14 September 2017
EMA/648982/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zejula

International non-proprietary name: niraparib

Procedure No. EMEA/H/C/004249/0000

Note

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

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List of abbreviations

ADR	adverse drug reactions
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AME	absorption, metabolism, excretion
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCN	allele specific copy number
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
AUC	area under the plasma concentration-time curve
AUCtau	area under the plasma concentration-time curve over the dosing interval
BBB	blood brain barrier
BCS	Biopharmaceutics Classification System
BER	base excision repair
BRCA	breast cancer susceptibility gene
BSEP	bile salt export pump
CA-125	cancer antigen-125
CEP	Certificate of Suitability of the EP
CFI	chemotherapy-free interval
CFU	Colony Forming Units
CHMP	Committee for Human Medicinal Products
CI	confidence interval
CIPC	Critical in-process control
CL/F	apparent clearance
Cmax	maximum concentration
CNS	central nervous system
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	complete response
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
Ctrough	trough concentration
CYP	cytochrome P450
DA	dopamine
DAT	dopamine transporter
DDI	3rug-drug interaction
DLT	dose-limiting toxicity
DNA	3eoxyribonucleic acid
DoE	Design of experiments
EAR	excess absolute risk
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ENGOT	European Network of Gynaecological Trial (groups)
EQ-5D-5L	European Quality of Life Scale, 5-Dimensions
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FE	food effect
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FOSI	Functional Assessment of Cancer Therapy – Ovarian Symptom Index
FT-IR	Fourier Transform Infrared Spectroscopy
gBRCAmut	germline BRCA mutation
GC	Gas Chromatography
GCP	goof clinical practise
HDPE	High Density Polyethylene
hERG	human Ether-a-go-go-related gene
HMHDPE	High Molecular Weight High Density Polyethylene
HPLC	High performance liquid chromatography
HR	hazard ratio
HRD	homologous recombination deficient
HRDneg	homologous recombination deficient negative

HRDpos	homologous recombination deficient positive
HUI	Health Utility Index
IC	inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IND	Investigational New Drug
IPC	In-process control
IRC	Independent Review Committee
ITT	intent-to-treat
KF	Karl Fischer titration
KM	Kaplan-Meier
LC-MS	Liquid chromatography mass spectrometry
LDPE	Low density polyethylene
LDPE	Low Density Polyethylene
LOH	loss of heterozygosity
MA	Marketing Authorisation Application
MAD	multiple ascending dose
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MSD	Merck Sharpe and Dohme
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	not estimated
NET	norepinephrine transporter
NHEJ	non-homologous end joining
NMR	Nuclear Magnetic Resonance
Non-gBRCAmut	without a germline BRCA mutation
NOR	Normal Operating Range
OAT	organic anion transporter
OATP	organic anion transport polypeptide
OCT	organic cation transporter
OCT Pool	ovarian cancer treatment pool
OS	overall survival
OVAT	One variable at a time
PAR	Proven Acceptable Range
PARP-1, -2	poly (ADP-ribose) polymerase 1, 2
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PDX	patient-derived xenograft
PFS	progression-free survival
PFS2	progression-free survival 2
PGI	Potentially genotoxic impurities
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
popPK	population pharmacogenetics
PR	partial response
PRO	patient-reported outcome
PVC	Poly vinyl chloride
Q/F	Intercompartmental clearance (a population pharmacokinetic term)
QbD	Quality by design
QD	once daily
QOL	quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTPP	Quality target product profile
RBC transfusion	red blood cell transfusion
RECIST	Response Evaluation Criteria in Solid Tumours
RH	Relative Humidity
rpm	revolutions per minute
RRT	Relative retention time
SAE	serious adverse event
SIRS	standardized incidence ratios
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA queries

SNP	single nucleotide polymorphism
TAMC	Total Aerobic Microbial Count
TEAE	treatment-emergent adverse event
TFST	time to first subsequent therapy
TPP	Target product profile
TSE	Transmissible Spongiform Encephalopathy
TSST	time to second subsequent therapy
TYMC	Total Combined Yeasts/Moulds Count
UGT	uridine-5'-diphospho-glucuronosyltransferases
US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet
V2/F	Apparent volume of distribution of central compartment (a population PK term)
V3/F	Apparent volume of distribution of peripheral compartment (a population PK term)
Vd/F	apparent volume of distribution
VEGF	vascular endothelial growth factor
VMD	volume mean diameter
WBC	white blood cell
Wt	Wildtype
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Tesaro UK Limited submitted on 4 October 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Zejula, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 June 2015.

Zejula was designated as an orphan medicinal product EU/3/10/760 on 4 August 2010 in the following condition: treatment of ovarian cancer.

The applicant applied for the following indication:

Zejula is indicated for the maintenance treatment of adult patients with platinum-sensitive recurrent high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Zejula as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that niraparib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance niraparib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 19 September 2017. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

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

- The application was received by the EMA on 4 October 2016.
- The procedure started on 27 October 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 January 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 27 January 2017
- During the meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 23 February 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 April 2017.
- The following GMP inspection were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

  - A GMP inspection at QS Pharma LLC (formerly known as:Charles River Laboratories Contract Manufacturing PA, LCC, USA between 14 – 16 February 2017. The outcome of the inspection carried out was issued on 12 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 May 2017.
- During the PRAC meeting on 9 June 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 June 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 July 2017 and 11 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 August 2017.
- During the meeting on 14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zejula.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed therapeutic indication is: “Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum based chemotherapy ”.

Platinum sensitivity was defined by complete response (CR) or partial response (PR) for more than six months to their penultimate (next to last) platinum-based therapy. To be eligible for niraparib treatment the patient should be in response (CR or PR) following completion of last platinum based chemotherapy.

2.1.2. Epidemiology

Ovarian cancer is the deadliest of gynaecologic cancers; in women, it is the fifth overall cause of cancer-related deaths representing 5% of all such deaths [Siegel et al 2014]. In 2016, it was estimated that there would be 22,280 new cases of ovarian cancer and an estimated 14,240 women would die of this disease in the US [NCI, 2016]. In 2012 (the latest data available), 42,716 died in Europe from ovarian cancer [IARC, 2012].

Ovarian cancer is predominantly a disease of postmenopausal women with the majority (>80%) of cases being diagnosed in women over 50 years and the median age at diagnosis being 63 years.

First-line treatment regimens result in high response rates, but most patients with advanced disease will recur within 2 years. The median PFS in the front-line setting is approximately 16 to 18 months from initiation of platinum-based chemotherapy [Coleman et al 2013]. Relapse rates for epithelial ovarian cancer are 62% overall, but can be as high as approximately 85% for patients diagnosed with advanced disease [Birrer et al 2016].

2.1.3. Biologic features

Platinum predominantly causes large-scale DNA intra-strand cross-links which require a competent homologous recombination pathway for effective repair. Given that platinum sensitivity and PARP inhibitor sensitivity may converge at the homologous recombination pathway, it was possible that platinum responsiveness may be also enrich for PARP inhibitor sensitivity [Mukhopadhyay et al 2010]. Clinical data support this hypothesis, platinum sensitive tumours are more sensitive to PARP inhibitors than platinum resistant tumours [Matulonis et al 2016]. Thus, while BRCA mutations and HRD might represent biological markers of sensitivity to PARP inhibitors, platinum responsiveness may be a clinical indicator of sensitivity to these compounds.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Early stage ovarian cancer is often asymptomatic and therefore difficult to detect. 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. Thus, ovarian cancer is often first detected in advanced stages when prognosis is poor.

The 5-year overall survival rate of ovarian cancer patients is 46% across all stages and only 29% in patients diagnosed with distant metastatic disease. Most patients will die within 3 to 4 years of diagnosis [Coleman et al 2013].

2.1.5. Management

The majority of patients with ovarian cancer receive surgery to remove or debulk the tumour. The primary treatment of advanced-stage ovarian cancer in the first-line setting is platinum (cisplatin or carboplatin) plus a taxane (paclitaxel or docetaxel) with or without bevacizumab. However, platinum-based chemotherapy can cause serious side effects this may negatively impact patients' ability to lead a productive life.

Once a patient has recurrence of their ovarian cancer, chemotherapy is an option for reducing disease-related symptoms. Both the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend re-treatment of patients with a platinum-based combination chemotherapy when relapse occurs >6 months after initial platinum-based treatment.

The treatment options for patients with prior platinum-sensitive relapsed ovarian cancer are described below:

- Following response to second-line chemotherapy, one of the options per NCCN and ESMO guidelines is to monitor for disease progression while managing the patient's symptoms and providing no active anti-cancer treatment. Importantly, patients during the surveillance period are not asymptomatic as they continue to have signs and symptoms associated with their underlying ovarian cancer as well as residual side effects of their prior chemotherapy. Further, during the observation period ovarian cancer survivors report emotional problems, including psychological distress (40%), anxiety about CA-125 testing (54%), and fear of recurrence (56%); 26% had scores suggestive of post-traumatic stress disorder [Ferrell et al 2003]. The primary challenge with this approach is that the duration of the chemotherapy-free interval after platinum therapy is short and becomes progressively shorter; therefore, these patients will inevitably require retreatment with platinum-based chemotherapy.
- Bevacizumab is approved in the EU for patients with recurrent ovarian cancer in combination with chemotherapy with continuation as maintenance after 6 cycles of combination. Bevacizumab in combination with gemcitabine plus carboplatin improved median PFS by 4 months compared to gemcitabine plus carboplatin alone in patients with platinum-sensitive recurrent ovarian cancer [Aghajanian et al 2012]. Of note, as bevacizumab is initiated at the time of platinum-based chemotherapy, the reported PFS interval includes the time during which the patient is receiving platinum-based chemotherapy (~4.5 months). Importantly, for patients who received bevacizumab in the first-line setting, this therapy is not an option for this patient group which have platinum-sensitive recurrent ovarian cancer.
- Olaparib was approved in the EU as maintenance monotherapy for patients with platinum-sensitive, relapsed, ovarian cancer with a BRCA mutation (either germline or tumour) who are in response (CR or PR) to platinum-based chemotherapy [Ledermann et al 2014]. Olaparib is not approved as maintenance treatment in the US, but was recently approved for treatment of patients who have had at least 3 prior treatment regimens for ovarian cancer. Median prolongation in PFS of olaparib maintenance treatment was 6.9 months (11.2 months in olaparib arm vs 4.3 months in placebo arm) for patients with the BRCA mutation. Recently, olaparib OS data after more than five years follow up have been published [Ledermann et al 2016], showing beneficial treatment effect in the olaparib arm

as compared to placebo for the gBRCA group of patients (HR 0.62 34.9 months in olaparib arm vs 30.2 months in placebo arm).

About the product

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 section 5.1 of the SmPC).

The indication for Zejula as initially proposed by the applicant was as follows:

“Zejula is indicated for the maintenance treatment of adult patients with platinum-sensitive recurrent high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.”

The final indication as approved by the CHMP following review of the application is:

“Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum based chemotherapy.”

Treatment with Zejula should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

The dose is three 100 mg hard capsules once daily, equivalent to a total daily dose of 300 mg. The capsules should be swallowed whole with water. The capsules should not be chewed or crushed.

Patients should be encouraged to take their dose at approximately the same time each day. Niraparib can be taken without regard to meals. Bedtime administration may be a potential method for managing nausea.

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

If patients miss a dose, they should take their next dose at its regularly scheduled time.

Recommendations for the management of adverse reactions are provided in Table 1. In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to reduce the dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended that Zejula be discontinued. If adverse reactions are not manageable with this strategy of dose interruption and reduction, it is recommended that Zejula be discontinued.

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.

The recommended dose modifications for adverse reactions are listed in Tables 1 and 2.

Table 1: Dose modifications for non-haematologic adverse reactions	
Non-haematologic CTCAE* ≥ Grade 3 treatment-related adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	First occurrence: • Withhold Zejula for a maximum of 28 days or until resolution of adverse reaction. • Resume Zejula at a reduced dose (200 mg/day).
	Second occurrence: • Withhold Zejula for a maximum of 28 days or until resolution of adverse reaction. • Resume Zejula at a reduced dose (100 mg/day).
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered Zejula 100 mg/day	Discontinue treatment.

*CTCAE=Common Terminology Criteria for Adverse Events

Table 2: Dose modifications for haematologic adverse reactions	
Haematologic adverse reactions have been observed during the treatment with Zejula especially during the initial phase of the treatment. It is therefore recommended to monitor complete blood counts (CBCs) weekly during the first month of treatment and modify the dose as needed.After the first month, it is recommended to monitor CBCs monthly and periodically after this time (see section 4.4 of the SmPC). Based on individual laboratory values, weekly monitoring for the second month may be warranted.	
Haematologic adverse reaction requiring transfusion or haematopoietic growth factor support	• For patients with platelet count ≤ 10,000/µL, platelet transfusion should be considered. If there are other risk factors for bleeding such as co-administration of anticoagulation or antiplatelet medicinal products, consider interrupting these substances and/or transfusion at a higher platelet count. • Resume Zejula at a reduced dose.
Platelet count < 100,000/µL	First occurrence: • Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • Resume Zejula at same or reduced dose based on clinical evaluation. • If platelet count is < 75,000/µL at any time, resume at a reduced dose.
	Second occurrence: • Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • Resume Zejula at a reduced dose. • Discontinue Zejula if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil < 1,000/µL or Haemoglobin < 8 g/dL	• Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥ 1,500/µL or haemoglobin returns to ≥ 9 g/dL. • Resume Zejula at a reduced dose. • Discontinue Zejula if neutrophils and/or haemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	• Permanently discontinue Zejula.

Type of Application and aspects on development

Niraparib was granted orphan designation for the indication of ovarian cancer in August 2010 in the EU (EU/3/10/760).

Confirmation on the applicability of the class waiver for paediatric investigations was received on 01 April 2016.

The pivotal trial NOVA was designed in accordance with International Council for Harmonization (ICH) guidelines for robust study design including the Guideline on Evaluation of Anticancer Medicinal Products in Man (EMA/CHMP/205/95) and Methodological considerations for using PFS as primary endpoint in confirmatory trials (EMA/CHMP/27994/2008).

The Applicant sought advice from the Committee for Human Medicinal Products (CHMP) in Europe during development of niraparib.

Table 3: **EU Regulatory Interactions**

Type	Date	Description
Scientific Advice (CHMP)	19 Sep 2013	Scientific Advice received regarding non-clinical and clinical aspects. Non-clinical aspects included the adequacy of the non-clinical package according to ICH S9 guideline and on embryofetal toxicity studies. Clinical aspects were focused on the proposed dose and design of the NOVA study, this included advice regarding local gBRCA testing confirmed by central lab testing,
PDCO Decision	1 Apr 2016	Confirmation of the applicability of the class waiver under the scope of EMA Decision CW/1/2011

Abbreviations: BRCA=breast cancer susceptibility gene; CHMP=Committee for Medicinal Products for Human Use; EMA=European Medicines Agency; gBRCAmut=germline BRCA mutation; non-gBRCAmut=without a germline BRCA mutation; PDCO=Paediatric Committee.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 100 mg of niraparib (as tosylate monohydrate) as active substance.

Other ingredients in the capsule content are magnesium stearate and lactose monohydrate. Ingredients of the capsule shell are: titanium dioxide (E 171), gelatin, brilliant blue FCF (E 133), erythrosine (E 127) and tartrazine (E 102). Ingredients of the printing ink are: shellac (E 904), propylene glycol (E 1520), potassium hydroxide (E 525), black iron oxide (E 172), sodium hydroxide (E 524) and povidone (E 1201).

The product is available in Aclar/PVC/aluminium foil perforated unit dose blisters, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of niraparib tosylate monohydrate is 2-{4-[(3*S*)-piperidin-3-yl]phenyl}-2H-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1) corresponding to the molecular formula $C_{19}H_{20}N_4O \cdot C_7H_8O_3S \cdot H_2O$. It has a relative molecular mass of 510.61 and the following structure:

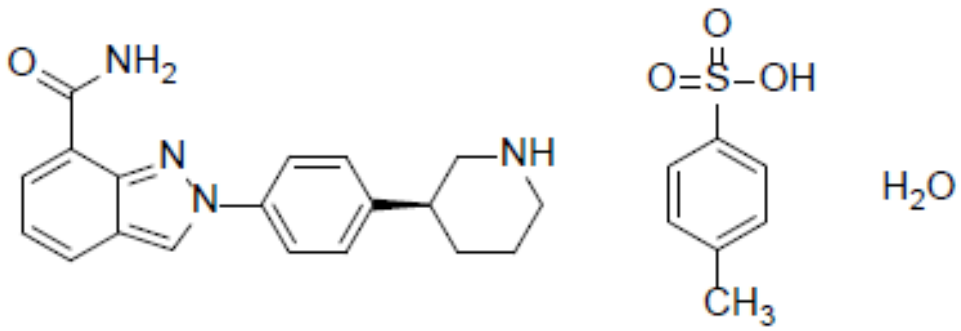


Figure 1: active substance structure

The chemical structure of niraparib tosylate monohydrate was elucidated by a combination of nuclear magnetic resonance spectroscopy (NMR), liquid chromatography–mass spectrometry (LC-MS), and single crystal X-ray crystallography with confirmatory data from elemental analysis, Fourier transform infra-red (FT-IR) spectroscopy, and ultraviolet (UV) spectroscopy.

The active substance is a white to pale brown powder; it is non-hygroscopic, with low, pH independent solubility in aqueous media. Based on the high permeability, it is classified as BCS Class II compound. Due to low solubility, particle size distribution is controlled in the active substance specification. Particle size distribution supports product manufacturability and it is based on the analysis of batches used in the pivotal clinical study.

Niraparib exhibits stereoisomerism due to the presence of a single chiral centre. The stereochemistry originates and is controlled in the synthesis.

Polymorphism has been observed. The anhydrate form has been detected by DSC but is only formed at very high temperatures. The crystallization ensures routine production of the monohydrate form which is conformed routinely by XRPD.

Manufacture, characterisation and process controls

Niraparib is synthesized from well-defined starting materials with acceptable specifications. One starting material was red-defined during the procedure in response to a major objection from CHMP as not enough of the process has been included for the regulatory to understand the control and fate of impurities. The revised process, along with impurity (including genotoxic impurities) fate and purge studies ensures that sufficient steps are included in the process description, and that the control strategy is adequate to ensure the quality of the active substance. Three manufacturers carry out the manufacture of the active substance. The active substance is synthesized in six main steps.

