)	215 (87.4)
Event rate, n (%)	16 (6.5)	10 (7.9)	48 (9.9)	31 (12.6)
p-value[c]	0.2323		0.1238	
Hazard ratio (95% CI)[d]	0.61 (0.265, 1.388)		0.70 (0.442, 1.106)	

Source: CSR PR-30-5017-C Table 14.2.2.1
Abbreviations: CI=confidence interval; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient tumors; ITT=intent-to-treat; NE=not estimable.
[a] Time to Death is defined as the date of randomization to the date of death by any cause. Patients known to be alive were censored at the last known follow-up date.
[b] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.



Source: CSR PR-30-5017-C Figure 14.2.2.1
Abbreviations: CI=confidence interval; ITT=intent-to-treat.

Figure 34. Kaplan-Meier plot of Overall Survival in the Overall population (ITT population)

- Time to first subsequent therapy (TFST)

Table 39. Time to First Subsequent Therapy (ITT population)

Parameter Statistic	HRDpos		Overall	
	Niraparib (N=247)	Placebo (N=126)	Niraparib (N=487)	Placebo (N=246)
TFST (months)[a,b]				
75th percentile (95% CI)	NE (NE, NE)	NE (20.3, NE)	NE (NE, NE)	NE (20.3, NE)
Median (95% CI)	NE (24.7, NE)	13.7 (11.6, 19.3)	18.6 (15.8, 24.7)	12.0 (10.3, 13.9)
25th percentile (95% CI)	12.6 (10.8, 15.8)	8.2 (6.6, 9.7)	9.1 (7.9, 10.2)	6.7 (6.3, 7.9)
Censored observations, n (%)	171 (69.2)	60 (47.6)	277 (56.9)	108 (43.9)
Event rate, n (%)	76 (30.8)	66 (52.4)	210 (43.1)	138 (56.1)
p-value[c]	<0.0001		0.0001	
Hazard ratio (95% CI)[d]	0.46 (0.330, 0.640)		0.65 (0.521, 0.802)	

Source: CSR PR-30-5017-C Table 14.2.4.1

Abbreviations: CI=confidence interval; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient tumors; ITT=intent-to-treat; NE=not estimable; TFST=time to first subsequent therapy.

[a] Time to first subsequent therapy is defined as the time from the date of randomization to the date of first dose of follow-up anti-cancer treatment or death, whichever occurs first. Patients alive and not starting a first follow-up anti-cancer treatment will be censored at the date last known alive.

[b] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.

[c] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR), and homologous recombination deficiency test status (for Overall cohort only).

[d] Based on stratified Cox proportional hazards model using randomization stratification factors as above.

- Progression-Free Survival-2 (PFS-2)

Table 40. Progression-free survival-2 (PFS-2) (ITT population)

Parameter Statistic	HRDpos		Overall	
	Niraparib (N=247)	Placebo (N=126)	Niraparib (N=487)	Placebo (N=246)
PFS2 (months)[a,b]				
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (25.3, NE)	NE (NE, NE)	27.2 (25.3, NE)	NE (NE, NE)
25th percentile (95% CI)	24.0 (19.0,27.2)	NE (16.3, NE)	19.8 (17.2, 24.0)	17.3 (14.9, NE)
Censored observations, n (%)	210 (85.0)	106 (84.1)	395 (81.1)	193 (78.5)
Event rate, n (%)	37 (15.0)	20 (15.9)	92 (18.9)	53 (21.5)
p-value[c]	0.5311		0.2242	
Hazard ratio (95% CI)[d]	0.84 (0.485,1.453)		0.81 (0.577,1.139)	

Source: CSR PR-30-5017-C Table 14.2.3.1

Abbreviations: CI=confidence interval; CR=complete response; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient tumors; ITT=intent-to-treat; NE=not estimable; PFS2=progression-free survival-2; PR=partial response.

[a] Progression-free survival 2 is defined as date of randomization to the earlier date of assessment of progression on the next anti-cancer therapy following study treatment or death by any cause.

[b] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.

[c] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR), and homologous recombination deficiency test status (for Overall cohort only).

[d] Based on stratified Cox proportional hazards model using randomization stratification factors as above.

- Outcomes for next anticancer therapy following study treatment

No data have been included in the submitted documentation for this secondary endpoint.

As follow-up anticancer therapy, the majority of patients in both the niraparib arm and the placebo arm in both the HRDpos population and the Overall population received a platinum (most commonly carboplatin with around 25-30% in the niraparib arm and 30-33% in the placebo arm), paclitaxel (10-12% of the arms in the Overall population; 6-7% of the arms of the HRDpos population), pegylated liposomal doxorubicin hydrochloride (12% in the arms of the Overall population and 8-10% in the arms of the HRDpos population) and gemcitabine (11-12% in both arms in the Overall population and 8-9% in the arms of the HRDpos population).

More patients in the Overall population received bevacizumab as follow-up anticancer therapy (8% in the niraparib arm vs. nearly 13% in the placebo arm) compared to the HRDpos patients (ca. 5% in the niraparib group vs. ca. 7% in the placebo group).

Few patients in both arms in both populations received PARP-inhibitors as follow-up anticancer therapy (a total of 1.4% in the niraparib arm vs. 4.5% in the placebo arm in the Overall population vs. 2.8% in the niraparib arm vs. 5.6% in the placebo arm in the HRDpos population).

- Patient Reported Outcomes (PROs)

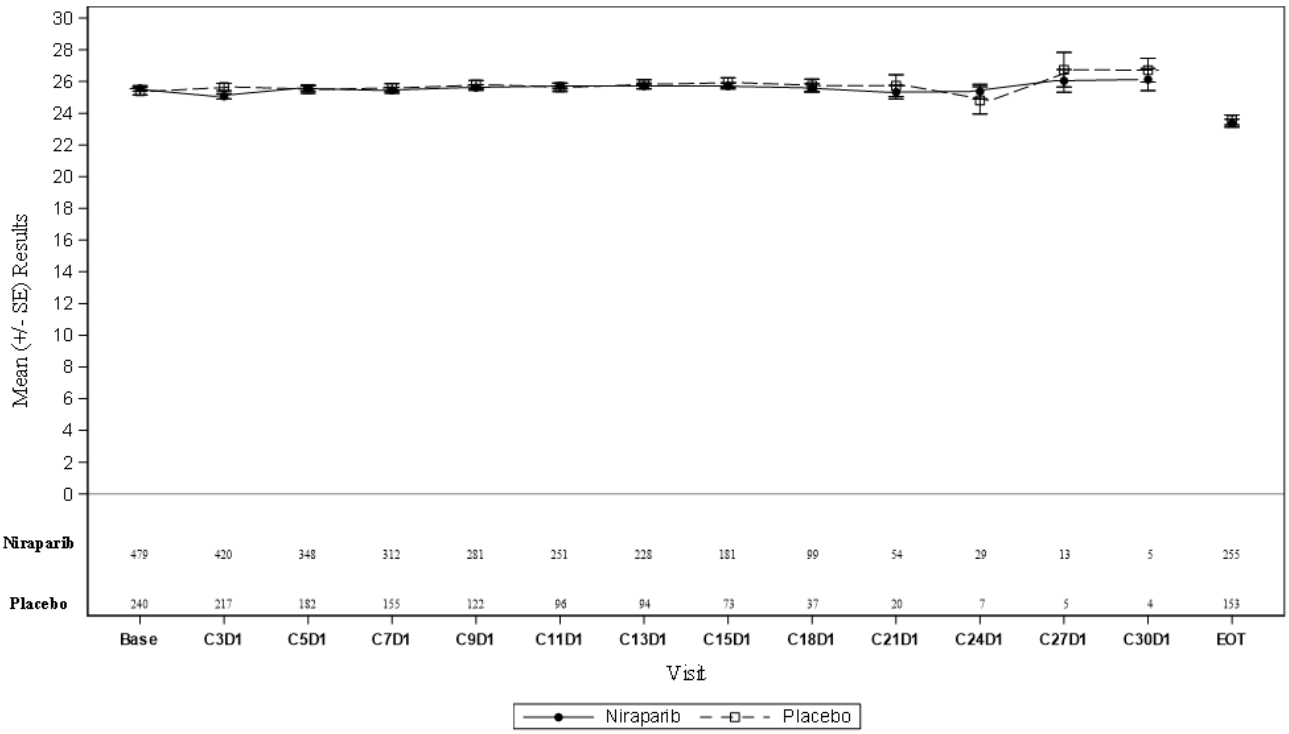
Symptoms of ovarian cancer were assessed in the PRIMA study using the functional assessment of cancer therapy–ovarian symptom index (FOSI), and quality of life was assessed using the EQ-5D-5L health utility index (HUI) and the visual analog scale (VAS). In addition, the EORTC-QLQ-C30 and the EORTC-QLQ-OV28 were used to measure symptoms, function, and health-related QoL. The latter was designed specifically for ovarian cancer patients.

PROs were collected every 8 weeks (± 7 days) for 56 weeks beginning on C1D1, then every 12 weeks (± 7 days) thereafter while the patient was receiving study treatment.

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

Baseline symptoms and quality of life were equivalent between placebo and niraparib patients in the overall population (overall FOSI niraparib mean=25.6 [SD=3.73] versus placebo mean=25.4 [SD=3.51]). Similar results were observed throughout the study with no observed differences in changes from baseline during the treatment period (p>0.05 for each assessment and each treatment arm on each patient outcome with one exception: Cycle 3 of the FOSI [p=0.0447] where placebo had a higher value.

Baseline symptoms and quality of life were also equivalent between placebo and niraparib in patients with HRDpos tumors (FOSI niraparib mean=25.6 [SD=3.64] versus placebo mean=25.3 [SD=3.54]).



Abbreviations: Base=baseline; C=cycle; D=day; EOT=end of treatment; FOSI=Functional Assessment of Cancer Therapy – Ovarian Symptom Index; ITT=intent-to-treat; SE=standard error.

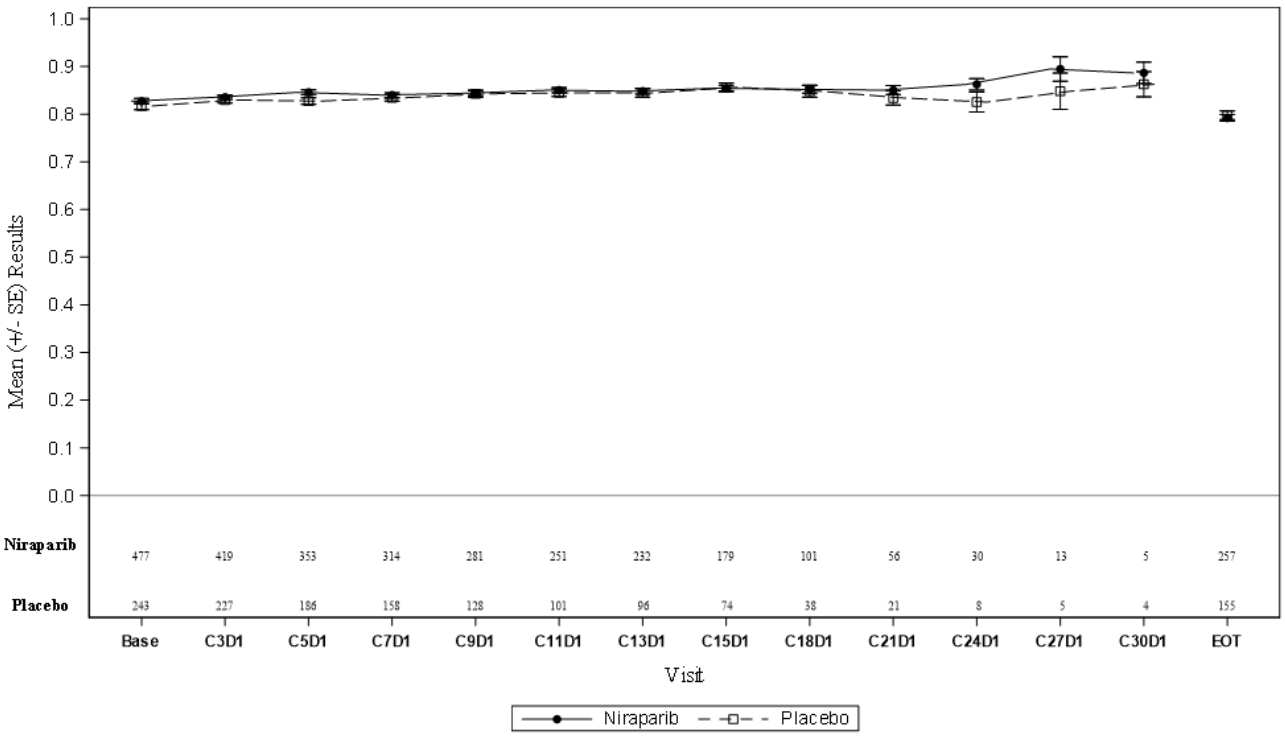
Figure 35. Adjusted means and associated standard error for FOSI by study visit in Overall population (ITT population)

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

Baseline EQ-5D-5L scoring was similar between placebo and niraparib patients in the overall population (health utility index [HUI] niraparib mean=0.827 [SD=0.1229] versus placebo mean=0.817 [SD=0.1245]; visual analog scale [VAS] niraparib mean=75.5 [SD=17.24] versus placebo mean=74.8

[SD=17.10]). Similar results were observed throughout the study in the overall population with no observed differences in changes from baseline during the treatment period (p>0.05 for each assessment and each treatment arm on each patient outcome with 1 exception: Cycle 5 of the HUI [p=0.0234] where niraparib had the higher value).

Baseline EQ-5D-5L scoring was also similar between placebo and niraparib patients with homologous recombination-deficient tumours (HUI niraparib mean=0.832 [SD=0.1207] versus placebo mean=0.818 [SD=0.1303]; VAS niraparib mean=76.5 [SD=17.29] versus placebo mean=75.9 [SD=16.74]).



Abbreviations: Base=baseline; C=cycle; D=day; EOT=end of treatment;EQ-5D-5L=European Quality of Life scale, 5-Dimensions; ITT=intent-to-treat.

Figure 36. Adjusted means and associated standard error for EQ-5D-5L by study visit in Overall population (ITT population)

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC-QLQ-C30 and EORTC-QLQ-OV28)

Baseline global health status/quality of life were equivalent between placebo and niraparib patients in the overall population (overall EORTC-QLQ-C30 niraparib mean=71.5 [SD=18.86] versus placebo mean=70.2 [SD=18.66]). Similar results were observed throughout the study in the Overall population with no consistent observed differences during the treatment period on most assessment (p>0.05 for each assessment at each visit). Exceptions were observed in gastrointestinal related assessments. Constipation, nausea/vomiting and appetite loss were reported as significantly worse in niraparib treated patients. Diarrhea was reported as significantly worse in placebo treated patients. Similar results were observed throughout the study in the homologous recombination deficient population with no consistent observed differences during the treatment period for most assessments.

The QLQ-C30 supplement OV28, designed specifically for ovarian cancer patients, did not indicate any consistent differences in health-related quality of life scores between niraparib- and placebo-treated patients in the overall population or patients with homologous recombination deficient tumours.

Ancillary analyses

Biomarker and subgroup analyses of PFS in the Overall and HRDpos populations

Table 41. Progression-free survival based on BICR assessment based on homologous recombination deficiency status and BRCA subgroup (ITT population)

Population Statistic	Overall	
	Niraparib (N=487)	Placebo (N=246)
HRDpos (homologous recombination deficient)		
*BRCA*mut		
N	152	71
Median PFS (months) (95% CI)[a,b]	22.1 (19.3, NE)	10.9 (8.0, 19.4)
p-value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.40 (0.265, 0.618)	
*BRCA*wt		
N	95	55
Median PFS (months) (95% CI)[a,b]	19.6 (13.6, NE)	8.2 (6.7, 16.8)
p-value[c]	0.0064	
Hazard ratio (95% CI)[d]	0.50 (0.305, 0.831)	
HRDneg (homologous recombination proficient)		
N	169	80
Median PFS (months) (95% CI) [a,b]	8.1 (5.7, 9.4)	5.4 (4.0, 7.3)
p-value[c]	0.0203	
Hazard ratio (95% CI)[d]	0.68 (0.492, 0.944)	
HRD-not determined		
N	71	40
Median PFS (months) (95% CI)[a,b]	11.0 (7.4,13.9)	8.3 (5.7,12.5)
p-value[c]	0.5577	
Hazard ratio (95% CI)[d]	0.85 (0.509, 1.432)	

Abbreviations: BICR=blinded independent central review; *BRCA*=breast cancer gene; *BRCA*wt=*BRCA* wildtype CI=confidence interval; HRD-not determined=homologous recombination deficiency status not determined; HRDneg=homologous recombination deficiency test negative, referring to homologous recombination proficient tumors; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient tumors; ITT=intent-to-treat; NE=not estimated; PFS=progression-free survival.
[a]Progression-free survival was defined as the time in months from the date of randomization to progression or death.
[b]Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[c]Based on stratified log-rank test using randomization stratification factors: administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR).
[d]Based on stratified Cox proportional hazards model using randomization stratification factors as above.

Subgroup: HRDneg population

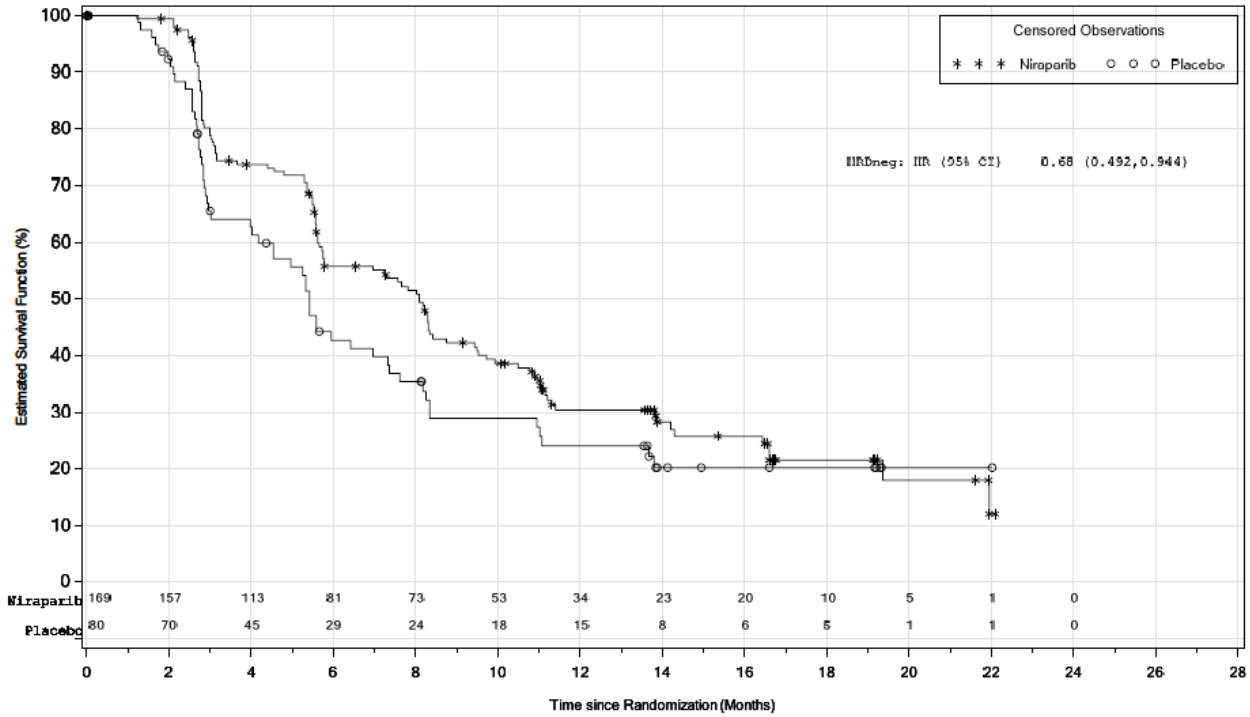
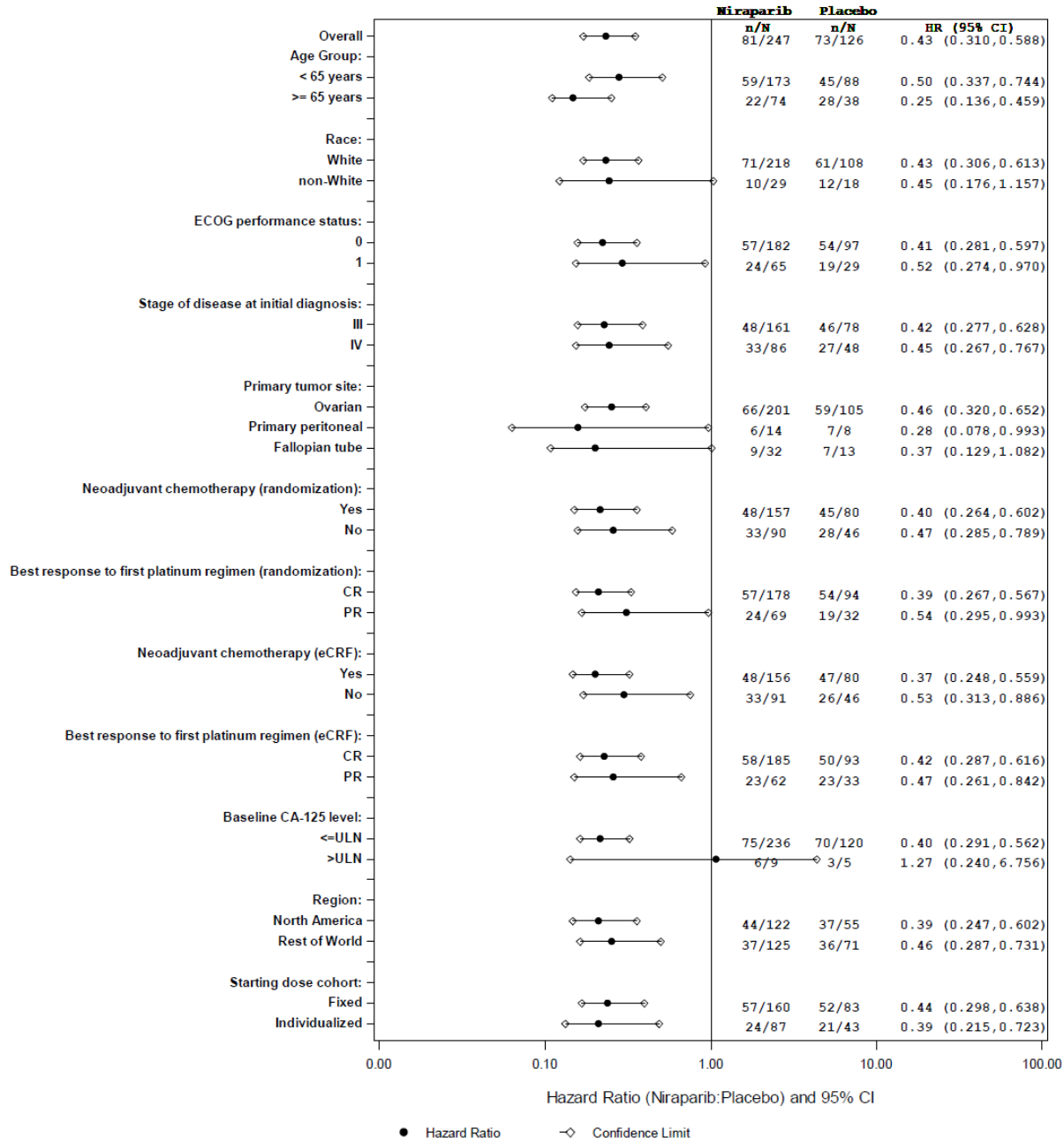


Figure 37. Kaplan-Meier plot of Progression-Free Survival by BICR in HRDneg subgroup (ITT population)

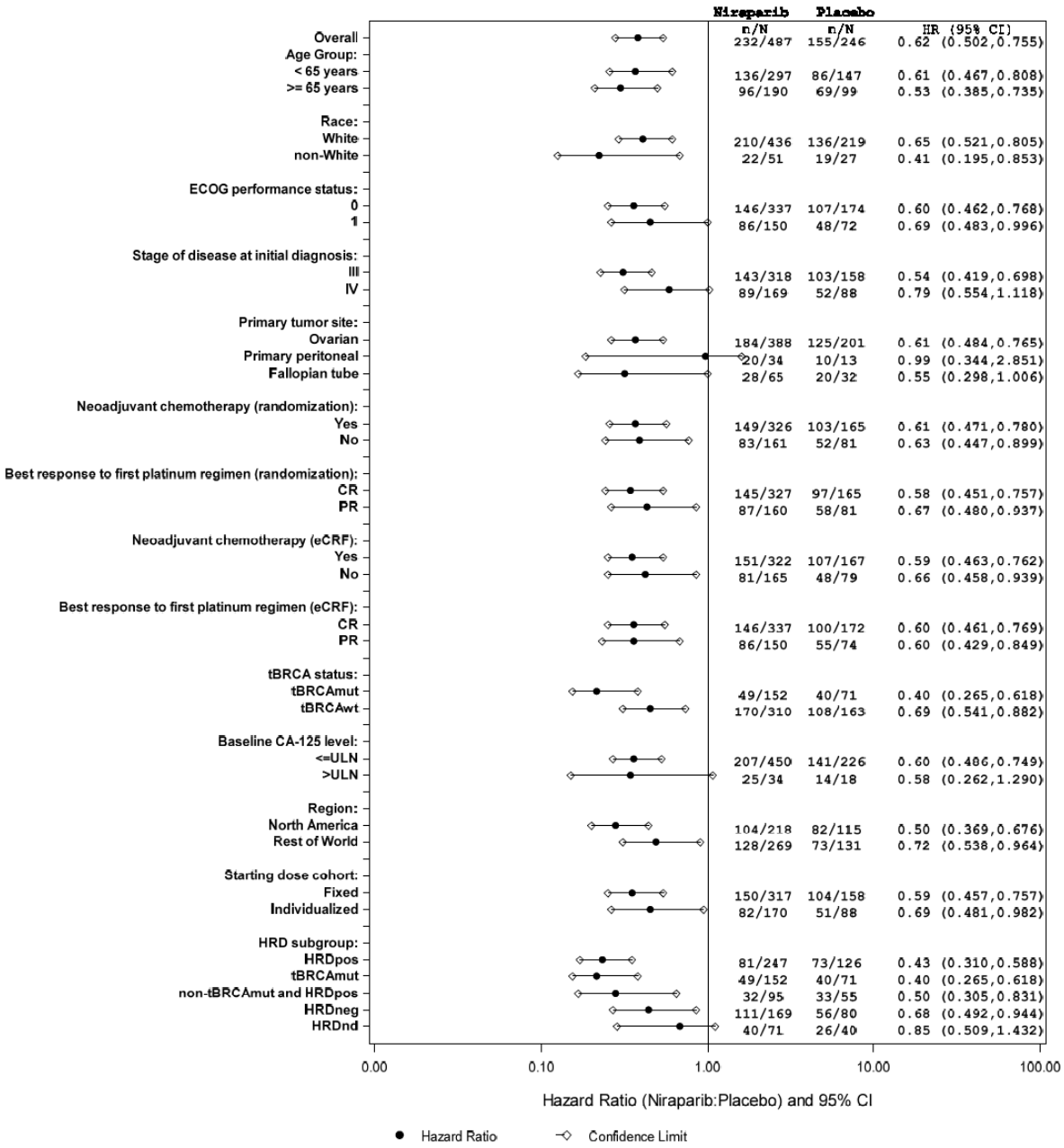
The forest plots below present HRs (95% CI) for PFS (niraparib:placebo) as assessed by BICR for the homologous recombination deficient (HRDpos) and Overall populations.



Source: CSR PR-30-5017-C Figure 14.2.1.9

Abbreviations: CA-125=cancer antigen 125; CI=confidence interval; CR=complete response; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; HR=hazard ratio; ITT=intent-to-treat; PFS=progression-free survival; PR=partial response; ULN=upper limit of normal.

Figure 38. Forest plot of hazard ratios (95% CI) for PFS by subgroup for patients with homologous recombination deficient (HRDpos) tumors (ITT population)



Source: CSR PR-30-5017-C Figure 14.2.1.9

Abbreviations: CA-125=cancer antigen 125; CI=confidence interval; CR=complete response; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; HR=hazard ratio; ITT=intent-to-treat; PFS=progression-free survival; PR=partial response; ULN=upper limit of normal.

Figure 39. Forest plot of hazard ratios (95% CI) for PFS by subgroup in the Overall population (ITT population)

Subgroup analyses by starting dose and baseline body weight and baseline platelet counts

Additional *post-hoc* analyses were presented to characterise the efficacy for each starting dose subgroup by baseline body weight and baseline platelet counts for each of the three populations; Overall population, HRDpos population and HRDneg population, as outlined below:

A. Fixed Starting Dose subgroup (300 mg starting dose) with body weight (BW) ≥ 77kg and platelet count (PC) ≥ 150K/µL

B. Individualised Starting Dose subgroup (300 mg starting dose) with BW ≥ 77kg and PC ≥150K/µL

C. Fixed Starting Dose subgroup (300 mg starting dose) with BW <77kg or PC <150K/µL

D. Individualised Starting Dose subgroup (200 mg starting dose) with BW <77kg or PC <150K/µL

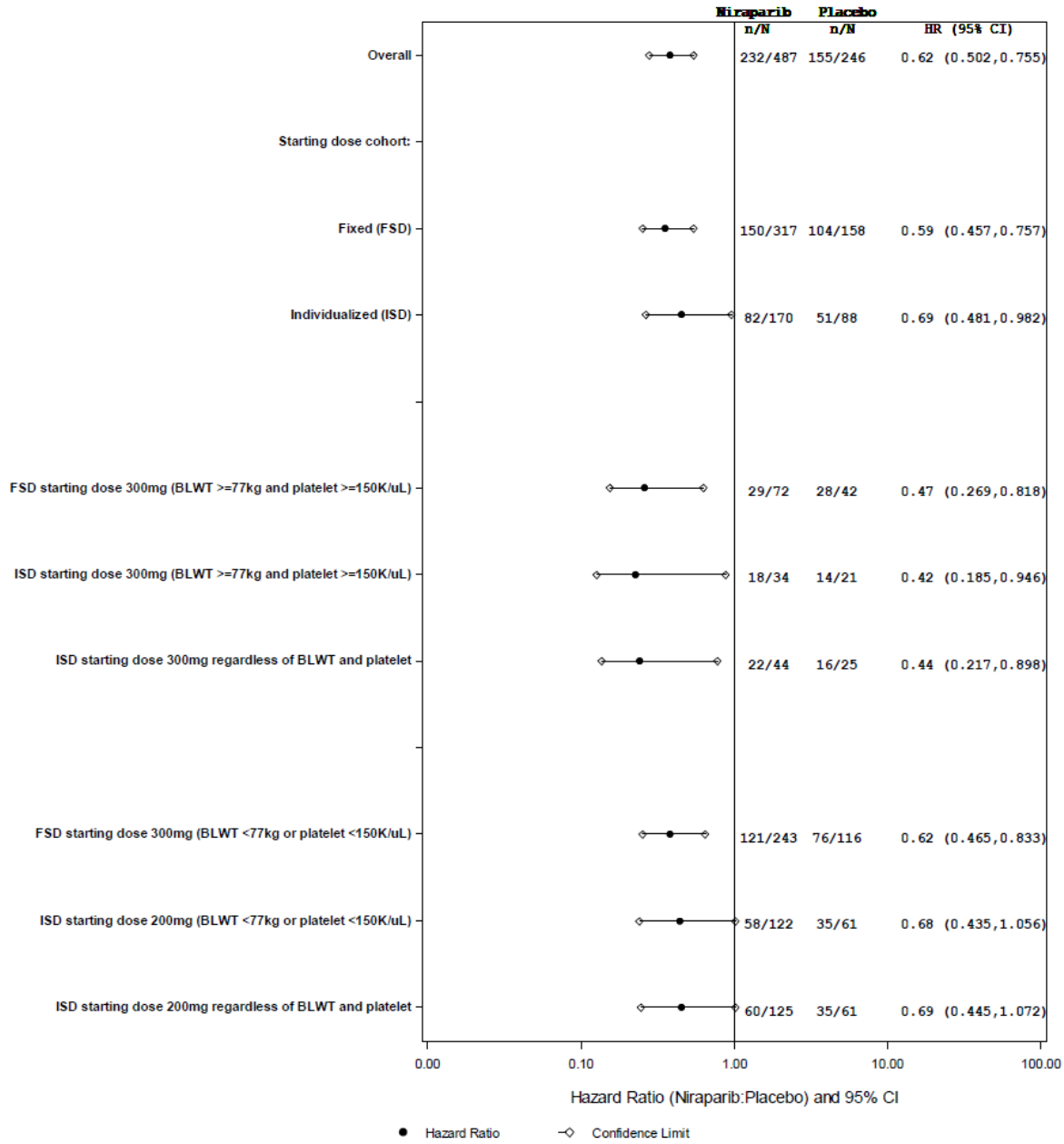
E. Individualised Starting Dose subgroup (300 mg starting dose) for all patients (regardless of their baseline body weight and platelet counts)

F. Individualised Starting Dose subgroup (200 mg starting dose) for all patients (regardless of their baseline body weight and platelet counts)

A proportion of 76% (N=542/711) of the patients had body weight <77kg or platelet counts <150K/µL and 24% (N= 169/711) had body weight ≥77kg or platelet counts ≥150K/µL.

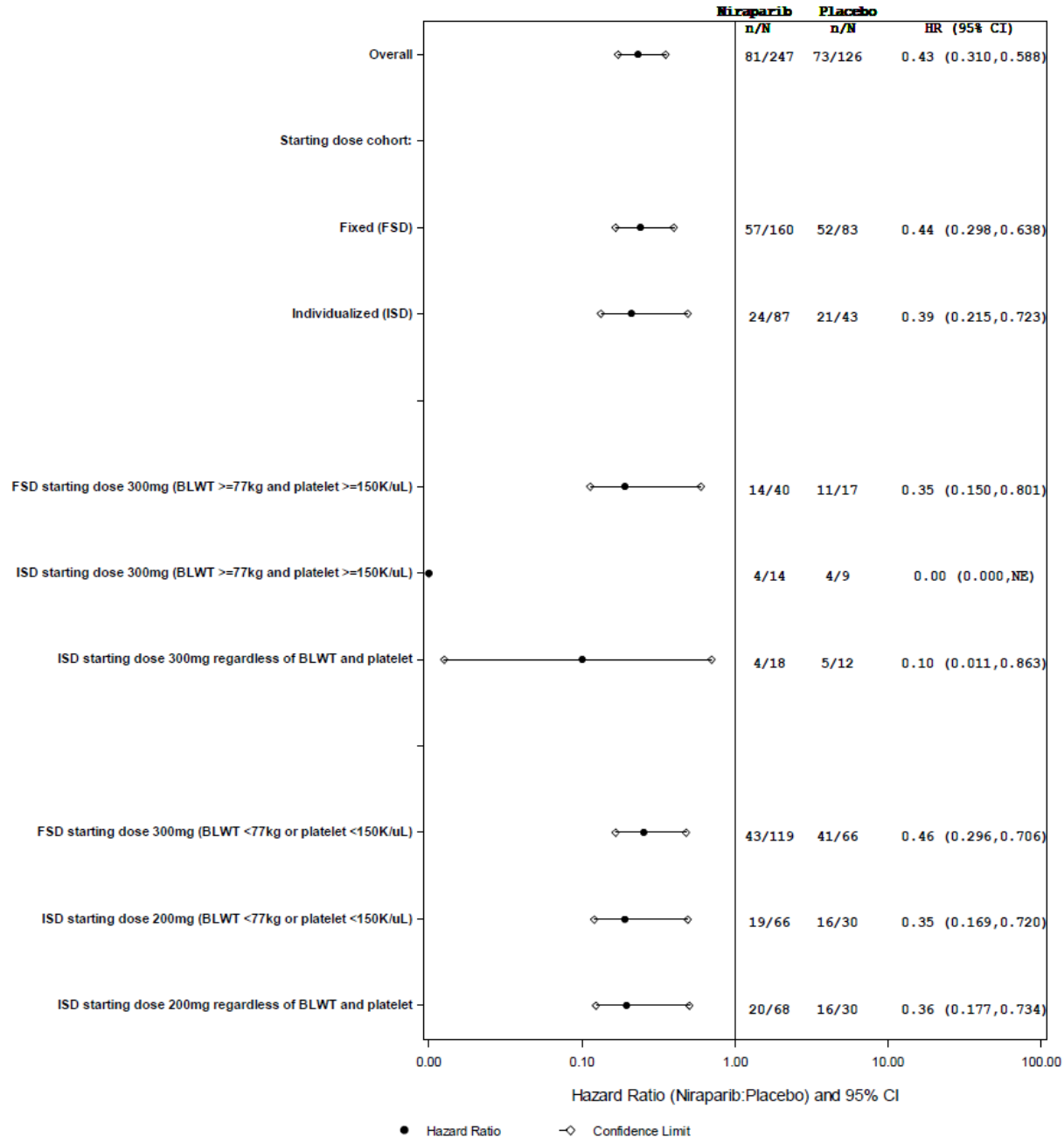
Summaries of patient disposition, demographics, biomarker status and other baseline disease characteristics split by the subgroups A-D generally reflected what was seen in the fixed and individualised starting dose groups (this is displayed for subgroups C and D further below, but not shown for subgroups A-B and E-F).

Efficacy analyses by starting dose and baseline weight/platelet subgroup



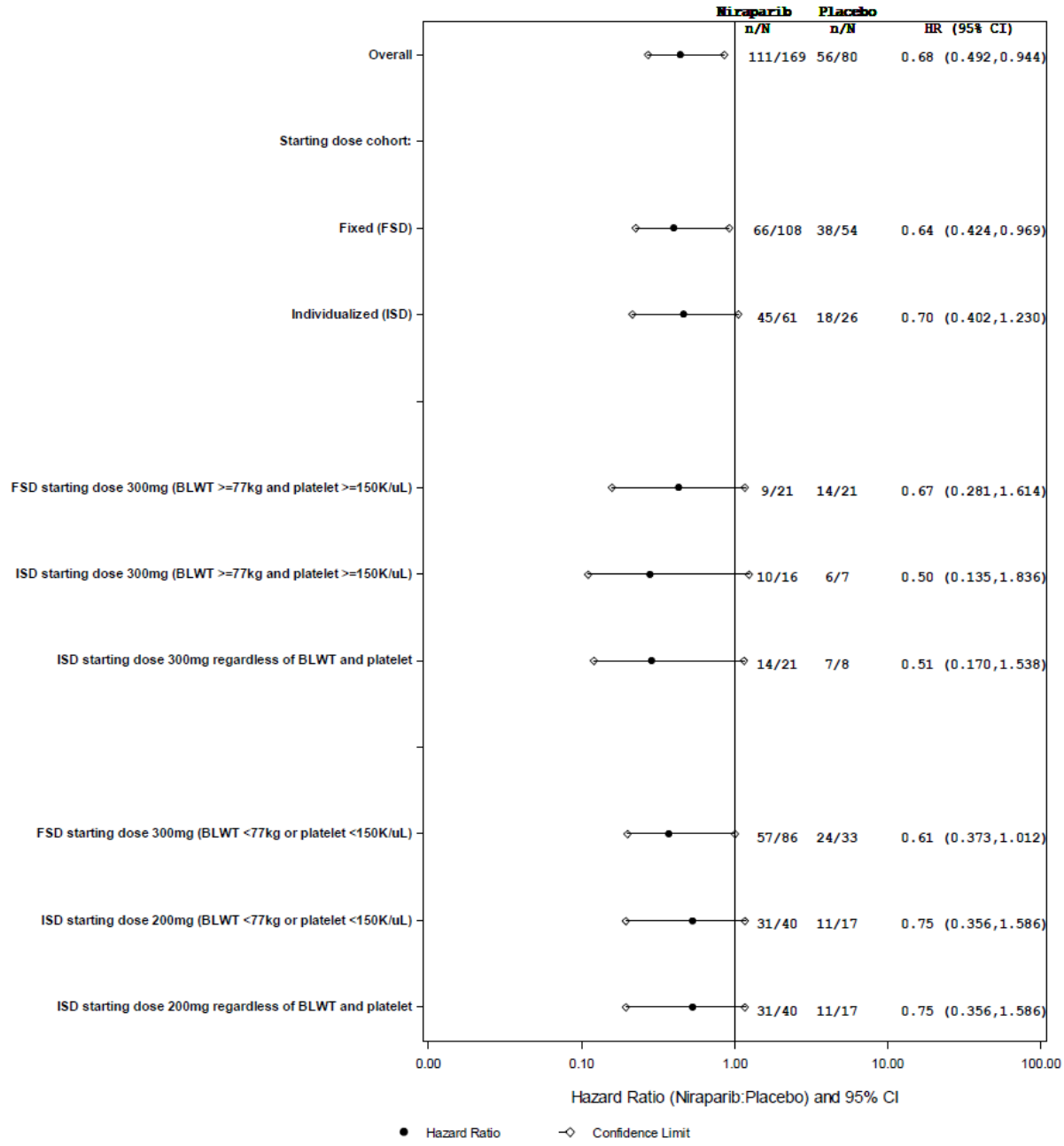
n = number of events, N = number of patients in the subgroup, BLWT = Baseline Weight

Figure 40. PFS Hazard Ratios by Starting Dose and baseline weight/platelet subgroup for the Overall population (ITT population)



n = number of events, N = number of patients in the subgroup, BLWT = Baseline Weight

Figure 41. PFS Hazard Ratios by Starting Dose and baseline weight/platelet subgroup in Homologous Recombination Deficient (HRDpos) population (ITT population)



n = number of events, N = number of patients in the subgroup, BLWT = Baseline Weight

Figure 42. PFS Hazard Ratios by Starting Dose and baseline weight/platelet subgroup in Homologous Recombination Proficient (HRDneg) population (ITT population)

Efficacy of the applied 200 mg dose

In the subgroup C "Fixed Starting Dose subgroup (300 mg starting dose) with BW <77kg or PC <150K/µL" patients received 300 mg although they should have received 200 mg to be in accordance with the MAH's body weight/platelet algorithm.

In the subgroup D "Individualised Starting Dose subgroup (200 mg starting dose) with BW <77kg or PC <150K/µL" the patients received 200 mg in accordance with the algorithm.

Considering the applied dose of 200 mg for all patients (except those patients weighing ⩾ 77 kg and ⩾ 150K/µL), it is therefore of special interest to compare patient demographics and baseline characteristics and efficacy results for the two subgroups C and D.

Table 42. Patient demographics and baseline characteristics by baseline weight and platelet count – Individualised and Fixed Starting Dose Subgroups C and D (ITT population)

	Baseline weight < 77 kg or Platelet < 150,000/µL			
	Fixed 300 (Subgroup C)		**ISD 200 (Subgroup D)**	
	Niraparib n, (%)	**Placebo n, (%)**	**Niraparib n, (%)**	**Placebo n, (%)**
N	243	116	122	61
Age at time of screening (median)	63	63	63	61
Min, Max	34, 88	34, 88	39, 88	33, 82
ECOG PS				
0	175 (72.0)	87 (75.0)	83 (68.0)	42 (68.9)
1	68 (28.0)	29 (25.0)	39 (32.0)	19 (31.1)
Cancer stage (FIGO) at time of diagnosis				
III, not otherwise specified	1 (0.4)	2 (1.7)	3 (2.5)	0 (0.0)
IIIA	3 (1.2)	4 (3.4)	5 (4.1)	5 (8.2)
IIIB	143 (58.8)	67 (57.8)	73 (59.8)	33 (54.1)
IIIC	4 (1.6)	3 (2.6)	2 (1.6)	0 (0.0)
IV	92 (37.9)	40 (34.5)	39 (32.0)	23 (37.7)
Primary tumor site				
Ovarian	189 (77.8)	96 (82.8)	99 (81.1)	48 (78.7)
Primary peritoneal	40 (16.5)	15 (12.9)	12 (9.8)	8 (13.1)
Fallopian tube	14 (5.8)	5 (4.3)	11 (9.0)	5 (8.2)
NACT				
Y	167 (68.7)	88 (75.9)	84 (68.9)	38 (62.3)
N	76 (31.3)	28 (24.1)	38 (31.1)	23 (37.7)
Response after chemotherapy				
CR	178 (73.3)	85 (73.3)	75 (61.5)	39 (63.9)
PR	65 (26.7)	31 (26.7)	47 (38.5)	22 (36.1)
HRD status				
Pos	119 (49.0)	66 (56.9)	66 (54.1)	30 (49.2)
Neg/not determined	124 (51.0)	50 (43.1)	56 (45.9)	31 (50.8)

Abbreviations: FIGO= International Federation of Gynecology and Obstetrics; HRDpos= homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat

Efficacy results of subgroups C and D:

Overall population

Table 43. Progression-Free Survival by BICR for patients of baseline weight <77 kg or baseline platelet count <150K/µL starting dose on 300mg in the Fixed Starting Dose Subgroup of the Overall population (SAF population)

Parameter	Statistic	Niraparib (N=243)	Placebo (N=116)
Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	NE (21.9,NE)	NE (16.6,NE)
	Median (95% CI)	14.2 (11.2,19.4)	8.2 (5.9,10.4)
	25th Percentile (95% CI)	5.7 (5.5,8.1)	3.9 (2.8,5.4)
Survival Distribution Function (SDF) [3]	SDF (95% CI)		
6-month		0.74 (0.68,0.79)	0.59 (0.49,0.67)
12-month		0.55 (0.48,0.61)	0.37 (0.28,0.46)
18-month		0.44 (0.37,0.51)	0.29 (0.20,0.38)
24-month		0.31 (0.22,0.41)	0.25 (0.16,0.36)
30-month		0.31 (0.22,0.41)	0.25 (0.16,0.36)
Censored Observations	n (%)	122 (50.2)	40 (34.5)
Event Rate, Overall	n (%)	121 (49.8)	76 (65.5)
Death	n (%)	0	1 (0.9)
Progression	n (%)	121 (49.8)	75 (64.7)
p-value [4]		0.0013	
Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	0.62 (0.465,0.833)	

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 1.2.5.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR), and HRD status (HRDpos or HRDneg/HRDnd).
[5] Based on stratified Cox proportional hazards model using randomization stratification factors as above.
Note: NE = Not Evaluable.

Table 44. Progression-Free Survival by BICR for patients of baseline weight <77 kg or baseline platelet count <150K/µL starting dose on 200mg in the Individualised Starting Dose Subgroup of the Overall population (SAF population)

Parameter	Statistic	Niraparib (N=122)	Placebo (N=61)
Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	14.0 (13.9,NE)	NE (11.0,NE)
	Median (95% CI)	11.4 (9.7,14.0)	8.3 (6.1,11.1)
	25th Percentile (95% CI)	5.6 (3.0,7.2)	5.4 (3.1,6.1)
Survival Distribution Function (SDF) [3]	SDF (95% CI)		
6-month		0.70 (0.60,0.77)	0.66 (0.52,0.77)
12-month		0.46 (0.35,0.56)	0.31 (0.18,0.45)
18-month		0.11 (0.01,0.36)	0.31 (0.18,0.45)
24-month		0.11 (0.01,0.36)	0.31 (0.18,0.45)
30-month		0.11 (0.01,0.36)	0.31 (0.18,0.45)
Censored Observations	n (%)	64 (52.5)	26 (42.6)
Event Rate, Overall	n (%)	58 (47.5)	35 (57.4)
Death	n (%)	0	0
Progression	n (%)	58 (47.5)	35 (57.4)
p-value [4]		0.0858	
Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	0.68 (0.435,1.056)	

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 1.2.5.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR), and HRD status (HRDpos or HRDneg/HRDnd).
[5] Based on stratified Cox proportional hazards model using randomization stratification factors as above.

HRDpos population

Table 45. Progression-Free Survival by BICR for patients of baseline weight <77 kg or baseline platelet count <150K/µL starting dose on 300mg in the Fixed Starting Dose Subgroup of the HRDpos population (SAF population)

Parameter	Statistic	Niraparib (N=119)	Placebo (N=66)
Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	NE (NE,NE)	NE (16.7,NE)
	Median (95% CI)	22.1 (16.6,NE)	8.2 (6.7,16.7)
	25th Percentile (95% CI)	11.0 (6.9,13.8)	5.4 (2.8,5.7)
Survival Distribution Function (SDF) [3]	SDF (95% CI)		
6-month		0.84 (0.75,0.89)	0.64 (0.51,0.74)
12-month		0.72 (0.62,0.79)	0.40 (0.28,0.52)
18-month		0.61 (0.50,0.70)	0.33 (0.21,0.46)
24-month		0.46 (0.31,0.60)	0.28 (0.16,0.42)
30-month		0.46 (0.31,0.60)	0.28 (0.16,0.42)
Censored Observations	n (%)	76 (63.9)	25 (37.9)
Event Rate, Overall	n (%)	43 (36.1)	41 (62.1)
Death	n (%)	0	0
Progression	n (%)	43 (36.1)	41 (62.1)
p-value [4]		0.0003	
Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	0.46 (0.296,0.706)	

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 1.2.5.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), and best response to platinum therapy (CR or PR).
[5] Based on stratified Cox proportional hazards model using randomization stratification factors as above.
Note: NE = Not Evaluable.

Table 46. Progression-Free Survival by BICR for patients of baseline weight <77 kg or baseline platelet count <150K/µL starting dose on 200mg in the Individualised Starting Dose Subgroup of the HRDpos population (SAF population)

Parameter	Statistic	Niraparib (N=66)	Placebo (N=30)
Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	14.8 (14.0,NE)	NE (11.1,NE)
	Median (95% CI)	14.0 (11.9,NE)	10.9 (8.0,NE)
	25th Percentile (95% CI)	11.2 (5.8,14.0)	5.9 (3.1,10.4)
Survival Distribution Function (SDF) [3]	SDF (95% CI)		
6-month		0.86 (0.74,0.93)	0.75 (0.55,0.87)
12-month		0.66 (0.48,0.78)	0.37 (0.18,0.56)
18-month		0.21 (0.01,0.57)	0.37 (0.18,0.56)
24-month		0.21 (0.01,0.57)	0.37 (0.18,0.56)
30-month		0.21 (0.01,0.57)	0.37 (0.18,0.56)
Censored Observations	n (%)	47 (71.2)	14 (46.7)
Event Rate, Overall	n (%)	19 (28.8)	16 (53.3)
Death	n (%)	0	0
Progression	n (%)	19 (28.8)	16 (53.3)
p-value [4]		0.0030	
Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	0.35 (0.169,0.720)	

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 1.2.5.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), and best response to platinum therapy (CR or PR).
[5] Based on stratified Cox proportional hazards model using randomization stratification factors as above.
Note: NE = Not Evaluable.

HRDneg population

Table 47. Progression-Free Survival by BICR for patients of baseline weight <77 kg or baseline platelet count <150K/µL starting dose on 300mg in the Fixed Starting Dose Subgroup of the HRDneg population (SAF population)

Parameter	Statistic	Niraparib (N=86)	Placebo (N=33)
Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	16.6 (11.3,NE)	11.1 (5.9,NE)
	Median (95% CI)	8.3 (5.8,11.1)	4.5 (2.8,7.4)
	25th Percentile (95% CI)	5.4 (3.0,5.7)	2.7 (2.4,2.9)
Survival Distribution Function (SDF) [3]	SDF (95% CI)		
6-month		0.62 (0.50,0.71)	0.39 (0.22,0.56)
12-month		0.35 (0.25,0.46)	0.25 (0.11,0.41)
18-month		0.25 (0.15,0.36)	0.21 (0.08,0.37)
24-month		0.14 (0.04,0.30)	0.21 (0.08,0.37)
30-month		0.14 (0.04,0.30)	0.21 (0.08,0.37)
Censored Observations	n (%)	29 (33.7)	9 (27.3)
Event Rate, Overall	n (%)	57 (66.3)	24 (72.7)
Death	n (%)	0	0
Progression	n (%)	57 (66.3)	24 (72.7)
p-value [4]		0.0531	
Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	0.61 (0.373,1.012)	

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 1.2.5.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), and best response to platinum therapy (CR or PR).
[5] Based on stratified Cox proportional hazards model using randomization stratification factors as above.
Note: NE = Not Evaluable.

Table 48. Progression-Free Survival by BICR for patients of baseline weight <77 kg or baseline platelet count <150K µL starting dose on 200mg in the Individualised Starting Dose Subgroup of the HRDneg population (SAF population)

Parameter	Statistic	Niraparib (N=40)	Placebo (N=17)
Progression-free Survival (months) [1] [2]	75th Percentile (95% CI)	10.5 (7.2,NE)	8.3 (5.4,NE)
	Median (95% CI)	5.5 (2.9,8.2)	5.4 (2.7,8.3)
	25th Percentile (95% CI)	2.8 (2.6,3.0)	2.7 (1.6,5.4)
Survival Distribution Function (SDF) [3]	SDF (95% CI)		
6-month		0.44 (0.29,0.59)	0.44 (0.19,0.67)
12-month		0.17 (0.06,0.32)	0.12 (0.01,0.40)
18-month		0.17 (0.06,0.32)	0.12 (0.01,0.40)
24-month		0.17 (0.06,0.32)	0.12 (0.01,0.40)
30-month		0.17 (0.06,0.32)	0.12 (0.01,0.40)
Censored Observations	n (%)	9 (22.5)	6 (35.3)
Event Rate, Overall	n (%)	31 (77.5)	11 (64.7)
Death	n (%)	0	0
Progression	n (%)	31 (77.5)	11 (64.7)
p-value [4]		0.4761	
Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	0.75 (0.356,1.586)	

[1] Progression-free Survival is defined as the time in months from the date of randomization to progression or death. See section 1.2.5.1 of the statistical analysis plan for censoring conventions.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), and best response to platinum therapy (CR or PR).
[5] Based on stratified Cox proportional hazards model using randomization stratification factors as above.
Note: NE = Not Evaluable.
Source: Listing 16.2.6.2

Updated 6 months data based on data cut-off date 17 November 2019 (only PFS data as assessed by Investigator are available):

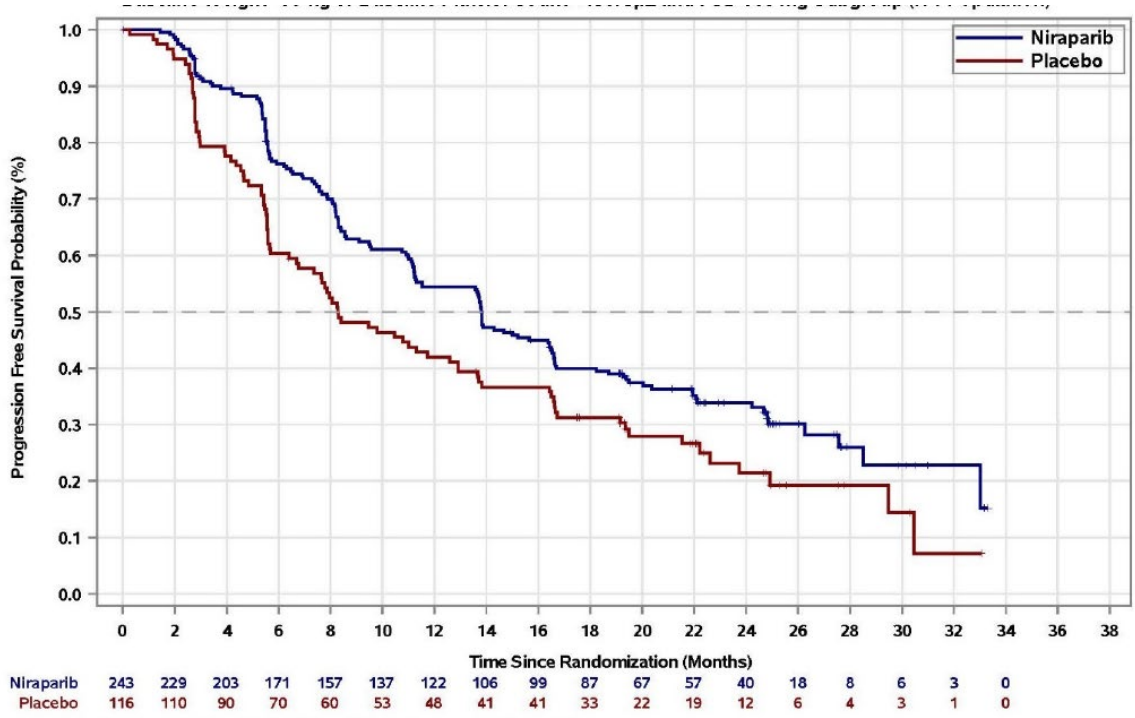
Table 49. Investigator-assessed PFS for low W/P population

HR (95% CI) mPFS (NIR vs PBO months)	Overall		HRd		HRp	
	Original Data Cut	Updated Data Cut	Original Data Cut	Updated Data Cut	Original Data Cut	Updated Data Cut
Group C FSD 300 mg (n=359)	0.68 (0.52, 0.90) 13.8, 8.3	0.69 (0.53, 0.91) 13.8, 8.3	0.54 (0.36, 0.81) 20.4, 10.4	0.52 (0.36, 0.77) 21.9, 10.4	0.60 (0.37, 0.99) 10.9, 5.3	0.65 (0.41, 1.03) 10.9, 5.3
Group D ISD 200 mg (n=183)[1]	0.67 (0.44, 1.04) 11.9, 8.4	0.67 (0.45, 1.00) 12.5, 8.4	0.48 (0.24, 0.96) 14.0, 12.7	0.53 (0.29, 0.98) 19.4, 13.4	0.46 (0.24, 0.91) 5.5, 5.4	0.43 (0.22, 0.83) 5.5, 5.4

Source: IR Table T_14_sNDA, T_14_sNDA6m, T_15_sNDA, T_15_sNDA6m, T_18_sNDA, T_18_sNDA6m, T_19_sNDA, T_19_sNDA6m, T_22_sNDA, T_22_sNDA6m, T_23_sNDA, T_23_sNDA6m.
Abbreviations: CI=confidence interval; FSD=fixed starting dose; HRd=homologous recombination-deficient; HRp=homologous recombination-proficient; ISD=individualized starting dose; Low W/P=low baseline weight and platelet counts; mPFS=median PFS; PFS=progression-free survival.
[1] There were 14 patients with Low W/P in the ISD who started with 300 mg; these patients are excluded from Group D.