Niraparib tosylate monohydrate is a genotoxic compound and is administrated to patients with advanced cancer at a daily dose of up to 300 mg. In accordance with Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, both the identification (0.10 %) and qualification thresholds (0.15 %) stated in ICH Q3A will be applied to niraparib impurities including other potential genotoxic impurities (PGIs).

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. There have been three slightly different variations of the same synthetic route to manufacture niraparib tosylate monohydrate active substance. The synthetic approaches for Processes I to III all employ the same carbon-carbon bond and carbon-hetero bond formation steps. The order of some chemical transformations has varied between processes, as has the selection of isolated intermediates. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. Active substance batches manufactured using Process III were used in clinical studies, as primary stability batches, and for commercial product.

The manufacturing process has been developed using a combination of traditional and enhanced approach to pharmaceutical development, in line with ICH Q11 Guideline. The early development work in establishing the commercial route for niraparib synthesis primarily used the traditional approach to screen and select reagents, solvents, catalysts, and reaction temperature, as well as to optimize the process for early stage production. When appropriate, an enhanced approach, such as the use of statistical design of experiment and one variable at a time (OVAT) studies has been conducted to understand the sensitivity of the process to various parameters and ensure that the process is robust across the defined normal operating ranges (NORs), proven acceptable ranges (PARs) and critical process parameters (CPPs). Although aspects of enhanced approach to pharmaceutical development have been used, no design space or regulatory flexibility is applied for.

The active substance is packaged in HMHDPE or ArmorFlex® 116 bags inside of LDPE bags. All primary packaging material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, identification, identification of toluene sulfonic acid (HPLC), assay (HPLC), achiral related impurities (HPLC), chiral impurity (chiral HPLC), residual solvents (GC), water content (KF), elemental impurities (ICP-MS), particle size (laser diffraction), solid form (XRPD) and residue on ignition/sulfated ash (gravimetric Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Analysis data from 22 commercial and pilot scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The microbiological quality of three out of six registration batches of the active substance was consistently below 100 CFU/g (TAMC) and 10 CFU/g (TYMC) and given the oral route of administration, no routine test is required.

Stability

Stability data from three commercial scale batches of active substance from each of the proposed manufacturers stored in the intended commercial package for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, assay, achiral related substances, chiral impurity, water content, particle size and solid form. The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

Photostability testing following the ICH guideline Q1B was performed on two batches showing that the active substance is not photosensitive. Forced degradation studies were carried out by exposing the active substance to heat, light, acid, base and oxidative conditions. Niraparib tosylate monohydrate is stable in the solid state and did not show significant degradation in basic/acidic aqueous solutions but degrades in aqueous solution with an oxidant.

All tested parameters were within the specifications. Stability data is representative for all suppliers and there are no differences in stability data between the active substance manufacturers.

The stability results justify the proposed retest period in the proposed container.

Comparability exercise for Active Substance

Not applicable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as hard capsules containing 100 mg of niraparib (as tosylate monohydrate) as active substance. The dimensions of hard capsules are approximately 22 mm x 8 mm; they have a white body with “100 mg” printed in black ink and purple cap with “Niraparib” printed in white ink.

The aim of the pharmaceutical development was to deliver a robust formulation and manufacturing process with an appropriate control strategy that meets all aspects of the Target Product Profile (TPP) and the Quality Target Product Profile (QTPP).

Pharmaceutical development of the finished product followed an enhanced approach with QbD elements.

Niraparib tosylate monohydrate is classified as having low solubility based on the experimentally determined solubility over the pH range according to the BCS guidelines (BCS Class II).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Compatibility of the active substance with the finished product excipients is demonstrated through ongoing stability studies

A dissolution method was developed and validated for the release and stability testing of niraparib 100 mg capsules. The discriminatory power of the dissolution method has been demonstrated.

The general process used to manufacture all niraparib clinical trial material and the commercial product has remained unchanged over the course of development. During the MAA review process, a development effort to further enhance the robustness of the commercial manufacturing process and optimize efficiency by targeting increasing yields was initiated.

With the exception of capsule colour and ink printing, the niraparib 100 mg capsule composition has remained unchanged throughout clinical development and is identical to the intended

commercial formulation. A 10 mg capsule was developed and used during early clinical studies. This formulation contained the same excipients which differed in ratios compared to the formulation used in pivotal clinical trial and selected for commercialisation.

The primary packaging is Aclar/PVC/aluminium foil perforated unit dose blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: screening of components, blending, encapsulation and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Full scale validation activities will be completed prior to commercial launch in accordance with the site master validation plan and protocols which was found acceptable. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form appearance (visual), identification (FT-IR, HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units (HPLC), dissolution (HPLC), water content (KF), elemental impurities (ICP-MS) and microbial enumeration (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 18 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the approved release specifications, through traditional final product release testing.

Stability of the product

Stability data from six commercial batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH), for up to 9 months at intermediate (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Data on batches of the finished product manufacturer using the active substance by different suppliers were provided (3 per supplier) in order to support their equivalence in terms of quality.

Samples were tested for the same parameters and using the same methods as for release. The analytical procedures used are stability indicating.

No significant changes have been observed for most of the tested parameters. Changes were observed for batches stored through to 6 months of storage at 40 °C/75 % RH as the known crosslinking within the hard gelatin capsule shell was observed at this accelerated condition. In accordance with ICH Q1E, failure to meet acceptance criteria for dissolution is not considered to be

a significant change since it is unequivocally due to the cross-linking of the gelatin capsule. Since there was little or no change over time, statistical analysis of the data was deemed unnecessary. With the exception of crosslinking of the hard gelatin capsule shell, there were no significant physical and chemical changes to any other measured parameters and on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, a single batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The data show no changes in the fully exposed test samples, with the exception of dissolution where cross linking, a known phenomenon for gelatin capsules, was observed. Therefore, with the exception of gelatin capsule cross linking, there were no observed changes on stability and the niraparib 100 mg capsules do not require light protection.

Based on available stability data, the shelf-life of 24 months and 'do not store above 30 °C', as stated in the SmPC (section 6.3) are acceptable.

Comparability exercise for finished medicinal drug product

Not applicable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Niraparib was evaluated in a series of biochemical and cell-based studies to determine its potency and selectivity against the PARP family of enzymes. Further, daily oral niraparib dosing was evaluated in cell line xenograft and patient-derived xenograft (PDX) models of ovarian cancer, as monotherapy, and in combination with platinum-based chemotherapy. Finally, niraparib-related effects on secondary pharmacological parameters and safety pharmacology endpoints were evaluated.

Primary pharmacodynamic studies

In vitro

Potency and selectivity of niraparib (studies PD001, 1001, PARP-05232016)

Niraparib demonstrated potent and selective PARP-1 and PARP-2 inhibition in biochemical and cell-based assays vitro, with IC_{50} of <4 nM, and displayed >100-fold window over the other PARP-family members.

Table 4: Activity of niraparib on PARP family members

PARP isoform[a]	IC_{50} (nM)[b]
hPARP-1	3.76 ± 1.6 (n = 9)
hPARP-2	2.15 ± 0.70 (n = 5)
hPARP-3	1250 ± 34.0 (n = 7)
h-vPARP	334 ± 101 (n = 5)
hTANK-1	567 ± 381 (n = 6)

[a] h= human.; vPARP = vault PARP (or PARP4); TANK-1 = tankyrase-1 (or PARP5a)
[b] Each value represents the mean ± SD derived from the indicated number (n) of experiments.

The primary circulating metabolite of niraparib in rats and dogs, the carboxylic acid M1, did not inhibit PARP-1 or PARP-2 *in vitro* at concentrations up to 10 µM.

Table 5: Inhibitory effects of niraparib and metabolite M1 on PARP activities

PARP	IC_{50}		
	Study 1001	Study PARP-05232016	
	Niraparib	Niraparib	M1
PARP1	2.8 nM	1.1 nM	>10 µM
PARP2	0.6 nM	0.4 nM	>10 µM
PARP3	5.2 µM	-	-
TNKS1	1.4 µM	-	-
TKNS2	1.4 µM	-	-
PARP6	>10 µM	-	-
PARP7	>10 µM	-	-

PARP8	>10 µM	-	-
PARP10	2.1 µM	-	-
PARP11	>10 µM	-	-
PARP12	>10 µM	-	-
PARP14	>10 µM	-	-
PARP15	>10 µM	-	-

PARP inhibition in human HeLa cells (study PD002)

Niraparib inhibited intracellular PARylation in HeLa human cervical cancer cells with an IC_{50} and IC_{90} of 4 and 37 nM, respectively. Similar results have been reported for niraparib in the A2780 ovarian tumour cell line and in the BRCA-2mut CAPAN-1 pancreatic tumour cell line (Jones et al, 2015).

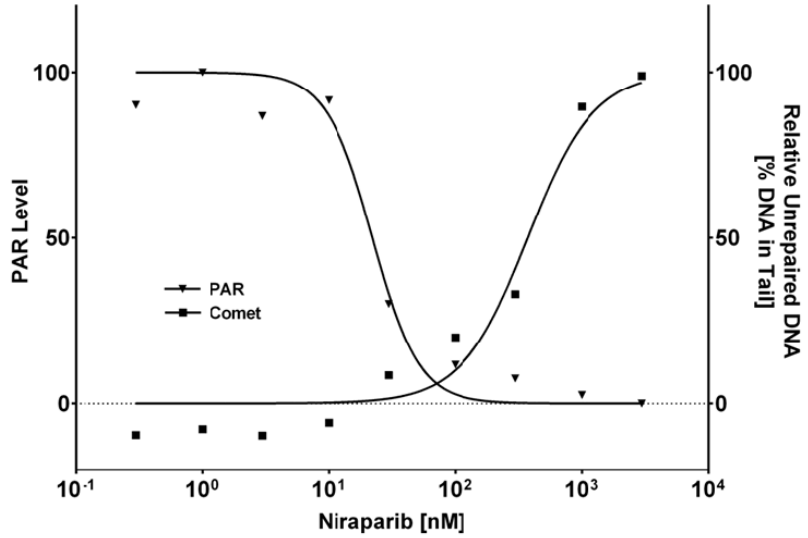
Table 6: Inhibition of PARylation in tumour cell lines (Jones et al, 2015)

cell line	BRCA status	PARylation IC_{50} (nM)	PARylation IC_{90} (nM)
HeLa	wild type	4 ± 2	46 ± 6
A2780	wild type	4 + 1	52 ± 5
CAPAN-1	BRCA2 deficient	3.5 ± 1	50 ± 9

Values represent the mean ± SD derived from a minimum of three experiments.

Niraparib functionally inhibits PARylation and single-stranded DNA break repair (study TSR2016082)

Niraparib inhibited intracellular PARylation in Jurkat cells (human immortalised T lymphocytes) with an IC_{50} and IC_{90} of 22 and 56 nM, respectively. DNA repair was not inhibited until PAR levels were suppressed by approximately 90%.



Jurkat cells were pretreated with niraparib at indicated concentration for 1 hour and stimulated with H_2O_2 for 15 minutes to induce DNA damage. After one hour PAR levels were measured by ELISA (Trevigen 4520-096-K) and DNA SSBs were quantified by single cell gel electrophoresis (Trevigen 4252-040-K). DNA repair was normalized to DMSO sample 15 and 75 minutes after H_2O_2 treatment as minimum and maximum repair, respectively.

Figure 2 Correlation of niraparib-induced PAR suppression with suppression of DNA SSB repair

Antiproliferative activity of niraparib on cancer cells and normal cells (studies PD003, TSR-01)

Cell proliferation was selectively inhibited in cancer cell lines (uterine cervical, non-small cell lung, breast, pancreas) that were either BRCA-1- or BRCA-2 deficient (IC_{50} <74 nM), with ≥18-fold selectivity window over corresponding BRCAwt cell lines.

Table 7: Niraparib selectively inhibits proliferation of BRCA-1-deficient HeLa and BRCA-2-deficient A549 cells as compared to wild-type pairs

Cell Line	Tumor Type	CC_{50} (nM)[a]
Wild-type HeLa	Cervical carcinoma	852 ± 262 (n = 52)
HeLa BRCA-1-deficient	Cervical carcinoma	34 ± 17 (n = 52)
Wild-type A549	NSCLC	1760 ± 670 (n = 3)
A549 BRCA-2-deficient	NSCLC	11 ± 5 (n = 3)

[a] Proliferation was measured 5-7 days after addition of niraparib to the medium using the CellTiter-Blue™ assay (Promega). Values represent the mean CC50 ± Sdev derived from the indicated number (n) of experiments.

Compared to BRCA-1/-2-deficient cancer cells, niraparib exhibited only weak anti-proliferative activity on normal human cells, including human renal, prostate, and mammary epithelial cells, with IC_{50}s of ≥2.9 µM.

Table 8: Activity of niraparib on normal epithelial cells

Cells	CC_{50} (nM)[a]
HRE (human renal epithelial)	2900 ± 16 (n = 2)
PREC (human prostate epithelial)	> 4000 (n = 1)
HMEC (human mammary epithelial)	> 5000 (n = 1)

[a] Proliferation was measured using the CellTiter-Blue™ assay (Promega) according to manufacturer's instructions. Values represent the mean CC50 ± Stdev derived from the indicated number (n) of experiments.

Niraparib and olaparib had similar effects on both erythroid and myeloid progenitors with an IC_{50} of approximately 1 µM in each of the tested cell populations.

Table 9: Effects on niraparib and olaparib on normal haematopoietic cells

CFU Assay	Olaparib IC50 (nM)	Niraparib IC50 (nM)	Niraparib Selectivity Margin (fold change vs BRCAmut)[a]
Human megakaryocyte	490	460	13
Human erythroid	3800	1300	38
Human myeloid	1300	1100	32
Mouse megakaryocyte	1700	1000	29
Mouse myeloid[b]	5400	1000	29

[a] The average CC50 in BRCAmut tumor cells was 34 nM (Table 5)
[b] Frequency of mouse erythroid population too low to determine IC50

Normal, human megakaryocytes were, however, more sensitive relative to mouse (IC_{50}s of 0.46 and 1 µM, respectively).These data indicate a ≥13-fold selectivity margin when comparing the average BRCAmut tumour cell.

In vivo

Efficacy of niraparib in BRCA-1/-2 mutant human cell-line xenograft models (studies PD005, PD007)

Tumour regression was observed in a cell line derived human xenograft model of breast cancer with a functional BRCA-1 mutation with one month oral niraparib administration (100 mg/kg/day, either as QD or BID). When niraparib was dosed at 80 mg/kg QD for one, two, three, or four weeks, significant inhibition of tumour growth was observed in all groups, while continuous

treatment for 3 and 4 weeks resulted in an increase in regressions and remissions. This indicates that sustained inhibition of PARP is required for maximum anti-tumour efficacy in this model.

Cells can develop HR deficiency by a variety of mechanisms including the loss of function or inactivation of tumour suppressor genes BRCA-1 or BRCA-2. Similarly, the loss of function or inactivation of other genes involved in the HR pathway can lead to an HR deficient (HRD) phenotype within a tumour. The Applicant has applied a sequencing test, the myChoice HRD test, to identify HRD-status in breast and ovarian cancers by detecting variants in the BRCA1 and BRCA2 genes and quantitating genomic scarring of the tumour that can occur as a consequence of the error-prone non-homologous end joining repair pathway. An experimentally determined threshold (HRD Score cutoff) derived from molecular data and comparison with HRD scores from tumours with BRCA mutations was used to determine the HRD state and define a binary test output (HRD-positive or HRD-negative). This threshold value was selected to have a high sensitivity for detecting HRD in treatment-naïve breast and ovarian tumours as defined by BRCA-1 and BRCA-2 deficiency.

Activity of niraparib in orthotopic high-grade serous ovarian cancer patient-derived xenograft (PDX) models (study 3000-09-002)

To evaluate the potential therapeutic effect of single-agent niraparib in HRD-positive high-grade serous ovarian cancers, mice bearing treatment-naïve patient-derived orthotopic xenografts (PDX) were administered oral niraparib at 60 mg/kg/day for up to 28 days. Each tumour was tested for HRD status using the Myriad myChoice HRD test, to evaluate the potential utility of using this tumour classifier to identify patients that may benefit from niraparib therapy. Niraparib caused tumour regression in 7 out of 27 models overall (26%) and 7 out of 16 HRD positive models (44%). None of the HRD negative tumours responded to niraparib treatment.

Table 10: Niraparib response in orthotopic ovarian PDX models

Model#	HRD status[a]	BRCA-1/-2 mutation status[a]	Fold-change from baseline[b]	Tumor response[c]
PH054	positive	BRCA-1mut	0.08	PR
PH039	positive	wt	0.14	PR
PH088	positive	BRCA-1mut	0.17	PR
PH242	positive	wt	0.24	PR
PH013	positive	wt	0.54	PR
PH077	positive	BRCA-2mut	0.54	PR
PH056	positive	wt	0.62	PR
PH038	positive	wt	1.11	SD
PH331	negative	wt	1.35	PD
PH235	negative	wt	1.42	PD
PH048	negative	wt	1.42	PD
PH044	negative	wt	1.43	PD
PH087	negative	wt	1.45	PD
PH080	negative	wt	1.51	PD
PH095	positive	BRCA-2mut	2.05	PD
PH063	positive	wt	2.14	PD
PH098	negative	wt	2.33	PD
PH026	negative	wt	2.76	PD
PH233	positive	wt	2.91	PD
PH061	positive	wt	3.43	PD
PH045	negative	wt	3.48	PD
PH134	positive	wt	3.99	PD
PH249	positive	wt	4.58	PD
PH247	negative	wt	5.31	PD
PH231	positive	wt	5.66	PD
PH081	negative	wt	7.38	PD
PH291	positive	wt	10.60	PD

[a] from Myriad myChoice HRD test, positive tumors have BRCA-1/-2mut or HRD scores ≥42 [1]
[b] tumor area at day 0/ tumor area at day 28
[c] progressive disease (PD, FC >1.20), stable disease (SD, FC=1.20-0.70), or partial response (PR, FC < 0.70)

When using a threshold of 50% tumour growth inhibition (TGI) relative to vehicle treatment as a marker for anti-tumour effect, 4 out of 11 HRD negative tumour models (36%) were found niraparib responsive. The rate was 46%, and the response rate in HRD positive models was 52%.

Table 11 Overall niraparib response rate

Ovarian PDX model	Tumour regression[a, b]	>50% TGI[c, d]
All models	7/27 (26%)	14/30 (46%)
HRD positive	7/16 (43%)	10/19 (52%)
HRDnegative	0/11 (0%)	4/11 (36%)

TGI: Tumour growth inhibition
a: Defined as reduced tumour size at end of treatment relative to before treatment
b: defined as >50% TGI at end of treatment (relative to vehicle control)
c: data from study 3000-09-002
d: data from studies 3000-09-002 and PH-ON-TSB-5OVC

Efficacy of niraparib maintenance therapy in a BRCA-2mut high grade serous ovarian cancer patient derived xenograft (PDX) model (study 3000-09-003).

To assess the potential for niraparib as combination therapy with platinum-treatment, or as a maintenance therapy following platinum-based treatment, one BRCA-2mut high grade serous ovarian cancer PDX model and one HRD-positive, BRCA-wt PDX model were selected. The tumour

models were sensitive to niraparib single therapy, with tumour shrinkage to 36% and 8% of baseline, respectively. Tumour regression was also observed after four weeks of treatment with carboplatin/paclitaxel alone, and in combination with niraparib. The growth trajectories were not significantly different between carboplatin/paclitaxel and niraparib/carboplatin/paclitaxel. Tumours without maintenance treatment exhibited rapid regrowth 11 weeks after end of the 4-week platinum-treatment. In contrast, in mice randomized to niraparib maintenance treatment, tumours (n=4) became undetectable. An additional study was conducted to assess niraparib activity in three tumour models derived from patients who had experienced recurrence following platinum based treatment, but whose tumours were still responsive at some level to platinum. Following a single dose of carboplatin or carboplatin plus paclitaxel on day 1, daily niraparib monotherapy from day 8 was considered effective in maintaining tumour suppression in ovarian cancer after platinum treatment. These observations suggest that niraparib may have a role in the maintenance setting after primary treatment of high grade serous ovarian cancers, while its role in combination with primary platinum-based therapy is less clear.

Inhibition of PARP activity in tumour xenografts and peripheral blood mononuclear cells (studies PD009, PD010)

In vivo effect on tumour growth was seen in BRCA-mut and BRCAwt HRD ovarian tumour models with once daily oral administration of niraparib at a dose level sufficient to suppress 90% of PARP-1 enzymatic activity in the tumour at 8 hours post dose, and to >50% inhibition of PARP activity in PBMCs at 8 hours post dose. Consequently, PARP inhibition levels in PBMCs may potentially be considered as a surrogate marker for tumour response.

Secondary pharmacodynamic studies

In vitro secondary pharmacodynamics (studies PD011, PD012)

Niraparib was assessed for binding to ion channels, transporters and other G-protein coupled receptors to evaluate the potential for off-target activity. Six endpoints exhibited IC_{50} values below 5 µM. Niraparib was further assessed for functional activity against the two most potent targets identified in the primary assay, the dopamine transporter (DAT) and the norepinephrine transporter (NET) Niraparib was shown to inhibit the uptake of dopamine and norepinephrine with IC_{50} values of 24 and 130 nM, respectively. As a follow-up, three rodent studies were conducted to evaluate the effects of niraparib administration on brain monoamines.

Pharmacological effects of niraparib on monoamines in the mouse brain (study PD014)

Niraparib did not significantly change levels of dopamine, monoamines/metabolite levels or dopamine turnover in the striatum or hippocampus relative to the positive control amphetamine in mice following a single ip administration. Niraparib did not impact dopamine release, but increased intracellular dopamine and metabolite (DOPAC and HVA) levels in the cortex by 330%, 295% and 236%, respectively. These results suggest that niraparib can cause a build-up of intracellular dopamine in the cortex without increasing dopamine availability at its site of action in the CNS.

In vivo measurement of niraparib binding to the central dopamine transporter (DAT) in mice (study PD015)

Niraparib occupancy of DAT *in vivo* was measured by PET in the mouse brain using the DAT specific tracer [^{11}C]-CFT (PD015). Niraparib did not occupy DAT in the striatum at anti-tumour exposure levels, measured by PET on the mouse brain.

A comparison of niraparib and d-amphetamine induced locomotor behaviour (study PD013)

Niraparib was examined for its ability to influence motor activity compared to amphetamine as a positive control in mice (PD013). While amphetamine significantly increased the total distance travelled by the mice in a dose-dependent manner, niraparib significantly decreased distance travelled. Further, no niraparib-related behavioural or neurological findings were observed following 3 months repeated dosing in rats and dogs. Therefore, niraparib did not have behavioural or neurochemical effects consistent with enhanced DA availability in the CNS.

Safety pharmacology programme

Three safety pharmacology studies was performed to examine for potential effects of niraparib on the central nervous (CNS) and cardiovascular (CV) systems.

Effects of niraparib on hERG (potassium channel) expressing CHO cells (study ID TT #07-4734, non GLP)

In this study it was demonstrated that niraparib inhibited hERG current with an IC_{50} value of 10 µM (3200ng/mL).The positive control (cisapride 30 nM) inhibited 54 % of the hERG tail current, and confirmed the validity of the experiment.

Cardiovascular effects in dogs (study ID TT #07-5300, non-GLP)

Niraparib was evaluated in a cardiovascular study in anesthetized dogs for potential pharmacological activity after intravenous (IV) administration. Niraparib did not induce any significant changes in ECG parameters in conscious dogs at doses up to 10 mg/kg.

Effect of niraparib on neurological function in mice (study ID TT #07-5362)

Niraparib was evaluated in a neurological function study using a functional battery of tests. Niraparib had no effect on neurological function in conscious female mice at a single oral dose of 100 mg/kg.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were conducted with niraparib.

2.3.3. Pharmacokinetics

Single dose pharmacokinetic (PK) studies were conducted in male rats, dogs and monkeys *in vivo*, and in experimental species and human *in vitro*. Repeat-dose PK studies have not been conducted, but toxicokinetic (TK) analysis of niraparib and the main metabolite M1 were conducted as part of the pivotal repeat-dose toxicity studies.

Absorption

Niraparib was rapidly absorbed following oral administration in rats and dogs (T_{max} ~ 2 and 0.5 hrs, respectively). In rats, iv niraparib demonstrates a moderate plasma clearance (28 mL/min/kg), a high volume of distribution (6.9 L/kg), and a moderate half-life (3.4 hours). In dogs, iv niraparib exhibited a high clearance (31 mL/min/kg), a high volume of distribution (12.3 L/kg), and a moderate half-life (5.7 hours). The oral bioavailability of niraparib was low in rats (27%) and moderate in dogs (57%).

Distribution

Conventional tissue distribution studies have not been conducted. Niraparib was moderately bound to plasma proteins (~71.6 - 84.0%), and red blood cells (blood-to-plasma concentration ratios of 1.1-1.7) across species. Niraparib is highly cell membrane-permeable, with the counter efflux from P-glycoprotein (P-gp) being evidently limited.

Niraparib is readily distributed to the brain of rats and the cerebrospinal fluid (CSF) of monkeys. Brain-to-plasma C_{max} ratios in rats were 0.77 and 0.64 following PO doses of 10 and 30 mg/kg, respectively. In monkeys, CSF-to-plasma C_{max} and $AUC_{0\text{-}inf}$ ratios were approximately 0.31 and 0.19, respectively, after a PO dose of 10 mg/kg.

Metabolism

All metabolites formed by human hepatocytes have been detected in the species used in the toxicity studies, with M1, a carboxylic acid metabolite formed by the carboxylesterases (CEs), being the major primary metabolite in circulation.

Diverse metabolic pathways, mediated by enzymes in several classes with non-CYP enzymes being principal, were detected. The minor oxidative pathways were primarily mediated by CYP1A2 and CYP3A4/5 with a possibly minor contribution from CYP2D6. This warrants a minimal risk for the drug-drug interaction for niraparib when being concurrent with CYP inhibitory and/or inductive agents.

Excretion

Niraparib was primarily eliminated unchanged via faecal (biliary) and renal routes in rats, while being mainly eliminated as M1 via renal excretion in dogs. In addition, findings in faeces in bile-cannulated rats and dogs indicate intestinal excretion, likely via the action of the efflux transporter, P-gp. The overall recoveries in rats and dogs were high and virtually identical (~ 80% for 5-day collections for both species), suggestive of minimal long term body retention.

Pharmacokinetic drug interactions

The potential interaction of niraparib with major drug-metabolizing enzymes and the interaction with drug transporters were evaluated in vitro. Data are discussed under the clinical section.

2.3.4. Toxicology

The toxicology dossier provided for niraparib, comprises repeat dose toxicity studies in rats and dogs up to 3 months, genotoxicity studies *in vitro* and *in vivo* and phototoxicity studies. All the pivotal studies were performed according to GLP.

Single dose toxicity

No single dose toxicity study has been submitted.

Repeat dose toxicity

Repeat-dose toxicity studies with daily oral (gavage) administration of niraparib for up to three months were conducted in rats and dogs.

Table 12: Repeat dose toxicity studies with niraparib

Species/ strain/ Study ID (GLP)	Dose (mg/kg/day) Route (Vehicle)	n/sex /group	Duration	Major findings
Rat (F)/ Crl:CD(SD) TT # 07-2516 Non-GLP	0, 10, 100, 750 Oral (gavage) (0.5% methylcellulose in deionized water)	5F/group	7 days	≥10mg/kg: ↓ white blood cells (neutrophils, eosinophils, monocytes, and lymphocytes) (slight). 100 mg/kg: ↓ in erythroid parameters (RBC, HGB, and HCT) (slight to moderate), ↓ in reticulocytes and leukocytes (severe) with corresponding changes in differential count on Day 8. Salivation (from day 3) and ↓ food consumption (from day 6). ↓ ASAT (very slight) and ↑ ALP (very slight-slight) on day 8. Histopathological findings included ↓ hematopoietic tissue of the bone marrow and necrosis of the mucosa of the small intestine. 750 mg/kg: Treatment-related mortality or early sacrifice occurred in all animals on Days 5 and 6. ↓ food consumption, salivation, ↓ activity, distended abdomen, unkempt appearance, faecal staining, urine staining, and red discharge from the nose or mouth from Day 2 or 4. Histopathologic findings included ↓ amount of haematopoietic tissue of the bone marrow, necrosis of the mucosa of the small intestine, atrophy of skeletal muscle, depletion of the lymphoid tissue of the spleen, atrophy of the mucosa of the large intestine, and glandular dilation of the glandular mucosa of the stomach, which correlated with distention of the stomach noted at gross examination. **NOAEL:** 10 mg/kg/day
Rat / Crl:CD(SD) TT # 07-9826 GLP	0, 5, 10, 50 Oral (gavage) (0.5% methylcellulose in deionized water)	15/sex/ Group 5/sex/ recovery group	1 month + 2 weeks recovery period	10 mg/kg: ↑urine volume (moderate) (M). 50 mg/kg: 4M died during treatment period, 1 M died during recovery. ↓activities, piloerection, convulsion-like activity, increased respiration rate, discharge from eye and/or nose, swollen muzzle and/or ear pinna, salivation, and unformed faeces were observed before death. ↓ body weight gain, ↓ food consumption, pale fundus in the ophthalmic examinations, ↓ RBC and WBC parameters (slight to severe), ↓ reticulocytes (severe). Changes in serum chemistry parameters (very slight to slight), ↑ urine volume (moderate). ↑ heart weight, ↑ adrenal weight (M), ↓ thymus and ovary weights. ymphoid depletion in thymus, spleen, and lymph nodes (very slight to marked) with or without histiocytosis, depletion in red pulp in spleen (M, very slight), ↓ spermatogenic epithelium in testes (very slight to slight), depletion of the bone marrow (slight to marked). Septicaemia (septic emboli and/or septic necrosis in 1 or more organs/tissues) were confined to the dead males. Septic emboli and/or septic necrosis with or without oedema corresponded to grossly observed adhesion of the heart, grey-white discoloration/foci of the heart, liver, kidney, and spleen, and scab or thickened area (at the muzzle) in the skin with or without red discoloration. Haemorrhage with septic meningeal inflammation in spinal cord, focal necrosis with septic embolus in liver. Cortical hypertrophy in the adrenal, Kupffer cell hypertrophy and hepatocellular vacuolation, ↓uterus, ↓ number of corpus luteum. Recovery: There was treatment-related very slight to slight arterial hypertrophy in the heart of female and male rats and very slight to marked increased amount of trabecula in the bone (femur) of female and male rats at the end of dosing period. Other treatment-related postmortem changes observed in rats from the 50-mg/kg/day group at the interim necropsy were not observed at the end of the recovery period, or were demonstrated reversibility. **NOAEL:** 5 mg/kg/day (M), 10 mg/kg/day (F).
Rat / Crl:CD(SD) 12-2328 incl. Amend ment 1	0, 5, 10, 30 (F), 30/20 (M) Oral (gavage) (0.5% (w/v) methylcellulose in	10-15/sex/ group 3-6/sex /group for TK	3 months + 4 weeks recovery	≥10 mg/kg: ↓ in red cell mass (haemoglobin, haematocrit, and/or red blood cells) and ↑ platelets (M). Bone marrow depletion (minimal, 1M) ↑creatinine and phosphorus at the end of dosing. 30/20 mg/kg: mortality (2F), severe anaemia (M). ↓ red cell mass (haemoglobin, haematocrit, and/or red blood cells), ↑

GLP	deionized water) In the high dose group (M) after a dose holiday on Days 29-33 (total 5 days) the dosage was lowered to 20 mg/kg/day starting on Day 34 (referred to as 30/20 mg/kg/day).	evaluation		platelets (F), ↑ red cell distribution width (RDW). ↓ neutrophils, lymphocytes and/or monocytes. ↓ total protein (albumin and globulins), triglycerides, sodium, chloride, and calcium and increases in albumin to globulin ratio and potassium. Bone marrow depletion (minimal to marked). Testicular germ cell depletion with ↓ sperm and cell debris in the epididymis, ↓ testicular weights. Lymphoid depletion (minimal to moderate) in the spleen. Recovery: Partially or complete recovery was demonstrated, with the exception of: ↓ red blood cell and ↑ in MCV, MCH and RDW, ↓lymphocytes (M), ↓ total protein and globulins (F), ↓ testicular and epididymal weights, depletion of germ cells. **NOAEL:** 10 mg/kg/day.
Dogs, Beagle TT # 07-9943 Non-GLP	Dose escalating regimen for consecutive 3-day intervals at 4.5, 13.5, and 40.5 mg/kg/day. (0.5% methylcellulose in deionized water)	2F	9 day	≥ 4.5 mg/kg: ↓in reticulocytes (moderate to marked). 13.5 mg/kg: ↓in neutrophils (moderate). 40.5 mg/kg: emesis, body weight losses (slight), ↓ in haemoglobin and haematocrit value (very slight), and ↓ in leukocytes moderate.↓ haematopoietic tissue in bone marrow. **NOAEL**: < 4.5 mg/kg/day.
Dogs Beagle TT # 07-6050 GLP	0, 3, 6 and 15 Oral (gavage) (0.5% methylcellulose in deionized water)	5/sex/group	One month with a 15-day recovery period.	≥ 6 mg/kg: ↓ amount of the spermatogenic epithelium. 15 mg/kg: ↓ in reticulocytes (marked), ↓ in erythrocytes, haemoglobin, and haematocrit (slight). Recovery: The changes were reversible following recovery. A decreased amount of the spermatogenic epithelium was observed at 15 mg/kg/day at the interim necropsy and in the 6 mg/kg/day and 15 mg/kg/day groups at the final necropsy. This change was considered reversible by the sponsor after longer term cessation of dosing since spermatogonia was present in all the sections that were examined histomorphologically. **NOAEL:** 3 mg/kg/day (M), 6 mg/kg/day (F)
Dogs Beagle 12-3110, incl. amendment 1 GLP	0, 1.5, 4.5, 12 Oral (gavage) (0.5% (w/v) methocel)	6/sex/ Group 1 and 4, 4/sex/Group 2 and 3	Three months with 28 days recovery	12 mg/kg: testicular hypospermatogenesis (moderate to marked) , ↓ of epididymal sperm content (slight to marked), bone marrow hypocellularity (slight) correlating with ↓ (minimal) in erythroid precursors (bone marrow smear analysis), ↓ in red cell mass (minimal to slight,), ↓ reticulocytes (M). Recovery: recovery was observed after 28-day recovery period. **NOAEL:** 4.5 mg/kg/day (M), 12 mg/kg/day (F).

The results indicate that bone marrow is the main target organ for toxicity, with subsequent reduction in RBC and WBC parameters and lymphoid depletion in the bone marrow, spleen, thymus and lymph nodes. Infections and septicaemia observed in the one-month rat study are considered secondary to the lymphoid depletion, leading to mortality in male rats.

The testes were also identified as a target organ for toxicity in both species, with effects seen as reduced spermatogenesis and a decreased amount of spermatogenic epithelium in rats and dogs. This is in agreement with the proposed role of PARP in chromatin modifications during spermatogenesis (Dantzer 2006, Celik-Ozenki 2013).

Interspecies comparison showed that both rats and dogs were exposed to niraparib as well as to main human metabolites M1 and M10 at exposure levels below human levels at intended therapeutic dose. In rats, the AUC of M1 was approximately 15- to 50-fold less than the AUC of niraparib, while in dogs the AUC of M1 reached approximately 15-fold the AUC of niraparib. The similarity of safety profiles and nature of the adverse findings in both species, despite a difference in parent/M1 exposure ratio, suggest low contribution of M1 to the adverse findings of niraparib.

Genotoxicity

Niraparib in hydrochloride salt form was clearly positive in two non-GLP Ames tests, indicating a mutagenic potential. Niraparib in tosylate salt form, however, was negative in three GLP-compliant Ames tests.

Niraparib (independent of salt form) is considered clastogenic in mammalian test systems *in vitro* and in a micronucleus test *in vivo*, as expected for a PARP-1/PARP-2 inhibitor, at plasma exposure levels below therapeutic exposure levels.

Carcinogenicity

No Carcinogenicity study has been submitted.

Reproduction Toxicity

No reproductive and developmental toxicity study has been performed. In a paper, referred to by the applicant, it was shown that PARP-1 and PARP-2 double knockout mutant embryos die around the onset of gastrulation and that PARP-1 and PARP-2 is essential during early embryogenesis (Menissier de Murcia et al, 2003). The PARP-1/PARP-2/PARP-3 inhibitor olaparib was shown to be teratogenic at low doses and to produce total embryo lethality at levels below human exposure (Lynparza EPAR, 2014). Niraparib is clastogenic and bone marrow is the main target organ for toxicity. An overall evaluation of the data is that, in compliance with ICH S9, it is not necessary to perform reproductive and developmental toxicity studies with niraparib.