Updated 6 months data: Kaplan-Meier plots for the Overall, HRDpos and HRDneg patient populations are shown below for the two dosing subgroups C and D (only PFS data as assessed by the Investigator is available):

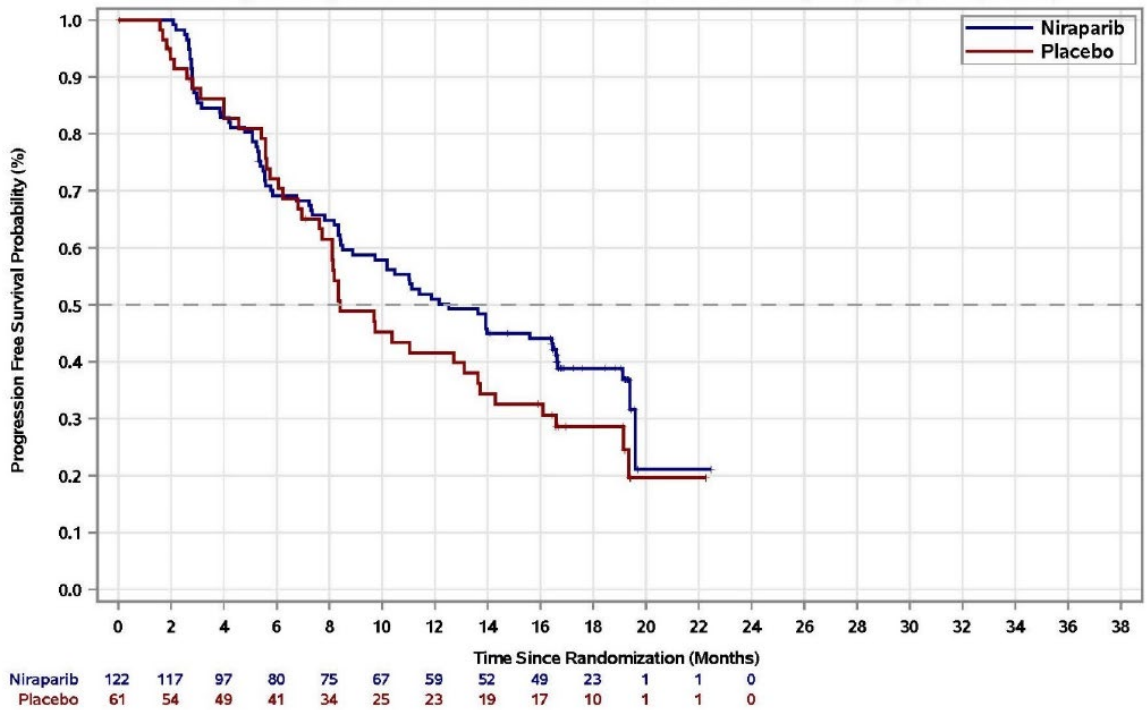
Subgroup C (300 mg) - Overall population



Source: Figure 2.14 (data cut date: 17 Nov 2019)

Figure 43. Progression free survival by Investigator assessment – Low W/P, Fixed starting dose subgroup (Subgroup C, ITT population)

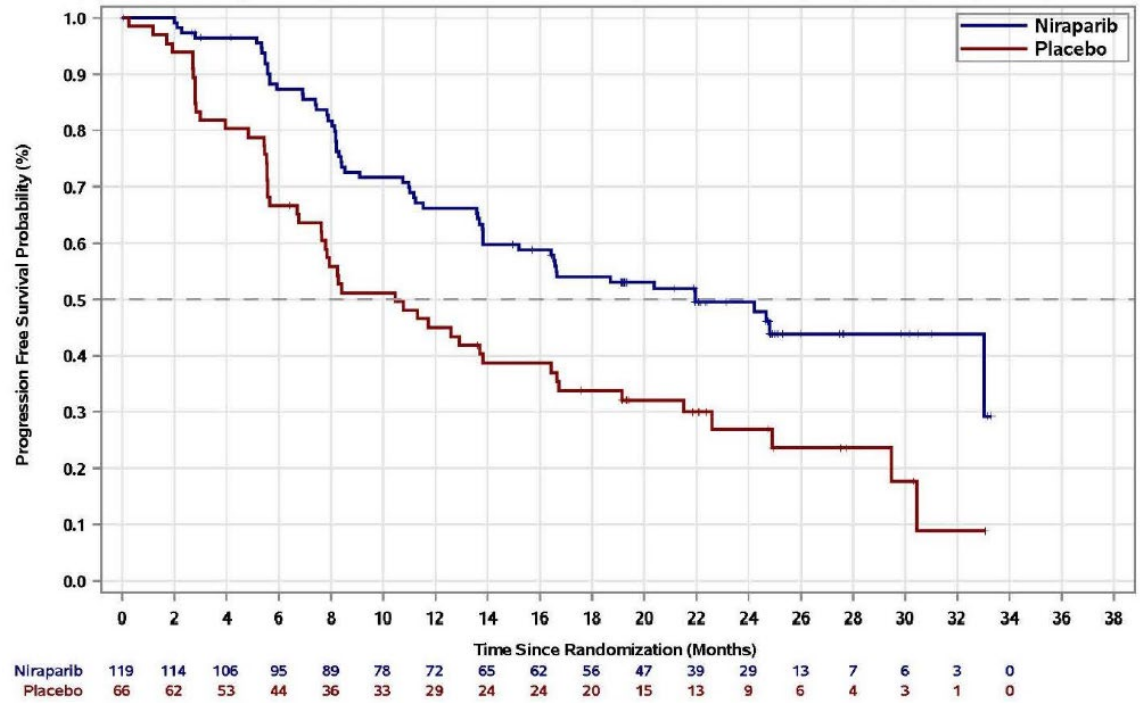
Subgroup D (200 mg) – Overall population



Source: Figure 2.15 (data cut date: 17 Nov 2019)

Figure 44. Progression free survival by Investigator assessment – Low W/P, Individualised starting dose subgroup (Subgroup D, ITT population)

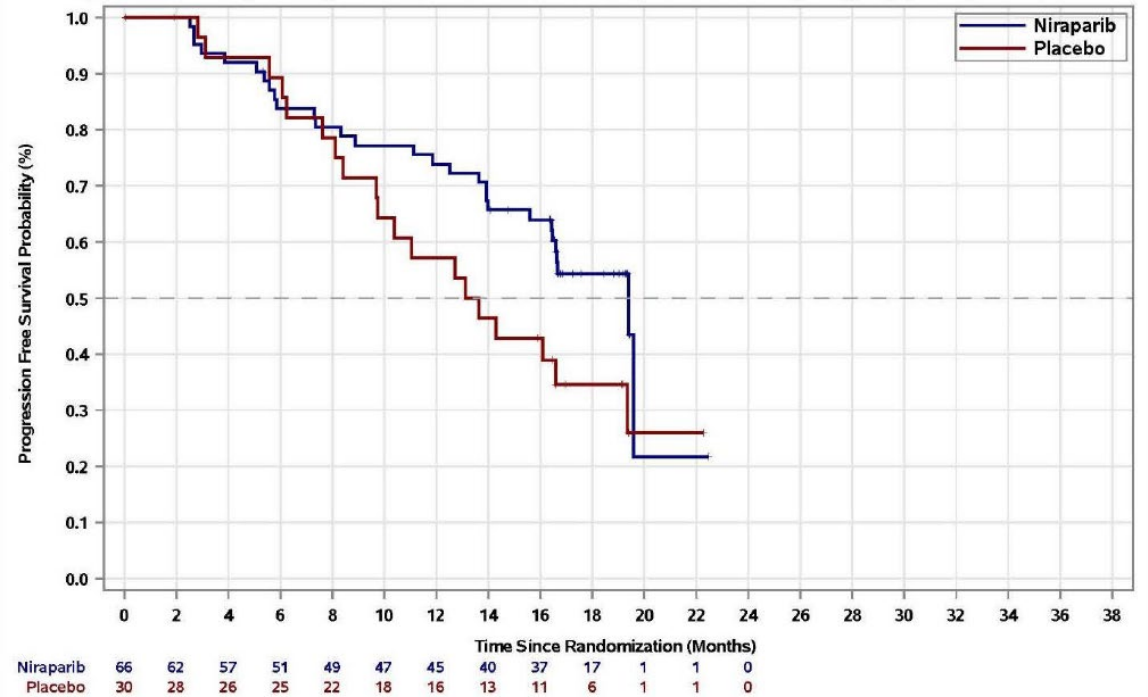
Subgroup C (300 mg) – HRDpos population



Source: Figure 2.16 (data cut date: 17 Nov 2019)

Figure 45. Progression free survival by Investigator assessment in HRDpos patient population – Low W/P, Fixed starting dose subgroup (Subgroup C)

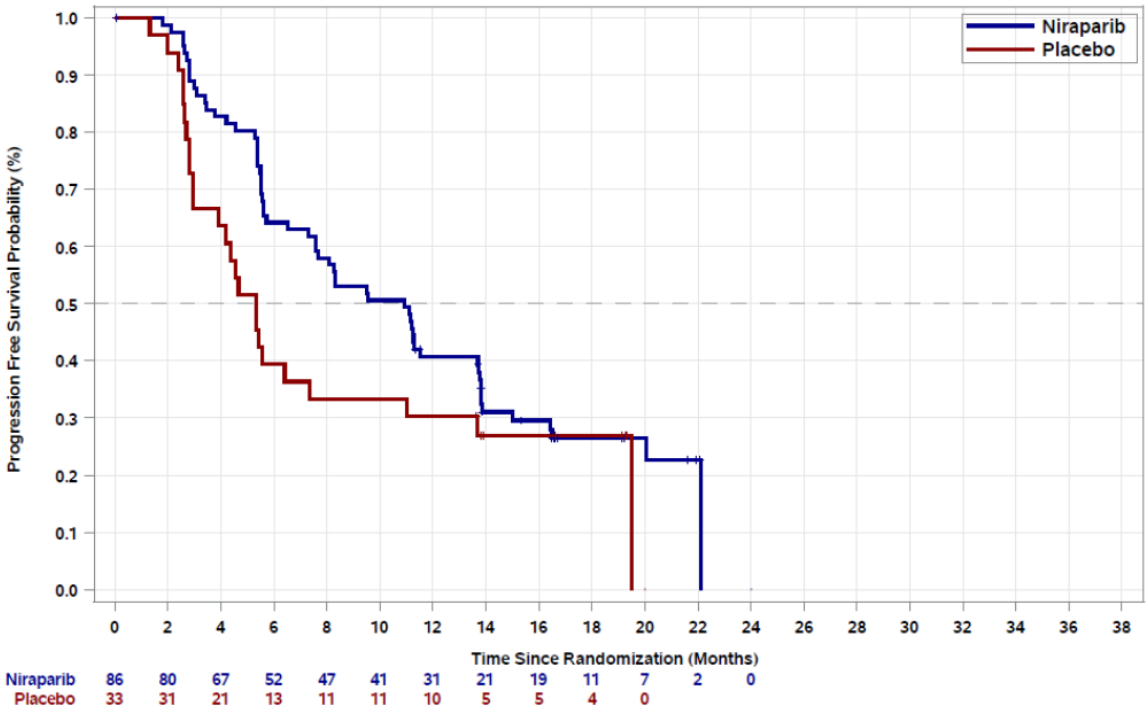
Subgroup D (200 mg) – HRDpos population



Source: Figure 2.18 (data cut date: 17 Nov 2019)

Figure 46. Progression free survival by Investigator assessment in HRDpos patient population – Low W/P, Individualised starting dose subgroup (Subgroup D)

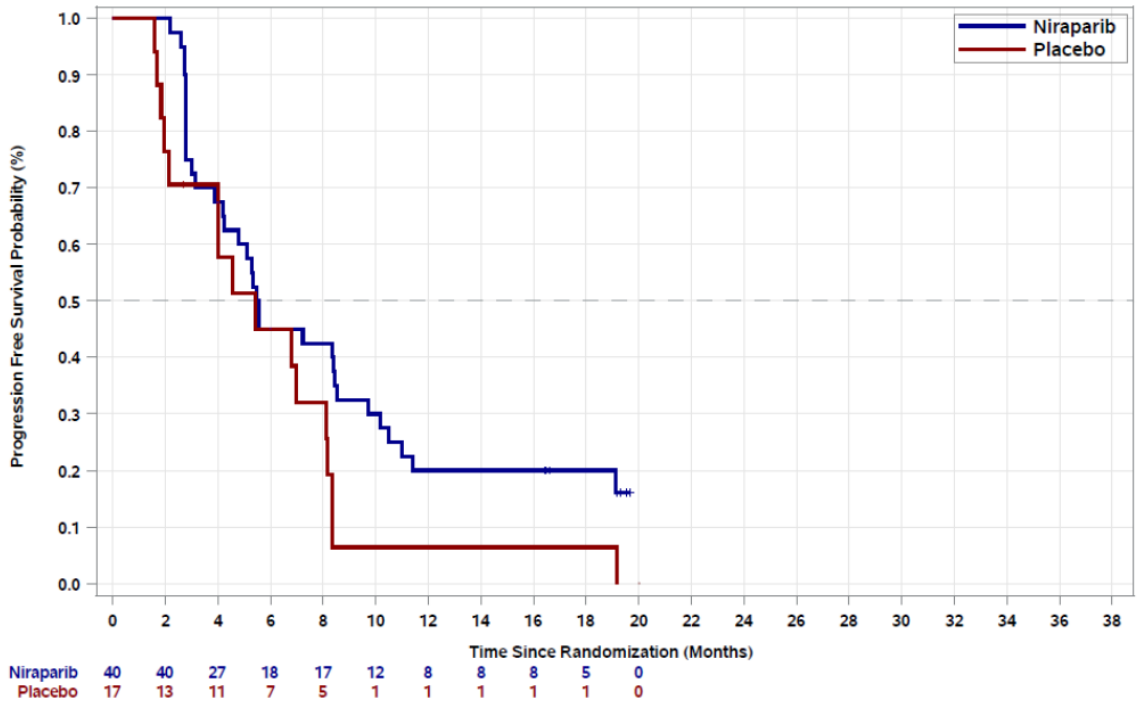
Subgroup C (300 mg) – HRDneg population



Source: Figure 2.17 (data cut date: 17 Nov 2019)

Figure 47. Progression free survival by investigator assessment in HRDneg patient population - low W/P, Fixed starting dose subgroup (Subgroup C)

Subgroup D (200 mg) – HRDneg population



Source: Figure 2.19 (data cut date: 17 Nov 2019)

Figure 48. Progression free survival by investigator assessment in HRDneg patient population - low W/P, Individualised starting dose subgroup (Subgroup D)

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 50. Summary of efficacy for trial PR-30-5017-C (PRIMA)

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy		
Study identifier	PR-30-5017-C	
Design	Randomized, double-blinded Phase III	
	Duration of main phase:	Approximately 3 years
Hypothesis	Superiority; Placebo as surrogate for "watch and wait" in clinical practice; The primary objective of this study was to evaluate the efficacy of niraparib versus placebo as maintenance treatment, measured by progression-free survival (PFS), in patients with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) with a complete response (CR) or partial response (PR) following front-line platinum-based chemotherapy treatment.	
Treatments groups	Niraparib	Niraparib 300 mg (or 200 mg)*; maintenance treatment until progression or adverse event not allowing further dose reduction or other , randomized 487 * Per Protocol Amendment 2, the starting dose of study treatment was either 300 mg or 200 mg based upon the subject's baseline body weight and/or baseline platelet count; subjects with a baseline body weight <77 kg or baseline platelet count <150,000/µL were dosed at 200 mg.
	Placebo	Placebo; maintenance treatment until progression or adverse event not allowing further dose reduction or other, randomized 246

Endpoints and definitions	Primary endpoint – Progression-free survival	PFS	The time from treatment randomization to the earlier date of assessment of progression (by blinded central review) or death by any cause in the absence of progression.
	Secondary – Overall Survival	OS	The time from randomization to the date of death by any cause.
	Secondary- time to first subsequent therapy (TFST)	TFST	The time from the date of randomization to the date of the first subsequent anticancer therapy or death.
	Secondary- time to progression on the next anticancer therapy (PFS2)	PFS2	The time from the date of randomization to the date of disease progression on the next anti-cancer therapy following study treatment or death due to any cause.
	Secondary- Patient-reported outcomes (PROs)	PROs	Quality of Life assessed with tools: FOSI, EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28
	Secondary -- Safety		Safety parameters evaluated included the following: TEAEs, clinical laboratory results (hematology, chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications.
Database lock	17 May 2019 (data cut-off date) , DB lock July 3rd 2019		

Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Hierarchical testing in homologous recombination deficient (HRDpos), then Overall ITT population for PFS. OS tested only when statistical significance was shown for PFS in both populations.				
Efficacy statistics-Primary endpoint PFS		Niraparib HRDpos N=247	Placebo HRDpos N=126	Niraparib Overall N=487	Placebo Overall N=246
	PFS (months)[a,b] Median (95% CI)	21.9 (19.3, NE)	10.4 (8.1,12.1)	13.8 (11.5,14.9)	8.2 (7.3,8.5)
	Survival distribution function (95% CI)[c]				
	6-month	0.86 (0.81,0.90)	0.68 (0.59,0.76)	0.73 (0.69,0.77)	0.60 (0.53,0.66)
	12-month	0.72 (0.65,0.77)	0.42 (0.33,0.51)	0.53 (0.48,0.58)	0.35 (0.29,0.42)
	18-month	0.59 (0.50,0.66)	0.35 (0.25,0.45)	0.42 (0.36,0.47)	0.28 (0.21,0.35)
	24-month	0.47 (0.36,0.58)	0.26 (0.14,0.39)	0.32 (0.25,0.39)	0.23 (0.14,0.32)
	30-month	0.47 (0.36,0.58)	0.26 (0.14,0.39)	0.32 (0.25,0.39)	0.23 (0.14,0.32)
	Censored observations, n (%)	166 (67.2)	53 (42.1)	255 (52.4)	91 (37.0)
	Event rate, n (%)	81 (32.8)	73 (57.9)	232 (47.6)	155 (63.0)
	p-value[d]	<0.0001		<0.0001	
	Hazard ratio (95% CI)[e]	0.43 (0.310,0.588)		0.62 (0.502,0.755)	
	Source: Table 14.2.1.1 and Table 14.2.1.2 Abbreviations: BICR=blinded independent central review; CI=confidence interval; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; NE=not estimable; PFS=progression free survival. [a] Progression-free survival is defined as the time in months from the date of randomization to progression or death. [b] Confidence intervals from Brookmeyer and Crowley method with log-log transformation. [c] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation. [d] Based on stratified log-rank test using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy and homologous recombination deficiency test status (for overall population only). [e] Based on stratified Cox proportional hazards model using randomization stratification factors.				
Efficacy Statistics-Secondary endpoint OS [interim analysis due data immature; 11% data maturity]		Niraparib HRDpos N=247	Placebo HRDpos N=126	Niraparib Overall N=487	Placebo Overall N=246
	Time to Death (months)[a,b] Median (95% CI)	30.3 (30.3, NE)	NE (25.0, NE)	30.3 (30.3, NE)	NE (25.0, NE)
	Censored observations, n (%)	231 (93.5)	116 (92.1)	439 (90.1)	215 (87.4)
	Event rate, n (%)	16 (6.5)	10 (7.9)	48 (9.9)	31 (12.6)
	p-value[c]	0.2323		0.1238	

	Hazard ratio (95% CI)[d]	0.61 (0.265,1.388)	0.70 (0.442,1.106)
	Source: Table 14.2.2.1 and Table 14.2.2.4 Abbreviations: CI=confidence interval; HRDneg=homologous recombination deficiency test negative; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; NE=not estimable. [a] Time to Death is defined as the date of randomization to the date of death by any cause. Subjects known to be alive were censored at the last known follow-up date. [b] Confidence intervals from Brookmeyer and Crowley method with log-log transformation. [c] Based on stratified log-rank test using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy, and homologous recombination deficiency test result status (for overall population only). [d] Based on stratified Cox proportional hazards model using randomization stratification factors.		

Efficacy Statistics-Secondary endpoint TFST [interim analysis due data immature; 47% data maturity]		Niraparib HRDpos N=247	Placebo HRDpos N=126	Niraparib Overall N=487	Placebo Overall N=246
	TFST (months)[a,b] Median (95% CI)	NE (24.7, NE)	13.7 (11.6,19.3)	18.6 (15.8,24.7)	12.0 (10.3,13.9)
	Censored observations, n (%)	171 (69.2)	60 (47.6)	277 (56.9)	108 (43.9)
	Event rate, n (%)	76 (30.8)	66 (52.4)	210 (43.1)	138 (56.1)
	p-value[c]	<0.0001		0.0001	
	Hazard ratio (95% CI)[d]	0.46 (0.330, 0.640)		0.65 (0.521,0.802)	
	Source: Table 14.2.4.1 Abbreviations: CI=confidence interval; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; NE=not estimable; TFST=time to first subsequent therapy. [a] Time to first subsequent therapy is defined as the time from the date of randomization to the date of first dose of follow-up anti-cancer treatment or death, whichever occurs first. Subjects alive and not starting a first follow-up anti-cancer treatment will be censored at the date last known alive. [b] Confidence intervals from Brookmeyer and Crowley method with log-log transformation. [c] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR), and homologous recombination deficiency test status (for Overall cohort only). [d] Based on stratified Cox proportional hazards model using randomization stratification factors as above.				

Efficacy Statistics-Secondary endpoint PFS-2 [interim analysis due data immature; 20% data maturity]		Niraparib HRDpos N=247	Placebo HRDpos N=126	Niraparib Overall N=487	Placebo Overall N=246
	PFS-2 (months)[a,b] Median (95% CI)	NE (25.3, NE)	NE (NE, NE)	27.2 (25.3, NE)	NE (NE, NE)
	Censored observations, n (%)	210 (85.0)	106 (84.1)	395 (81.1)	193 (78.5)
	Event rate, n (%)	37 (15.0)	20 (15.9)	92 (18.9)	53 (21.5)
	p-value[c]	0.5311		0.2242	
	Hazard ratio (95% CI)[d]	0.84 (0.485,1.453)		0.81 (0.577,1.139)	
	Source: Table 14.2.3.1 Abbreviations: CI=confidence interval; CR=complete response; HRDpos=homologous recombination deficiency test positive, referring to homologous recombination deficient (HR-deficient) tumors; ITT=intent-to-treat; NE=not estimable; PFS2=progression-free survival-2; PR=partial response. [a] Progression-free survival 2 is defined as date of randomization to the earlier date of assessment of progression on the next anti-cancer therapy following study treatment or death by any cause. [b] Confidence intervals from Brookmeyer and Crowley method with log-log transformation. [c] Based on stratified log-rank test using randomization stratification factors: Administration of neoadjuvant chemotherapy (yes/no), best response to platinum therapy (CR or PR), and homologous recombination deficiency test status (for Overall cohort only). [d] Based on stratified Cox proportional hazards model using randomization stratification factors as above.				

Analysis performed across trials (pooled analyses and meta-analysis)

No such analyses have been carried out.

Clinical studies in special populations

No specific studies are carried out.

Supportive study(ies)

No supportive efficacy studies are carried out.

2.4.3. Discussion on clinical efficacy

Zejula (niraparib) is currently approved 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. This approval was mainly based on data from the Phase 3 NOVA clinical trial.

The MAH is seeking authorisation to extend the indication of Zejula (niraparib) to include first-line treatment: "for the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy."

Currently, the general recommended and approved starting dose is 300 mg once daily (to be adjusted in case of adverse reactions). However, in connection with the applied extension of the indication, the MAH also seeks to change the posology, by recommending a general starting dose of 200 mg once daily. For those patients weighing ≥ 77 kg **and** having baseline platelet count ≥ 150 000/µL though, the recommended starting dose is 300 mg once daily (see discussion on clinical pharmacology). During the initial MA application review for Zejula, low body weight and low baseline platelet count were identified as potential risk factors for treatment-emergent adverse events (TEAEs). Consequently, the MAH included a statement in the SmPC suggesting that a starting dose of 200 mg for patients weighing less than 58 kg may be considered. It was advised that the MAH should further investigate alternative dosing strategies to reduce adverse events (AEs) for niraparib while still maintaining clinical efficacy. As a result, the MAH submitted a Type II Variation (procedure no. EMEA/H/C/004249/II/0006) where a starting dose of 200 mg niraparib was recommended for the subset of ovarian cancer patients with body weight <77 kg or platelet count <150,000/µL. This alternative dosing strategy was introduced in order to reduce the risk of high-grade TEAEs, such as Grade 3 or 4 thrombocytopenia, while not compromising the efficacy. The data submitted in support of the change in posology was based on exposure-efficacy models. However, as serious limitations of these models were found, it was not possible to conclude about the efficacy of the proposed posology. The CHMP concluded that without the support of a prospective study, the new dosage regimen could not be accepted. The variation EMEA/H/C/004249/II/0006 was withdrawn.

The current claims of extension of indication and change in posology are mainly based on one pivotal Phase 3 study called PRIMA.

Design and conduct of clinical studies

The PRIMA study is a Phase 3, randomised, double-blinded, placebo-controlled, multicentre, global clinical trial. Primary objective was to evaluate the efficacy and safety of niraparib as first-line maintenance treatment for patients with ovarian, primary peritoneal or fallopian tube cancer who were in complete response (CR) or partial response (PR) to their last platinum-based chemotherapy. Subjects were randomised 2:1 to receive either niraparib or placebo and stratified by best response to platinum therapy (CR or PR), administration of neoadjuvant chemotherapy (yes or no) and homologous recombination deficiency (HRD) status (positive or negative/not determined). Central HRD test results as assessed by a clinical trial assay (Myriad HRD test) were required for randomisation as it was a stratification factor. Subjects with documented gBRCA1/2 or sBRCA1/2 mutation by local testing were considered to have HRDpos tumours and have been randomised as such. The MAH was asked to discuss the concordance of the local test results with the central test. The MAH clarified that 120 patients had locally reported gBRCA1/2 or sBRCA 1/2 mutations. For these 120 patients, the central test produced 110 HRDpos, 4 HRDneg and 6 HRDnd results. Of the 10 HRD negative or HRDnd results, 8 patients (3 HRDneg and 5 HRDnd) were randomized to HRDpos stratum (based on the locally reported BRCA mutations). The primary analysis of PFS in the ITT population was performed based on randomized HRD stratum and a sensitivity analysis was conducted based on the strata derived from the actual eCRF data which included the HRD stratum determined by the myChoice CDx result. Consistent results were observed between both analyses.

In connection with the review of the MAA for Zejula, it was a concern that the HRD test did not provide sufficient sensitivity to select patients for niraparib treatment (see EPAR Zejula). The MAH was therefore recommended to further explore validated biomarkers of HR deficiency that could be incorporated in clinical practice in order to identify those patients that would benefit from niraparib therapy. In 2019, this test was approved by the FDA and used in the QUADRA study that formed the basis for FDA approving Zejula for treatment of ovarian cancer patients treated with ≥ 3 chemotherapy regimens and whose cancer was associated with HRDpos status (indication not approved in EU). However, this test is not at present commonly available and used in EU. Furthermore, the sensitivity of the test to select patients for niraparib treatment has not been further discussed as part of this application.

All subjects in the PRIMA study had to have received frontline or neoadjuvant/adjuvant platinum-based therapy (including at least two post-operative cycles of platinum-based therapy after interval debulking surgery), with a physician-assessed response of CR or PR after at least three cycles of therapy. Cross-over of patients from the placebo-arm was not allowed. All patients, independent of the BRCA or HRD status, were randomised within 12 weeks of the first day of the last cycle of chemotherapy, meaning that 'platinum-free interval' could be maximum 3 months. There was no pre-selection of patients with HR-deficiency based on platinum sensitivity (defined as PFI>6 months).

The inclusion and exclusion criteria were generally well defined, reflecting the study population intended for maintenance treatment after first-line platinum-based chemotherapy. Stage III and IV patients were eligible, except stage III patients that had complete cytoreduction.