Local Tolerance

No local tolerance study has been performed

Other toxicity studies

Phototoxicity studies

Results from the 3T3 NRU *in vitro* assay indicate that niraparib has a phototoxic potential but the results from an *in vivo* study with Long Evans pigmented rats showed no evidence of cutaneous or ocular phototoxicity.

Immunotoxicity

Immunotoxicity was observed as effects on the bone marrow in the preclinical studies. Separate immunogenicity studies have not been conducted. This is acceptable, and in accordance with ICH S8.

Impurities

No specific impurity studies were conducted. Two impurities are above the qualification threshold; impurity A and a niraparib tosylate monohydrate enantiomer. Because impurity A is identical to the main metabolite M1 in humans and animals, the proposed specification limits in drug substance and drug product are considered adequately qualified.

The enantiomer was present at 0.10% in the batch used for the 3-month rat and dog studies. Based on the highest dose levels of niraparib administered in these studies (30 mg/kg/day and 12 mg/kg/day in rats and dogs, respectively), and the intended clinical dosing of niraparib at 300 mg/day, the proposed specification of NMT 0.20% are acceptable from a non-clinical point of view.

2.3.5. Ecotoxicity / environmental risk assessment

Table 13 Summary of main study results of an OECD-compliant study

Substance (INN / Invented Name): Niraparib					
CAS-number (if available): 1038915-60-4					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 5: -0.6 pH 7: 0.2 pH 9: 2.1			Potential PBT: N
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, refined	0.0435	µg/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

A PEC_{SW} has been calculated to above the action limit of 0.01 µg/L, thus a Phase II Tier A environmental fate and effects analysis is required. The environmental risk assessment for Zejula requires further investigations, and the Applicant is recommended to submit an updated ERA by the end of Q2 2018.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Primary pharmacodynamics

In vitro data indicate that BRCA-deficient tumour cells are more sensitive to niraparib than BRCA wild-type tumour cells, and normal epithelial and haematopoietic cells. Human megacaryocytes, however, appear more sensitive to niraparib than other human and murine haematopoietic cells and murine megacaryocytes, with IC_{50} at 460 nM and IC_{90} at 1000 nM. Although this is 13-fold higher than for the BRCA-deficient cells, expected human plasma levels of niraparib at intended therapeutic dosing is about 2-fold higher than IC_{90} for human megacaryocytes, indicating a potential for thrombocytopenia. Similarly, reversible findings compatible with bone marrow suppression have been observed in repeat-dose toxicity studies without margins of safety. Thrombocytopenia is an adverse event often seen in clinical studies with niraparib, and has been adequately reflected in the proposed SmPC for Zejula.

Thrombocytopenia is also listed as an adverse event in the SmPC for Lynparza (olaparib), but appears to be a more frequent event for niraparib than olaparib. Based on *in vitro* data with human megacaryocytes, there are no apparent difference in IC_{50} values, or in selectivity margins (ratio between IC_{50} values for megacaryocytes and tumour cell growth) for olaparib and niraparib, respectively. However, IC_{90} values could suggest that the human megacaryocytes are more sensitive to niraparib than olaparib.

Homologous recombination (HR) is a type of genetic recombination most widely used by cells to accurately repair harmful breaks that occur on both strands of DNA, known as double-strand breaks. In cells with a deficiency in homologous recombination repair (HRD), such as those with BRCA-1 and BRCA-2 mutations, PARP inhibition leads to irreparable DSBs, use of the error prone NHEJ pathway, resultant genomic instability, and ultimately cell death. The Applicant has applied a test to score the HR deficiency in tumour cells. No validation data has been provided for the Myriad myChoice HRD test. According to the Applicant, however, the test provides a HRD score which is an unweighted sum of three independent DNA-based measures of genomic instability based on loss of heterozygosity (LOH), telemetric allelic imbalance (TAI) and large-scale state transitions (LST). A HRD score of ≥42 (the 5th percentile of the HRD scores in a combined ovarian and breast training set of tumours with known BRCA1/2 deficiencies and/or BRCA1 or BRCA2 mutation) is by the Applicant defined as an indication for homologous repair deficiency (Telli et al., 2016).

The indication sought for niraparib is broader than the approved indication for olaparib, not limited to the treatment of BRCA-1/-2 deficient (due to mutation, low expression or deletion) tumour type. Based on clinical (and non-clinical) data it is agreed that niraparib responsiveness goes beyond the BRCA mutation status (as measured with the myChoice test). The Applicant is 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.

The Applicant has provided results of a study assessing niraparib activity in tumours derived from patients who had experienced recurrence following platinum based treatment, but whose tumours were still responsive at some level to platinum. From data presented in study E0322-U1509 is it not possible to evaluate the tumour response to carboplatinum single administration and thus it is not possible to draw any conclusion on the non-clinical correlation between niraparib response vs platinum response (in other terms whether platinum sensitivity could be a predictive factor of niraparib response besides being a prognostic disease factor). Clinically, however, platinum sensitivity is considered a sufficient marker for niraparib responsiveness.

In study 3000-09-003, PH077 responded to niraparib maintenance therapy (following primary 4-week treatment with platinum+paclitaxel+niraparib): data for PH039 are not available. Although both HRD+ PDXs resulted sensitive to niraparib monotherapy (study 3000-09-002), tumour growth inhibition was more marked for PH077 that is also BCRA 2mut respect to PH039 that is BCRA wt. The BCRA mutation status may play a relevant role also for the positive response to niraparib as

maintenance treatment after a previous niraparib treatment, rather than tumour aggressivity as suggested by the Applicant.

None of the HRD-negative tumour models in study 3000-09-002 were found niraparib sensitive, defined as tumour regression. However, when using a threshold of 50% tumour growth inhibition (TGI) relative to vehicle treatment as a marker for anti-tumour effect, 4 out of 11 HRD negative tumour models (36%) were found niraparib responsive. However, such an exercise is questioned for study 3000-09-002, considering the highly variable number of animals (2-16) between treatment groups and tumour models, and extensive variability in duration of treatment (7-28 days).

The Applicant has discussed a number of plausible reasons for the apparent niraparib responsivity in HRD-negative tumours, including false negatives, altered genetic properties after HRD-testing, and high PARP-1 expression. Taken together, the true HRD status of the tumour models classified as HRD negative by the MyChoice test is unknown. Consequently, due to the uncertainties related to the MyChoice test, the deficiencies in the Applicant's response regarding potential niraparib responsivity in tumour models classified as HRD negative will not be further pursued.

In vivo effects on tumour growth were seen in BRCA-mut and BRCAwt HRD ovarian tumour models with once daily oral administration of niraparib at a dose level sufficient to suppress 90% of PARP-1 enzymatic activity in the tumour at 8 hours post dose, and to >50% inhibition of PARP activity in PBMCs at 8 hours post dose. Consequently, PARP inhibition levels in PBMCs may potentially be considered as a surrogate marker for tumour response. The reason for the enhanced level of PARP suppression in tumours relative to PBMC is not known, but a potential explanation proposed by the Applicant is a preferential distribution of niraparib to tissues relative to plasma. Distribution studies have, however, not been conducted.

M1 is a major human metabolite, with clinical M1 to niraparib exposure ratios of 1.3-2.2 fold in plasma, and with a mean $T_{1/2}$ of 88h. *In vitro* studies indicate that M1 has no inhibitory effect on PARP1 or PARP2 (IC_{50} <10 µM). Potential secondary effects have not been evaluated. This is considered acceptable, in view of the intended indication.

Secondary pharmacodynamics

Niraparib readily crosses the BBB in rodents, and inhibits the DAT transporter *in vitro* with an IC_{50} level (24 nM) below human C_{max} levels (free fraction) at intended therapeutic dose. Niraparib did not occupy DAT in striatum in mice following single doses, and did not change levels of dopamine, monoamines/metabolite levels or dopamine turnover in the striatum or hippocampus in mice (study PD014). However, increased intracellular levels of DA and metabolites have been observed in cortex (study PD014), indicating a potential build-up of intracellular dopamine in this region. The long-term consequence of such a build-up is not known. It has, however, been suggested that accumulation of intracellular DA may trigger oxidative stress and neurotoxicity (Lohr et al, 2017).

In mice, single ip doses of niraparib increased intracellular levels of DA and metabolites in cortex. No effect on neurological function, including general behaviour, neural reflexes, spontaneous activity and thermoregulation were observed in mice in a 24-hour period following a single oral dose of 100 mg/kg. However, reduced locomotor activity was seen in mice following single ip doses. No effect on behavioural and/or neurological parameters were observed in repeat-dose toxicity studies in rats and dogs at estimated CNS exposure levels similar to or below expected therapeutic exposure level (see section 5.3 of the SmPC), and margins of safety cannot be established.

Safety pharmacology

Niraparib tosylate salt inhibited hERG current in a GLP assay, with an IC_{50} value of 15 µM. Considering observed C_{max} levels at intended therapeutic dose in patients of 4.37 µM (clinical study

PN001), and plasma protein binding fraction of 83%, the IC_{50} value is only 13.5-fold free fraction in humans (3200ng/mL).

Niraparib did not induce any significant changes in ECG parameters in conscious dogs at doses up to 10 mg/kg. Peak average plasma concentrations measured in dogs during infusion at 10 mg/kg (15.3 µM) was only 3.5-fold higher than observed C_{max} levels at intended therapeutic dose in patients, leading to low margins of safety. Taken together, niraparib inhibits the hERG current with low margins of safety. A potential clinical relevance of this finding cannot be excluded due to low margins of safety to exposure levels at the highest dose administered in the negative ECG study in dogs.

Pharmacokinetics

Absorption

Single-dose PK data from rats and dogs indicate substantial distribution ($V_{d,ss}$ of 6.9 and 12.3 L/kg, respectively). Further, brain distribution studies in rats and Rhesus monkeys indicate that niraparib is readily distributed across the BBB. Although *in vitro* data indicate that niraparib is a P-gp substrate, the brain:plasma ratio in rats increases over time, suggesting a sustained brain distribution.

Metabolism

The data provided by the Applicant regrading *in vivo* metabolism is rather limited. Study PK003 is a study on metabolism and excretion of niraparib in male rats and dogs following IV administration, and is mostly addressing excretion. While the levels of niraparib and metabolites were quantified in urine, bile and faeces, the plasma levels were not quantified. Further, the route of administration in PK003 is IV, and not the intended clinical route of administration. Consequently, metabolism of niraparib following oral administration has not been addressed by the Applicant. However, data from study PK003 do indicate that the major circulating metabolite in rats and dogs following po administration of niraparib is M1, and its glucuronide metabolite M10.

Based on TK data from the 3-month repeat-dose toxicity studies, niraparib was the major circulating compound in rats. Although the plasma levels of M1 generally were slightly higher in males than in females and appeared to be greater after repeated administration of niraparib, M1 comprised less than 10% of the parent compound in rats. In dogs, however, the plasma levels of M1 generally appeared to be independent of dose and sex, and were similar after single and repeated oral (gavage) administration. M1 comprises the major plasma component, with a systemic exposure level approximately 15-fold higher than to the parent substance.

Toxicology

Repeat-dose toxicity

The choice of rat and dog as species for non-clinical testing of niraparib is considered acceptable according to ICH S9.

In repeat -dose oral toxicity studies, niraparib was administered daily for up to 3 months' duration in rats and dogs. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral haematology parameteres.

The adverse findings on bone marrow are expected effects as a result of PARP inhibition and is considered to reflect the pharmacology of niraparib. The testes were also identified as a target organ for toxicity in both species (reversible decreased spermatogenesis), the relevance is however limited as the target clinical population consists of female patients.

These findings were dose related, occurred at exposure levels below those seen clinically, and were largely reversible within 4 weeks of cessation of dosing (see section 5.3 of the SmPC). They are

also in line with observations from animal studies with the PARP inhibitor olaparib (marketed as Lynparza).

At NOAEL, exposure levels to bound + unbound niraparib free base were below human levels at intended therapeutic dose (i.e., C_{max} 1144 ng/ml; AUC 21255 ng·h/ml from clinical study PN001). Clinical exposure level to M1 following repeated dosing has not been presented by the Applicant. However, plasma exposure ratio of M1 to niraparib following a single dose of niraparib was approximately 1.3-2.2 in clinical study PR-30-5015-C. Taken together, there are no margins of safety for the observed findings in rats and dogs.

Genotoxicity/carcinogenicity

Niraparib was not mutagenic in a bacterial reverse mutation assay (Ames) test but was clastogenic in an *in vitro* mammalian chromosomal aberration assay and in an *in vivo* rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of niraparib and indicates potential for genotoxicity in humans (see section 5.3 of the SmPC).

No genotoxicity studies were performed with the M1 metabolite. This is acceptable, considering that niraparib is genotoxic, and in view of the intended patient population.

Carcinogenicity studies are not required to support a marketing application for the proposed patient population (in line with ICH S9 guideline). In addition, the patients with ovarian cancer receiving niraparib have received prior therapy with multiple cycles of platinum-containing chemotherapy that is known to be genotoxic. The omission of such studies is therefore considered acceptable.

Reproductive and developmental toxicity

Studies on reproductive and developmental toxicity studies have not been conducted. PARP-1 and PARP-2 is considered essential during embryogenesis, and animal studies with the PARP-1/PARP-2/PARP-3 inhibitor olaparib have demonstrated embryolethal and teratogenic effects. Consequently, embryotoxic and teratogenic effects of niraparib is expected and niraparib should not be used during pregnancy (see section 4.6 of the SmPC). The lack of reproductive and developmental toxicity studies is therefore considered acceptable.

The environmental risk assessment for Zejula requires further investigations as a phase II Tier A has not been submitted. The applicant is recommended to submit an updated ERA by the end of Q2 2018.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data provided during the procedure support marketing authorisation.

The CHMP considers the following measures necessary to address the non-clinical issues:

- The Applicant is 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.

- The Applicant is recommended to submit an updated ERA including the Phase II Tier A.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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.

Table 14 Tabular overview of clinical studies included in the submssion

Study ID	No. of Centers (Location)	Study Dates (Status)	Total Enrollment (Planned/ Actual)	Design / Control	Route and Regimen	Indication	No. of Patients by Treatment (Entered/ Treated)	Median Treatment Duration (cycles, days, or months)	Sex (M/F) Age (Range) Race
Phase 1									
PN001	3 (US, UK)	15 Sep 2008 – 14 Sep 2011 Completed	50 to 342/104	Open-label MAD	Niraparib: 30, 40, 60, 80 , 110, 150, 210, 290, 300, 400 mg PO QD	Advanced ST or hematologic malignancies	Total: 104/104	58.5 days	31/73 35-75 W: 99 B: 2 A: 1 Unk: 2
PN008	2 (US, UK)	13 Jul 2010 - 04 Jul 2011 Terminated	105/12	Open-label MAD	Niraparib: 40, 60, 80, 110 mg PO QD for 4 days each 21-day cycle starting 2 days before carboplatin administered on Day 3	Advanced ST	Total: 12/12 3/dose level (40, 60, 80, 110 mg)	6 cycles	2/10 30-74 W: 11 B: 1
PN011	3 (US, Israel)	17 Nov 2010 - 14 Sep 2011 Terminated	90/6	Open-label MAD	Niraparib: 30 or 40 mg QD PO on Days 1-16 of 28-d cycles Pegylated liposomal doxorubicin: 40 mg/m^2 IV on Day 3 of every 28-day cycle	Advanced ST	Total: 6/6 3/dose level (30 and 40 mg)	3.5 cycles (Days 1-16 of 28-d cycles)	3/3 44-67 W: 6
PN014	3 (US)	28 Feb 2011 - 14 May 2012 Terminated	64/19	Open-label MAD	Niraparib: 30, 40, 70 mg QD PO on Days 1-8 of 28-day cycles Temozolomide: 150 mg/m^2 IV on Days 4-8 of every 28-day cycle	Advanced ST	Total: 19/19 6 (30 mg) 10 (40 mg) 3 (70 mg)	30 mg: 41.5 days 40 mg: 37.5 days 70 mg: 46.0 days	5/14 25-78 W: 17 B: 2
PR-30-5015-C AME	1 (Nether-lands)	29 Jan 2015 - Ongoing (Data cut off: 15 Feb 2016)	Part 1: 6/6 Part 2: 6/6 Extension: 12/11	Open-label 2-part: AME, absolute BA with treatment extension	Niraparib: Part 1: SD 300 mg PO + IV [^{14}C] 100 µg Part 2: [^{14}C] SD 300 mg PO Extension: 300 mg QD PO	Advanced ST	Total Part 1 and Part 2: 12/12 Extension: 11/11 (3 ongoing)	Parts 1 and 2: Single dose Extension: 67 days	0/12 33-71 W: 12
Phase 2									
PR-30-5020-C QUADRA	39 (US)	27 Mar 2015 - Ongoing (Data cut: 20 May 2016)	400/311	Open-label Treatment	Niraparib: 300 mg QD PO in continuous 28-day cycles	Advanced, relapsed (≥3prior lines of therapy), high grade serous epithelial OC	311/291 (139 ongoing on study)	1.9 months	0/291 29-90 W: 243 B: 18 A: 9 AI: 1 Unk: 20
Phase 3									
PR-30-5011-C NOVA	107 (North America Europe, Israel)	26 Aug 2013 - Ongoing (Data cut: 30 May 2016; Data lock: 20 June 2016)	490/553	Randomized, double-blind, placebo-controlled Maintenance	Niraparib: 300 mg QD PO in continuous 28-day cycles	Women with platinum-sensitive recurrent OC with CR or PR to their most recent platinum-based therapy	553/546 (382 ongoing) Niraparib: 372/367 (266 ongoing on study) Placebo: 181/179 (116 ongoing on study)	Niraparib: 250 days Placebo: 163 days	0/546 33-84 W: 480 B: 7 A: 19 AI: 1 Unk: 46
PR-30-5011-C1-QTC QTc sub-study	4 (US)	28 May 2015 - Ongoing (Data cut off: 30 May 2016)	20/26	Open-label ECG evaluation with treatment extension	Niraparib: 300 mg QD PO	Women previously treated with recurrent OC	26/26 (10 ongoing on study)	151.5 days	0/26 46-76 W: 21 B: 3 A: 1 AI: 1

PR-30-5010-C BRAVO	109 (North America, Europe, Israel)	08 Apr 2014 - Ongoing (Data cut off: 15 Mar 2016)	306/141	Randomized, open-label versus Physician's choice	Niraparib: 300 mg QD PO Eribulin, vinorelbine, gemcitabine, or capecitabine	Adults with previously-treated advanced, metastatic, HER2-negative gBRCAmut breast cancer	Total: 141[a]	NA[a]	NA[a]
PR-30-5011-C2-FE FE sub-study	6 (US)	05 Aug 2013 – 20 Oct 2015 Complete	12/17	Open-label Fasted vs fed crossover with treatment extension	Niraparib: 300 mg SD PO For extension: 300 mg QD PO	Women with previously treated recurrent OC with no standard therapy options	17/17	42 days	0/17 47-69 W: 15 B: 1 NH: 1

Abbreviations: A=Asian; AI=American Indian or Alaska Native; AME=absorption, metabolism, and excretion; B=Black; BA=bioavailability; CR=complete response; d=day; FE=food effect; gBRCAmut=germline BRCA mutation; =HER2=hu man epidermal growth factor receptor 2; IV=intravenous; MAD=multiple-ascending dose; NA=not applicable; NH=Native Hawaiian or other Pacific Islander; OC=ovarian cancer; PO=oral; PR=partial response; QD=once daily; QTc=QT interval corrected for heart rate; SD=single-dose; ST=solid tumour; UK=United Kingdom; Unk=unknown; US=United States; W=White

[a]BRAVO study is still open to enrolment and has not yet completed its primary efficacy analysis (final progression-free survival analysis and overall survival analysis). As such, and in agreement with the Sponsor partner in the study (Breast International Group and EORTC), the Sponsor is blinded to aggregate data by study arm to avoid perception of impact to the conduct of the study.

2.4.2. Pharmacokinetics

A total of five clinical studies with pharmacokinetic data are submitted, with a total of 524 subjects (94% women) receiving niraparib. However, thorough PK data has only been presented in the dossier for three studies (133 subjects).

One population pharmacokinetic and pharmacodynamic modelling report (Niraparib PPK) was submitted, using data from studies PN001, PR-30-5011-C, PR-30-5011-C1 and PR-30-5011-C2.

Absorption

Niraparib was rapidly absorbed with median Tmax occurring at 2.5-4 hours postdose. The absolute bioavailability of niraparib was determined to be 71.7%. Following a single-dose administration of 300 mg niraparib under fasting conditions, niraparib was measurable in plasma within 30 minutes and the mean peak plasma concentration (C_{max}) for niraparib was reached in about 3 hours [804 ng/mL (% CV:50.2 %)]. Following multiple oral doses of niraparib from 30 mg to 400 mg once daily, accumulation of niraparib was approximately 2 to 3 folds.

The systemic exposures (C_{max} and AUC) to niraparib increased in a dose-proportional manner when the dose of niraparib increased from 30 mg to 400 mg. The absolute bioavailability of niraparib is approximately 73 %, indicating minimal first pass effect.

Influence of food:

A concomitant high-fat meal did not significantly affect the pharmacokinetics of niraparib after administration of 300 mg of niraparib.

Distribution

Niraparib was moderately protein bound in human plasma (83.0 %). In a population pharmacokinetic analysis of niraparib, the Vd/F was 1,074 L in cancer patients, indicating extensive tissue distribution of niraparib. The blood-to-plasma concentration ratio was 1.6. Overall, niraparib

exhibited higher human serum albumin (HSA) binding than alpha1-acid glycoprotein (AGP) binding in human plasma.

Elimination

The carboxylesterases-catalysed amide hydrolysis is the major primary metabolic pathway, followed by the UDP-glucuronosyltransferases-mediated glucuronidation and other minor secondary pathways. Niraparib is metabolised primarily by carboxylesterases (CEs) to form a major inactive metabolite, M1.

The minor pathway of oxidative metabolism of niraparib was primarily mediated by CYP1A1/2 and CYP3A4/5 with minor contribution from CYP2D6.

In a mass balance study, M1 and M10 (the subsequently formed M1 glucuronides) were the major circulating metabolites. Niraparib is eliminated with $t_{1/2}$ varying between 36 and 96 hours in different studies. Apparent total body clearance (CL/F) is 8-17 L.

Following a single oral 300-mg dose of niraparib, the mean terminal half-life ($t_{½}$) of niraparib ranged from 48 to 51 hours (approximately 2 days) (food effect study PR30-5011-C2-FE). In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of niraparib was 16.2 L/h in cancer patients.

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following an oral administration of a single 300-mg dose of [^{14}C]-niraparib, on average 86.2 % (range 71 % to 91 %) of the dose was recovered in urine and feces over 21 days. Radioactive recovery in the urine accounted for 47.5 % (range 33.4 % to 60.2 %) and in the feces for 38.8 % (range 28.3 % to 47.0 %) of the dose. In pooled samples collected over 6 days, 40.0 % of the dose was recovered in the urine primarily as metabolites and 31.6 % of the dose was recovered in the feces primarily as unchanged niraparib.

The major primary metabolite M1 exhibited a comparable to (AUC and Cmax) or possibly slightly higher exposure (AUC) than niraparib, and $t_{1/2}$ of M1 to be analogous to the parent.

Dose proportionality and time dependencies

- **Dose proportionality**

Study **P001** was designed to establish the safety, tolerability, PK, pharmacodynamics (PD), and recommended Phase 2 dose of niraparib in patients with advanced solid tumours. The first part of the study (Part A) was a dose escalation and confirmation scheme to determine the MTD and recommended Phase 2 dose of niraparib in patients with advanced solid tumors. A total of 60 patients were treated in Part A QD at 10 dose levels ranging from 30 mg to 400 mg. The MTD determined in Part A was 300 mg QD. A total of 40 patients were treated in Part B at the MTD of 300 mg QD as determined in Part A. The recommended Phase 2 dose determined on the basis of cumulative data from Part A and Part B was 300 mg QD. Due to a decision to suspend enrolment (unrelated to any safety reasons), Part C did not enrol any patients. A total of 4 patients were enrolled and treated in Part D, with 300 mg QD.

Table 15: **Summary statistics for pharmacokinetic parameters of niraparib following multiple QD oral doses of niraparib to cancer patients (study P001, parts A and B)**

Dose (mg)	N (Day 1 / Final Intensive)	$AUC_{0\text{-}24}$ (nM•hr)[a]		Ratio $AUC_{0\text{-}24}$ [d]	C_{max} (nM)[a]		Ratio C_{max} [d]	C_{24} (nM)[a]		Ratio C_{24} [d]	T_{max} (hr)[b]		Apparent $t_{1/2}$ (hr)[c]
		Cycle 1 Day 1	Final Intensive	Final Intensive/ C1D1	Cycle 1 Day 1	Final Intensive	Final Intensive/ C1D1	Cycle 1 Day 1	Final Intensive	Final Intensive/ C1D1	Cycle 1 Day 1	Final Intensive	Final Intensive
30	6 / 5	1777.86 ± 1038.54	5003.12 ± 3266.54	3.21 (1.98, 4.18	147.81 ± 93.13	325.68 ± 201.50	2.54 (1.64, 3.68)	49.93 ± 26.92	178.47 ± 96.97[f]	3.71 (2.11, 5.67)[f]	3.0 (1.5, 4.1)	1.5 (3.0, 4.0)	--[e]
40	3 / 3	2545.86 ± 1338.90	9680.95 ± 2491.82	4.22 (2.98, 6.64)	200.83 ± 114.92	644.84 ± 217.59	3.62 (2.50, 5.65)	72.29 ± 35.38	287.76 ± 55.40	4.38 (2.98, 7.19)	3.0 (3.0, 3.1)	2.0 (1.0, 3.0)	--[e]
60	7 / 6	4559.04 ± 1675.85	13600.13 ± 7465.88	2.85 (2.24, 5.07)	354.88 ± 129.25	833.86 ± 449.13	2.27 (1.65, 4.19)	131.38 ± 53.95	445.93 ± 276.75	3.36 (2.79, 5.80)	3.1 (1.5, 4.0)	1.5 (3.0, 4.0)	44.3 ± 78.9[g]
80	6 / 5	6099.31 ± 2569.75	17487.54 ± 4932.58	2.96 (2.29, 3.57)	531.75 ± 223.34	1174.96 ± 318.97	2.21 (1.74, 2.78)	178.30 ± 72.97	636.53 ± 222.36	3.62 (2.76, 5.52)	3.0 (3.0, 3.2)	3.0 (1.0, 3.0)	40.9 ± 7.6[h]
110	5 / 3	10998.45 ± 4424.52	25465.69 ± 12306.74	2.93 (2.73, 3.19)	1029.69 ± 487.45	1760.36 ± 898.19	2.39 (1.90, 2.91)	296.14 ± 103.89	1087.50 ± 563.78	3.46 (2.87, 4.42)	3.3 (3.0, 4.0)	2.0 (1.5, 3.0)	36.8 ± 12.4[i]
150	6 / 4	16036.09 ± 5926.22	31550.04 ± 22782.34	1.99 (0.91, 3.77)	1346.51 ± 477.69	2041.34 ± 1430.26	1.55 (0.85, 2.93)	475.60 ± 219.53	1104.14 ± 876.70	2.31 (0.87, 4.77)	3.0 (1.5, 4.1)	3.5 (2.0, 4.0)	35.1 ± 22.4
210	6 / 5	21697.65 ± 14235.63	54849.02 ± 52949.96	2.52 (1.69, 3.44)	1844.72 ± 1077.27	3160.19 ± 2799.43	1.71 (0.94, 2.46)	611.66 ± 416.10	1753.10 ± 1707.20	2.99 (2.23, 4.14)	3.0 (2.0, 4.1)	4.0 (2.0, 6.0)	32.8 ± 30.9
290	5 / 3	19151.76 ± 8320.65	67142.32 ± 35665.02	2.90 (2.27, 3.37)	1858.70 ± 978.90	4345.86 ± 1413.13	1.88 (1.74, 2.22)	532.30 ± 221.81	2004.67 ± 1267.57	3.09 (2.52, 3.88)	3.0 (3.0, 6.2)	3.0 (3.0, 6.1)	34.6 ± 14.7
300 Part A	10 / 10	27067.67 ± 10542.56	66813.70 ± 28612.71	2.41 (1.70, 5.34)	2400.83 ± 1087.76	4367.55 ± 1898.54	1.79 (1.13, 3.97)	828.45 ± 370.42	2143.93 ± 945.66	2.60 (1.71, 5.92)	3.0 (1.5, 4.1)	3.5 (2.0, 4.2)	36.2 ± 14.6
300 Part B	38 / 26	14117.66 ± 6200.04[k]	28709.16 ± 9074.57[k]	2.24 (0.62, 4.00)[k]	1921.60 ± 862.01	3102.65 ± 854.52	1.82 (0.53, 3.27)	922.46 ± 439.74[k]	1980.32 ± 752.14[k]	2.49 (0.72, 4.41)[k]	3.1 (2.0, 6.1)	4.0 (2.0, 12.0)	--[e]
400	6 / 4	26581.46 ± 5494.01	79055.48 ± 20899.21	3.16 (2.47, 5.38)	2121.55 ± 552.76	4448.42 ± 990.00	2.37 (1.67, 4.88)	806.80 ± 184.44	2546.66 ± 830.49	3.35 (2.80, 4.80)	3.6 (1.5, 6.0)	3.5 (3.0, 6.0)	46.0 ± 44.3[j]

[a]Arithmetic mean ± SD; [b]Median (min, max); [c]Geometric mean ± CV% of geometric mean; [d]Geometric mean ratio (min, max) calculated by PPDM; [e]Intensive PK sampling was not collected; [f]N=4; [g]N=2; [h]N=4; [i]N=2; [j]N=2; [k]$AUC_{0\text{-}12hr}$ and C_{12hr} reported due to PK sampling ending at 12 hours for C2D1 All treatments other than "300 Part B" were for patients in Part A.

Following multiple oral doses of 30-400 mg doses of niraparib for 21 days (parts A and B), niraparib was rapidly absorbed with a median Tmax ranging from 3.0-3.6 hours on Day 1 and 1.5-4.0 hours on Day last. Mean t1/2 ranged from 32.8-46.0 hours, based on the plasma samples collected for 96 hours starting on day 21 over the 60-400 mg dose range.

An exploratory analysis of dose proportionality indicated no dose dependent trends in dose-normalized area under the plasma concentration-time curve from 0 to 24 hours (AUC0-24) and the maximum concentration (Cmax), suggesting approximate dose-proportional increases in exposure across the range of doses studied.

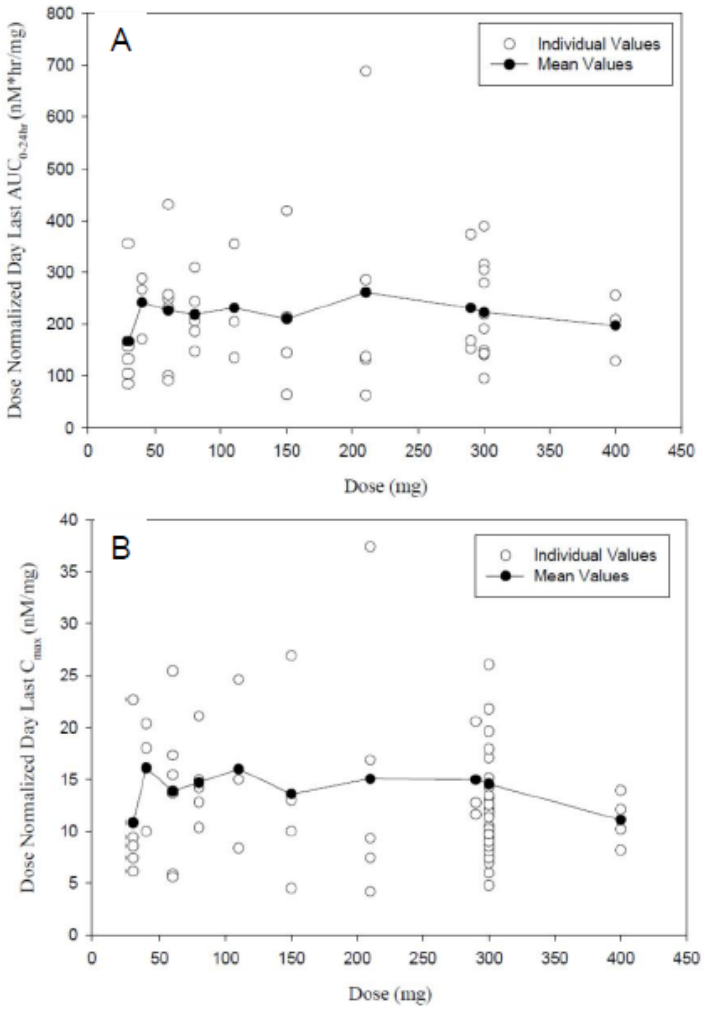


Figure 3: **Dose-normalized AUC0-24 h (A) and Cmax (B) on day last following multiple dose administration of niraparib to cancer patients (study P001)**

- **Time dependency**

In study **PN001**, the average plasma concentration profiles following multiple doses decreased in an approximately biphasic manner and trough concentrations (C_{trough}) generally approach steady state by day 12 of intensive sampling across all dose levels. Consistent with its t1/2, niraparib displayed moderate accumulation over 21 days of daily doses. Over the entire dose range studied (30-400 mg), the AUC0-24 and Cmax geometric mean accumulation ratios (Day 21/Day 1) after 21 days of dosing ranged from 1.99 to 4.22 and 1.55 to 3.62 for AUC0-24 and Cmax, respectively. For the 30-400 mg dose range studied, AUC0-24 and Cmax geometric mean accumulation ratios (day last/day 1) after 21 days of dosing ranged from 1.99–4.22 and 1.55–3.62 for AUC0-24 and Cmax, respectively.