As the majority of high-grade ovarian, fallopian tube or primary peritoneal cancer are of epithelial origin, it was requested that "epithelial" was added to the indication. It was also clarified that niraparib is used in "monotherapy" and "advanced" refers to FIGO stages III and IV. To make sure that the study population indeed were high-grade patients, the MAH was asked to present tumour grade at diagnosis for both arms in the HRDpos and Overall population, in addition to the fixed and individualised dosing groups. Based on the additional information provided, it was concluded that, overall, the study population consisted of high-grade patients. It is therefore considered justified that high-grade is reflected in the indication wording.

Furthermore, Stage III patients who had complete cytoreduction after primary surgery were excluded from the pivotal study. As these patients have a clearly different prognosis, the MAH was requested to

justify a positive B/R in that population and as such the inclusion in the indication. The MAH explained that Stage III patients who had no visual residual disease (NVRD) at the time of primary debulking surgery (PDS) were excluded in order to try to minimize the time required to reach the number of events triggering outcomes analysis. However, Stage III patients with neoadjuvant chemotherapy (NACT) and who had NVRD post interval debulking surgery (IDS) were allowed into the study. An exploratory PFS analysis was performed for these patients. Even though the analysis is exploratory and the subset of patients is relatively limited and should therefore be interpreted with caution, the results indicated a benefit of niraparib in this subset of patients (HR=0.58 [95%CI: 0.374, 0.902], median PFS of 19.3 months in the niraparib arm [n=128] vs. 11.0 months in the placebo arm [n=62]). The MAH also referred to the beneficial results from the SOLO-1 study for another PARP-inhibitor, olaparib. In this study, Stage III patients with PDS and NVRD were included, and the PFS analysis indicated a clear benefit of olaparib compared to placebo (HR of 0.32, 95%CI 0.20, 051). It is acknowledged that olaparib and niraparib have similar mechanism of action, and it is therefore not considered unreasonable to anticipate that niraparib and olaparib would, to some degree, have similar effect in the same patient population. Taken together, it can be accepted that the data presented by the MAH indicate a positive B/R of niraparib for the whole Stage III population. However, it is still considered relevant to inform the physicians that this type of Stage III patients has actually not been treated in the PRIMA study. It is therefore stated in section 5.1 of the SmPC that these Stage III patients were excluded.

Amendment 1 (01 December 2016 after 44 subjects were enrolled) included several changes to the original protocol; some were modifications to the inclusion/exclusion criteria. The most extensive change was to include patients independent of HRD status as in the original protocol patient enrolment was limited to those with HR deficient status. The rationale for changing this was based on results from the NOVA trial where clinical benefit from niraparib therapy was consistently demonstrated in a broad population of ovarian cancer patients regardless of HRD status. Germline BRCA testing was not required and it is therefore unknown if tumour BRCA mutations were somatic or germline. It appears that the myChoice HRD test identifies germline and somatic variants in the tumour but does not distinguish between the two. However, this information is not strictly required for the study population and data analyses.

There is a priori biological rationale and evidence indicating that HR-deficiency biomarker can be a plausibly predictive factor of therapeutic response for niraparib in ovarian cancer, more particularly when patient's platinum sensitivity could not be established.

The inclusion of only HRDpos patients early in the study may have resulted in a slightly overestimated outcome in the Overall population as HRDpos patients are expected to respond favourably to PARP-inhibitors. Since the changes were implemented early in the PRIMA trial, they are considered acceptable.

At the time of study initiation (01 December 2016), all patients received 300 mg as the starting dose. However, on 16 November 2017 (Amendment 2) the dosing scheme was revised. A dosing of either 200 mg or 300 mg based on an algorithm comprising the patient's weight and/or platelet counts was implemented. This entailed that patients weighing ≥ 77 kg and having baseline platelet count ≥ 150 000/µl should receive 300 mg daily, while patients < 77 kg or baseline platelet count < 150 000/µl should receive 200 mg. However, at the time point this change was introduced, a total of 473 patients had already received the fixed starting dose of 300 mg (whereof 315 in the niraparib group). The hypothesis regarding dosing strategy was changed during enrolment and conduct of the study without increasing sample size to ensure sufficient power for the individualised dosing group. This clearly affects the interpretation of the efficacy data for the lower dose.

A substantial higher number of patients with at least one important protocol deviation was reported in the niraparib arm as compared to the placebo arm. The MAH was therefore asked to discuss details and possible reasons for this discrepancy and if it could somehow have impacted study integrity, in particular

in relation to the efficacy analyses and timing of the radiographic assessments. The main difference between the two study arms was in the category "study visits/procedures" with a reported difference of 13.7% (26.3% in the niraparib arm vs. 12.6% in the placebo arm). According to the MAH, the reason for this discrepancy was mainly due to missed weekly complete blood count (CBC) blood drawing after haematological toxicity resolution in the niraparib group. This deviation was not observed in the placebo group. Concerning protocol deviations (PDs) that could possibly affect the timing of the radiographic assessments, the MAH stated that there were proportionally similar percentages of deviations between the niraparib arm and the placebo arm in regard to RECIST assessment not done per protocol requirements. No detailed information was provided. However, a sensitivity analysis using the mid-point between progression time and previous assessment for unscheduled assessments has been performed and showed no impact on the primary efficacy analysis.

Placebo was used as comparator and this was found acceptable by the SAWP/CHMP. The only currently approved maintenance regimen for the first-line ovarian population, not limited to patients positive for BRCA mutations and/or HRD, is bevacizumab. At the time of study initiation (2016) bevacizumab treatment in combination with carboplatin and paclitaxel followed by bevacizumab maintenance was used to various extent in the EU and was not approved in all regions where the PRIMA study was performed (e.g., approved in 2018 in the US). Bevacizumab was therefore not considered suitable as comparator by the MAH. This reasoning can be accepted. Nevertheless, it could have been possible to consider bevacizumab as a treatment option under discretion of investigator and according to local practice. This could have given further insights into the extent of the efficacy of the treatment with niraparib when compared to bevacizumab. Olaparib, another PARP inhibitor, is also approved for first-line maintenance treatment in patients with ovarian cancer (however, not until June 2019), but only in patients with a mutation in the BRCA gene. Olaparib was therefore not viewed as a suitable comparator in this study. Overall, it is considered acceptable that placebo was used as comparator.

Primary endpoint was progression-free survival (PFS) and the analyses of PFS were based on the HRDpos population and the ITT population ("Overall population"). CHMP/SAWP concluded that PFS was an acceptable primary endpoint provided that the treatment effect was large and clearly outweighed the toxicity of maintenance therapy. Furthermore, it is not influenced by the impact of post progression therapy. Overall survival (OS) was a key secondary endpoint. Other secondary endpoints were patient-reported outcomes (PROs), time to first subsequent treatment (TFST), outcomes for the next anticancer therapy following study treatment and PFS-2. Crossover to niraparib was not permitted within the study design. However, patients could not be prevented from being switched to niraparib or a PARP inhibitor outside of the study. OS and PFS 2 analysis will thus be diluted by cross-over and multiple subsequent lines of therapy.

A blinded independent review committee (BIRC) was used to assess study imaging based on RECIST (version 1.1) and available clinical data for the primary analysis.

The sample size calculations were based on PFS in the HRDpos group and an event-based analysis. The sample size was adjusted when amending the protocol to change inclusion criteria. However, it was not changed when adjusting the dosing scheme to give a fully powered analysis only including patients included after the change.

The primary PFS analysis is not in accordance with EMA guidelines (CHMP/EWP/205/95 REV. 3): "outcome data should be collected according to the intended schedule of assessment and the date of progression or recurrence should be assigned based on the time of the first evidence of objective progression or recurrence regardless of violations, discontinuation of study drug or change of therapy". However, the required analyses not censoring events after change in therapy or missed assessments were included among the performed sensitivity analyses.

Efficacy data and additional analyses

The data cut-off date for the primary data analysis in the PRIMA study was 17 May 2019 with a database lock date of 3 July 2019. A total of 733 patients (487 subjects/niraparib and 246 subjects/placebo) were randomised into the study, however 256 patients were recorded as screen failures. The MAH clarified that the main part of patients who were screen failures did not meet the clinical or laboratory inclusion criteria. Of the 234 patients for whom data were available, the majority of patients (62/234; 26%) failed due to lack of "having either CA-125 in the normal range or CA-125 decreased by more than 90% during their frontline therapy that was stable for more than 7 days". In total, 728 patients received intervention (484 patients in the niraparib arm vs. 244 patients in the placebo arm). Of these 728 patients, 370 (~50%) were categorised as HRDpos (245 in the niraparib arm vs. 125 in the placebo arm). The main reason for discontinuing the study was disease progression.

As previously mentioned, 473 subjects (315 niraparib, 158 placebo) had received the 300 mg starting dose (nominated "Fixed starting dose" or FSD) prior to the change of dosing strategy (Amendment 2 of the protocol). After the amendment, 238 patients (156 in the niraparib group and 82 in the placebo group) received either 200 mg or 300 mg in accordance with the algorithm of body weight and platelet count (nominated "Individualised starting dose group" or ISD). Of the 156 niraparib patients, it was 122 (i.e., 78%) patients vs. 61/82 (i.e., 74%) patients in the placebo group that specifically received the applied 200 mg starting dose in accordance with the algorithm of body weight/platelet count. The proportions of patients discontinuing the study and specifically discontinuing due to disease progression for both the fixed and individualised starting dose group were mainly comparable to that reported in the Overall population and HRDpos population.

In the ITT population, baseline patient demographic and disease/tumour characteristics as well as all stratification factors were, in general well balanced between the two treatment arms, both in the HRDpos and the Overall population. History of debulking surgery (timing and outcome) was also compared across treatment arms in both cohorts and no significant difference was revealed.

The number of prior lines of chemotherapy, and CR/PR to primary platinum-based chemotherapy were also balanced between the niraparib and placebo treatment arms in both populations.

Discrepancies for stratification factors between the randomisation list and screening eCRF occurred (*data not shown*). However, they were well balanced across both arms in the Overall population. Overall, discrepancies were seen in 8.6% of subjects for the best response to first platinum regimen (CR or PR), and 4.1% of the subjects for neo-adjuvant chemotherapy (yes or no) and 1.2% of subjects for HRD test status (pos or neg).

The disease characteristics of the patients were consistent with an advanced ovarian cancer population and in line with the proposed indication wording. The study population was stratified for HRD status and as such, this factor was well balanced between the treatment arms. Fifty (~50) percent of the subjects were HRDpos, of these, 30% had mutation in the BRCA gene. BRCAmut subtypes included BRCA1 (21.6% niraparib subjects and 17.5% placebo subjects, respectively) and BRCA2 mutations (9.7% niraparib subjects and 11.4% placebo subjects, respectively). The remaining patients were HRDneg (~35%) and ~15% had HRD status not determined. The latter was applied if test results were inconclusive (e.g. due to insufficient tumour specimen) or the test was not done.

Generally, in both the HRDpos and Overall population there were no noteworthy differences in baseline characteristics between patients who received a fixed starting dose (300 mg) compared with those who received an individualised starting dose (200 mg or 300 mg) in either treatment arm. The only exception that might have consequences for the interpretation of the data was that fewer patients (both in the niraparib and the placebo group) in the individualised starting dose group had a complete response to first-line platinum based chemotherapy (~62%) compared to in the fixed starting dose group (~74%) in

the Overall population. However, it should be noted that the patients were not randomised when they were assigned to the different starting dose groups as this was based on cut-off values for weight and/or baseline platelet counts.

According to the protocol, patients who had received bevacizumab with their 1L chemotherapy but were unable to receive bevacizumab as maintenance for any reason could have been included in the study as long as the last dose of bevacizumab was received 28 >days prior ICF. The MAH was asked to summarise and discuss data (efficacy and safety) in the patients treated with bevacizumab. The data showed consistency with the overall population data (data not shown). However, the prior use of bevacizumab as part of the adjuvant/neo-adjuvant platinum regimen prior to enrolment in the PRIMA study concerned only 6 patients in the niraparib arm. This information has been added to section 5.1 of the SmPC.

The PRIMA study met its primary efficacy objective.

In HRD positive subjects, treatment with niraparib prolonged median PFS by 11.5 months compared to placebo, independent of starting dose. Median PFS as determined by BICR based on RECIST (version 1.1), was 21.9 months (95% CI: 19.3, NE) in the niraparib arm and 10.4 (95% CI: 8.1, 12.1) months in the placebo arm (HR 0.43 [95% CI: 0.310, 0.588]; p<0.0001).

In the Overall population, treatment with niraparib prolonged median PFS by 5.6 months compared to placebo. Median PFS as determined by BICR based on RECIST (version 1.1) was 13.8 (95% CI: 11.5, 14.9) months in the niraparib arm and 8.2 (95% CI: 7.3, 8.5) months in the placebo arm (HR 0.62 [95% CI: 0.502, 0.755]; p<0.0001). The outcomes in both populations are considered clinically relevant in a disease with unmet medical need.

Per request, the MAH provided reasons for censoring in the different populations. Among the HRDpos patients, the total number of censored patients was 166/247 (67.2%) in the niraparib arm and 53/126 (42.1%) patients in the placebo group. For the overall population, the number was 255/487 (52.4%) in the niraparib arm vs. 91/246 (37.0%) in the placebo arm. The most common reason for censoring in both arms in all populations was "last tumour assessment". This comprised patients who had not progressed or died and had not started subsequent anti-cancer therapy and who were censored at the date of the latest evaluable radiological assessment. Censoring due to this reason was more common in the niraparib arm than in the placebo arm (in the ITT population: HRDpos: 132/247, 53.4% vs. 43/126, 34.1% in the placebo arm and in the Overall population: 192/487, 39.4% in the niraparib arm vs. 72/246, 29.3% in the placebo arm). This difference could be viewed as a reflection of the observed increased treatment effect of niraparib as compared to placebo.

Both investigator assessed PFS and sensitivity analyses were consistent with the primary efficacy results.

The concordance between BICR and investigator-assessed PFS was high in both the overall and HRDpos patient populations in both the niraparib (88.8%, 88.2% respectively) and placebo (86.6%, 84.9% respectively) treatment arms. In both the overall and HRDpos populations, patients were more likely to be considered to have an event by investigator than by BICR in both treatment arms.

Compared to the results in the primary analyses, similar median PFS outcomes were seen in both the HRDpos and overall population in the fixed starting dose group - FSD (encompassed 65% of the total ITT population).

For the individualised starting dose group - ISD (i.e., comprises both those patients receiving 200 mg and those patients receiving 300 mg starting dose in accordance with the algorithm), the median prolongation in PFS appears to be shorter as compared to the fixed starting dose group for niraparib treatment, even though quite similar hazard ratios were presented for both the HRDpos and the Overall population. The individualised starting dose group had a shorter follow-up time as of data cut-off (median PFS follow up time 11.1 months in the individualised starting dose group as compared to 16.6 months in the fixed

starting dose group). The number of patients censored was relatively high, as they had not yet had an event, thus it was not possible to interpret these data. Updated efficacy analyses were provided by the MAH, see further below under "Subgroups" for more details.

The MAH argued that since the test of interaction between the starting dose groups (fixed vs. individualised) showed non-significant p-values (0.7486 in the HRDpos population and 0.2957 in the Overall population), the change in dose had no significant effect on PFS for these populations. However, it has to be emphasized that a high p-value in this context cannot be used to conclude on similarity between the two starting dose groups. The PRIMA study was neither designed nor powered to draw any conclusions on the treatment effect of the different starting doses.

Secondary endpoints

All the secondary endpoints (i.e., OS, TFST, PFS-2 and outcomes for next anticancer therapy) were immature at the data cut-off date. Hence, these data were not informative enough to exclude a potential detrimental effect in the ITT population or in the subgroups. As resistance mechanisms might occur in ovarian cancer patients after exposure to PARP-inhibitors, this could possibly affect the efficacy of next line therapy. Therefore, the immaturity of these data makes the long-term outcomes uncertain. As the initial efficacy assessment is based on PFS, it requires further investigation and a new condition is imposed for the MAH to submit updated analyses for all of the secondary endpoints when 60% maturity has occurred for OS (submission by 31 December 2025, Annex II condition).

The PRO analyses are considered exploratory and no statistical inference can be made. Overall, what can be inferred from these data are that gastrointestinal symptoms such as constipation, nausea/vomiting and appetite loss were reported of a higher proportion of patients in the niraparib arm as compared to patients in the placebo arm (please refer to Clinical Safety below).

Subgroups

Main subgroup analyses (data cut-off date 17 May 2019)

In general, a PFS benefit of niraparib with HR<1 was observed in the majority of subgroups indicating efficacy independent of baseline and disease characteristics.

As anticipated, based on knowledge of efficacy outcomes in the NOVA study, the tBRCAmut subgroup in the Overall population had the most promising outcome with median PFS of 22.1 months [95%CI: 19.3, NE] vs. 10.9 months [95%CI: 8.0, 19.4] in the niraparib arm vs. the placebo am, respectively; HR of 0.40 [95%CI: 0.265, 0.618], p<0.0001).

In non-tBRCAm/HRDpos patients, HR was 0.5 (95% CI: 0.3; 0.83) p=0.0064. These data highlight that the efficacy of niraparib was not driven solely by the patients with BRCAmut tumours.

A positive effect of niraparib treatment was also observed in the HRDneg subgroup (N=249) with median PFS of 8.1 months [95%CI: 5.7, 9.4] vs. 5.4 months [95%CI: 4.0, 7.3] in the niraparib arm vs. the placebo am, respectively; HR of 0.68 [95%CI: 0.492, 0.944], p=0.0203). This is indicative of a positive effect of niraparib in the Overall population even though the effect was less than for the HRDpos population. This is also observed for the HRDneg patients in the Fixed starting dose group and the Individualised starting dose group (HR of 0.64 [95% CI: 0.424, 0.969]) and 0.70 [95%CI: 0.402, 1.230], respectively).

Among the biomarker subgroups, the HRD not determined (nd) population (~15%) derived the less benefit of niraparib with median PFS of 11.0 months [95%CI: 7.4, 13.9] vs. 8.3 months [95%CI: 5.7, 12.5] in the niraparib arm vs. the placebo am, respectively; HR of 0.85 [95%CI: 0.509, 1.432], p=0.5577). The reason for this is unclear, and the MAH discussed that it could be due to an (unknown) imbalanced composition of the homologous recombination (HR) status in each treatment group.

Furthermore, the MAH argued that since the composition of HR-status is unknown in these tumours, this hazard ratio cannot be attributed to any of the biomarker subgroups and does not have a meaningful interpretation. It is acknowledged that further understanding of the poor response and molecular basis of this subgroup is difficult with the current data and knowledge. Data concerning the baseline patient and disease characteristics for the HRDnd patients showed that there was a higher proportion of patients who received NACT in the HRDnd subgroup than others – 88-93% vs. 59-65%, respectively. Furthermore, stratified and un-stratified covariate-adjusted analyses were performed and the results of both analyses reduced the hazard ratio estimate from 0.85 to 0.68-0.70.

Additional post-hoc efficacy analyses of starting dose subgroups (data cut-off date 17 May 2019)

Additional *post-hoc* analyses were submitted by the MAH to characterise the efficacy for each starting dose subgroup by baseline body weight and baseline platelet counts.

It was of particular interest, to compare efficacy results for the two subgroups nominated C (=patients with BW <77kg or PC <150K/µL taking 300 mg as fixed starting dose) and D (=patients also with BW <77kg or PC <150K/µL but taking 200 mg as an individualised starting dose). Of note, there were relatively few patients in subgroup D (122 patients in the niraparib arm vs. 61 in the placebo arm).

When comparing subgroup C vs. subgroup D, it was observed that the HRs were quite similar for the two dosing regimens for both the HRDpos and the Overall population. For the HRDneg population, however, the HR was clearly lower in subgroup D compared to HR in subgroup C, i.e., 0.61 vs. 0.75, respectively.

When looking at the differences in median PFS between the niraparib group and the placebo group in the two subgroups C and D, it appeared that the gain in median PFS was consistently smaller for subgroup D compared to subgroup C for all patient populations and with the largest difference between the two dosing groups in the HRDneg population. For the 200 mg starting dose group, fewer patients had reached sufficient follow-up time and thus updated analyses were requested.

Updated efficacy analyses (data cut-off date 17 November 2019)

Updated 6-month efficacy results were provided for all 3 patient populations (i.e. Overall, HRDpos and HRDneg), in the FSD dosing group, the ISD dosing group and the two dosing subgroups C and D. This led to an increase in the median follow-up time from 11.2 to 17.0 months (ISD) and from 17.1 to 22.4 months (FSD). The data maturity rate increased to > 60% in both the FSD and ISD subgroups. The updated analyses showed that it was mainly the body weight criterion that determined which patients who were to receive 200 and 300 mg in the PRIMA study, while the platelet count criterion only had influence on the dose in 2% of the patients. In contrast to the analyses based on the original data cut-off date (i.e., 17 May 2019), the 6-month update (data cut-off date 17 November 2019) is based on investigator assessed (IA) PFS. According to the MAH, it was not possible to provide updated data based on BICR.

Consistency between BICR and investigator-assessed PFS (used in the updated efficacy analyses)

Based on analyses performed by the MAH, consistency was found between BICR and IA PFS for all 3 patient populations (i.e., Overall, HRDpos and HRDneg) for the dosing group FSD at the original data cut off. For the dosing group ISD, consistency was, overall, also quite high between BICR and IA PFS for the Overall and HRDpos populations. For the HRDneg population, on the other hand, the results between the BICR and IA PFS for the dosing group ISD was less consistent due to a lower (and thereby seemingly more beneficial) point estimate of HR when based on IA PFS compared to when based on BICR PFS (HR 0.59 vs. HR 0.70, respectively). This inconsistency was even more marked for dosing subgroup D (HR by BICR was 0.75 vs. 0.46 by IA and for the updated analyses HR was estimated to 0.43 by IA). The reason for this diversion in HR point estimates by BICR and IA for the HRDneg population has not been specifically discussed by the MAH. However, it is realised that the HRDneg population in subgroup D is of

limited size (40 patients in the niraparib arm vs. 17 in the placebo arm). In such a small data set, one or two outliers could impact heavily on the results. There is also no biological rationale to expect that lower doses of niraparib should lead to higher efficacy in HRDneg patients or that the efficacy should be more beneficial in HRDneg compared to HRDpos patients. Consequently, it is doubted that the point estimate for HR in this population represents the true treatment effect of the 200 mg dose.

Updated efficacy analyses for the FSD and ISD groups

Of note, due to the proposed dosing algorithm, the ISD dosing group consisted not only of patients receiving 200 mg, but also some patients receiving 300 mg (this was dependent upon the patient's baseline body weight and platelet count).

The updated point estimates for HR were relatively similar between the FSD and the ISD for the Overall population (0.62 vs. 0.68, respectively) and only slightly lower for FSD compared to ISD for the HRDpos population (0.46 vs. 0.54, respectively). Based on these HR point estimates, it appears that the loss in treatment effect for the ISD group compared to the FSD group could be considered to be relatively modest. When comparing differences in point estimates in medians between niraparib and placebo, the median prolongation in PFS always favoured the niraparib arm, although the difference between niraparib and placebo was longer in the FSD group compared to what was observed in the ISD group for both patient populations (5.7 months vs. 4.3 months, respectively for the Overall population and 14 months vs. 6.5 months, respectively for the HRDpos population). The updated KM plots, showed that the effect for the FSD and the ISD dosing groups seems quite similar for the Overall and HRDpos population in the niraparib arm.

For the HRDneg population, the updated point estimates for HR in the ISD group was 0.56 vs. 0.64 in the FSD group. However, considering the inconsistency between the BICR and IA assessed PFS for the original data cut, this HR estimate is, as already mentioned above, questioned. The median prolongation in PFS for the HRDneg population was stated to be 1.1 months in the ISD group vs. 5.4 months in the FSD group. Moreover, for the HRDneg population, the KM curve for the niraparib arm in the ISD dosing group seems to be inferior to the niraparib arm in the FSD dosing group. However, at 8-10 months, there are very few patients left, making the result less reliable.

Updated efficacy analyses for the dosing subgroups C and D

The point estimates for HR were quite similar between subgroup C and subgroup D for the Overall and HRDpos patient populations (both for original and updated data). Based on these HR point estimates, it therefore appeared, as a potential loss in treatment effect for the 200 mg dosing group compared to the 300 mg dosing group could be considered negligible. Although always in favour of the niraparib arm, the gain in median PFS (as compared to the placebo arm) wasconsistently lower in subgroup D compared to the corresponding populations in subgroup C.

In the HRDneg population, there was no clinical relevant difference in median PFS between the niraparib arm and the placebo arm in subgroup D (5.5 months vs. 5.4 months, respectively). As already stated above, the low point estimates of HR for the HRDneg patients in subgroup D are considered to be unreliable and not supported by the KM plot.

The updated KM plots showed a smaller treatment effect for the 200 mg dose (subgroup D) compared to the 300 mg dose (subgroup C) for all 3 patient populations. For the Overall and HRDpos populations, the curves in subgroup D started to diverge first at around 7-8 months. In contrast, for the 300 mg subgroup, the curves were separating early in the study. No explanation has been offered for this observation. The HRs for subgroup D might be underestimated. Even if a reduced treatment effect for the 200 mg dose is seen for all 3 patient population, the greatest loss in efficacy is observed for the HRDneg patient population.

Overall conclusion

Taken together, it seems reasonable to conclude that, based on the available data and current knowledge, it cannot be affirmably stated that there is no loss of efficacy with the 200 mg starting dose. Compared to the 300 mg starting dose, the efficacy seems to not be fully maintained at the 200 mg starting dose for the Overall and HRDpos population. However, the potential loss of efficacy appears to be rather modest. For the HRDneg population the 200 mg dose seems to be of lower efficacy compared to 300 mg. The available data are not sufficiently robust to allow any definite conclusion on efficacy of the 200 mg dose for this patient group in comparison to the 300 mg dose.

The PRIMA study was not initially designed with the intent of studying different starting doses and considering that the lower dose has only been tested in limited number of subjects, it is realised that the study does not have the statistical power to allow any firm conclusions to be drawn in regards to the 200 mg starting dose compared to the 300 mg starting dose. Consequently, the results of these analyses are flawed by uncertainty. Furthermore, for subgroups not based on stratification factors, the results also may be confounded by imbalance in the baseline characteristics.

However, overall, it could be inferred by the data that the modified dosage regimen, when compared to placebo, niraparib still showed a PFS benefit.

2.4.4. Conclusions on the clinical efficacy

In general, the outcomes of the primary analyses in the overall population are encouraging in a patient group, which currently has limited treatment options. However, the documentation for the proposed dosing scheme of 200 mg as a starting dose for nearly all patients (with the exception of those weighing $\geqslant$ 77kg and having platelet count $\geqslant$ 150K/µL) is not sufficiently robust to conclude with certainty on whether the lower dose will reduce efficacy of niraparib compared to 300 mg starting dose. Nevertheless, the potential loss of efficacy appears to be rather modest and the benefit observed remains clinically relevant.

The current data seem to indicate that, compared to the 300 mg dose, the 200 mg dose could lead to lower efficacy of niraparib, in the HRDneg patients. As HRDneg patients do not harbour a deficiency in the HR machinery, they are probably not as sensitive to PARP inhibitors as HRDpos patients. Thus, a different dose-response relationship is expected in these patients and, independent of dose, the treatment effect in the HRDneg patients is lower than in HRDpos patients. Information regarding the seeming lower efficacy of the 200 mg for HRDneg patients has been stated in section 5.1 of the SmPC.

Overall, the risk of a reduced treatment effect by using a 200 mg starting dose group vs. using a 300 mg starting dose has to be weighed against the benefit of a reduced risk of experiencing severe thrombocytopenia grade 3 or 4 (and thereby avoiding possible hospitalization, transfusions, interventions, and early discontinuation of niraparib) with the 200 mg dose (see discussion on benefit/risk balance).

Furthermore, relative to placebo, the totality of evidence based on efficacy data with the modified dosage regimen is considered to support a clinically relevant improvement in outcome.

All the secondary endpoints (i.e., OS, TFST, PFS-2 and outcomes for next anticancer therapy) were immature at the data cut-off date. Therefore, the following measure is considered necessary to address issues related to clinical efficacy:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate the efficacy of niraparib in the maintenance treatment of adult patients with advanced epithelial	31 December 2025

(FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy, the MAH should submit the final analysis for OS and updated analyses for TFST, PFS-2 and outcomes for next anticancer therapy from study PRIMA.	

2.5. Clinical safety

Introduction

Zejula is currently 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 (posology 300 mg capsule QD). The main safety data in support of this indication was derived from the NOVA trial. The NOVA study included 553 patients (546 treated) who had recurrent platinum-sensitive ovarian cancer with a CR or PR to their last platinum-based chemotherapy treatment and randomized patients 2:1 to niraparib or placebo.