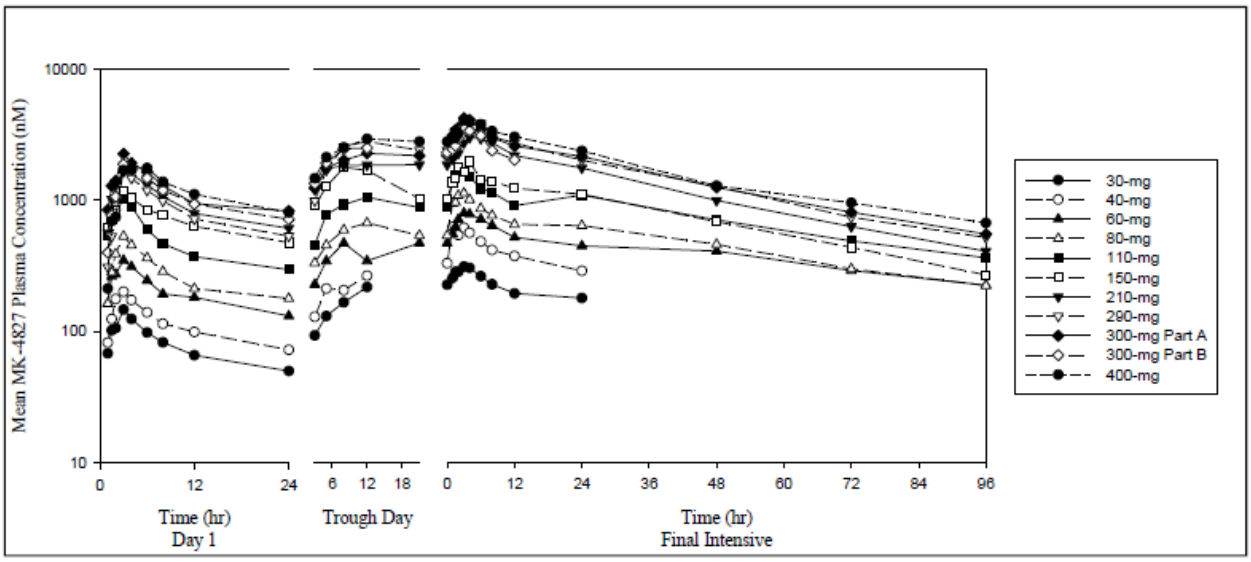


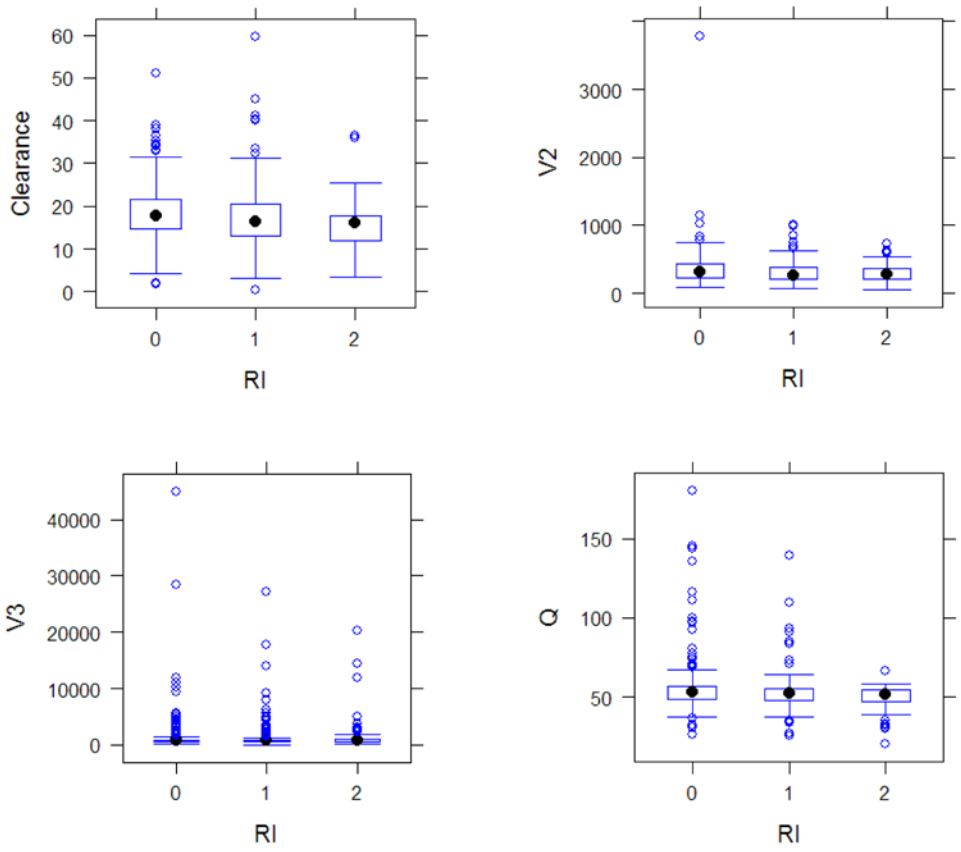
Figure 4: Arithmetic mean concentration-verses-time profiles of niraparib following multiple dose administration to cancer patients (semi-log scale) (study P001)

Special populations

No specific studies have been undertaken or planned to investigate the influence of age, weight or race on niraparib.

- **Impaired renal function**

There is no formal study of niraparib in patients with renal impairment. However, in the population pharmacokinetic and pharmacodynamic modeling report, creatinine clearance was evaluated as a parameter of renal function. Creatinine clearance in the range of 33 to 236 mL/min had no significant impact on the pharmacokinetics of niraparib. The pharmacokinetics of niraparib have not been assessed in patients with severe renal impairment end-stage renal disease undergoing haemodialysis.



RI, renal impairment;

0, normal function (CRCL ≥ 90 ml/min); 1, mild impairment (90 ml/min > CRCL ≥ 60 ml/min); 2, moderate impairment (60 ml/min > CRCL ≥ 30 ml/min)

Figure 5 :**Effect of renal impairment on niraparib pharmacokinetics (Figure from Niraparib PPK)**

- **Impaired hepatic function**

There is no formal study of niraparib in patients with hepatic impairment. However based on population PK analysis from pooled Phase1 and 3 studies (PN001 and PR-30-5011-C), baseline serum albumin, AST, total bilirubin, and ALT levels did not have a clinically important effect on niraparib pharmacokinetics in patients with various degrees of hepatic impairment. The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment.

- **Gender**

Based on the population PK analysis using the data combined from Phase 1 and Phase 3 studies (PN001 and PR-30-5011-C), gender had no significant impact on the PK of niraparib.

- **Race**

Based on the population PK analysis using the data combined from Phase 1 and Phase 3 studies (PN001 and PR-30-5011-C), race had no significant impact on the PK of niraparib.

- **Weight**

Based on the population PK analysis using the data combined from Phase 1 and Phase 3 studies (PN001 and PR-30-5011-C), weight had no significant impact on the PK of niraparib.

- **Elderly**

Based on the population PK analysis using the data combined from Phase 1 and Phase 3 studies (PN001 and PR-30-5011-C), age had no significant impact on the PK of niraparib. There are limited clinical data in patients aged 75 or over.

- **Children**

No study has been conducted to investigate the pharmacokinetics of niraparib in paediatric patients.

Inter and intraindividual variability

Interindividual variability was moderate to high for the pharmacokinetic parameters. The cause of the variability is not explained.

Intraindividual variability was determined to be 36.9% in the popPK model.

Pharmacokinetic interaction studies

No specific in vivo drug-drug interaction studies were performed.

To evaluate the substrate and/or inhibitor potential of niraparib and M1 for the transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), organic anion transporters 1 and 3 (OAT1 and OAT3), organic cation transporters 1 and 2 (OCT1 and OCT2), and bile salt export pump (BSEP), HEK (human embryonic kidney 293) cell lines were transfected with each of the uptake transporters of interest (OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2) (15TESAP1R2). The uptake of a transporter-specific probe substrate was studied with and without niraparib or M1 in transporter- and vector-transfected control cells.

Cytochrome p450 enzymes
Niraparib as a substrate of CYPs (CYP1A2 and CYP3A4)

Niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs) *in vivo*. Oxidative metabolism of niraparib is minimal *in vivo*. Oxidative metabolism of niraparib is minimal *in vivo*.

Inhibition of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4)

Neither niraparib nor M1 is an inhibitor of any active substance-metabolising CYP enzymes, namely CYP1A1/2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

Even though any inhibition of CYP3A4 in the liver is not expected, in the intestine where niraparib concentrations could be higher, this effect is not established.

Induction of CYPs (CYP1A2 and CYP3A4)

Neither niraparib nor M1 is a CYP3A4 inducer *in vitro*. *In vitro,* niraparib weakly induces CYP1A2 at high concentrations and the clinical relevance of this effect would not be completely ruled out. M1 is not a CYP1A2 inducer.

Transporters
Niraparib as a substrate or inhibitor of efflux transporters (P-gp, BCRP, BSEP and MATE1/2)

Evaluation of niraparib and M1 as a substrate of P-gp and BCRP was carried out in MDR1-MDCK, BCRP-MDCK and MDCK cells (study 15TESAP1R2). Permeability was evaluated in both the apical-to-basolateral and basolateral-to-apical directions.

Niraparib is a substrate of P gp and BCRP. However, due to its high permeability and bioavailability, the risk of clinically relevant interactions with medicinal products that inhibit these transporters is unlikely..

Niraparib and its major primary metabolite are not substrates of BSEP. The major primary metabolite M1 is not a substrate of P gp, BCRP, or BSEP. Niraparib is not a substrate of MATE 1 or 2, while M1 is a substrate of both.

Niraparib is not an inhibitor of BSEP. *In vitro,* niraparib inhibits P-gp very weakly and BCRP with an IC_{50} = 161 µM and 5.8 µM, respectively.

Niraparib is an inhibitor of MATE1 and -2 with IC50 of 0.18 µM and ≤ 0.14 µM, respectively. Increased plasma concentrations of co-administered medicinal products that are substrates of these transporters (e.g. metformin) cannot be excluded.

The major primary metabolite M1 does not appear to be an inhibitor of P-gp, BCRP, BSEP or MATE1/2.

Niraparib as a substrate or inhibitor of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)

Neither niraparib nor M1 are substrates of OATP1B1, OATP1B3, or OCT1.

Neither niraparib nor M1 are inhibitors of OATP1B1 or OATP1B3. *In vitro,* niraparib weakly inhibits the OCT1 with an IC_{50} = 34.4 µM.

Niraparib as a substrate or inhibitor of renal uptake transporters (OAT1, OAT3, and OCT2)

Neither niraparib nor M1 is a substrate or inhibitor of OAT1, OAT3, and OCT2.
The combination of niraparib with vaccines or immunosuppressant agents has not been studied.
The data on niraparib in combination with cytotoxic medicinal products are limited.

2.4.3. Pharmacodynamics

The PD of niraparib is based on non-clinical *in vitro* and *in vivo* studies. Clinical PD investigations include an assessment of its inhibition of PARP *in vivo* in peripheral blood mononuclear cells (PBMC) (**PN001**), QTc prolongation (**PR-30-5011-C1-QTC**) and exposure-response in terms of PFS and safety in patients with platinum ovarian cancer (**PR-30-5011-C**). Data from two studies (**PN001**, **C-30-5011-C**) were used to develop and evaluate a popPK model and to explore the PK/PD relationship.

Mechanism of action

Niraparib is an inhibitor of poly(ADP-ribose) polymerase (PARP)-1 and -2. PARP inhibition is thought to induce cytotoxicity by blocking base excision DNA repair. In tumours deficient of a functional high fidelity homologous recombination (HR) DNA repair system e.g. due to a germline or somatic BRCA mutation, the repair is instead performed by more error prone mechanisms (e.g. NHEJ) resulting in genomic instability and subsequent cell death. The proposed mechanism of action is supported by in vitro and in vivo non-clinical data. PARP inhibition in PBMCs has also been shown in the in vivo clinical study PN001.

Primary and Secondary pharmacology

Primary pharmacology

The results from study PN001 informed the RD2P and dose reduction recommendations. The maximum tolerated dose (MTD) of niraparib was 300 mg, and this dose was selected for further clinical studies.

Of the 104 patients, across all dose levels, who received at least one dose of study drug, 14 patients achieved confirmed or unconfirmed PR by RECIST and/or by CA-125 criteria. An additional 41 patients had stable disease by RECIST. Among the remaining 49 patients, 36 had progressive disease, and 13 had unknown response, due to discontinuation prior to post-baseline assessments.

Among the 50 ovarian cancer patients in the study, 22 had BRCA mutations. Eight of these 22 patients responded by RECIST (with 7 of the 8 having CA-125 response as well), for a response rate of 36.4% (95% CI: 17.2%, 59.3%). Among the 28 ovarian cancer patients who did not have BRCA mutations or whose BRCA mutation status was unknown, 2 patients achieved confirmed PR by RECIST and by CA-125, and another 2 patients achieved unconfirmed CA-125 PRs, for a response rate of 14.3% (95% CI: 4.0%, 32.7%).

PARP inhibition in PBMCs were apparently documented at doses of ≥ 60 mg QD and ≥ 80 mg QD, respectively. No data regarding the validation or qualification of the analytical method used for measurement of PARP activity has been provided.

Secondary pharmacology

Due to the mutagenic potential of niraparib, its effect on cardiac repolarisation was investigated in ovarian cancer patients (pivotal study). Based on a pooled analysis of intensive ECG measurements, the administration of single dose niraparib at the therapeutic dose of 300 mg appears not to prolong the QT interval. The QTc data collected as part of the Phase 3 trial for niraparib was evaluated via a graphical and regression approach (data not shown). These data are derived from patients receiving single (Cycle 1 Day 1) and multiple doses (Cycle 2 Day 1) of niraparib. The regression plots show that there is no relationship between increasing niraparib concentrations and QTcF. The higher exposure (i.e. plasma centration), after single dose on Day 1 and after multiple daily doses at steady state, did not lead to the elevated QTcF.

Pharmacodynamic interactions with other medicinal products or substances

No pharmacodynamic interactions studies have been conducted.

PK/PD relationship

The PKPD relationship between individual niraparib exposure parameters and the measures of efficacy and safety responses was explored using a popPK model. The 2-compartment model was based on data from studies PC-30-5011-C (365 patients), PC-30-5011-C1-QTc (26 patients), PC-30-5011-C2-FE (17 patients) and PN001 (104 patients). The niraparib exposure parameters used in the PKPD analyses were C_{max} on Day 1 (2hrs postdose) and at steady state, C_{trough} and AUC_{tau} over the dosing interval at steady state.

Exposure-PFS

Exploratory subgroup analyses were carried out for low and high niraparib exposure groups (from study PR-30-5011-C) based on median values for popPK model predicted Ct_{rough}, C_{max}, and AUC_{tau}. KM estimates were used to examine PFS response in the two niraparib exposure-defined subgroups. The low and high niraparib exposure groups were further subdivided into *gBRCA*mut, non-*gBRCA*mut, and HRD-positive groups.

The median PFS for the high vs. low niraparib exposure groups in the *gBRCA*mut cohort was:

- 21.3 vs. 13.5 months with HR 0.81 (95% CI of 0.49-1.35) based on steady-state C_{trough},
- >15.7 vs. 13.8 months with HR 0.72 (95% CI of 0.43-1.22) based on steady-state C_{max},
- >15.7 vs. 15.9 months with HR 0.91 (95% CI of 0.54-1.52) based on steady-state AUC_{tau}.

The median PFS for the high vs. low niraparib exposure groups in the non-*gBRCA*mut cohort was:

- 10.7 vs. 8.2 months with HR 0.94 (95% CI of 0.66-1.34) based on steady-state C_{trough}

- 11.3 vs. 7.5 months with HR 0.72 (95% CI of 0.51-1.03) based on steady-state C_{max}
- 11.5 vs. 7.5 months with a HR of 0.70 (95% CI of 0.49-0.99) based on steady-state AUC_{tau}

The median PFS for the high vs. low niraparib exposure groups in the HRDpos subset was:

- 15.7 vs. 9.4 months with HR 0.78 (95% CI of 0.46-1.33) based on steady-state C_{trough}
- 15.4 vs. 9.4 months with HR 0.70 (95% CI of 0.41-1.19) based on steady-state C_{max}
- 16 vs. 9.4 months with HR 0.74 (95% CI of 0.43-1.26) based on steady-state AUC_{tau}.

During the procedure,n the applicant was requested to provide a Monte-Carlo simulation PK/PD study associated with a PTA (Probability Target Attainment) given the POP-PK and the efficacy endpoint.

A population pharmacokinetic model using full profiles from the phase I study PN001 (n=104) and sparse samples from the phase III NOVA study (n=408) was developed and was used to perform simulations within NONMEM. Data sets of 5000 patients each receiving either 100 mg, 200 mg, or 300 mg to steady-state were created for the simulations. The final model parameter estimates as well as the variability estimates were used for the simulations.

Figure 6presents a summary of the niraparib AUC for the simulated dose regimens. It demonstrates that niraparib exposure bands of the 100 mg, 200 mg, and 300 mg dose groups were largely overlapping. These simulation results are consistent with the observed sparse data for the NOVA study and with the full profiles from the PN001 study.

Figure 7 presents the % of patients achieving various AUC values for each simulated dose group. In the absence of a definitive exposure threshold needed to maintain efficacy, three AUC bins (12,000 ng*hr/mL) are shown. The AUC of 12,000 ng*hr/mL was selected as the target exposure for the analysis based on the previous population PK report. In the population PK analysis, the median AUC for the exposure response relationship was approximately 12,000 ng*hr/mL in both the gBRCA and nongBRCA cohorts. The exposure-response analyses in the population PK report showed a trend towards increased efficacy with increased exposure, most notably in the non-gBRCA cohort. Figure 7 indicates that >80% patients in the 300 mg group and < 50% patients in the 200 mg group would achieve exposure higher than the population median. It is important to note, that while these data support the recommended starting dose of 300 mg, efficacy was maintained in patients in NOVA who were dose reduced per the current dose modification guidance in the SmPC.

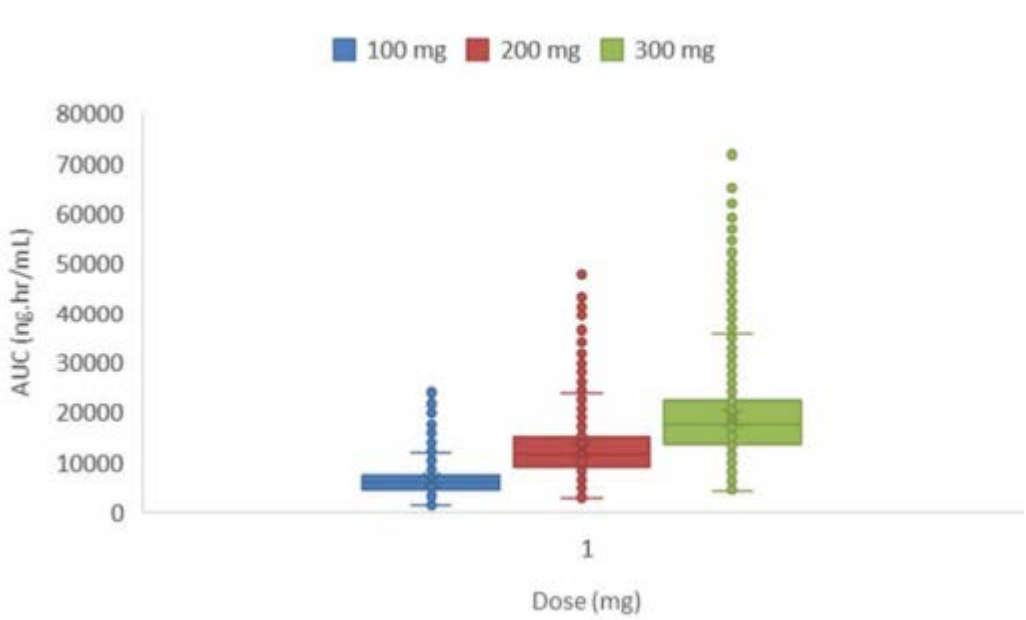


Figure 6: Box plots of simulated AUC of niraparib following 100, 200 and 300 mg daily on day 14

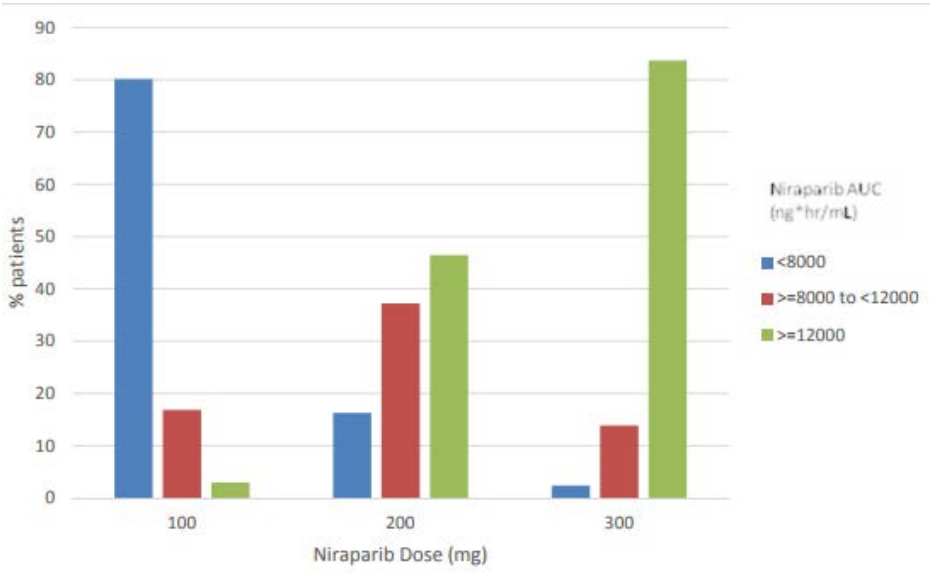


Figure 7: Percentage of patients at various niraparib AUC levels by simulated dose group

Exposure-safety

Patient incidence of treatment-emergent AEs by preferred term and worst grade was summarised by descriptive statistics in the two niraparib exposure groups. The relationships between AEs of interest, including thrombocytopenia, neutropenia, anemia, nausea, and fatigue and niraparib exposure were explored using logistic regression models. The predicted steady-state AUC_{tau}, C_{max} and C_{trough} were tested. Adverse events (≥ Grade 1 and ≥ Grade 3) were evaluated.