The major factors limiting the tolerability of niraparib are haematological toxicity (most notably thrombocytopenia, anaemia and neutropenia), and gastrointestinal events such as nausea/vomiting, in addition to fatigue, which lead to frequent dose modifications (>70% of patients). Warnings in SmPC section 4.4 are in place for the following ADRs: haematological toxicity, myelodysplastic syndrome/acute myeloid leukaemia, hypertension including hypertensive crisis.

The applicant is seeking to extend the current indication to first-line patients. The recommended starting dose for the first-line indication is proposed to be 200 mg QD, except for patients who weigh $\geqslant$ 77 kg and have baseline platelet count $\geqslant$ 150,000/mcL, where the recommended starting dose is 300 mg QD.

The purpose of this safety evaluation is to assess the safety and tolerability of niraparib in the sought indication, and at the proposed dosing regimen, which is different from the dosing regimen in the approved indication.

The primary data to support the safety of treatment with niraparib in the proposed indication are derived from the PRIMA study (PR-30-5017-C), where 733 patients were randomised 2:1 to receive niraparib (484 patients) or placebo (244 patients). Initially, patients were enrolled at a fixed starting dose (FSD) of 300 mg QD niraparib or placebo. The dosing strategy was subsequently changed by a trial amendment, to an individualised starting dose (ISD), where patients received niraparib 200 mg QD or placebo, except for patients who weighed $\geqslant$ 77 kg and had baseline platelet count $\geqslant$ 150,000/mcL, where the starting dose was 300 mg QD or placebo. In the PRIMA trial, 315 patients were treated with the FSD of niraparib (300 mg QD), and 169 patients were treated with the ISD of niraparib (200/300 mg QD).

Because two different starting dose regimens were used in the PRIMA trial (fixed; FSD and individualised; ISD), the safety populations have been presented in different ways as described in Table 51. In addition to the primary data from the PRIMA trial, supporting safety data from the NOVA trial is presented in the safety tabulations, along with pooled data from the PRIMA trial and NOVA trial. Note that the PRIMA and NOVA study pool does not contain safety data from the ISD subgroup; only data from the FSD pools (300 mg QD) are included in this pool.

Table 51. Niraparib Safety Data Presentation

Population Name	Description
PRIMA "All"	Safety data from the overall safety population in the PRIMA study, ie, combined data from patients treated with both fixed (300 mg/day) and individualized (200 or 300 mg/day) starting doses
PRIMA "Individualized"	Safety data from patients treated with the individualized starting dose (200 or 300 mg/day (n=169), based on the baseline weight and baseline platelet count level, in the PRIMA study
PRIMA "Fixed"	Safety data from patients treated with the fixed starting dose of 300 mg/day (n=315) in the PRIMA study
NOVA "Fixed"	Safety data from patients in the NOVA study, all of whom were treated with the fixed starting dose of 300 mg/day (n=367)
Pooled (also referred to as the PRIMA and NOVA Study Pool).	Integrated safety data from patients treated with the fixed starting dose of 300 mg/day in the PRIMA (n=315) and NOVA (n=367) studies (total n=682)

Some data are also presented per dosing subgroups in the PRIMA trial. This refers to subdivisions of the FSD and ISD safety data according to the baseline weight and platelet count of the patients, as follows: Subgroup A: patients with a baseline body weight ≥77 kg and a baseline platelet count of ≥ 150,000/µL who received FSD 300 mg; Subgroup B: patients with a baseline body weight ≥77 kg and a baseline platelet count of ≥150,000/µL who received ISD 300 mg; Subgroup C: patients with a baseline body weight <77 kg or a baseline platelet count of <150,000/µL who received FSD 300 mg; Subgroup D: patients with a baseline body weight <77 kg or a baseline platelet count of <150,000/µL who received ISD 200 mg.

Patient exposure

Safety data in this report are based on a data cut-off date of 17 May 2019, unless indicated. 246 patients in the PRIMA study and 39 patients in the NOVA study remain on treatment. Updated safety data from the PRIMA trial were subsequently submitted including data up to a cut-off date of 17 November 2019. Tables including data from the 17 Nov 2019 cut-off date are indicated with the DCO date.

Table 52. Summary of Overall Exposure to Study Drug (PRIMA and NOVA Study Pool)

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Parameter	All	All	Individualized	Fixed	All	Fixed[a]	All	Fixed
Number of cycles started, n	244	484	169	315	179	367	423	682
Mean (StD)	10.8 (6.66)	11.7 (7.38)	9.8 (5.41)	12.7 (8.09)	9.8 (12.28)	16.3 (17.50)	10.4 (9.45)	14.6 (14.07)
Median	9.0	12.5	12.0	13.0	6.0	9.0	7.0	11.0
Min, Max	1, 31	1, 32	1, 18	1, 32	1, 72	1, 65	1, 72	1, 65
Overall treatment duration (months)[b], n	244	484	169	315	179	367	423	682
Mean (StD)	9.5 (5.93)	10.3 (6.63)	8.6 (4.81)	11.3 (7.26)	8.7 (11.24)	14.9 (16.09)	9.2 (8.58)	13.2 (12.91)
Median	8.3	11.1	11.0	11.5	5.4	8.2	7.0	9.5
Min, Max	0, 28	0, 29	0, 16	0, 29	0, 65	0, 61	0, 65	0, 61
Actual treatment duration (months)[c], n	244	484	169	315	179	367	423	682
Mean (StD)	9.4 (5.88)	9.7 (6.50)	8.2 (4.75)	10.6 (7.14)	8.7 (11.20)	14.3 (15.97)	9.1 (8.54)	12.6 (12.81)
Median	8.3	10.4	10.0	10.7	5.3	7.8	6.7	9.2
Min, Max	0, 28	0, 29	0, 16	0, 29	0, 65	0, 60	0, 65	0, 60
Dose intensity (mg/day)[d], n	244	481	168	313	178	364	422	677
Mean (StD)	259.9 (50.66)	174.7 (67.31)	162.1 (57.98)	181.4 (70.99)	289.8 (26.01)	193.8 (70.13)	272.5 (44.55)	188.1 (70.75)
Median	290.6	181.3	178.6	181.8	297.7	194.4	295.7	189.9
Min, Max	58, 327	31, 350	31, 350	73, 307	141, 340	45, 360	58, 340	45, 360
Relative dose intensity (%)[e], n	244	481	168	313	178	364	422	677
Mean (StD)	94.9 (13.74)	64.8 (24.81)	72.7 (24.99)	60.5 (23.66)	96.6 (8.67)	64.6 (23.38)	95.6 (11.89)	62.7 (23.58)
Median	98.9	62.6	66.4	60.6	99.2	64.8	99.1	63.3
Min, Max	19, 144	16, 175	16, 175	24, 102	47, 113	15, 120	19, 144	15, 120

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Parameter	All	All	Individualized	Fixed	All	Fixed[a]	All	Fixed
Dose reduction (%), n	244	484	169	315	179	367	423	682
Any reason	30 (12.3)	362 (74.8)	111 (65.7)	251 (79.7)	11 (6.1)	269 (73.3)	41 (9.7)	520 (76.2)
Due to AE	19 (7.8)	342 (70.7)	105 (62.1)	237 (75.2)	10 (5.6)	268 (73.0)	29 (6.9)	505 (74.0)
Dose interruption (%), n	244	484	169	315	179	367	423	682
Any reason	58 (23.8)	385 (79.5)	120 (71.0)	265 (84.1)	35 (19.6)	298 (81.2)	93 (22.0)	563 (82.6)
Due to AE[f]	39 (16.0)	376 (77.7)	116 (68.6)	260 (82.5)	31 (17.3)	294 (80.1)	70 (16.5)	554 (81.2)

Abbreviations: AE=adverse event; StD=standard deviation.

a All patients randomized to niraparib in the NOVA study were treated with a starting dose of 300 mg/day.
b Overall treatment duration = last dose date - first dose date + 1.
c Actual treatment duration = last dose date - first dose date – duration of dose interruption(s) + 1.
d Dose intensity (mg/day) = sum of total daily doses actually consumed / overall treatment duration.
e Relative dose intensity (%) = dose intensity / (assigned starting dose in mg) * 100.
f Planned interruptions include dose interruption after a Grade 3 or 4 AE, and a non-hematologic AE which the Investigator considers to be related to administration of study drug.

Dose interruptions were required for any patient with a platelet count <100×10^9/L, neutrophil count <1.0×10^9/L, hemoglobin <8 g/dL, or any non-hematologic NCI CTCAE (version 4.02 for NOVA and 4.03 for PRIMA) Grade ≥ 3 TEAE that the Investigator considered to be related to the study drug. If Grade 3 or 4 non-hematologic toxicity was appropriately resolved to baseline or Grade 1 or less within 28 days of interruption, the patient was allowed to restart study treatment but with a dose level reduction. The minimum niraparib daily dose was 100 mg/day.

Dose modifications for the patients on niraparib with baseline weight under 77 kg or baseline platelet count less than 150 000/µL in the PRIMA study are shown in Table 53.

Table 53. Dose Modifications for the low W/P Population (DCO 17 November 2019)

Dose Modification, n (%)	FSD (300 mg Starting Dose) Group C; N=243	ISD (200 mg Starting Dose) Group D; N=122
Dose Interruption	212 (87.2%)	83 (68.0%)
Dose Reduction	204 (84.0%)	73 (59.8%)

Source: Table 14.3.5.14a and Table 14.3.5.14b
Abbreviations: FSD=fixed starting dose; ISD=individualized starting dose; Low W/P=low baseline weight and platelet counts.

Following the implementation of ISD with Amendment 2, 10 patients with baseline weight <77 kg or a baseline platelet count of <150,000/μL incorrectly received a 300 mg starting dose. Overall, the rate of dosing error based on the ISD dosing algorithm was 13 patients out of 258 (5.0%) who were eligible to receive the individualized starting dose and received the incorrect dose.

For patients whose starting dose was 200 mg QD, escalation to 300 mg QD was permitted if no treatment interruption or discontinuation was required during the first 2 cycles of therapy. Thirteen patients, 7 of whom who received niraparib and 6 who received placebo, had their dose escalated to 300 mg during Cycle 3 or 4. At the time of data cut-off, 8 of these patients had discontinued study treatment (5 niraparib and 3 placebo patients). Of the 7 patients who dose escalated niraparib, 3 experienced adverse events 1-2 months after receiving the 300 mg dose. This included 1 patient with grade 2 arthralgia and 1 with grade 3 anaemia which led to dose interruption and reduction. The 3rd patient experienced grade 3 thrombocytopenia but discontinued study treatment due to disease progression.

Demographics/baseline characteristics

An overview of the baseline characteristics of the patients included in the PRIMA study is presented in the clinical efficacy part of this AR (refer to baseline data section of 2.4.2).

Per protocol, all patients in the PRIMA study had received 1 prior line of platinum-based therapy, with most having undergone 6 cycles of 1L platinum-therapy (≥6 and ≤9 cycles specified in Protocol Amendment 1, at least 4 cycles were required per original protocol). A total of 97% patients had received taxane as part of their prior therapy, 96% received carboplatin, and 8% received cisplatin. Seven patients received bevacizumab with chemotherapy during 1L treatment, but bevacizumab was not continued during maintenance when they enrolled in the trial.

History of myelosuppression in the PRIMA and NOVA is shown in Table 54.. Niraparib and placebo treatment arms were well balanced with regard to history of myelosuppression, with >87% of patients within each treatment arm reporting this event in the PRIMA study (Table 54.). A history of thrombocytopenia was noted in >44% of patients across the treatment arms; a history of Grade 3 or 4 thrombocytopenia was observed in ~5-6% of patients in each treatment arm. The most commonly reported history of a Grade 3 or 4 hematologic abnormality was reported for neutropenia, occurring in 33% to 37% of patients across the treatment arms.

Table 54. Prior History of Myelosuppression and Baseline Haematology (PRIMA and NOVA study pool)

Parameter	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
	All n (%)	All n (%)	Individualized n (%)	Fixed n (%)	All n (%)	Fixed[a] n (%)	All n (%)	Fixed n (%)
Prior myelosuppression, n	244	484	169	315	179	367	423	682
Yes	213 (87.3)	425 (87.8)	151 (89.3)	274 (87.0)	142 (79.3)	298 (81.2)	355 (83.9)	572 (83.9)
No	31 (12.7)	59 (12.2)	18 (10.7)	41 (13.0)	37 (20.7)	69 (18.8)	68 (16.1)	110 (16.1)
Baseline platelet count ($\times 10^9$/L), n	244	484	169	315	179	367	423	682
Mean (StD)	244.2 (87.77)	243.0 (77.88)	248.4 (80.98)	240.1 (76.14)	231.9 (82.35)	233.5 (82.38)	239.0 (85.64)	236.6 (79.57)
Median	224.5	234.0	233.0	235.0	219.0	215.0	222.0	222.5
Min, Max	110, 776	100, 662	100, 538	101, 662	101, 612	85, 648	101, 776	85, 662
Baseline hemoglobin (g/L), n	244	484	169	315	179	367	423	682
Mean (StD)	117.1 (9.92)	118.9 (10.26)	118.7 (9.76)	119.0 (10.53)	118.3 (10.70)	117.2 (10.88)	117.6 (10.26)	118.0 (10.75)
Median	118.0	119.0	118.0	120.0	119.0	117.0	118.0	118.6
Min, Max	88, 147	93, 160	93, 147	96, 160	89, 153	90, 152	88, 153	90, 160

Abbreviations: StD=standard deviation.
a All patients randomized to niraparib in the NOVA study were treated with a starting dose of 300 mg/day.
Note: Myelosuppression values are provided only for patients with history of myelosuppression within the year before study entry.
Source: ISS Table 1.1.7.

Adverse events

Standard safety evaluations were conducted in the NOVA and PRIMA studies, including monitoring for TEAEs, clinical laboratory evaluations, vital signs, concomitant medication usage, physical examinations, and quality-of-life questionnaires. AEs were recorded in PRIMA through 30 days post end of treatment (EOT), and in NOVA until EOT (30 days post EOT for SAEs). An ECG sub-study was conducted with data from the NOVA study, indicating no clinically meaningful difference in terms of QTc-effect. Hence, ECG assessments were only performed at screening in the PRIMA study. Tabulations were classified by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term (PT) using MedDRA version 20.0. Lab abnormalities were based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade criteria v4.03.

PRIMA study

Most patients in both treatment arms in the PRIMA study experienced at least 1 TEAE, including 478 (99%) of 484 patients who received niraparib and 224 (92%) of 244 patients who received placebo.

Patients who received niraparib were more likely to experience treatment-related TEAEs (96% vs 69%), CTCAE Grade ≥3 TEAEs (71% vs 19%), treatment-related Grade ≥3 TEAEs (65% vs 7%), SAEs (32% vs 13%), treatment-related SAEs (24% vs 3%), TEAEs leading to treatment interruption (80% vs 18%), TEAEs leading to dose reduction (71% vs 8%), and TEAEs leading to study drug withdrawal (12% vs 3%) when compared to patients receiving placebo.

There were no on-treatment deaths reported in the PRIMA study. Two niraparib patients and 1 placebo patient (<1% each) experienced TEAEs leading to death, all were assessed by the Investigator as unrelated to study drug. Deaths are further discussed in the section below.

Serious adverse events and TEAEs of grade 3-4 were decreased in patients receiving the individualized starting dose as compared to the fixed starting doses (27% vs 35% and 60% vs 76%, respectively).

PRIMA and NOVA studies

When considering the PRIMA and NOVA studies, the incidence of patients experiencing at least 1 TEAE was high, with 680 (~100%) of 682 patients in the pooled niraparib group and 396 (94%) of

423 patients in the pooled placebo group reporting at least 1 TEAE. Patients who received niraparib were more likely to experience treatment-related TEAEs (98% vs 70%), CTCAE Grade ≥3 TEAEs (76% vs 21%), treatment-related Grade ≥3 TEAEs (69% vs 6%), SAEs (34% vs 14%), treatment-related SAEs (22% vs 2%), TEAEs leading to treatment interruption (76% vs 17%), TEAEs leading to dose reduction (72% vs 7%), and TEAEs leading to study drug withdrawal (15% vs 2%) when compared to patients receiving placebo.

Summary statistics for TEAEs were largely similar in the PRIMA and NOVA studies, but some differences were noted when comparing the niraparib fixed dosing strategy in the PRIMA study with that of the NOVA study: more patients in the PRIMA trial experienced TEAEs leading to dose interruptions and TEAEs leading to dose reductions (84% and 76%, respectively) compared to patients in the NOVA study (69% and 69%, respectively). Slightly more patients receiving niraparib in the NOVA trial experienced a TEAE leading to drug withdrawal (17%) compared to patients receiving the niraparib fixed dosing regimen in the PRIMA trial (11%).

Table 55. Most Common (⩾ 10% Incidence Rate in Either Treatment Group) Treatment-emergent Adverse Events by MedDRA Preferred Term (PRIMA and NOVA Study Pool)

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Preferred Term	All n (%) N=244	All n (%) N=484	Individualized n (%) N=169	Fixed n (%) N=315	All n (%) N=179	Fixed[a] n (%) N=367	All n (%) N=423	Fixed n (%) N=682
Any TEAE with ≥10% incidence rate	208 (85.2)	472 (97.5)	162 (95.9)	310 (98.4)	154 (86.0)	366 (99.7)	362 (85.6)	676 (99.1)
Nausea	67 (27.5)	278 (57.4)	90 (53.3)	188 (59.7)	65 (36.3)	273 (74.4)	132 (31.2)	461 (67.6)
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)
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)
Constipation	46 (18.9)	189 (39.0)	53 (31.4)	136 (43.2)	38 (21.2)	153 (41.7)	84 (19.9)	289 (42.4)
Fatigue	72 (29.5)	168 (34.7)	56 (33.1)	112 (35.6)	58 (32.4)	176 (48.0)	130 (30.7)	288 (42.2)
Vomiting	29 (11.9)	108 (22.3)	28 (16.6)	80 (25.4)	31 (17.3)	132 (36.0)	60 (14.2)	212 (31.1)
Headache	36 (14.8)	126 (26.0)	37 (21.9)	89 (28.3)	21 (11.7)	104 (28.3)	57 (13.5)	193 (28.3)
Insomnia	35 (14.3)	119 (24.6)	35 (20.7)	84 (26.7)	16 (8.9)	91 (24.8)	51 (12.1)	175 (25.7)
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)
Abdominal pain	75 (30.7)	106 (21.9)	30 (17.8)	76 (24.1)	56 (31.3)	94 (25.6)	131 (31.0)	170 (24.9)
Decreased appetite	20 (8.2)	92 (19.0)	32 (18.9)	60 (19.0)	27 (15.1)	97 (26.4)	47 (11.1)	157 (23.0)
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)
Diarrhoea	55 (22.5)	91 (18.8)	23 (13.6)	68 (21.6)	38 (21.2)	82 (22.3)	93 (22.0)	150 (22.0)
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)
Dyspnoea	30 (12.3)	88 (18.2)	27 (16.0)	61 (19.4)	15 (8.4)	72 (19.6)	45 (10.6)	133 (19.5)
Cough	35 (14.3)	74 (15.3)	22 (13.0)	52 (16.5)	10 (5.6)	67 (18.3)	45 (10.6)	119 (17.4)
Dizziness	26 (10.7)	71 (14.7)	18 (10.7)	53 (16.8)	14 (7.8)	68 (18.5)	40 (9.5)	121 (17.7)
Asthenia	31 (12.7)	78 (16.1)	26 (15.4)	52 (16.5)	16 (8.9)	63 (17.2)	47 (11.1)	115 (16.9)

Preferred Term	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
	All n (%) N=244	All n (%) N=484	Individualized n (%) N=169	Fixed n (%) N=315	All n (%) N=179	Fixed[a] n (%) N=367	All n (%) N=423	Fixed n (%) N=682
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)
Arthralgia	47 (19.3)	85 (17.6)	29 (17.2)	56 (17.8)	23 (12.8)	55 (15.0)	70 (16.5)	111 (16.3)
Back pain	24 (9.8)	64 (13.2)	17 (10.1)	47 (14.9)	23 (12.8)	60 (16.3)	47 (11.1)	107 (15.7)
Viral upper respiratory tract infection	25 (10.2)	49 (10.1)	16 (9.5)	33 (10.5)	15 (8.4)	49 (13.4)	40 (9.5)	82 (12.0)
Abdominal pain upper	22 (9.0)	41 (8.5)	10 (5.9)	31 (9.8)	18 (10.1)	40 (10.9)	40 (9.5)	71 (10.4)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
a All patients randomized to niraparib in the NOVA study were treated with a starting dose of 300 mg/day.
Note: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.

Table 56. Grade ≥ 3 Treatment-emergent Adverse Events Reported in ⩾ 5% of Patients in Either Treatment Group by MedDRA System Organ Class and Preferred Term (PRIMA and NOVA Study Pool)

MedDRA SOC Preferred Term	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
	All n (%) N=244	All n (%) N=484	Individualized n (%) N=169	Fixed n (%) N=315	All n (%) N=179	Fixed[a] n (%) N=367	All n (%) N=423	Fixed n (%) N=682
Any Grade ≥3 TEAE	46 (18.9)	341 (70.5)	102 (60.4)	239 (75.9)	42 (23.5)	280 (76.3)	88 (20.8)	519 (76.1)
Blood and lymphatic system disorders	6 (2.5)	255 (52.7)	65 (38.5)	190 (60.3)	2 (1.1)	190 (51.8)	8 (1.9)	380 (55.7)
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)
Anemia	4 (1.6)	150 (31.0)	38 (22.5)	112 (35.6)	0	96 (26.2)	4 (0.9)	208 (30.5)
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)
Investigations	8 (3.3)	99 (20.5)	25 (14.8)	74 (23.5)	9 (5.0)	89 (24.3)	17 (4.0)	163 (23.9)
Platelet count decreased	0	63 (13.0)	12 (7.1)	51 (16.2)	0	29 (7.9)	0	80 (11.7)
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)
Vascular disorders	4 (1.6)	32 (6.6)	11 (6.5)	21 (6.7)	4 (2.2)	44 (12.0)	8 (1.9)	65 (9.5)
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)
General disorders and administration site conditions	4 (1.6)	21 (4.3)	7 (4.1)	14 (4.4)	3 (1.7)	35 (9.5)	7 (1.7)	49 (7.2)
Fatigue	1 (0.4)	9 (1.9)	4 (2.4)	5 (1.6)	0	22 (6.0)	1 (0.2)	27 (4.0)

Abbreviations: CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class; TEAE=treatment-emergent adverse event.
a All patients randomized to niraparib in the NOVA study were treated with a starting dose of 300 mg/day.
Note: If a patient experienced more than 1 event in a given SOC, that patient was counted once for the SOC. If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.

Table 57. Grade ≥3 Haematologic Toxicities for the low W/P Population (PRIMA study; DCO 17 Nov 2019)

Hematologic Event, n (%)	FSD (300 mg Starting Dose) Group C; N=243		ISD (200 mg Starting Dose) Group D; N=122	
	Grade 3/4	Grade 4	Grade 3/4	Grade 4
Thrombocytopenia	127 (52.3%)	95 (39.1%)	21 (17.2%)	8 (6.6%)
Anemia	86 (35.4%)	1 (0.4%)	25 (20.5%)	1 (0.8%)
Neutropenia	67 (27.6%)	26 (10.7%)	18 (14.8%)	1 (0.8%)

Source: Table 14.3.1.17h, Table 14.3.1.17g, Table 14.3.3.10, and Table 14.3.3.11
Abbreviations: FSD=fixed starting dose; ISD=individualized starting dose; Low W/P=low baseline weight and platelet counts.

Adverse drug reactions

Adverse drug reactions in the PRIMA study were evaluated using relative risk assessment for the niraparib treatment arm versus the placebo arm in addition to medical-pharmacological assessment of ADRs.

The relative risk and 95% confidence interval (CI) were provided for TEAEs reported in ≥1% of patients and Grade ≥3 TEAEs reported in ≥1% of patients in either treatment arm, respectively (CSR, data not shown). Based on the TEAE rates observed in patients who received placebo, the population enrolled in this study had a high background rate of TEAEs related to the burden of prior chemotherapy and disease.

No new ADRs were identified in PRIMA as compared to previous studies with niraparib.

Adverse reactions (ADRs) of all grades occurring in ⩾ 10 % of the 851 patients receiving Zejula monotherapy in the pooled PRIMA (either 200 mg or 300 mg starting dose) and NOVA trials were nausea, anaemia, thrombocytopenia, fatigue, constipation, vomiting, headache, insomnia, platelet count decreased, neutropenia, abdominal pain, decreased appetite, diarrhoea, dyspnoea, hypertension, asthenia, dizziness, neutrophil count decreased, cough, arthralgia, back pain, white blood cell count decreased, and hot flush.

The incidence of the most common ADRs and laboratory abnormalities in the PRIMA study (i.e., ADRs occurring in ⩾10% of patients, and laboratory abnormalities occurring in ⩾25% of patients) were consistent with those previously identified in other niraparib studies.

The adverse reactions noted in the group of patients who were administered a 200 mg starting dose of Zejula based on baseline weight or platelet count were of similar or lesser frequency compared to the group administered a fixed starting dose of 300 mg.

Serious adverse events and deaths

Table 58. Serious Treatment-emergent Adverse Events Reported in ≥2% of Patients in Either Pooled Treatment Group by MedDRA System Organ Class and Preferred Term (PRIMA and NOVA Study Pool)

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
MedDRA SOC Preferred Term	All n (%) N=244	All n (%) N=484	Individualized n (%) N=169	Fixed n (%) N=315	All n (%) N=179	Fixed[a] n (%) N=367	All n (%) N=423	Fixed n (%) N=682
Any SAE	32 (13.1)	156 (32.2)	45 (26.6)	111 (35.2)	27 (15.1)	123 (33.5)	59 (13.9)	234 (34.3)
Blood and lymphatic system disorders	0	87 (18.0)	22 (13.0)	65 (20.6)	0	56 (15.3)	0	121 (17.7)
Thrombocytopenia	0	59 (12.2)	7 (4.1)	52 (16.5)	0	40 (10.9)	0	92 (13.5)
Anemia	0	27 (5.6)	14 (8.3)	13 (4.1)	0	15 (4.1)	0	28 (4.1)
Gastrointestinal disorders	12 (4.9)	24 (5.0)	9 (5.3)	15 (4.8)	14 (7.8)	28 (7.6)	26 (6.1)	43 (6.3)
Small intestinal obstruction	5 (2.0)	14 (2.9)	3 (1.8)	11 (3.5)	4 (2.2)	9 (2.5)	9 (2.1)	20 (2.9)
Investigations	0	23 (4.8)	5 (3.0)	18 (5.7)	0	3 (0.8)	0	21 (3.1)
Platelet count decreased	0	20 (4.1)	5 (3.0)	15 (4.8)	0	1 (0.3)	0	16 (2.3)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SOC=system organ class.
a All patients randomized to niraparib in the NOVA study were treated with a starting dose of 300 mg/day.
Note: If a patient experienced more than 1 event in a given SOC, that patient was counted once for the SOC. If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.

Deaths

In the PRIMA and NOVA study pool, a total of 226 (33%) patients in the pooled niraparib group and 119 (28%) patients in the pooled placebo group had died at the time of the data cutoff of 17 May 2019, and 5 TEAEs leading to death were reported in niraparib-treated patients. No on-treatment deaths were reported in either study.

In the PRIMA study, 2 patients treated with niraparib and 1 patient treated with placebo experienced TEAEs that led to death. The events leading to death were intestinal perforation (Patient in niraparib arm) which likely occurred secondary to bowel obstruction. This is a common sequela of high grade tubo-ovarian cancer. The other event of pleural effusion (Patient in niraparib arm) was likely due to lung metastases. An event of intentional overdose with hydromorphone occurred in the placebo arm. None of these events were assessed as related to study treatment by the investigator.

Between the previous DCO of 30 May 2016 and DCO of 17 May 2019, 3 niraparib patients in the NOVA study experienced TEAEs leading to death. Two patients died of AML; both these deaths were assessed as related to study drug. Refer to section on adverse events of special interest: MDS/AML for more information. Another patient died of chronic obstructive pulmonary disease, dyspnea, pneumonia, sepsis, and acute kidney injury; the events of sepsis and acute kidney injury were assessed as likely related to study drug. The case was confounded by pre-existing history of COPD.

Other Significant Events

In the PRIMA and NOVA studies, particular attention was paid to monitoring patients for AESIs, including MDS/AML, secondary primary malignancies other than MDS/AML, pneumonitis, and embryo-fetal toxicity. In addition to AESIs, myelosuppression events (thrombocytopenia events, anemia events, neutropenia events, leukopenia events, and pancytopenia events), hypertension events, and thromboembolic events were grouped for analysis as events of medical interest. These AESIs were selected based on the known safety profile of niraparib and other PARP inhibitors.

MDS/AML

Cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) have been observed in patients treated with Zejula monotherapy or combination therapy in clinical trials and post-marketing. There are 1,785 subjects who have been exposed to monotherapy niraparib treatment or maintenance in clinical trials as of DCO 17 May 2019. MDS/AML events data from PRIMA (N=728; niraparib: 484 and placebo: 244) is presented in context with data from QUADRA (N=463; niraparib), NOVA (N=546; niraparib: 367 and placebo: 179) and with pooled clinical data of subjects exposed to niraparib monotherapy treatment or maintenance in other clinical studies (N=536; niraparib: 471 and physician’s choice: 65) as of 17 May 2019 data cutoff.

As of DCO 17 May 2019, 15 cases of myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) have been reported in clinical trials in patients who received niraparib.

Germline BRCA status was not available for all subjects across the clinical trials; therefore, the incidence of MDS and/or AML in subjects who are BRCAmut vs. BRCA wild type was not evaluated.

In the PRIMA study, 1 new case of MDS/AML was reported. One niraparib patient with a homologous recombination-deficient tumor experienced MDS reported as Grade 4 on study. In the NOVA study, a total of 14 reports of MDS/AML have been reported since study start.

Table 59. Summary of AEs of MDS and/or AML Occurring Across the Niraparib Monotherapy Clinical Program (DCO: 17 May 2019)

Data Source	TEAEs[a] + AEs After 30 Day Follow-up			
	Niraparib		Placebo	
	Number of AEs	Incidence	Number of AEs	Incidence
PRIMA N=484 niraparib[b] N=244 placebo	1	0.2	0	0
QUADRA N=463 niraparib	3	0.6	NA	NA
NOVA[c] N=367 niraparib N=179 placebo	11	3.0	3	1.7
Other Monotherapy Studies [d] (N=471)	0	0	0	0
Overall Niraparib Monotherapy Pool N=1,785 niraparib N=488 placebo/physician's choice treatment	15	0.8	3	0.6

Source: Table 1.1,Table 1.2

Abbreviations: AE=adverse event; AML =acute myeloid leukaemia; DCO=data cut-off; MDS=myelodysplastic syndrome; N=total number of patients; NA=not applicable; TEAE=treatment emergent adverse event.

[a] TEAEs are events occurring on-study treatment or during 30-day follow-up after the last dose of study treatment.

[b] Includes all patients treated with individualised and fixed starting doses of niraparib.

[c] All patients were treated with fixed starting dose of niraparib.

[d] Data is from NOVA-QTc, NOVA-FE, AME, TABLET, PN001, HEPATIC, BRAVO, JASPER, NEOADJUVANT studies.

Second Primary Malignancies Other Than Myelodysplastic Syndrome and Acute Myeloid Leukemia

In the PRIMA study, a total of 7 new malignancies other than MDS/AML were reported. The incidence of new malignancies other than MDS/AML was similar in the niraparib arm (4 of 484 patients, <1%) and the placebo arm (3 of 244 patients, 1%). In the PRIMA and NOVA study pool, the analysis identified 9 (1%) patients in the pooled niraparib group and 4 (1%) patients in the pooled placebo group with events in this category. There was no specific trend suggesting a different frequency for any given type of tumor in pooled niraparib vs pooled placebo patients.

Pneumonitis

A total of 5 patients (1%) treated with niraparib in the PRIMA study experienced pneumonitis events compared to no patients who received placebo. All events were Grade 1 or 2 in intensity and reported as serious as instructed per study protocol. Two patients were diagnosed with pneumonitis based on routine study imaging, and 2 were diagnosed due to symptoms of dyspnea, cough, or chest pain. Events led to dose interruption/reduction in 1 patient, drug withdrawn in 1 patient, and no change in 2 patients. Three patients experienced Grade 2 events that were assessed as related or possibly related to study treatment.

In the NOVA study, 4 events in the pneumonitis category were identified. Pneumonitis events were reported in 3/367 (1%) patients in the niraparib group and in 1/179 (<1%) patient in the placebo group.

All events were Grade 1 or 2. One patient who received niraparib in the NOVA study experienced a nonserious pneumonitis event that was assessed likely related to study treatment. All other pneumonitis events were considered unrelated to study treatment.

Embryo-Foetal Toxicity

In the PRIMA and NOVA study pool, a total of 4 events were reported in this category. None of the 4 terms (chloasma [verbatim term: melasma], gene mutation [verbatim term: vaginal gene defect], ichthyosis, and mastitis) were reported for women of childbearing potential or were associated with pregnancies; therefore, these events are not considered embryo-fetal toxicities. All 4 events were considered by the Investigator as unrelated to study drug.

Hypertension

In the PRIMA study, the incidence of hypertension events in patients receiving niraparib was 18% (87/484 patients). In comparison, 7% of patients receiving placebo experienced hypertension events. Grade 3/4 hypertension occurred in 6% of Zejula-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 50 days (range: 1 to 589 days) and with a median duration of 12 days (range: 1 to 61 days. Treatment was not withdrawn due to grade 3/4 events. In the individualized starting dose group, the rate of Grade ⩾3 hypertension was 5% in patients in the niraparib arm compared to 2% in the placebo arm.

One patient treated with niraparib experienced a hypertension event Grade 3 that was reported as an SAE; none of the patients who received placebo experienced a hypertension event that was reported as an SAE.

Eight patients in the niraparib arm (2%) underwent dose interruption and 4 (1%) underwent dose reduction for hypertension. No patients were discontinued from study drug due to hypertension. No events of hypertensive crisis were reported in the PRIMA study.

Overall, in the PRIMA and NOVA study pool, hypertension was reported as a TEAE in 144 (21%) of the 682 patients in the niraparib pooled group and in 27 (6%) of the 423 patients in the placebo pooled group. Grade ⩾3 hypertension was reported in 54 (8%) of the 682 patients, Grade ⩾3 hypertensive crisis was reported in 2 (<1%) patients, and Grade ⩾3 blood pressure increased was reported in 1 (<1%) patient in the pooled niraparib group compared with 7 patients (2%) with Grade ⩾3 hypertension and no Grade ⩾3 hypertensive crisis or Grade ⩾3 blood pressure increased in the pooled placebo group.

A review of increases from baseline in systolic and diastolic blood pressure in the PRIMA study revealed that the changes occurred during the first 15 days of treatment.

Thromboembolic events

In the PRIMA study, 3 (0.6%) patients experienced thromboembolic events in the niraparib arm compared with 1 (0.4%) patient in the placebo arm. All 3 thromboembolic events in the niraparib arm were reported as Grade ⩾3; no Grade ⩾3 events were reported in the placebo arm. The Grade ⩾3 thromboembolic events included singular TEAE reports of pulmonary embolism, embolism, and thrombosis. None of the 3 events was assessed as related to niraparib by Investigator.

In the PRIMA and NOVA study pool, 11 (2%) pooled niraparib patients experienced thromboembolic events compared with 2 (0.5%) placebo patients. Of these, 6 (1%) pooled niraparib patients and no placebo patients experienced events that were considered Grade ⩾3.

Myelosuppression Adverse Events of Interest

Table 60. presents the overall incidence of myelosuppression events by type of event reported in the PRIMA and NOVA studies by category.

Table 60. Incidence of Myelosuppression Treatment-Emergent Adverse Events by Type of Event (PRIMA and NOVA Study Pool)

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
Myelosuppression Event Preferred Term	All n (%) N=244	All n (%) N=484	Individualized n (%) N=169	Fixed n (%) N=315	All n (%) N=179	Fixed[a] n (%) N=367	All n (%) N=423	Fixed n (%) N=682
Thrombocytopenia events	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)
Anemia events	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 events	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 events	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 events	0	2 (0.4)	0	2 (0.6)	0	8 (2.2)	0	10 (1.5)
Myelodysplastic syndrome	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)

Abbreviations: MedDRA=medical dictionary for regulatory activities; PT=preferred term; SMQ=Standardized MedDRA Query

Note: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.

Note: since both leukopenia events and neutropenia events used MedDRA preferred terms in the Haematopoeitic leukopenia SMQ (broad), the preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis are reported under both leukopenia and neutropenia myelosuppression events.

a All patients randomized to niraparib in the NOVA study were treated with a starting dose of 300 mg/day.

Thrombocytopenia events

Incidence of thrombocytopenias events

Overall in the PRIMA study, a total of 321 (66%) patients treated with niraparib experienced a thrombocytopenia event compared to 12 (5%) patients who received placebo (Table 71). The incidence

rate of thrombocytopenia events by PEY was 0.92 for patients who received niraparib and 0.05 for those who received placebo. 39% of Zejula-treated patients experienced Grade 3/4 thrombocytopenia compared to 0.4% of placebo-treated patients with a median time from first dose to first onset of 22 days (range: 15 to 335 days) and with a median duration of 6 days (range: 1 to 374 days).

21 (4%) patients had treatment with niraparib withdrawn due to a thrombocytopenia event, all of these were of Grade ⩾3. No patients in the placebo group withdrew treatment due to thrombocytopenia. Thrombocytopenia events were reported as SAEs in 79 (16%) patients who received niraparib; none of the patients who received placebo experienced a thrombocytopenia event that was reported as an SAE.

FSD vs ISD

203 patients (73%) experienced a thrombocytopenia event in the FSD group, compared to 91 patients (53%) in the ISD group. The rate of Grade ⩾3 thrombocytopenia events was 48% in patients who received the fixed starting dose compared to 21% in patients who received the individualized starting dose.

Characterization of Thrombocytopenia Events

In the PRIMA study, thrombocytopenia events generally occurred early during niraparib treatment (during Cycle 1) with the incidence decreasing rapidly thereafter; during Month 1 of niraparib therapy, the incidence of overall thrombocytopenia events was 53% (258 of 484 patients); this decreased to 8% (34 of 454 patients) during Month 2 and then was <5% for Months 3, 4, 5, and ⩾6.

At study baseline in the PRIMA study, 94% of patients in the niraparib and placebo arms had platelet laboratory values in the normal range; Grade 1 thrombocytopenia was noted in 6% of patients in each arm. In the niraparib arm, shifts to Grade 3 or 4 thrombocytopenia occurred in 181 (38%) of the 483 patients who had baseline and post-baseline results. No patient in the placebo arm had a shift to Grade 3 or 4 thrombocytopenia on treatment.

Mean decreases in platelets were observed during Cycle 1 in patients treated with niraparib, with recovery noted starting at Cycle 2. By Cycle 5, mean platelet counts were near baseline and remained stable in the niraparib arm for the remainder of the study.

Management of thrombocytopenia

In general, thrombocytopenia events were manageable with few patients discontinuing study drug due to these TEAEs; 21 patients (4%) who received niraparib and no patients who received placebo had study drug withdrawn as a result of thrombocytopenia. As required by protocol, study drug interruptions and dose reductions were mandated for patients with low platelet counts. Also per protocol, platelet transfusions may have been considered for patients with platelet count ≤10,000/μL. Overall, 94 patients (19%) required platelet transfusions. 67 patients (14%) requiring a platelet transfusion had platelet counts <10,000/ μL. All of the platelet transfusions were in patients receiving niraparib.

In the niraparib arm, study drug interruption for these events occurred in 269 patients (56%) and dose reduction occurred in 229 patients (47%). There were no study drug interruptions or dose reductions for thrombocytopenia for patients who received placebo.

Anaemia events

Anaemia events include reports of anemia, anemia macrocytic, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased.

Incidence of anaemia events

In the PRIMA study, a total of 311 patients (64%) treated with niraparib experienced an anemia event

compared with 43 patients (18%) who received placebo (Table 71). The incidence rate of anemia events by PEY was 1.68 for patients who received niraparib and 0.26 for those who received placebo.

In PRIMA, 31% of Zejula-treated patients experienced Grade 3/4 anaemia compared to 2% of placebo-treated patients with a median time from first dose to first onset of 80 days (range: 15 to 533 days) and with a median duration of 7 days (range: 1 to 119 days). 5 patients (1%) had treatment with niraparib withdrawn due to these Grade 3/4 events. In contrast, no patients treated with placebo had their treatment withdrawn due to an anaemia event. Anaemia events were reported as SAEs in 27 patients (6%) treated with niraparib and in none of the patients who received placebo. Overall, 9 patients (2%) who received niraparib and no patients who received placebo had study drug withdrawn as the result of anemia.

ISD vs FSD

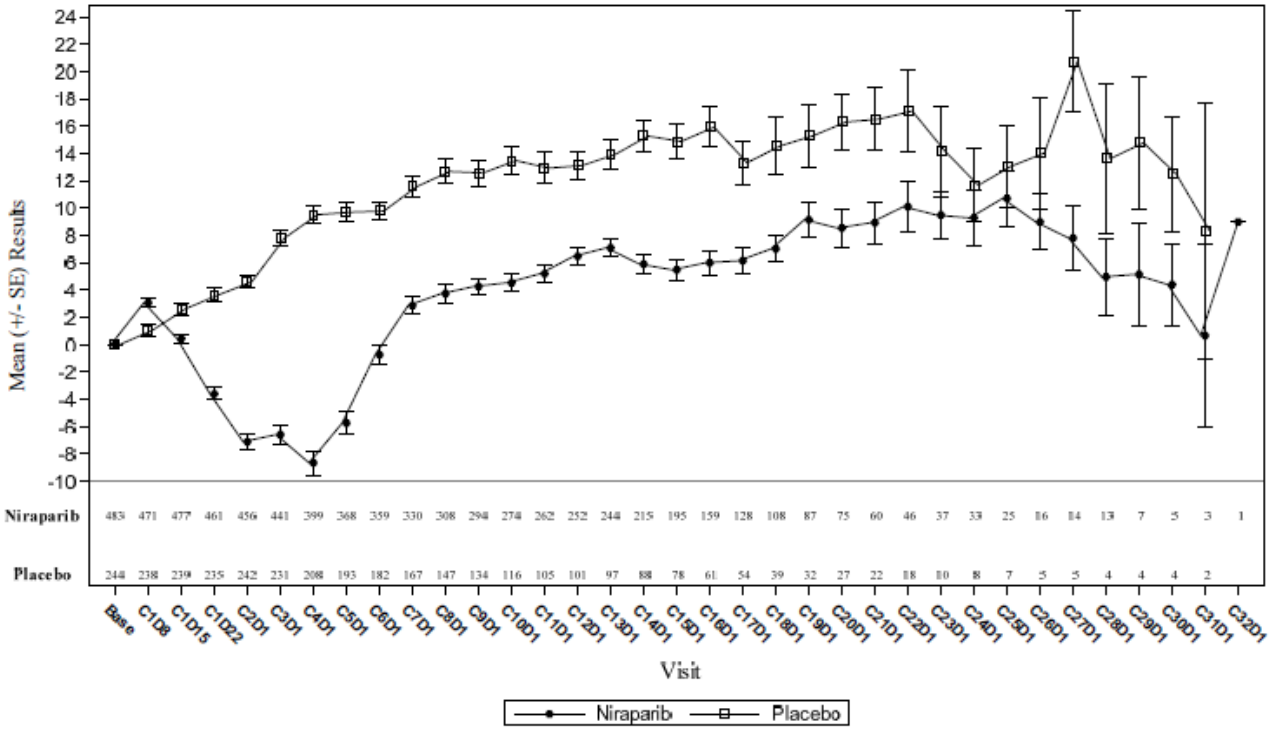
The rate of Grade ⩾3 anemia events was 36% in patients who received the fixed starting dose as compared to 23% in patients who received the individualized starting dose. The PEY adjusted incidence rate of anaemia events (regardless of grade) was 2.02 in the FSD subgroup and 1.16 in the ISD subgroup.

Characterisation of anaemia events

At study entry in the PRIMA study, most patients had Grade 0 or 1 hemoglobin concentrations; 2% of patients in the niraparib arm and 3% of patients in the placebo arm entered the study with Grade 2 anemia. In the niraparib arm, shifts to Grade 3 anemia occurred in 140 (29%) of the 483 patients with baseline and post-baseline data available. Only 3 patients (1%) in the placebo arm had a shift to Grade 3 anemia. None of the patients in either the niraparib or placebo arms had laboratory shifts to Grade 4 anemia.

In the PRIMA study, the onset of anemia events tended to occur early during niraparib treatment with the incidence decreasing over time; during Month 1 of niraparib therapy, the incidence of anemia events was 31% (148 of 484 patients); this decreased to 11% (50 of 454 patients) during Month 2 and 13% (55 of 437 patients) during Month 3. The incidence was 8%, 1%, and 6% for Months 4, 5, and ⩾6, respectively. As shown in Figure 49, decreases in hemoglobin were observed starting during Cycle 1 of niraparib treatment; mean hemoglobin levels remained below baseline until approximately Cycles 6-7.

Figure 49. Change from Baseline (+/-SE) in Hemoglobin (g/L) Over Time (PRIMA study)



Management of anaemia

Overall, anaemia events in the PRIMA study were manageable, with few patients discontinuing study drug due to these TEAEs; 9 patients (2%) who received niraparib and no patients who received placebo had study drug withdrawn as the result of anemia. As required by the protocol, study drug interruptions and dose reductions were employed for patients with low hemoglobin levels. In the niraparib arm, study drug interruption for anemia events occurred in 152 patients (31%) who received niraparib and study drug dose reduction occurred in 131 patients (27%). Two patients (<1%) who received placebo experienced a dose interruption and 2 patients (<1%) experienced a dose reduction due to these events.

Leukopenia events

Leukopenia events include reports of neutropenia, neutrophil count decreased, white blood cell count decreased, leukopenia, lymphocyte count decreased, lymphopenia, febrile neutropenia, eosinophil count decreased, neutropenic sepsis, and monocyte count decreased.

Incidence of leukopenia events

In the PRIMA study, a total of 241 patients (50%) treated with niraparib experienced a leukopenia event compared with 32 patients (13%) who received placebo (Table 71). The incidence rate of leukopenia events by PEY was 0.15 for patients who received niraparib and 0.07 for those who received placebo. Among niraparib patients in the PRIMA study, 105 (22%) experienced a Grade 3 or 4 leukopenia event. In contrast, 4 (2%) placebo patients experienced a Grade 3/4 leukopenia event. Leukopenia events were reported as SAEs in 11 patients (2%) who received niraparib; none ofthe patients who received placebo experienced a leukopenia event that was reported as an SAE.

FSD vs ISD

The rate of Grade ⩾3 leukopenia events was 25% in patients who received the fixed starting dose of niraparib compared to 16% in patients who received the individualized starting dose. PEY-adjusted leukopenia rates (all grades) were similar in the two niraparib dosing subgroups.

Characterisation of leukopenia events

In the PRIMA study, leukopenia events tended to occur early during niraparib treatment, with the

incidence decreasing over time; the overall incidence of leukopenia events during Month 1 of niraparib therapy was 33% (158 of 484 patients); this decreased to 13% (57 of 454 patients) during Month 2 and then was <3% for months 3, 4, 5, and ⩾6.

Management of leukopenia
Overall, leukopenia events were manageable, with few patients discontinuing study drug due to these TEAEs; 10 patients (2%) who received niraparib and no patients who received placebo had study drug withdrawn as the result of a leukopenia event. In the niraparib arm, study drug interruption occurred in 97 patients (20%) and dose reduction occurred in 68 patients (14%). Study drug interruption and reduction for leukopenia events were uncommon for patients who received placebo (<2% each).

Neutropenia events

Neutropenia events include neutropenia, neutrophil count decreased, neutropenic sepsis, and febrile neutropenia Table 60.

Incidence of neutropenia events
In the PRIMA study, a total of 205 patients (42%) treated with niraparib experienced a neutropenia event compared to 19 patients (8%) who received placebo (Table 71). The incidence rate of neutropenia events by PEY was 0.39 for patients who received niraparib and 0.09 for those who received placebo. Febrile neutropenia was reported in 4 (1%) niraparib patients and in no placebo patient.

21% of Zejula-treated patients experienced Grade 3/4 neutropenia compared to 1% of placebo-treated patients with a median time from first dose to first onset of 29 days (range: 15 to 421 days) and with a median duration of 8 days (range: 1 to 42 days). Neutropenia events were reported as SAEs in 11 patients (2%) treated with niraparib and none of the patients who received placebo.

FSD vs ISD
The rate of Grade ⩾3 neutropenia events was 24% in patients who received a fixed starting dose compared to 15% in patients who received an individualized starting dose. No remarkable differences in PEY-adjusted neutropenia rates (all grades) were seen for patients receiving niraparib in the individualised dosing group (0.34) compared to the fixed dosing subgroup (0.28).

Characterisation of neutropenia events
In the PRIMA study, neutropenia events tended to occur early during niraparib treatment 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 with dose modifications. The overall incidence of neutropenia events during Month 1 of niraparib therapy was 26% (128 of 484 patients); this decreased to 13% (59 of 454 patients) during Month 2 and then was ⩽2% for Months 3, 4, 5, and ⩾6.

Most patients in both treatment arms had Grade 0 or 1 neutrophil counts at study entry; Grade 2 neutropenia was noted in approximately 2% of patients in each treatment arm at baseline. In the niraparib arm, shifts to Grade 3 or 4 neutropenia occurred in 112 (23%) of the 483 patients who had baseline and post-baseline results. Only 2 patients in the placebo arm had a shift from baseline to a Grade 3 neutropenia on treatment. Decreases in neutrophils were observed starting during Cycle 1 of niraparib treatment; mean neutrophil levels remained below baseline until approximately Cycles 4-5.

Management of neutropenia
In the PRIMA study, study drug interruption occurred in 93 patients (19%) who receive niraparib and dose reduction occurred in 65 (13%). Study drug interruption and reduction for neutropenia events were uncommon for patients who received placebo (~1% each).

Discontinuations due to neutropenia were reported in 9 patients (2%) who received niraparib and no patients who received placebo.

Pancytopenia events

Pancytopenia events included reports of pancytopenia, aplastic anemia, bone marrow failure, and MDS.

Incidence of pancytopenia events
Two pancytopenia events (<1%) were reported during the PRIMA study (Table 71) and both were in patients with homologous recombination-deficient tumors in the niraparib arm and reported as Grade 3 or 4 SAEs. The pancytopenia events included 1 TEAE report of MDS and 1 report of pancytopenia. Both events were reported in patients who received the fixed starting dose. The case of MDS is considered under the MDS/AML heading above.

Characterisation of pancytopenia events
During Month 1 of niraparib therapy, the incidence of overall pancytopenia events in pooled niraparib patients (PRIMA and NOVA studies) was <1% (3 of 682 patients, respectively). No events occurred during Months 2, 3, 4, and 5, and the incidence was 1% (7 in 492 patients) for Months ⩾6.

Management of pancytopenia
No patients in the PRIMA trial withdrew from treatment with niraparib due to pancytopenia. The action taken in the patient with pancytopenia was reported as dose reduced from 300 mg QD to the 100 mg QD dose level. In the NOVA trial, a total of 5 (1%) patients discontinued study drug as a result of pancytopenia events; all pancytopenia events leading to study drug discontinuation occurred in the niraparib group, and all were Grade ≥3. Study drug interruption for pancytopenia events occurred in 3 (<1%) pooled niraparib patients and no pooled placebo patients while dose reductions occurred in 2 (<1%) pooled niraparib patients and no pooled placebo patients.

Analysis of other adverse events

Other TEAEs that were reported with a higher incidence rate (⩾10%) in niraparib patients than in placebo patients included nausea, constipation, vomiting, fatigue, headache, decreased appetite and insomnia. Similar incidence rates were noted for these TEAEs when considering the PRIMA study and the PRIMA and NOVA study pool.

In general, gastrointestinal disorders were reported with a higher incidence rate in pooled niraparib patients than in pooled placebo patients (90% vs 72%). The most commonly reported gastrointestinal TEAEs in niraparib patients with corresponding incidence in placebo patients were nausea (68% vs 31%), constipation (42% vs 20%), and vomiting (31% vs 14%). The majority of these events were Grade 1 or 2 in severity, and these gastrointestinal events were serious or resulted in study drug discontinuation in ⩽ 1% of niraparib patients.

Fatigue was reported in 288 (42%) niraparib patients and in 130 (31%) placebo patients; the events were assessed by the Investigator as Grade ⩾3 in 4% of niraparib patients and in <1% of placebo patients. All but one event of fatigue in a niraparib patient were considered nonserious; in 12 (2%) of niraparib patients and in none of the placebo patients, the event of fatigue resulted in discontinuation of study drug.

Headache was reported in 193 (28%) niraparib patients and in 57 (14%) placebo patients. The majority of these events were Grade 1 or 2 in severity, except in 3 (<1%) niraparib patients. All events of

headache were considered nonserious, and TEAEs of headache resulted in study drug discontinuation in 4 (<1%) niraparib patients and in none of the placebo patients.

Insomnia was reported in 175 (26%) niraparib patients and in 51 (12%) placebo patients. The majority of events of insomnia were Grade 1 or 2 in severity; 5 patients who received niraparib and 1 of the patients who received placebo experienced Grade ⩾3 events of insomnia. All but 1 event of insomnia in niraparib patient were considered nonserious, and insomnia resulted in study drug discontinuation in 3 (<1%) niraparib patients and in 1 (<1%) placebo patient.

Decreased appetite was reported in 157 (23%) niraparib patients and in 47 (11%) placebo patients. The majority of these events were Grade 1 or 2 in severity; all but one event of decreased appetite in a placebo patient were considered nonserious. Events of decreased appetite resulted in study drug discontinuation in 5 (<1%) niraparib patients and none of the placebo patients.

Laboratory findings

Hematology

Changes in hematology laboratory values were expected over the course of treatment given the known safety profile of niraparib from completed and ongoing single-agent clinical studies and of other PARP inhibitors. Changes from baseline in platelet count, hemoglobin concentrations, neutrophil counts, and leukocyte counts are discussed with the corresponding medically significant hematologic events above. Results of shift analyses for platelet count, hemoglobin concentrations, neutrophil counts, and leukocyte counts are discussed with the corresponding AESI.

Blood chemistry

There were no clinically meaningful changes from baseline for blood chemistry parameters during the study for both PRIMA and NOVA. Summaries of shift analyses from baseline to maximum on-treatment CTCAE grade were conducted for blood chemistry parameters. The incidence of shifts to Grade 3 or 4 abnormalities was low for each clinical chemistry parameter examined.

Potential Hy's law cases

One patient in the niraparib arm met the criteria for drug-induced liver injury in the PRIMA study, based on elevated AST, ALT, and bilirubin values. The patient received the 300 mg startdose. Elevations up to Grade 3 in ALT and AST were noted. Total bilirubin was above the upper limit of normal. The patient developed toxic hepatitis (grade 2-3) after about 8 months on the study. Metastases in the liver were identified, which is a confounding factor.

In the pooled niraparib group, 4 patients had elevations of ALT >10×ULN to ⩽20×ULN and 2 patients had elevations of AST >10×ULN to ⩽20×ULN; no pooled placebo patients had elevations in ALT or AST >10×ULN to ⩽20×ULN. No patient in the pooled niraparib group had elevations of AST or ALT >20×ULN, but one patient in the niraparib individualized dose group and 1 patient in the pooled placebo group had elevations of AST and ALT >20×ULN.

Five niraparib patients and 3 placebo patients in the pooled niraparib group experienced elevations in bilirubin to >2×ULN and 90 niraparib patients and 17 placebo patients had elevations in ALP to >1.5×ULN. In addition, one patient in the niraparib individualised dose group experienced elevation in bilirubin to >2×ULN and 4 patients in the ISD group had elevations in ALP to >1.5×ULN. No events related to increased ALT, AST, ALP, or bilirubin increases led to discontinuation of treatment.

In the NOVA study, 4 potential candidates for Hy's Law were identified based on elevated AST,ALT, and bilirubin values, 1 in the placebo arm and 3 in the niraparib arm. The case in the placebo arm was related

to high doses of paracetamol. Two of the cases in the niraparib arm were diagnosed as cholestasis due to disease progression, and one case was an event of cholecystitis that resulted in cholecystectomy, subsequent biliary tract damage and liver failure. None of the cases in the NOVA trial met the criteria for Hy's law.

Safety in special populations

Intrinsic factors

There were no clinically meaningful differences in the overall incidence of TEAEs and SAEs, treatment-related TEAEs, TEAEs leading to study drug discontinuation, specific AESIs, or Grade ≥3 AESIs based on age or race.

Extrinsic factors

There were no clinically meaningful differences in the overall incidence of TEAEs and SAEs, treatment-related TEAEs, TEAEs leading to study drug discontinuation, specific AESIs, or Grade ≥3 AESIs based on number of prior chemotherapy courses.

Safety related to drug-drug interactions and other interactions

The effect of other drugs on niraparib across the niraparib program is described in the initial niraparib marketing application and labeling. Because of the minimal risk of drug interactions, no specific drug-drug interaction studies were provided with this application.