The probability of thrombocytopenia (≥ Grade 3) was not correlated with steady-state C_{trough} or AUC_{tau}. Similarly, the probability of high grade anemia (≥ Grade 3) was evidently not correlated with steady-state C_{trough}. There may be a positive trend between these events and C_{max} and AUC_{tau} although the relationship was not statistically significant. There were no apparent associations between niraparib exposure and lower grade thrombocytopenia and anemia as well as incidence of the other AEs of interest, neutropenia and fatigue in particular. There is no obvious difference in steady-state exposure between the patients who experienced high grade AEs of interest (thrombocytopenia, anemia, neutropenia, fatigue), and those who did not during the treatment. Graphical and tabular summary of the relationship between patient covariates and safety variables demonstrated that of all the key baseline covariates (PLTBL, NEUTBL, HGBBL, WTBL, AGE, ALBBL, BILIBL, ASTBL, ALTBL, ALPBL, and LDHBL) and platelet nadir (overall, across all study visits) was assessed; only baseline platelets had an impact on platelet nadir.

2.4.4. Discussion on clinical pharmacology

Overall, there are few studies with thorough PK data presented, however there are several ongoing studies with no PK data yet. From the submitted studies with PK data the inter-individual variability was moderate to high for the pharmacokinetic parameters. The variability can be exemplified by *e.g.* the mean apparent volume of distribution (Vd/F) of niraparib varying from 1220-2170 L and mean t1/2 varying between 36 and 96 hours in different studies. The cause of the observed high variability is currently unknown, however is consistent with other drugs of this class, such as olaparib and rucaparib.

Despite that hepatobiliary clearance and renal excretion are the major routes of niraparib elimination in humans, dedicated clinical studies investigating the impact of renal or hepatic impairment on niraparib 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. Creatinine clearance did not show a significant

effect on the PK of niraparib. No dose adjustment is necessary for patients with mild to moderate renal impairment. The pharmacokinetics of niraparib have not been assessed in patients with severe renal impairment end-stage renal disease undergoing haemodialysis; niraparib should be used with caution in these patients (see sections 4.2 and 5.2 of the SmPC).

Based on population pharmacokinetic modelling, baseline serum albumin, serum aspartate aminotransferase, total bilirubin, and aminotransferase levels did not have a clinically important effect on niraparib pharmacokinetics. No dose adjustment is needed in patients with mild to moderate hepatic impairment. The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment; niraparib should be used with caution in these patients (see sections 4.2 and 5.2 of the SmPC).

In the population pharmacokinetic and pharmacodynamic modelling report gender, race, ethnicity, body weight, age or age groups showed no significant effect on the pharmacokinetics of niraparib. No dose adjustment is necessary for elderly patients (≥ 65 years).

There is no study of niraparib in children or adults < 30 years old.

The applicant will continue to thoroughly evaluate the potential impact from the renal and hepatic impairment in the clinical studies.

Niraparib tosylate monohydrate has one chiral center of the S configuration. . Based on available data it is reasonable to conclude that neither niraparib nor the major metabolite M1 undergoes stereoconversion during the biotransformation in vivo. Based on the current knowledge it is unlikely that genetic polymorphism would play an important role in the PK of niraparib.

The carboxylesterases-catalysed amide hydrolysis is the major primary metabolic pathway, followed by the UDP-glucuronosyltransferases-mediated glucuronidation and the other minor secondary pathways. The major primary metabolite M1 exhibited a comparable to (AUC and Cmax) or possibly slightly higher exposure (AUC) than niraparib, and $t_{1/2}$ of M1 to be analogous to the parent. However, the pharmacokinetics of M1 are only analysed in single-dose studies

The specific carboxylesterase and UGT enzymes involved in the metabolism of niraparib and metabolites have not been presented. Niraparib is not an inhibitor of UGT 1A1, 1A4, 1A9 and 2B7.

An *in vitro* study to identify CE and UGT enzymes responsible for the metabolism of niraparib and M1 is currently ongoing, and data will be updated when available. No dose adjustment for niraparib is required when administered concomitantly with medicinal products known to inhibit (e.g. itraconazole, ritonavir, and clarithromycin) or induce CYP enzymes (e.g. rifampin, carbamazepine, and phenytoin).

Niraparib is a substrate of the transporters P-gp and BCRP. However, due to its high permeability and bioavailability, the risk of clinically relevant interactions with medicinal products that inhibit these transporters is unlikely. Therefore, no dose adjustment for Zejula is required when administered concomitantly with medicinal products known to inhibit P gp (e.g. amiodarone, verapamil) or BCRP (e.g. osimertinib, velpatasvir, and eltrombopag).

A clinically meaningful interaction related to an inhibition of P-gp and BCRP efflux transporters although unlikely, cannot be excluded. Caution is recommended when niraparib is combined with substrates of BCRP (irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate).

The impact of the substrate affinity of niraparib to P-pg with regards to the disposition and potential drug interactions have not been discussed. The possible involvement of P-pg in local tumour resistance is considered to be low.

However, since inhibition of CYP3A4 by niraparib cannot be ruled out in the intestine, caution is recommended when niraparib is combined with active substances the metabolism of which is

CYP3A4-dependent and, notably, those having a narrow therapeutic range (e.g. ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).

In addition since niraparib has been shown to weakly induce CYP1A2 in vitro, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (e.g. clozapine, theophylline, and ropinirole).
Niraparib and M1 are not substrates of OATP1B1, OATP1B3, OCT1, OAT1, OAT3 or OCT2. No dose adjustment for niraparib is required when administered concomitantly with medicinal products known to inhibit OATP1B1 or 1B3 (e.g. gemfibrozil, ritonavir), OCT1 (e.g. dolutegravir) OAT1 (e.g. probenecid), OAT3 (e.g. probenecid, diclofenac), or OCT2 (e.g. cimetidine, quinidine) uptake transporters.

As niraparib weakly inhibits OCT1, caution is recommended when it is combined with active substances that undergo an uptake transport by OCT1 such as metformin.

Due to its other pharmacodynamic effects, notably myelosuppression events, caution should be taken if niraparib is used in combination with a vaccine, immunosuppressant agents or other cytotoxic medicinal products.

In spite of the *in vitro* findings, no specific *in vivo* drug-drug interaction studies were performed.

The maximum steady state exposures observed on day 21 following multiple 300 mg doses of niraparib were 66814 nM·hr and 4368 nM for AUC0-24 and Cmax, respectively. No analysis is performed for M1 after multiple doses.

No dedicated PD study has been submitted. Combined PK/PD and efficacy studies have provided some information on the relationship between dose/exposure and response in terms of PFS and safety.

Several PARP-inhibitors resistance mechanisms have been described in the literature (e.g. Pgp overexpression, loss of 53BP1). Furthermore, cross-resistance to other anti-cancer agents including PARP inhibitors has been reported.

The rationale for using niraparib was initially only based on the principle of synthetic lethality that selectively exploits an acquired deficiency in the DNA repair apparatus in tumour cells. About 50% of serous ovarian carcinomas might be HRD and could thus be susceptible to PARP inhibitors (Mukhopadhyay 2012). Clinical responses of PARP inhibitors have been documented (although in less extent) in platinum-resistance tumours suggesting incomplete crossover of platinum sensitivity and PARP inhibitory response (Gelmon et al. 2011, Ledermann et al. 2012).

The applied indication includes patients with somatic or germline *BRCA* mutation, and patients with or without a competent HR DNA repair apparatus. The mechanism of action has been further clarified by the Applicant and provides a rationale for why tumour response is expected also in the HR competent patient population.

Platinum sensitivity is used in the pivotal study to select the target population. Platinum agents cause DNA crosslinks which are usually repaired either by nucleotide/BER or HR. Thus, in theory, combined therapy should result in synergism. Although no concomitant treatment with chemotherapy and niraparib is intended, long-lasting accumulation of platinum agents has been reported (Travis et al. 2010). However, to reduce adverse event burden on the patient, niraparib maintenance therapy after the patients have received maximum benefit from platinum therapy is a reasonable approach as is also the case for the already approved PARP inhibitor olaparib.

Several PARP-inhibitors resistance mechanisms have been described in the literature. Furthermore, cross-resistance to other anti-cancer agents including PARP inhibitors has been reported. This could have implications for subsequent use of chemotherapy as well as other PARP inhibitors.

The Applicant has performed a QTc analysis based on single dose data only. The Applicant has provided a regression analysis of the QTcF and PK data collected in the phase III NOVA study from patients receiving single and multiple doses of 300 mg QD niraparib. The sampling time of 2 hours postdose corresponds fairly well to the median Tmax (2.5-4 hours). No baseline comparison has been provided. No relationship between higher exposure with QTc was identified. Niraparib is not expected to have a significant effect on QTc.

2.4.5. Conclusions on clinical pharmacology

Niraparib pharmacokinetics are presented, however with some weaknesses. The interindividual variability was moderate to high for the pharmacokinetic parameters, and the cause of the variability is not known. The specific carboxylesterase and UGT enzymes involved in the metabolism of niraparib and metabolites have not been presented.

Pharmacokinetics of the main metabolite M1 is only presented from single-dose studies. Even though the metabolite is not regarded to be active, M1 might contribute to drug-drug interactions (see section 4.5 of the SmPC).

Despite that hepatobiliary clearance and renal excretion are presented as the major routes of niraparib elimination in humans, dedicated clinical studies investigating the impact of renal or hepatic impairment on niraparib have not been submitted. In vitro, niraparib exerted some induction of CYP1A2, was a substrate of P-gp and BCRP, an inhibitor of BCRP, a weak inhibitor of OCT1, and a very weak inhibitor of P-gp. M1 may be a substrate of P-gp and BCRP. In spite of the in vitro findings, no specific in vivo drug-drug interaction studies were performed.

Clinical pharmacodynamics (*i.e.* PARP inhibition, QTc prolongation, exposure-response) have been investigated in one phase I study and in the pivotal study.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- The applicant is recommended to submit the ongoing in vitro study to identify CE and UGT enzymes responsible for the metabolism of niraparib and M1.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No formal Phase II dose-ranging studies were conducted. The selection of the 300 mg starting dose of niraparib for the NOVA study was based on data from the phase I dose-escalating study PN001.

Study **PN001**: *A Phase I Study of MK-4827 in Patients with Advanced Solid Tumours or Hematologic Malignancies*

A multi-centre, open-label, non-randomised, cohort based, dose-escalation and confirmation study to establish a recommended Phase II dose (R2PD) based on safety and tolerability, PK and PD in patients with advanced and treatment refractory cancer.

The study included both a dose escalation phase and confirmation scheme to determine the MTD of niraparib in patients with advanced solid tumours (part A) and an dose expansion arm to further evaluate the selected dose in patients with platinum-resistant, recurrent, HGSOC or prostate cancer (part B). Part C and D are only briefly described, as the study was terminated with no/only a few patients enrolled in these parts.

Part A:

Patients were administred niraparib QD, continuously in 21-day cycles. An accelerated titration phase I clinical trial design was used, with 100% dose increments in single patient cohorts, beginning with the starting dose of 30 mg QD (*i.e.* 1/10 of the projected STD_{10} in rats). Under this accelerated scheme, one patient was to be entered per dose level until:

- a patient demonstrated ≥50% inhibition of PARP activity in PBMCs in Cycle 1,
- OR a patient experienced a DLT in any cycle,
- OR two patients (at any dose level) experienced treatment-related Grade 2 toxicities in any cycle.

Further dose escalations were to follow a modified 3+3 design (Ji et al. 2007) at approximately 40% dose increments.

Part B:

In Part B, patients began treatment at the RP2D of 300 mg QD. Patients took niraparib continuously in 21-day cycles. Dose modifications were performed as needed.

Part C and D:

In Part D, patients (n=4) began treatment at the RP2D of 300 mg QD. Patients took niraparib continuously 28-day cycles with no treatment holiday. No patients were enrolled in part C.

Results

Of 142 patients screened, 104 patients with advanced solid tumours were enrolled, including 60 patients during dose escalation over ten dose levels (30 mg to 400 mg) and 44 during expansion. Median age was 59 years, and 70.2% of patients were female. The population was heavily pretreated, with a median of five and up to 14 prior lines of therapy. The most common cancers represented was ovarian (n=48), prostate (n=23), and breast cancer (n=13). Overall, patients remained on treatment for a median of 59 days (10 to 590), and for a median of 3 cycles (1 to 28). Median duration of therapy for the 300 mg dose was 67 days (10-524).

The dose escalation stage (Part A) determined that 400 mg exceeded the MTD, thus a MTD of 300mg was determined for niraparib.

Sixty-one percent of patients required a dose interruption, reduction or withdrawal (50%, 33% and 7% of patients, respectively) due to an adverse event.

The PK profile supported a once daily dosing (dose proportional, terminal half-life 30-40 hrs). Fifty-six of patients were evaluated in the PD analysis. A significant PARP inhibition were seen at doses ≥ 80mg QD which supports a dose reduction scheme that allows patients to get the highest tolerable dose to start, but remain on a potentially efficacious dose if AE require dose interruption and reduction. For efficacy results, please refer to section 2.2.3 on primary pharmacology.

PopPK analysis

Individual niraparib exposure parameters were generated from the popPK analysis in order to explore the exposure-efficacy and exposure-safety relationships. The Applicant concluded that the 300 mg dose was supported by the efficacy and safety data from study **PR-30-5011-C**.

2.5.2. Main study

PR-30-5011-C (ENGOT-OV16) (NOVA study) - A phase 3, randomized, double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer.

The pivotal study (hereafter referred to as *NOVA study*) was a double-blinded, 2:1 randomized, placebo-controlled global clinical trial designed to evaluate the efficacy and safety of niraparib as maintenance treatment for patients with platinum-sensitive, relapsed, high-grade, ovarian cancer who had received at least 2 platinum-based regimens and were in response to their last platinum-based chemotherapy.

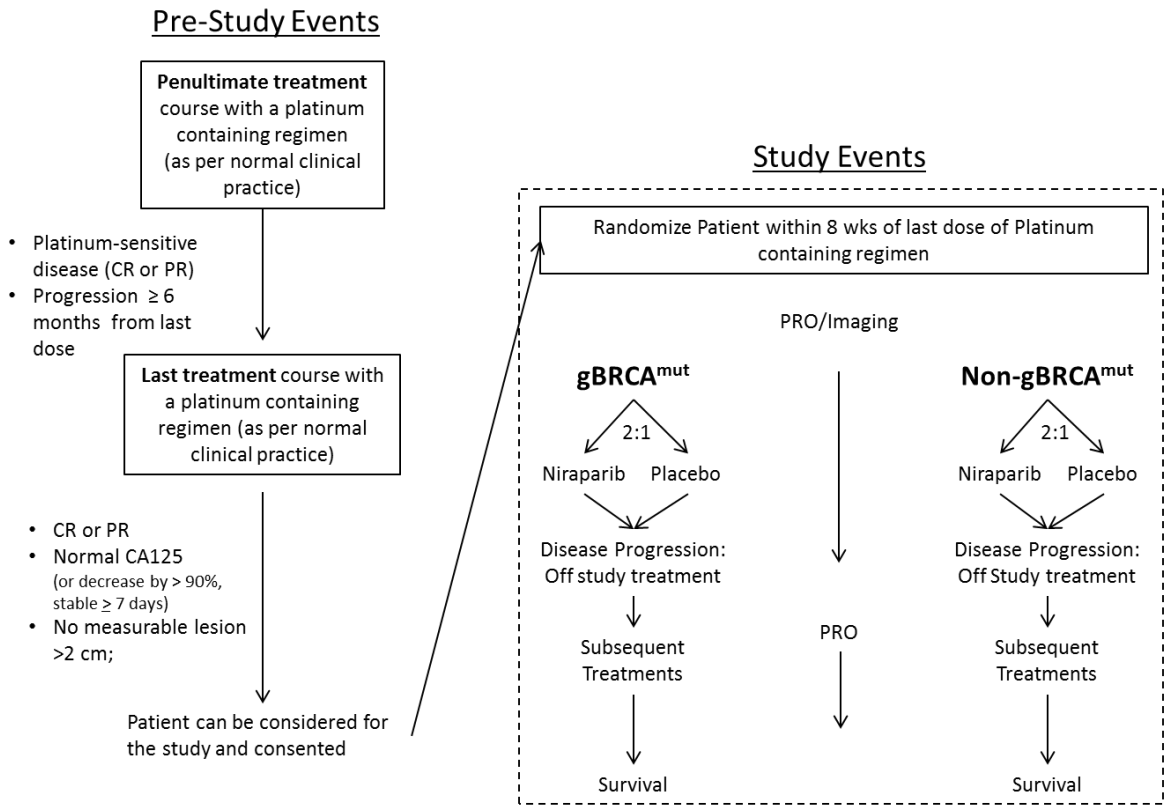


Figure 8: PR-30-5011-C (ENGOT-OV16) (NOVA) Study design

Methods

Study Participants

- **Key inclusion criteria**

1. Female, age at least 18 years

2. Patient agreed to undergo analysis of her g*BRCA* status.

3. Histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer

4. High-grade (or Grade 3) serous or high-grade predominantly serous histology or known to have g*BRCA*mut

5. Patients must have completed at least 2 previous courses of platinum-containing therapy:

    a. For the penultimate platinum-based chemotherapy prior to study enrollment:

i. A patient must have had platinum-sensitive disease after this treatment, defined as achieving a response (CR or PR) and disease progression >6 months after completion of her last dose of platinum therapy (documented 6 to 12 months or >12 months).

b. For the last chemotherapy prior to being randomized in the study:

i. Patients must have received a platinum-containing regimen for a minimum of 4 cycles

ii. Patients must have achieved a partial or complete tumor response (assessed according investigator clinical practice)

iii. Following the last regimen, patients must have had either

1. CA-125 in the normal range, OR

2. CA-125 decrease by more than 90% during the last platinum regimen, and which was stable for at least 7 days (ie, no increase >15%)

iv. Following the last regimen, patients could not have had any measurable lesion >2 cm at the time of study entry

c. Patients must have been randomized within 8 weeks after completion of their final dose of the platinum-containing regimen

- **Key exclusion criteria**
  - symptomatic, uncontrolled brain or leptomeningeal metastases
  - diagnosis, detection, or treatment of invasive cancer other than ovarian cancer ≤2 years prior to randomization
  - patients with a baseline QT prolongation >470 milliseconds
  - prior treatment with a known PARP inhibitor, including niraparib

Treatments

Subjects were randomized and assigned to either the niraparib or the placebo arm of the two cohorts based on the results of the Integrated BRACAnalysis test. This test sequences the BRCA1/2 genes to determine the presence of mutations.