Discontinuation due to adverse events

Table 61. Treatment-emergent Adverse Events Leading to Study Drug Discontinuation in ≥1% Pooled Patients by MedDRA System Organ Class and Preferred Term (PRIMA and NOVA Study Pool)

	PRIMA				NOVA		Pooled	
	Placebo	Niraparib			Placebo	Niraparib	Placebo	Niraparib
MedDRA SOC Preferred Term	All n (%) N=244	All n (%) N=484	Individualized n (%) N=169	Fixed n (%) N=315	All n (%) N=179	Fixed[a] n (%) N=367	All n (%) N=423	Fixed n (%) N=682
Any TEAE leading to drug discontinuation	6 (2.5)	58 (12.0)	23 (13.6)	35 (11.1)	4 (2.2)	64 (17.4)	10 (2.4)	99 (14.5)
Blood and lymphatic system disorders	0	27 (5.6)	9 (5.3)	18 (5.7)	1 (0.6)	18 (4.9)	1 (0.2)	36 (5.3)
Thrombocytopenia	0	18 (3.7)	4 (2.4)	14 (4.4)	1 (0.6)	8 (2.2)	1 (0.2)	22 (3.2)
Anaemia	0	9 (1.9)	5 (3.0)	4 (1.3)	0	5 (1.4)	0	9 (1.3)
Neutropenia	0	6 (1.2)	2 (1.2)	4 (1.3)	0	3 (0.8)	0	7 (1.0)
Gastrointestinal disorders	1 (0.4)	9 (1.9)	4 (2.4)	5 (1.6)	1 (0.6)	14 (3.8)	2 (0.5)	19 (2.8)
Nausea	0	6 (1.2)	4 (2.4)	2 (0.6)	0	7 (1.9)	0	9 (1.3)
Investigations	0	10 (2.1)	4 (2.4)	6 (1.9)	0	13 (3.5)	0	19 (2.8)
Platelet count decreased	0	3 (0.6)	1 (0.6)	2 (0.6)	0	6 (1.6)	0	8 (1.2)
Neutrophil count decreased	0	3 (0.6)	1 (0.6)	2 (0.6)	0	4 (1.1)	0	6 (0.9)
General disorders and administration site conditions	1 (0.4)	8 (1.7)	3 (1.8)	5 (1.6)	0	11 (3.0)	1 (0.2)	16 (2.3)
Fatigue	0	4 (0.8)	1 (0.6)	3 (1.0)	0	9 (2.5)	0	12 (1.8)
Nervous system disorders	0	5 (1.0)	2 (1.2)	3 (1.0)	0	4 (1.1)	0	7 (1.0)
Dizziness	0	3 (0.6)	0	3 (1.0)	0	2 (0.5)	0	5 (0.7)

Abbreviations: CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class; TEAE=treatment-emergent adverse event.

a All patients randomized to niraparib in the NOVA study were treated with a starting dose of 300 mg/day.

Note: If a patient experienced more than 1 event in a given SOC, that patient was counted once for the SOC. If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.

Post marketing experience

As described in the Periodic Safety Update Report No. 04 (data lock point 26 September 2019; Procedure no.: EMEA/H/C/PSUSA/00010655/201909), information relating to the benefit-risk profile of niraparib received in the reporting period of 27 March 2019 to 26 September 2019 has been reviewed and an overall assessment of risk has been made.

Based on sales figures and an assumed average daily dose of 200 mg (2 x 100-mg capsules), post-approval exposure during the time period 01-Jan-2019 to 30-Jun-2019 is estimated to be 1,385 patient-years. The algorithm used to derive post-approval exposure data is total number of capsules/2 x 365. This brings the cumulative exposure to 3,158 patient-years.

The results and conclusions from evaluations completed during the period for photosensitivity reaction, posterior reversible encephalopathy syndrome (PRES) and hypertensive crisis/malignant hypertension have been referred to the MAH safety governance and labelling boards for review and to inform action(s) to be taken, as applicable. Based upon the review of the post-marketing data for PSUR No. 4, no new safety concerns and/or new significant information was observed for the important identified risk or important potential risks which would alter the known safety profile of niraparib.

2.5.1. Discussion on clinical safety

The primary data to support the safety of treatment with niraparib in the proposed indication were derived from the ongoing PRIMA study (PR-30-5017-C), where 733 patients were randomised 2:1 to receive niraparib or placebo. A total of 484 patients received niraparib, including 315 patients who received a fixed starting dose of niraparib (300 mg), and 169 patients who received individualized starting doses of niraparib (200 mg or 300 mg) based on baseline body weight and platelet count; 244 patients received placebo. After introduction of the individualised dosing regimen, 13 patients out of 258 (5%) received an incorrect starting dose. This is not considered to impact on the safety data analyses.

The median overall treatment duration from the first to last dose was longer for patients in the niraparib group (11.1 months) compared to the placebo group (8.3 months). The median dose intensity (relative dose intensity) was 181 mg/day (63%) in the niraparib arm overall, consistent with the severe AE profile of niraparib which was managed by dose modifications. The overall exposure to niraparib and placebo in the PRIMA study is considered sufficient for a comparison of safety in the sought indication. Supportive safety data from the ongoing NOVA study (the basis of the initial MA application) were also presented.

In the PRIMA study, demographic and disease characteristics were generally well balanced between the niraparib and placebo arms. The median age was 62 years (range: 32 to 88 years), and 11% and 9% of niraparib and placebo patients, respectively, were ≥ 75 years of age. 69% of niraparib patients and 71% of placebo patients had an ECOG performance status of 0. The population baseline characteristics were also well balanced between ISD group and FSD group with regard to the median age, the proportion of ⩾ 75 years old patients, body weight baseline mean and ECOG status. The mean platelet count in the fixed-dose group was similar to that in the individualized-dose group (248.4 $\times 10^9$/L, vs. 240.1$\times 10^9$/L respectively). There were no remarkable differences in history of prior myelosuppression between patients who received a fixed starting dose compared with those who received an individualized starting dose in either treatment arm.

Overall, the most frequently reported AEs for niraparib in the PRIMA study were consistent with the known safety profile and included haematological and gastrointestinal events such as anaemia (63%), nausea (57%), thrombocytopenia (46%), and constipation (39%). The most frequently reported Grade 3/4 AEs in patients receiving niraparib were consistent with the known safety profile, i.e. anaemia (31%), thrombocytopenia (29%) and hypertension (6%). Consistent with the NOVA study, haematological events (thrombocytopenia, anaemia) were also the AEs generally responsible for frequent dose modifications. Dose interruptions occurred in 80% of patients in the niraparib group and dose reductions in 75%. In the placebo group, 24% and 12% of patients had a dose interruption and dose reduction (all reasons), respectively. Treatment discontinuations occurred in 12% overall in niraparib-treated patients.

Review of the data from the PRIMA study across cohorts for TEAE all grade and CTCAE grade ≥3 incidence shows that the results for the niraparib arm in general were similar in the HRD-positive cohort and overall (data not shown).

In the PRIMA study, 32% of the patients who received niraparib and 13% of the patients who received placebo experienced treatment emergent SAEs. The most common SAEs reported in niraparib-treated patients were consistent with the observed severe safety profile: thrombocytopenia (12%), anaemia (6%), and platelet count decreased (4%).

No on-treatment deaths were observed in the PRIMA study, but two deaths from TEAEs occurred (intestinal perforation and pleural effusion) in niraparib-treated patients in the PRIMA study; none were considered as related to study treatment. The pleural effusion was clearly due to disease progression

and/or infection and there was no evidence that any niraparib-induced lung toxicity could have caused the patient's condition to worsen and then lead to a fatal outcome.

Between the DCO date of 30 May 2016 and DCO of 17 May 2019, 3 patients who received niraparib in the NOVA study experienced TEAEs leading to death considered related to treatment with niraparib: two events of AML and one death due to chronic obstructive pulmonary disease, dyspnea, pneumonia, sepsis, and acute kidney injury. The events of sepsis and acute kidney injury were assessed as likely related to study drug by the investigator.

Overall, 15 cases of MDS/AML have been observed in the niraparib monotherapy clinical program as of the DCO date 17 May 2019. The incidence was slightly higher in the niraparib-treated patients compared to placebo-treated patients: 15 cases (0.8%) vs 3 cases (0,6%), respectively. Exposure to chemotherapy is a confounding factor, as all the patients have received at least one previous chemotherapy regimen.

The risk of MSD/AML with niraparib appears consistent with that reported for other PARP inhibitors, e.g. olaparib, and is described in SmPC section 4.4 of approved PARP inhibitor products, including the niraparib SmPC. Since MDS/AML diagnosis and progression may take years to develop after treatment initiation, the incidence of MDS/AML in the PRIMA trial is likely to rise with longer follow-up times. The duration of Zejula treatment in patients prior to developing MDS/AML varied from 0.5 months to > 4.9 years. The incidences of MDS/AML across the niraparib monotherapy trials is probably influenced by different exposures to niraparib and other DNA-damaging agents and varying follow-up times. MDS/AML is listed in the RMP as an important potential risk with niraparib. The MAH has committed to continuing to monitor MDS and/or AML, in addition to other secondary primary malignancies, through routine pharmacovigilance activities and the two category 3 post-authorization safety studies.

Pneumonitis was previously classified as an important potential risk with niraparib in the RMP. 5/484 patients on niraparib experienced pneumonitis events in the PRIMA trial and 3/367 experienced pneumonitis events in the NOVA trial (incidence 1% in both trials), compared to 1/423 patients in placebo-treated patients (incidence 0,2%). All events were grade 1 or 2 in intensity. Half of the events in niraparib-treated patients were considered as possibly, likely, or related to study treatment by the investigator. Pneumonitis has recently been included in section 4.8 of the SmPC after assessment of the available evidence (EMEA/H/C/004249/II/0020) and will continue to be monitored through routine pharmacovigilance.

Embryo-foetal toxicity is a safety issue that will continue to be monitored through routine pharmacovigilance. No cases consistent with embryo-foetal toxicity have been reported in the PRIMA and NOVA trials. The product information for Zejula contains warnings in section 4.4. and 4.6 concerning use during pregnancy and recommendations for use of reliable contraceptive methods in women of childbearing potential.

The incidence of hypertension events (all grade and $\geqslant$ grade 3) in patients treated with niraparib in PRIMA study was similar to the incidence in the niraparib pool (18% vs. 21% respectively). There was no difference in the incidence of TEAEs of hypertension between the individualised and fixed dosing subgroups. Hypertension is a very commonly occurring event with niraparib. The Zejula SmPC contains information concerning this risk, including a precautionary text for hypertension and hypertensive crisis in section 4.4. Guidance for blood pressure monitoring is included, which is considered sufficient.

Cancer patients are at risk for thromboembolisms. A higher incidence of thromboembolic events was observed in niraparib-treated patients in the PRIMA and NOVA study pool compared to the placebo arms: 11/682 (1.6%) vs 2/423 (0.5%), respectively. Six of the niraparib-treated patients and none of the placebo-treated patients experienced events that were of grade $\geqslant$3. None of the 9 events of thromboembolism which occurred in niraparib-treated patients in the NOVA study, were assessed as related to study drug. Although a higher incidence of thromboembolic events was observed in niraparib-

treated patients in the PRIMA and NOVA studies compared to those treated with placebo, this is not considered sufficient evidence to suggest a causal relationship between niraparib and the adverse event of thromboembolism.

Myelosuppression, including thrombocytopenia, is a main safety issue with niraparib. In the clinical programme, haematologic adverse reactions were managed with laboratory monitoring and dose modifications. The incidence of thrombocytopenia events was high in the PRIMA trial, including 188 patients (39%) on niraparib experiencing grade ⩾3 thrombocytopenia events, compared to none in the placebo group. 94 patients (19%) on niraparib treatment required a platelet transfusion, compared to none in the placebo-treated patients. Thrombocytopenia with niraparib occurs early. The mean decreases in platelets were observed during Cycle 1, with recovery noted starting at Cycle 2. By Cycle 5, mean platelet counts were near baseline and remained stable in the niraparib arm for the remainder of the study, corresponding to management through drug interruptions and dose reductions.

Consistent with the known safety profile, high incidences of anaemia were seen with niraparib in the PRIMA trial (64%). 31% of patients in the niraparib group experienced grade ⩾3 events. Anaemia appeared to be manageable in the PRIMA study, with relatively few patients in the niraparib group (2%) discontinuing treatment due to the event.

In the PRIMA study, the proportion of patients treated with niraparib who experienced a leukopenia events was slightly higher compared to niraparib pool (50% vs. 44%). The SmPC was amended accordingly to consider leukopenia as a very common adverse reaction. Overall, leukopenia events were manageable, with few patients discontinuing study drug due to these TEAEs; 10 patients (2%).

Pancytopenia is a potentially life-threatening ADR with niraparib. One PT of pancytopenia was reported in the niraparib FSD subgroup in the PRIMA trial, for which the action taken with the study drug was reported as dose reduced from 300 mg QD to 100 mg QD. In the NOVA study, 5 patients (1%) discontinued treatment with niraparib due to pancytopenia. Pancytopenia is included as and ADR in the Zejula SmPC section 4.8 with frequency uncommon and is also described under section 4.4 special warnings and precautions, haematologic adverse reactions, which is considered sufficient. If a patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, Zejula should be discontinued.

Gastrointestinal disorders are among the main factors limiting the tolerability of niraparib. The most commonly reported gastrointestinal TEAEs in niraparib patients in the PRIMA and NOVA study pool with corresponding incidence in placebo patients were nausea (68% vs 31%), constipation (42% vs 20%), and vomiting (31% vs 14%). Although the majority of these events were Grade 1 or 2 in severity, patient reported outcomes from the PRIMA study confirm that gastrointestinal related quality of life scores are significantly worse for patient treated with niraparib compared to placebo (refer to clinical efficacy section 5.4.2, subsection on patient reported outcomes).

For nausea and fatigue, the incidence of adverse events was lower in PRIMA study compared to PRIMA and NOVA Study Pool. For headache, insomnia, the incidence of adverse events was almost similar in both.

The incidence of decreased appetite adverse event in PRIMA was slightly lower (19%). The SmPC was amended to consider dysgeusia as common adverse event rather than very common.

Overall, except for pneumonitis, no new ADRs were identified from review of the TEAEs reported in the PRIMA study, or from a review of the combined PRIMA and NOVA study populations. However, based on updated incidence rates in the NOVA and PRIMA study pool, some changes have been made to the SmPC:

- The incidence of leukopenia events in patients who received the fixed starting dose was higher in PRIMA study compared to NOVA study (52.7% vs. 36.5%) and therefore leukopenia is considered as a very common adverse event.
- The SmPC was amended to consider dysgeusia as common adverse event rather than very common.
- Based on updated incidence rates of grade ≥3 elevations in ALT for niraparib in the PRIMA and NOVA study pool, the SmPC was amended so as the ALT increase is considered common grade ≥3 ADR.
- Dyspnoea and epistaxis are considered as uncommon grade ≥ 3 AE based on the available safety data.

In the PRIMA trial, there has been one patient with an event of toxic hepatitis who met the criteria for drug induced liver injury, although liver metastases was a confounding factor. In the NOVA trial, there were three potential Hy's law cases in niraparib-treated patients and one in a placebo-treated patient. None of the cases in the NOVA trial met the criteria for Hy's law. Two of the cases in the niraparib arm were diagnosed as cholestasis due to disease progression. The Zejula SmPC contains information in section 4.8 of liver function test increases with niraparib, including AST increased, ALT increased, gamma-glutamyl transferase increased and blood alkaline phosphatase increased; as well as grade ≥ 3 ADRs including GGT increased, ALT increased, AST increased and blood alkaline phosphatases increased. Currently, the evidence for DILI with niraparib is limited. Possible additional cases of DILI should be commented on in upcoming PSURs.

More patients in the niraparib arm than the placebo arm discontinued due to adverse events (12% vs 2%, respectively) in the PRIMA trial. The most common TEAEs leading to study drug withdrawal in niraparib treated patients were thrombocytopenia (4%), anaemia (2%), and nausea and neutropenia (1% each). None of the placebo patients were discontinued from study drug for these types of events. There were no notable differences in frequencies of TEAEs leading to study drug discontinuation for patients receiving niraparib in the HRD+ cohort compared to the overall population (data not shown).

Although no meaningful differences were noted overall in patients treated with niraparib based on age (<65 years vs ≥ 65 years), it is noted that few patients over 75 years have been treated with niraparib in the PRIMA and NOVA trials (60 patients, 9%, in the pooled niraparib population). Very few patients treated with niraparib in the PRIMA and NOVA trials were non-white, so safety results by race are not assessable.

Individualised vs. fixed starting dose

Patients with lower body weight or lower baseline platelet count may be at increased risk of Grade 3+ thrombocytopenia. In the PRIMA study, patients were initially enrolled at a fixed starting dose (FSD) of 300 mg QD niraparib or placebo. The dosing strategy was subsequently changed by a trial amendment, to an individualised starting dose (ISD), which is the proposed posology in the applied indication. Patients then received 200 mg QD niraparib or placebo, except for patients who weighed ≥ 77 kg and had baseline platelet count ≥ 150,000/μL, where the starting dose was 300 mg QD or placebo. Patients in the ISD subgroup had relatively fewer numbers of cycles and less overall and actual treatment exposure than those in the FSD subgroup. The introduction of the ISD at a later time point in the study also means that patients in the ISD group have a shorter follow-up time compared with patients in the FSD subgroup (11.1 months vs 16.6 months, respectively, as of the May 2019 DCO). The ISD subgroup was relatively small; 169 patients received treatment with niraparib under the ISD regimen. With the updated safety data with a DCO date 17 November 2019, the mean overall treatment duration was about 2 months longer than that included in the original dataset for both ISD and FSD groups. Only very minor changes

were noted in the updated dataset compared to the original, and the results were consistent between the updated and original dataset.

Dose reductions and dose interruptions were more frequent in the FSD group compared to the ISD group (80% and 84% vs 66% and 71%, respectively). Consistent with this, the median dose intensity (relative dose intensity) was similar in the ISD subgroup (179 mg/day, 66%) and the FSD subgroup (182 mg/day, 61%) Fewer dose reductions and dose interruptions due to thrombocytopenia (17% vs 38% and 24% vs 44%, respectively) and anaemia (20% vs 31% and 22% vs 36%, respectively) were seen in the ISD subgroup compared to the FSD subgroup. Dose modification per starting dose (200 mg vs 300 mg) over time supported an ameliorated dose modification profile of the 200 mg starting dose. In the low baseline weight/platelet dosing cohorts, dose interruptions and reductions dropped from 87% and 84% with the 300 mg starting dose, respectively, to 68% and 60% respectively, with the 200 mg starting dose. Those patients who will receive 300 mg under the ISD dosing regime, however, can expect more dose interruptions and reductions compared to those patients receiving the 200 mg starting dose: about 50% of patients receiving the 300 mg starting dose needed a dose reduction in the second month of treatment, compared to about 28% of patients receiving the 200 mg starting dose. By month 10 of treatment, only about 10% of patients in the 300 mg ISD subgroup received a dose of 300 mg, whereas for those patients in the 200 mg ISD subgroup, about 40% were receiving the dose they were started on (200 mg).

Although the protocol allowed for dose escalation to 300 mg after the first two treatment cycles, very few patients in the ISD subgroup had their dose escalated: 13 patients overall, 7 of these were in the niraparib arm. Of these 7, 3 experienced adverse events within 1-2 months after dose escalation which led to dose interruption and dose reduction in 2 patients. The last patient discontinued treatment due to disease progression. The low number of dose escalations could be expected, as in general, physicians may be wary of introducing toxicity when therapy is being tolerated.

All of the common TEAEs (incidence rate ≥ 10%) were less commonly reported in patients who received an individualized starting dose compared to patients who received a fixed starting dose. The incidence of anaemia and thrombocytopenia fell: from 71% and 52% in the FSD subgroup, to 50% and 34% in the ISD subgroup, respectively. The incidence of other common TEAEs, such as nausea and vomiting, fell less from the FSD subgroup (60% and 25% respectively) to the ISD subgroup (53% and 17%, respectively). Due to the mentioned differences in exposure times between the ISD and FSD subgroups, interpretation of differences in incidences of TEAEs between the ISD and FSD groups should be done with caution.

Exposure-adjusted incidence rates of the most commonly occurring TEAEs for the ISD and FSD groups indicate that the incidence rates per patient-exposure year (PEY) of anaemia and thrombocytopenia were almost twice as high in the FSD group (2.02 and 1.08, respectively) compared to the ISD group (1.16 and 0.65, respectively). For other haematological events, however, the PEY adjusted incidence rates are generally similar for FSD and ISD subgroups.

For other important TEAEs observed with niraparib, such as nausea, constipation and vomiting, only slight reductions in PEY adjusted incidence rates were observed in the ISD subgroup (1.45, 0.58, 0.27, respectively) compared to the FSD subgroup (1.63, 0.74, 0.34). The PEY adjusted incidence rate of fatigue was slightly higher in the ISD subgroup compared to the FSD subgroup (0.61vs 0.55, respectively). Unfortunately, gastrointestinal adverse events are among the main factors limiting the tolerability of niraparib. Patient reported outcomes from the PRIMA study confirm that gastrointestinal related quality of life scores were significantly worse in patients treated with niraparib compared to placebo.

Fewer patients reported any grade ≥ 3 TEAE in the ISD group (60%) compared to the FSD group (76%). Patients who were administered a starting dose of Zejula based on baseline weight or platelet count,

Grade ≥3 thrombocytopenia, anaemia and neutropenia were reduced from 48% to 21%, 36% to 23% and 24% to 15%, respectively, compared to the group administered a fixed starting dose of 300 mg.

Only relatively small differences between the subgroups in other reported grade ≥3 TEAEs were noted. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients.

A larger proportion of patients reported any SAE in the FSD subgroup compared to the ISD subgroup (35% vs 27%). There was a considerable reduction in SAEs of thrombocytopenia in the ISD subgroup, which fell from 17% in the FSD subgroup to 4% in the ISD subgroup. SAEs of anaemia, however, were not reduced in the ISD subgroup (8%) compared to the FSD subgroup (4%).

The assessment of differences in incidences for the most common TEAEs (≥10%), grade ≥ 3 TEAEs (≥5%) and SAEs between the ISD and FSD subgroups was not changed with receipt of updated safety data (including DCO date 17 November 2019).

Since the main benefit in terms of an individualised starting dose over a fixed starting dose appears to be the reduced frequency of thrombocytopenia and, to some extent, anaemia events, the sequelae of thrombocytopenia and anaemia are of importance in determining potential patient benefit in terms of a lower starting dose of niraparib. In addition to the reduction of thrombocytopenia SAEs in the ISD subgroup, the incidence of platelet transfusions was substantially decreased in the niraparib ISD subgroup (6.5%) compared to the FSD subgroup (19%). A review of bleeding events occurring concurrently with thrombocytopenia and grade ≥2 fatigue events concurrent with anaemia in the niraparib FSD and ISD subgroups of the PRIMA study were provided. The rates of bleeding concurrent with thrombocytopenia were reported in 9% of the overall safety population in the PRIMA study. Rates of bleeding events concurrent with thrombocytopenia decreased from 18.9% in the subgroup of patients with low weight/platelets who were dosed with FSD 300 mg, to 5.7% in the ISD 200 mg subgroup. There was no difference in grade ≥2 fatigue events concurrent with anaemia between the starting dose cohorts. The data support that the reduced 200 mg starting dose shows clinically meaningful reductions in sequelae of thrombocytopenia compared to the 300 mg starting dose in the low weight/platelet patient population.

As anaemia can lead to fatigue, analysis of grade ≥2 fatigue events occurring concurrently with anaemia was presented by the MAH. Overall, concurrent grade ≥2 fatigue events with anaemia occurred similarly amongst the 4 dosing cohorts (12-21%). No reduction in the frequency of concurrent grade ≥2 fatigue events with anaemia was seen with the lower starting dose.

In order to further characterize the extent of improved safety profile by lowering the starting dose, key safety parameters for 200 mg vs. 300 mg daily, were compared for these patients, using the most recently updated safety data (DCO 17 November 2019). The updated data were consistent with what was seen in the original dataset. Dose interruptions and dose reductions dropped from 87% and 84% with the 300 mg starting dose, respectively, to 68% and 60% respectively, with the 200 mg starting dose. Non-haematologic toxicity was not substantially reduced with the reduced starting dose, but grade 3/4 haematological toxicities were reduced with the 200 mg starting dose. The most remarkable reduction was in grade 3/4 thrombocytopenia, which was reduced from 52% with the 300 mg starting dose to 17% with 200 mg starting dose in the low w/p population. Notably, grade 4 thrombocytopenia was reduced from 39% to 7%. The MAH pointed out that, based on clinical trial and real-world experience with niraparib, high-grade thrombocytopenia leads to hospitalisation, transfusions, interventions and early discontinuation of niraparib, which are mitigated with the individualised starting dose. It is agreed that the reduction in thrombocytopenia seen with the 200 mg starting dose in the low w/p population is substantial and is likely to represent a benefit for those patients who will receive it.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of niraparib in the proposed indication is severe and consistent with the known safety profile.

The submitted data support clinically relevant advantages of the reduced starting dose of 200 mg QD compared to the currently approved starting dose of 300 mg QD in patients weighing less than 77 kg or having platelet counts lower than 150,000/µL.

In addition, the MAH should discuss possible additional cases of DILI in the next PSURs (routine pharmacovigilance).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Safety concerns

Table 62: Summary of the Safety Concerns (table from MAH RMP module SVIII)

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

Pharmacovigilance plan

Table 63: On-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

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				
3000-04-002: An integrated meta-analysis of	• The primary endpoint is to compare the	To provide additional safety information about the important	Final study report	Q1 2025

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
MDS/AML and other SPM incidence in patients with ovarian cancer who have been treated with niraparib Planned	incidence rate of MDS/AML in patients with ovarian cancer treated with niraparib versus any other treatment comparator. • The secondary endpoint is to compare the incidence rate of SPM in the same population. • The third endpoint is to estimate incidence of MDS/AML and other SPM in patients with ovarian cancer treated with niraparib in pooled TESARO clinical studies.	potential risks of MDS, AML and SPM.		
3000-04-001: PASS to evaluate the risks of MDS/ AML and other SPM in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula® (Niraparib). Planned	• Primary: To estimate the incidence rate of MDS/AML among a cohort of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with Zejula who are in a complete or partial response to platinum-based chemotherapy • Secondary: To estimate the incidence of SPM in the same cohort • Exploratory: To compare the incidence rate ratios of MDS/AML and other SPM in	To provide additional safety information about the important potential risks of MDS/AML and SPM other than MDS/AML in patients treated in clinical practice with existing medicines for ovarian cancer and patients treated with niraparib.	Final study report	Q1 2027

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	niraparib-treated patients to a retrospective cohort of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not been treated with a PARP inhibitor.			

Risk minimisation measures

Table 64: Risk minimisation measures 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** • SmPC sections 4.2; 4.4; 4.8 **PL** • Sections 2; 3; 4 **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: None Additional pharmacovigilance activities: None
Important identified risk: Hypertension	Routine risk minimisation measures: **SmPC** • SmPC sections 4.4; 4.8 **PL** • Section 2; 4 **Prescription status** • Prescription only medicine	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

	• Use restricted to physicians experienced in the use of anticancer medicinal products Additional risk minimisation measures: None	
Important potential risk: MDS and AML	Routine risk minimisation measures: **SmPC** • SmPC section 4.4 **PL sections** • Section 2 **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: • 3000-04-002: An integrated meta-analysis of MDS/AML and other SPM incidence in patients with ovarian cancer who have been treated with niraparib Final study report: Q1 2025 • 3000-04-001: PASS to evaluate the risks of MDS/AML and other second primary malignancies in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula (Niraparib) Final study report: Q1 2027
Important potential risk: SPM other than MDS and AML	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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A targeted questionnaire for SPM Additional pharmacovigilance activities: • 3000-04-002: An integrated meta-analysis of MDS/AML and other SPM incidence in patients with ovarian cancer who have been treated with niraparib Final study report: Q1 2025 • 3000-04-001: PASS to evaluate the risks of MDS/AML and other second primary malignancies in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula (Niraparib) Final study report: Q1 2027

2.7. Update of the Product information

As a result of this variation procedure, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.1 of the SmPC are

being updated. The Package Leaflet (PL) is updated accordingly. Annex II is also updated to add a new condition to the marketing authorisation.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Celsentri. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Zejula (niraparib) is "for the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy."

Additionally, a different posology is sought for the new indication; all first line ovarian cancer patients should receive 200 mg daily as starting dose (except patients weighing ≥ 77 kg and having baseline platelet count ≥ 150,000/µl who should receive 300 mg daily).

Ovarian cancer is the fifth overall cause of cancer death in women, representing 5% of all cancer deaths. Ovarian cancer is often asymptomatic in the early stages and is, therefore, first detected in advanced stages, when prognosis is poor (Fotopoulou 2014; Ovarian Cancer: Estimated Incidence, Mortality & Prevalence. WHO: International Agency for Research on Cancer 2016; Havrilesky *et al*. 2009). The 5-year overall survival (OS) rate in advanced ovarian cancer patients decreases from 42% for Stage IIIA, 32% for Stage IIIC, and 19% for Stage IV.

The primary objective of the treatment is to prolong progression-free survival (PFS). Extending the time to progression and hence the next chemotherapy regimen without compromising the patient's QoL can be regarded to be of clinical relevance also without an improvement in OS as long as there is no indication of detrimental effect on OS.

3.1.2. Available therapies and unmet medical need

The paradigm for first-line treatment of newly diagnosed ovarian cancer includes a combination of surgery and chemotherapy: either primary debulking surgery (PDS) followed by adjuvant platinum-based (cisplatin or carboplatin) plus a taxane (paclitaxel or docetaxel) chemotherapy regimen or neoadjuvant chemotherapy (NACT) with subsequent interval debulking surgery (IDS) followed by additional chemotherapy (NCCN Ovarian 2019). Worldwide, the use of NACT is increasing in patients with large volume Stage IIIC/IV disease, such that, 45%-60% of these patients will receive NACT.

Despite optimal upfront surgery and the administration of front-line paclitaxel–carboplatin chemotherapy, ~70% of patients will relapse in the first 3 years and become largely incurable (Ledermann *et al*., 2013).

Prolonging the benefit of first line platinum-based chemotherapy is currently the best chance these patients have to avoid recurrence and potentially improve survival outcomes.

Targeted treatments approved, at present, in the first line setting include maintenance olaparib for BRCAm patients only and bevacizumab for frontline and maintenance therapy regardless of BRCAm status. There is a remaining unmet clinical need regarding the treatment of patients with advanced ovarian cancer, particularly for patients with advanced ovarian cancer with DNA repair deficiency (i.e., HRD positive) not induced by BRCA mutation, and patients with HR-proficient (i.e., HRD negative) tumours.

3.1.3. Main clinical studies

The main evidence of efficacy is a single, pivotal trial (PRIMA) which is an ongoing Phase 3, double-blind, randomized (2:1 niraparib to placebo), study of niraparib vs. placebo with an effective data cut-off date of 17 May 2019. The study randomised 733 (487 niraparib and 246 placebo) patients with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) who had previously completed front-line platinum-based therapy with a physician-assessed response of CR or PR.

Randomisation was stratified by use of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (CR or PR), and tumour homologous recombination deficiency (HRD) status (positive or negative/not determined) as assessed by the myChoice assay. The primary efficacy endpoint in the PRIMA study was PFS, defined as the time from treatment randomisation to the earlier date of assessment of progression (by blinded central review) or death by any cause in the absence of progression. The primary endpoint, PFS by Blinded Independent Central Review (BICR), was tested hierarchically first in the HRDpos population and then in the ITT population by a stratified log-rank test at a one-sided 0.025 alpha level.

A proportion of about 65% (473/733) of the study population had been dosed with a fixed starting dose of 300 mg in the PRIMA study when the protocol was amended to implement an alternative dosing strategy. This alternative posology postulated 200 mg as a starting dose for all patients, except for those weighing ≥ 77 kg and having a platelet count ≥ 150,000/µL; for these patients the starting dose was 300 mg.

3.2. Favourable effects

All patients, regardless of dosing strategy

The primary endpoint PFS was met in the HRD positive (N=373; 247 in the niraparib group vs. 126 in the placebo group) with a HR of 0.43 (95% CI: 0.310 to 0.588, p<0.0001) in favour of the niraparib arm. The median PFS was 21.9 (95% CI: 19.3, NE) months for the niraparib arm versus 10.4 (95% CI: 8.1, 12.1) months in the placebo arm. This represents a prolongation in PFS of 11.5 months.

The primary endpoint PFS was met in the overall population (N=733; 487 in the niraparib group vs. 246 in the placebo group) with a HR of 0.62 (95% CI: 0.505 to 0.755, p<0.0001) in favour of the niraparib arm. The median PFS was 13.8 (95% CI: 11.5, 14.9) months for the niraparib arm versus 8.2 (95% CI: 7.3, 8.5) months in the placebo arm. This represents a prolongation in PFS of 5.6 months.

Niraparib showed effect in the HRDneg subgroup (N=249; 169 in the niraparib group vs. 80 in the placebo group) with a HR of 0.68 (95% CI: 0.492, 0.944; p=0.0203) and median PFS of 8.1 (95% CI: 5.7, 9.4) months in the niraparib arm vs. 5.4 (95% CI: 4.0, 7.3) months in the placebo arm. This represents a prolongation in PFS of 2.7 months.

The result for the Overall population for time to first subsequent treatment (TFST) indicated a prolongation of 6.6 months for the niraparib arm compared to the placebo arm (18.6 months [15.8, 24.7] vs. 12.0 months [10.3, 13.9], respectively; HR= 0.65 [95% CI: 0.521, 0.802], p<0.0001).

Results of the sensitivity analyses for progression-free survival were consistent with the primary efficacy results in both the HRDpos population and Overall population.

A PFS benefit of niraparib treatment over placebo with HR<1 was observed in the majority of subgroups, both in the HRDpos and overall population. The highest efficacy was observed in the *BRCAmut* subgroup (N=223) in the overall population with HR of 0.40 (95% CI: 0.265, 0.618; p<0.0001) and median PFS of 22.1 months (95% CI: 19.3, NE) in the niraparib arm vs. median PFS of 10.9 months (95% CI: 8.0, 19.4) in the placebo arm.

Fixed starting dose group (FSD)

The FSD group corresponds to ~65% of the total ITT population, whereof all received 300 mg as starting dose.

Data cut-off date 17 May 2019 (BICR assessed PFS):

- *HRDpos patients* (N=243): median PFS of 22.1 (95% CI: 19.6, NE) and 8.4 (95% CI: 7.6, 13.6) months in the niraparib and placebo arm, respectively with HR =0.44 (95% CI: 0.298, 0.638; p<0.0001).
- *Overall population* (N=475): median PFS of 14.7 (95% CI: 13.6, 19.4) and 8.2 (95% CI: 7, 9.8) months in the niraparib and placebo arm, respectively with HR =0.59 (95% CI: 0.457, 0.757; p<0.0001).
- *HRDneg patients* (N=162): HR of 0.64 (95% CI: 0.424, 0.969) (*of note; for this patient population, median PFS as assessed by BICR was not provided, however, median PFS as assessed by IA was found to be the same as stated below for the updated analysis from 17 November 2019*).

Data cut-off date 17 November 2019 (only PFS data as assessed by Investigator is available):

- *HRDpos patients* (N=243): median PFS of 24.8 and 10.8 months in the niraparib and placebo arm, respectively with HR =0.46 (95% CI: 0.32, 0.64).
- *Overall population* (N=475): median PFS of 13.9 and 8.2 months in the niraparib and placebo arm, respectively, HR =0.62 (95% CI: 0.49, 0.78).
- *HRDneg patients* (N=162): median PFS of 10.8 and 5.4 months in the niraparib and placebo arm, respectively, HR of 0.64 (95% CI: 0.44, 0.95).

Individualised starting dose group (ISD)

The ISD group corresponds to ~35% of the total ITT population, mixture of patients where 78% of the niraparib patients were given 200 mg and 22% were given 300 mg as starting dose, based on body weight and platelet count criteria.

Data cut-off date 17 May 2019 (BICR assessed PFS)*:

- *HRDpos patients* (N=130): HR =0.39 (95% CI: 0.215, 0.723; p=0.0019).
- *Overall population* (N=258): HR =0.69 (95% CI: 0.481, 0.982; p=0.0389).
- *HRDneg patients* (N=87): HR of 0.70 (95% CI: 0.402, 1.230).

Updated cut-off date 17 November 2019 (only PFS data as assessed by Investigator is available):

- *HRDpos patients* (N=130): median PFS of 19.4 and 12.9 months in the niraparib and placebo arm, respectively, with HR=0.54 (95% CI : 0.33, 0.91)
- *Overall population* (N=258): median PFS of 12.5 and 8.2 months in the niraparib and placebo arm, respectively with HR=0.68 (95% CI: 0.49, 0.94)
- *HRDneg patients* (N=87): median PFS of 6.6 and 5.5 months in the niraparib and placebo arm, respectively with HR =0.56 (95% CI: 0.34, 0.93)

Patients receiving 200 mg only and in accordance with the algorithm based on body weight/platelet count *(subgroup D):*

Data cut-off date 17 May 2019 (BICR assessed PFS)*:

- *HRDpos*: (N=96, 66 in the niraparib group and 30 in the placebo group): HR=0.35, (95% CI: 0.169, 0.720), p=0.0030.
- *Overall population:* (N=183, 122 in the niraparib group and 61 in the placebo group): HR=0.68, (95% CI: 0.435, 1.056), p=0.0858.
- *HRDneg*: (N=57, 40 in the niraparib group and 17 in the placebo group): HR=0.75, (95% CI: 0.356, 1.586) p=0.4761.

Data cut-off date 17 November 2019 (only PFS data as assessed by Investigator is available):

- *HRDpos*: (N=96, 66 in the niraparib group and 30 in the placebo group): median PFS of 19.4 and 13.4 months in the niraparib and placebo arm, respectively with HR=0.53, (95% CI: 0.29, 0.98).
- *Overall population:* (N=183, 122 in the niraparib group and 61 in the placebo group): median PFS of 12.5 and 8.4 months in the niraparib and placebo arm, respectively with HR=0.67, (95% CI: 0.45, 1.00).
- *HRDneg*: (N=57, 40 in the niraparib group and 17 in the placebo group): median PFS of 5.5 and 5.4 months in the niraparib and placebo arm, respectively with HR=0.43, (95% CI: 0.22, 0.83).

*(***** as the data for the individualised starting dose groups and the 200 mg dosing groups at data cut-off date 17 May 2019 were immature, only HRs were stated for these results).

3.3. Uncertainties and limitations about favourable effects

The dosing schedule of the PRIMA study was amended rather late in the course of the study. In total, approximately 25% (122/484) of the niraparib patients included in the study received the applied 200 mg dose in accordance with the algorithm based on body weight and/or platelet count. The PRIMA study was neither originally designed for testing multiple dosing strategies, nor powered to evaluate the treatment effect of the proposed lower starting dose of 200 mg. The candidate dosing strategies were not tested in parallel groups, but rather tested sequentially (prior to and after the time of the protocol amendment).

Whether the treatment effect of the 200 mg dose is fully maintained in the Overall and HRDpos patient populations is uncertain. A reduction of the efficacy with a 200 mg dose in these patient populations cannot be entirely excluded, however the potential reduction in treatment effect is anticipated to be relatively modest.

The exposure-response analyses did not indicate an exposure-response relationship over the range of exposures associated with 200 mg and 300 mg. However, due to limitations in the input data, mainly sparse PK sampling and a narrow exposure range under evaluation, they provide only limited supplementary evidence of efficacy at 200 mg.

For the HRDneg population, the 200 mg dose appears to have a low treatment effect. It is doubted that the stated point estimate of HR 0.43 represents the true treatment effect of the 200 mg dose for this population. This is due to the fact that the HR point estimate is lower than the corresponding HR point estimate in the 300 mg dosing group for HRDneg and also lower than the point estimate of HR for HRDpos in subgroup D (0.53). These results lack biological support. Adding to the uncertainties is also the very low number of patients in subgroup D (total of 57).

Analyses to characterise the efficacy for each starting dose subgroup by baseline body weight and baseline platelet counts were performed *post-hoc*.

Independent of dose, patients with HRD not determined status showed very little effect (a median prolongation of 2.7 months compared to placebo also in this group, however, HR was 0.85 and the 95% CI included 1).

As of the data cut-off for the primary analysis, OS data were immature with approximately 90% of events censored in both the HRDpos and the Overall population. The two other secondary endpoints TFST and PFS2 were also immature. No data regarding outcomes for next anticancer therapy following study treatment have been submitted. A new condition is imposed in Annex II to provide updated analyses by 31 December 2025 (Annex II).

3.4. Unfavourable effects

All patients

The most commonly reported adverse events in the PRIMA study were related to myelosuppression and gastrointestinal events, and were more frequently reported for niraparib compared to placebo: thrombocytopenia events (66%; grade 3/4: 29%), anaemia events (64%; grade 3/4: 31%), leukopenia events (50%; grade 3/4: 22%), nausea (57%), constipation (40%) and vomiting (22%). The majority of gastrointestinal adverse events were grade 1 or 2 in severity, but had important impact on tolerability, as seen by significantly worse GI-related quality of life scores in the niraparib-treated patients compared to placebo.

Other notable adverse events reported more commonly for niraparib than placebo were fatigue (35%), headache (26%), insomnia (25%), decreased appetite (19%), hypertension (17%; grade 3/4: 6%), and dyspnoea (18%).

Dose modifications in the form of dose interruptions and dose reductions were frequently required to manage AEs and occurred in 80% and 75% of niraparib-treated patients, respectively (vs 24% and 12% in the placebo group, respectively). The main reasons for dose interruptions and reductions with niraparib were thrombocytopenia (37% and 31%, respectively), anaemia (31% and 27%, respectively) and neutropenia (11% and 8%, respectively).

The incidence of SAEs in the PRIMA study was 32% in the niraparib arm and 13% in the placebo arm. The most common SAEs reported for niraparib were thrombocytopenia (12%), anaemia (6%), platelet count decreased (4%), and small intestinal obstruction (2%). None of the patients in the placebo arm reported SAEs of thrombocytopenia, anaemia or platelet count decreased.

Two patients treated with niraparib experienced TEAEs that lead to death, these were intestinal perforation and pleural effusion. Neither of these deaths were considered as related to treatment with niraparib.

Supportive updated data from the ongoing NOVA study were submitted with this application. A slightly larger proportion of patients in the pooled group of patients who received niraparib in the NOVA and

PRIMA studies have died compared to the pool of patients who received placebo (33% vs 28%, respectively).

In the NOVA study, there have been three deaths from TEAEs since the previous DCO date (30 May 2016), all of whom were assessed by the investigator as related to niraparib. There were two deaths from MDS/AML and one of related grade 5 events of sepsis and acute kidney injury. Overall, 158 cases of MDS/AML have been observed in the niraparib monotherapy clinical program as of the DCO date 17 May 2019. The incidence is slightly higher in the niraparib-treated patients compared to placebo-treated patients: 15 cases (0.8%) vs 3 cases (0.6%), respectively.

5/484 (1%) patients on niraparib experienced pneumonitis events in the PRIMA trial and 3/367 (1%) in the NOVA trial, compared to 1/423 (0.2%) patients in placebo-treated patients. All events were grade 1 or 2 in intensity. Half of the events in niraparib-treated patients were considered as possibly or likely related to study treatment by the investigator. The evidence for pneumonitis with niraparib was assessed in a parallel procedure (EMEA/H/C/004249/II/0020), where pneumonitis was identified as an ADR of niraparib.

Individualised vs fixed dosing

Dose reductions and dose interruptions were more frequent in the fixed starting dose (FSD) subgroup compared to the individualised starting dose (ISD) subgroup (80% and 84% vs 66% and 71%, respectively). All of the common TEAEs (incidence rate ≥ 10%) were more frequently reported in the FSD subgroup compared to the ISD subgroup. The incidence of anaemia and thrombocytopenia declined the most: from 71% and 52% in the FSD subgroup, to 50% and 34% in the ISD subgroup, respectively. More patients reported any grade $\geqslant$ 3 TEAE in the FSD subgroup (76%) compared to the ISD group (60%). The largest decrease was seen in the incidence of grade $\geqslant$ 3 thrombocytopenia and anaemia, which were reported in 21% and 23% of patients in the ISD subgroup, respectively, versus 48% and 36% in the FSD subgroup. A larger proportion of patients reported any SAE in the FSD subgroup compared to the ISD subgroup (35% vs 27%). There was a considerable reduction in SAEs of thrombocytopenia in the ISD subgroup, which fell from 17% in the FSD subgroup to 4% in the ISD subgroup. The incidence of platelet transfusions was substantially decreased in the niraparib ISD subgroup (6.5%) as well, compared to the FSD subgroup (19%).

Updated safety results including approximately six additional months of safety data (DCO 17 November 2019) also support an ameliorated safety profile for the 200 mg starting dose in terms of dose modifications and incidence of grade 3/4 thrombocytopenia. In patients with low baseline weight/platelets, dose interruptions and reductions dropped from 87% and 84% with the 300 mg starting dose, respectively, to 68% and 60% respectively, with the 200 mg starting dose. Grade 3/4 thrombocytopenia was reduced from 52% with the 300 mg starting dose to 17% with 200 mg starting dose. Grade 4 thrombocytopenia was reduced from 39% to 7%.

In the subgroup of patients who received 300 mg ISD (weight ≥ 77 kg and platelets ≥ 150 000/μL), about 50% of patients needed a dose reduction in the second month of treatment, compared to about 28% of patients receiving the 200 mg starting dose. By month 10 of treatment, only about 10% of patients in the 300 mg ISD subgroup received a dose of 300 mg, whereas for those patients in the 200 mg ISD subgroup, about 40% were receiving the dose they were started on (200 mg).

3.5. Uncertainties and limitations about unfavourable effects

The incidences of MDS/AML across the niraparib monotherapy trials varies by study and is probably influenced by different exposures to niraparib and other DNA-damaging agents and varying follow-up

times. The follow-up time in the PRIMA study is currently short. MDS/AML is a potential risk in the RMP, and two category 3 PASS studies are currently ongoing to follow up this safety concern.

A higher incidence of thromboembolic events was observed in niraparib-treated patients in the PRIMA and NOVA study pool compared to the placebo arm; 11/682 (1.6%) vs 2/423 (0.5%), respectively. Six of the niraparib-treated patients and none of the placebo-treated patients experienced events that were of grade ≥3. None of the events were assessed as related to treatment with niraparib by the investigators. Embolic and thrombotic events are a potential risk with niraparib and will continue to be followed up in upcoming PSURs.

The majority of the patients included in the PRIMA and previous studies with niraparib were Caucasian, and exposure in non-Caucasian patients is limited, thus limiting an assessment of safety by race.

Uncertainties and limitations pertaining to the dosing strategy

The introduction of the ISD regimen at a later time point in the study resulted in fewer numbers of treatment cycles and less overall and actual treatment exposure than those in the fixed starting dose (FSD) subgroup patients in the ISD subgroup have a shorter follow-up time compared with patients in the FSD subgroup (median 11.1 months vs 16.6 months, respectively, as of the May 2019 DCO).

The ISD subgroup was relatively small; 169 patients received treatment with niraparib under the ISD regimen. Sub-dividing the start dosing subgroups even further to elucidate potential safety benefits of the 200 mg starting dose, leads to an even smaller population (122 patients received 200 mg ISD and 34 patients received 300 mg ISD, in addition 13 patients received an incorrect starting dose and were therefore excluded from the safety analyses).

The proposed 300 mg starting dose in patients with body weight ⩾77 kg and platelet count ⩾150,000/µL is based on the observation that this subgroup appears to tolerate the 300 mg starting dose better than the remaining patients in terms of Grade 3+ thrombocytopenia risk. However, testing of the proposed dosing algorithm after the protocol amendment indicated poor performance in terms of identifying patients who will tolerate the 300 mg dose, as a notably high proportion of patients receiving the 300 mg starting dose required a dose reduction during the PRIMA study and had high incidences of grade ⩾3 TEAEs. Thus, with the proposed posology, patients with body weight ⩾77 kg and platelet count ⩾ 150,000/µL (~25% of the population) represents a subpopulation with a less beneficial safety profile and who could theoretically also benefit from the lower starting dose. A lower starting dose has, however, not been tested prospectively in this subgroup.

3.6. Effects Table

Table 62. Effects Table for Zejula in the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy (data cut-off: 17 May 2019)

Effect	Short description	Unit	Niraparib	Placebo	Uncertainties /Strength of evidence	References
Favourable Effects - All patients, regardless of dosing strategy						
HRDpos cohort						
PFS Progression free survival (HR)	From randomisation to progression or death (blinded		0.43 (p<0.0001)		OS, PFS2 and TFST data are immature	PRIMA-study

Effect	Short description	Unit	Niraparib	Placebo	Uncertainties /Strength of evidence	References
	independent review)					
PFS (median)		Months	21.9	10.4		PRIMA-study
Overall population						
PFS (HR)			0.62 (p<0.0001)			PRIMA-study
PFS (median)		Months	13.8	8.2	Sensitivity analyses support the primary analysis.	PRIMA-study
Unfavourable Effects						
G3/4 TEAEs		%	71	19		
SAEs		%	32	13		
G5		%	0.4	0.4		
Thrombocytopenia events	All grades	%	66	5		
	G3/4	%	39	0.4		
	SAEs	%	16	0		
	Treatment discontinuation	%	4	0		
Anaemia events	All grades	%	64	18		
	G3/4	%	31	2		
	SAEs	%	6	0		
	Treatment discontinuation due to anaemia events	%	2	0		
Leukopenia events	All grades	%	50	13		
	G3/4	%	22	2		
Nausea	All grade	%	57	28		
Constipation	All grade	%	40	19		
Vomiting	All grade	%	22	12		
Decreased appetite	All grade	%	19	9		
Hypertension	All grade	%	18	7		
Dyspnoea	All grade	%	18	12		
MDS/AML events	All grade	%	0.2	0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, in the primary effect analysis in the ITT population, maintenance therapy with niraparib resulted in a statistically significant and clinically relevant improvement of the BICR-based PFS for both the HRDpos population and the Overall population. These results are encouraging for a patient population with currently few treatment options.

As expected, when taking into account the biological rationale, niraparib showed the longest prolongation of PFS in patients with HRDpos status (+11.5 months, HR 0.43). Nevertheless, when taking into consideration the poorer prognosis of patients with HRDneg status, the increase in median PFS in this population, as demonstrated in the subgroup analysis (ITT), is also considered clinically relevant (+2.7 months, HR 0.68). Similar positive results for the HRDneg patients were observed during the review of the initial marketing authorisation for Zejula. However, as discussed further below, updated analyses for the applied dose of 200 mg seems to imply lower efficacy for the HRDneg patients as compared to the 300 mg dose.

Due to the absence of a bevacizumab maintenance comparator arm, it remains difficult to contextualise the overall magnitude of efficacy with niraparib, particularly in HRDneg patients.

With regards to the group of patients with undetermined HRD status, it still remains unexplained why they have a much lesser benefit of niraparib treatment compared to patients determined to be HRDneg. This could be due to an (unknown) imbalanced composition of the homologous recombination deficient (HRD) status in each treatment group. Although the composition of this group is unknown, some patients nonetheless seem to benefit from niraparib treatment, indicating that this is a heterogeneous group. Thus, there is no clear reason for excluding patients from niraparib treatment.

The secondary endpoints were all currently immature; hence, these data were not informative enough to exclude a potential detrimental effect in the ITT population or in the subgroups. As resistance mechanisms might occur in ovarian cancer patients after exposure to PARP-inhibitors, this could possibly affect the efficacy of next line therapy. As the initial efficacy assessment is based on PFS, it requires further investigation and a new condition is imposed to the MAH to provide the final OS analysis and updated analyses for the secondary endpoints by 31 December 2025 (Annex II).

Since niraparib is used as maintenance treatment, it is critical to optimise the dose to improve the patients' tolerability to the treatment during their period in remission. The application included several presentations of efficacy in various subgroups. The patients with body weight <77 kg or platelet count <150,000/µL who received the 200 mg starting dose (subgroup D) were compared to patients receiving 300 mg prior to the protocol amendment, meeting the same baseline characteristics in terms of body weight or platelet count cut-offs (subgroup C). Updated 6 months investigator efficacy analyses for all 3 patient groups (overall, HRDpos and HRDneg) were provided including comparisons of the FSD group vs. the ISD group as well as subgroup C vs. subgroup D.

For the Overall and HRDpos populations, the effect seemed quite similar in the niraparib arm between the FSD and ISD dosing groups (both in terms of point estimates of HR [but to a lesser degree in terms of median PFS, especially for the HRDpos] and the KM plots). When comparing the updated KM plots for subgroup C (300 mg) against subgroup D (200 mg), the treatment effect seemed to be smaller for the niraparib arm in subgroup D (although this was not reflected in the HR point estimates). There are several limitations associated with the analyses based on the two subgroups C and D; they were performed *post-hoc* and there were relatively few patients in subgroup D (122 patients in the niraparib arm vs. 61 in the placebo arm) compared to subgroup C (243 patients in the niraparib arm vs. 116 in the placebo arm). The PRIMA study was not initially designed with the intent of studying different starting doses and hence the study did not have the statistical power to allow any firm conclusions to be drawn regarding the 200 mg starting dose. Consequently, the results of these analyses are flawed by uncertainty. For the Overall and HRDpos populations, it cannot be affirmably stated that there is no loss of efficacy with the 200 mg dose compared to the 300 mg dose, however, the potential loss appears to be rather modest.

For the HRDneg population, the updated KM plots for both the FSD group vs. the ISD group and the subgroup C vs. subgroup D pointed in the same direction; the 200 mg dose appears to be of lower efficacy compared to the 300 mg dose. The HR point estimate, on the other hand, was low, but with wide

confidence intervals. Considering the small data set and the large uncertainties with these analyses, it is doubted that the low HR point estimate represents the true treatment effect of the 200 mg dose for the HRDneg population. The available data are not sufficiently robust to allow any definite conclusion on efficacy of the 200 mg dose compared to the 300 mg dose for this limited patient group. Furthermore, there is a biological rationale behind the notion that HRDneg patients would be less sensitive to PARP inhibitors compared to HRDpos patients, and thus a different dose-response relationship is expected in these patients.

However, the exploratory analyses showed that in patients treated with a starting dose of 200 mg or 300 mg per baseline weight or platelet count, niraparib still showed PFS benefit compared to placebo. Overall, the totality of evidence based on efficacy data with the modified dosage regimen is considered to support a clinically relevant improvement in outcome.

The data presented indicate that the main benefit of the reduced starting dose is in terms of reductions in haematological toxicity, most notably substantial reductions in thrombocytopenia-related events, which is also observed by an ameliorated dose modification profile for the 200 mg starting dose. When correcting for differences in time-exposure, it appears that other important adverse events, such as GI-events, are not markedly reduced. The improvements seen with the lower starting dose are considered to be of relevant clinical consequence for those patients who will receive it.

Neither body weight nor platelet counts have been identified as sources of variability in niraparib exposure. Still, it is proposed to dose by these factors. The proposed algorithm is derived from observed lower Grade 3+ thrombocytopenia incidences with increasing baseline body weight or increasing platelet count. If no loss of treatment effect at 200 mg could be confidently concluded, as claimed by the MAH, there would be no clear pharmacological reason not to allow all patients to benefit from the lower starting dose. However, with the remaining efficacy uncertainties at 200 mg, it could be argued that the thrombocytopenia risk (as predicted by body weight and platelet count) should determine whether the benefits of reducing the starting dose outweighs the risk of potential efficacy loss. Whether this shift occurs at the exact threshold values of 77 kg and 150,000/µL, respectively, has not been convincingly discussed, and the selected threshold values seem arbitrary. Despite its limited pharmacological basis, the proposed posology is considered acceptable as it seems to be the preferable option among the posology strategies that have been prospectively tested.

3.7.2. Balance of benefits and risks

The outcomes of the primary analyses in the Overall population are considered clinically relevant in the target population, which currently has limited treatment options. The overall safety profile is considered acceptable.

The benefits of an ameliorated safety profile with a 200 mg starting dose vs. a 300 mg starting dose outweigh the risk of potentially reduced efficacy in patients with body weight <77 kg or platelet count <150,000/uL. Furthermore, relative to placebo, the efficacy data of the modified dosage regimen is supportive of a clinically relevant improvement in outcome.

3.7.3. Additional considerations on the benefit-risk balance

The PRIMA study population consisted of patients with high-grade ovarian cancer. It is therefore considered justified that high-grade is reflected in the indication wording.

As the majority of high-grade ovarian, fallopian tube or primary peritoneal cancer are of epithelial origin, it was requested that "epithelial" was added to the indication. It was also clarified that niraparib is used in "monotherapy" and "advanced" refers to FIGO stages III and IV.

3.8. Conclusions

The overall B/R of Zejula 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, is positive.

The following measures are considered necessary to address issues related to efficacy:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate the efficacy of niraparib in 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, the MAH should submit the final analysis for OS and updated analyses for TFST, PFS-2 and outcomes for next anticancer therapy from study PRIMA.	31 December 2025

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the use of Zejula 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; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The MAH is also taking the opportunity to make minor corrections throughout the PI. The Package Leaflet is updated in accordance. Version 5.0 of the RMP to add the new indication, bring it in line with the RMP template Rev. 2.0.1 and update due dates for category 3 studies has been accepted. Annex II is updated with a new post-authorisation efficacy study (PAES).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following new condition:

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate the efficacy of niraparib in 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, the MAH should submit the final analysis for OS and updated analyses for TFST, PFS-2 and outcomes for next anticancer therapy from study PRIMA.	31 December 2025

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers by consensus that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.