Randomization was to occur within 8 weeks of the last dose of the final platinum-containing regimen.

Patients were administered with 300 mg niraparib or placebo (marked as equivalent dose) QD orally in continuous 28-day cycles. Drug was supplied as 100 mg niraparib capsules or appearance-matched placebo capsules.

Dose interruption and/or reduction could be implemented at any time for any grade toxicity considered intolerable by the patient. Treatment was required to be interrupted for any non-hematologic AE that was Grade 3 or 4, per National Cancer Institute (NCI)-CTCAE v.4.02 if the Investigator considered the event to be related to administration of study drug. If toxicity was appropriately resolved to baseline or Grade 1 or less within 28 days, the patient was allowed to restart treatment with study drug, but with a dose level reduction (300 mg to 200 mg). If the event recurred at a similar or worse grade, the patient's treatment was again to be interrupted; upon event resolution, a further dose reduction was required (200 mg to 100 mg). No more than 2 dose reductions were permitted for any patient.

Objectives

The primary study objective was to evaluate the efficacy of niraparib compared to placebo as maintenance treatment of patients with platinum-sensitive, recurrent ovarian cancer who were in response to platinum-based chemotherapy, as assessed by progression-free survival (PFS). The objective was independently evaluated in a cohort of patients with germline breast cancer susceptibility gene (BRCA) mutation tumors (gBRCAmut cohort) and in a cohort of patients with high-grade serous or high-grade predominantly serous histology, but who were not gBRCAmut carriers (non-gBRCAmut cohort).

Secondary efficacy objectives of the main study included the evaluation of additional measures of clinical benefit, including patient-reported outcomes (PROs), time to first subsequent treatment (TFST), Chemotherapy-free interval (CFI), progression-free survival 2 (PFS2), time to second subsequent treatment (TSST), and overall survival (OS).

Outcomes/endpoints

Descriptions of the study endpoints are presented in the table below:

Table 16 Primary and secondary efficacy endpoints – NOVA study

Primary efficacy endpoint	
Progression-free survival (PFS)	The primary efficacy endpoint PFS, defined as the time from the date of treatment randomization to the date of first documentation of progression or death by any cause, was assessed by IRC per RECIST v.1.1 criteria. The independent oncologist in addition reviewed relevant clinical data, including anatomic site(s) of prior radiotherapy, on-study cytology and/or histology results, on-study interventions (surgery, radiotherapy, etc), additional diagnostic test results, CA-125 values and clinical signs and symptoms of disease progression.
Secondary efficacy endpoints	
Time to first subsequent treatment (TFST)	Date of randomization in the current study to the start date of the first subsequent anti-cancer therapy after maintenance treatment
Chemotherapy-free interval (CFI)	The time from the last platinum therapy dose until initiation of the next anti-cancer therapy (excluding maintenance therapy)
Progression-free survival 2 (PFS2)	Date of randomization in the current study to the earlier date of assessment of progression on the next anti-cancer therapy following study treatment or death by any cause. If progression on next anti-cancer therapy was not determined, but the patient received a second subsequent anti-cancer therapy the date of the next line of therapy was used as a surrogate for PD.
Time to second subsequent treatment (TSST)	Date of randomization in the current study to the start date of the second subsequent anti-cancer therapy after maintenance treatment
Overall survival (OS)	Time from study randomization to the date of death by any cause
Patient-reported outcome (PRO)	• FOSI (PRO): Validated, 8-item measure of symptom response to treatment for ovarian cancer • EQ-5D-5L (PRO): Validated general preference-based health related QOL instrument in oncology, as well as other conditions, and is intended to compliment other QOL instruments • Neuropathy Questionnaire: As of the prior 7 days, patients provided a response on a scale of 0 (not at all) to 4 (very much), to “My feet feel numb or have prickling/ tingling feelings,” “My hands feel numb or have prickling/tingling feelings”

Clinical visits occur every 4 weeks ± 3 days and tumour assessment via CT or MRI scans will occur every 8 weeks ± 7 days until progression.

Progressive disease (PD) was determined if at least 1 of the following 3 criteria was met:

1. Tumour assessment by CT/MRI showed PD according to RECIST v.1.1 criteria.

2. Additional diagnostic tests (e.g., histology/cytology, ultrasound techniques, endoscopy, PET) identified new lesions or determined that existing lesions qualified for unequivocal PD and CA-125 progression, according to GCIG criteria.

3. Definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes (intractable cancer-related pain; malignant bowel obstruction/worsening dysfunction; or unequivocal symptomatic worsening of ascites or pleural effusion) and CA-125 progression according to GCIG criteria were present.

Note: CA-125 progression alone was not to be considered disease progression; at least 1 of the criteria defined above was necessary to determine PD.

In addition, exploratory endpoint analysis were conducted

- on patient subsets based on intrinsic and extrinsic factors
- on primary and secondary efficacy endpoints on the various mutational subgroups within the non-g*BRCA*mut cohort
- to assess the treatment effect on the primary endpoint of PFS in patients whose cancer had *BRCA* mutations present in their tumour (t*BRCA*).

Sample size

The gBRCAmut and non-gBRCAmut cohorts were treated as 2 independent cohorts/studies where each cohort was allocated 1-sided alpha = 0.025. For the sample size calculations, the assumptions used were based on published data provided for a placebo controlled trial of olaparib against placebo in a similar maintenance setting.

The gBRCAmut cohort sample size was determined based on the assumption that niraparib will result in an improvement in median PFS of 4.8 to 9.6 months (corresponding to an HR of 0.50 for niraparib relative to placebo). 98 PFS events will provide 90% power assuming a 2:1 randomization.

Sample size for the HRD positive subgroup in the non-gBRCAmut cohorts was determined based on the same PFS assumption as used for the gBRCAmut cohort: 98 PFS events will provide 90% power assuming a 2:1 randomization (Amendment 6). The overall non-gBCRAmut cohort sample size was determined to maintain the intended hierarchical testing procedure under the assumption that approximately 40% of the non-gBRCAmut cohort is expected to be classified as HRD positive. With a total of approximately 310 patients in the non-gBCRAmut cohort, the expected number of HRD positive patients would be 130.

In total the study planned to include approximately 490 patients.

Randomisation

Patients were to be randomized separately within each cohort based on results from the Integrated BRACAnalysis test using a 2:1 allocation of niraparib to placebo. Randomization was stratified by the following factors:

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

Blinding (masking)

Study patients, Investigators, study coordinators, and TESARO's study team and its representatives were blinded to the identity of the assigned treatment from the time of randomization until final database lock.

Statistical methods

The study objective was independently evaluated in a cohort of patients with germline breast cancer susceptibility gene (BRCA) mutation tumors (gBRCAmut cohort) and in a cohort of patients with high-grade serous or high-grade predominantly serous histology, but who were not gBRCAmut carriers (non-gBRCAmut cohort).

- **Hypothesis**

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

• H0: HR (niraparib/placebo) ≥ 1.

• Ha: HR (niraparib/placebo) < 1.

The statistical analysis of the primary endpoint of PFS for the non-gBRCAmut cohort was performed in a hierarchical manner, with statistical testing for the HRDpos group, as determined with the myChoice HRD test, performed first, followed by statistical testing of the overall non-gBRCAmut cohort, only if the first test on the HRDpos group was statistically significant. Therefore, the HRDpos group is referred to as the primary efficacy population within the non-gBRCAmut cohort.

Prospectively planned analysis

A stratified log-rank test using the randomization stratification factors was used to calculate the key efficacy endpoints. HR and 2-sided 95% CI were derived from a stratified Cox proportional hazards model and survivor function was estimated by the Kaplan-Meier method. In order to estimate PRO a mixed-effects growth-curve model adjusting for fixed and random covariates was used.

Within each cohort, the overall family-wise Type 1 error rate on the primary efficacy endpoint of PFS was controlled at 1-sided 0.025 significance level. A hierarchical testing method was used in the non-gBRCAmut cohort. First, the group of patients who were determined to have HRDpos tumours was analyzed for a statistically significant treatment group difference in PFS by the stratified log-rank test at alpha-level 0.025 1-sided. If that test was statistically significant, then the overall non-gBRCAmut cohort was evaluated by the same method, also at alpha-level 0.025 1-sided (this testing strategy was introduced with amendment 4).

The planned number of events was met on 30 May 2016, the data cut-off point for the study report, with 103 PFS events observed in the gBRCAmut cohort and 101 PFS events in HRDpos subgroup. At that time, enrollment was complete with 109 patients remaining on treatment and 273 in the follow-up phase.

All patients were to be followed off treatment every 3 months for subsequent anti-cancer treatment, including outcome of such therapy, any new malignancies, and survival status.

Sensitivity analyses

The ITT analysis is primary while the PP analysis is a sensitivity analyses.

Several sensitivity analyses were performed on PFS, using the ITT population:

• Unstratified log-rank testing along with Cox regression modeling using treatment only.

• Investigator assessment of PFS using a stratified log-rank and associated Cox regression model.

• An IRC analysis using only radiological assessment (RECIST v1.1) as progression.

• An IRC analysis treating censors due to subsequent anti-cancer treatment, discontinuation due to any reason, or missed tumour assessments as events. For this analysis, the date of progression was imputed as the date of initiation of subsequent anti-cancer treatment, the date of discontinuation, or the date of the last non-missing tumour assessment (in cases where the patient had no further assessments).

• Use of the scheduled assessment date to show progression if the actual assessment was conducted after the scheduled date and showed PD. This was done only for progression, not for censored observations, ie, if the last available observation was after a scheduled assessment and indicated that progression had not occurred, then that observation was used in this sensitivity analysis.

An additional sensitivity analysis has been performed where the patient who started subsequent anti-cancer treatment was considered as a progression and the event date was set as the date of initiation of the first subsequent anti-cancer treatment.

Results

Participant flow

A total of 553 patients (ITT population) were enrolled in the NOVA study where 372 were randomized to niraparib and 181 to placebo. The study was designed to evaluate niraparib as maintenance treatment in two independent cohorts of patients: those with germline BRCA mutation (gBRCAmut cohort) and those who were not germline BRCA mutation carriers (non-gBRCAmut cohort).

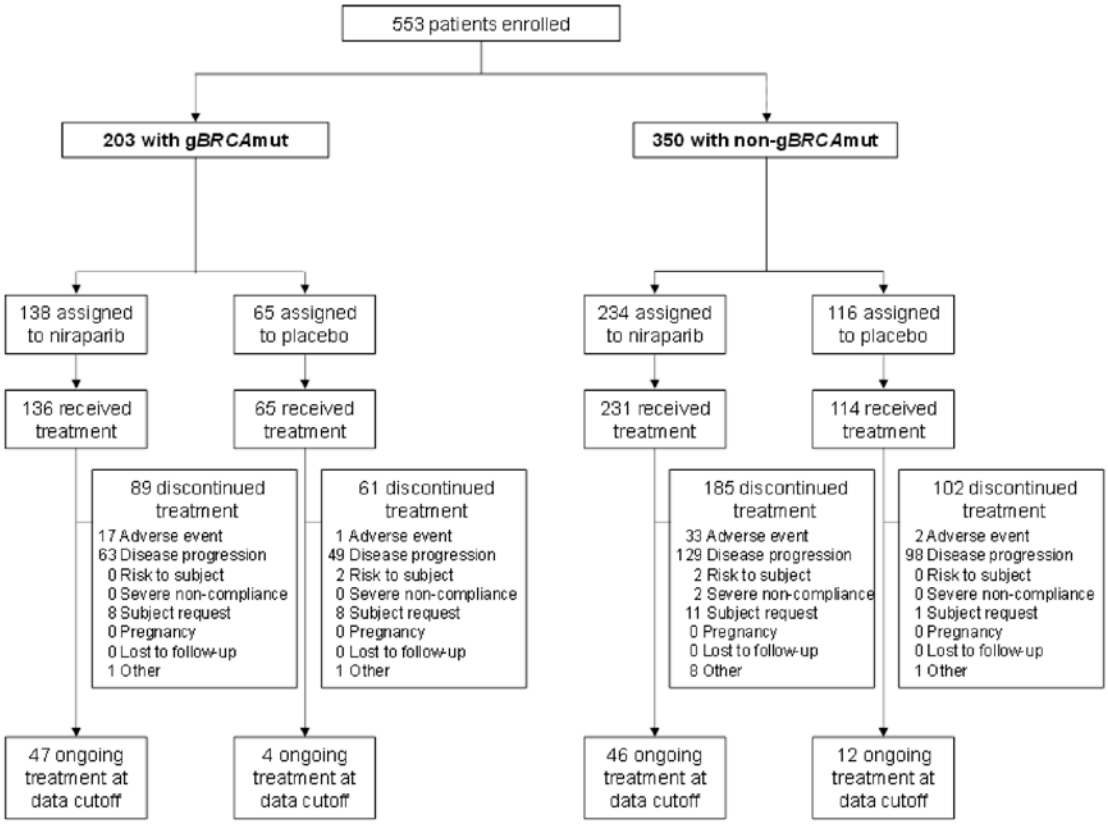


Figure 9 Patient disposition flowchart - NOVA study

Prior to randomization, a blood sample from each patient was tested centrally for germline BRCA mutation using Myriad's Integrated BRACAnalysis test. Based on the results from this test patients were divided into two study cohorts; gBRCAmut and non-gBRCAmut cohort.

During the conduct of the NOVA study, the myChoice HRD test was developed and identified as the biomarker classifier to define a patient population enriched for niraparib sensitivity in the non-gBRCAmut cohort. Prior to unblinding of the study, tumours of patients were tested for the presence of HRD using this experimental HRD test, which evaluates three indirect measures of tumour genome instability: loss of heterozygosity, telomeric allelic imbalance (TAI), and large-scale state transitions.

In order to determine HRD status as positive (HRDpos) or negative (HRDneg), tumour tissue samples from patients in both cohorts were evaluated using the test. Patients in this cohort were subsequently dived into subgroups (HRDpos/HRDneg) for data analysis.

Testing for tBRCA mutation and homologous recombination deficiency (HRD) was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis or at the time of recurrence.

Recruitment

The study was initiated at 128 sites globally and the following countries participated:

US (41 sites), Germany (13 sites), United Kingdom (10 sites), Canada (9 sites), Israel and Italy (8 sites each), France and Spain (7 sites each), Belgium and Poland (5 sites each), Denmark (4 sites), Austria, Hungary, and Sweden (3 sites each), Norway (2 sites).

Date first patient enrolled (signed informed consent): 26 Aug 2013.

Date last patient completed: study is ongoing.

Data cut-off date of 30 May 2016 and database lock date of 20 Jun 2016.

Conduct of the study

Protocol amendments

The main changes in the five global amendments to the protocol are described below:

- Amendment 1(date amendment final: 03 May 2013)
  - Disease progression (PFS, the primary efficacy endpoint) was originally required to be confirmed objectively by blinded central review in conjunction with RECIST v.1.1. Clinical criteria were added to the means of confirmation (ie, RECIST, clinical criteria, and blinded central review).
  - QTc Analyses were added to indicate that a formal analysis of ECG variables would be conducted and that a separate population PK analysis plan would be written to describe the relationship of ECG and PK variables.
  - PROs were to continue to be collected even after a patient discontinued treatment, regardless of progression status.
- Amendment 2 and 3 (date amendment final: 09 April 2014)
  - The Integrated BRACAnalysis was specified as the diagnostic test to determine germline BRCA mutation status; prior to this, local BRCA tests could be used.
  - The description of the Integrated BRACAnalysis was updated to include that DNA from the submitted sample(s) was going to be stored and could be used at a later time for additional biomarker testing, including the potential to bridge to candidate companion diagnostic assays.
- Amendment 4 (date amendment final: 04 Dec 2014)
  - In addition to germline BRCA testing, text was added in this amendment to indicate that patients would be tested (centrally) to classify their HRD status, and to indicate the timing of that testing.
  - It was further specified that HRDpos patients in the non-gBRCAmut cohort would be evaluated first for PFS, followed by all non-gBRCAmut patients.
  - Statistical methods were updated to indicate that superiority of niraparib relative to placebo in PFS would be evaluated in the gBRCAmut cohort using a 1-sided alpha equal to 0.025.
  - Concordance of a candidate companion HRD diagnostic test compared with the HRD diagnostic test used in this study would be assessed, if needed, and baseline samples for HRD analyses were to be collected and archived for possible bridging the study's HRD test to a candidate companion HRD diagnostic test.
  - The sample size for evaluation of PFS was expanded to include the original 180 gBRCAmut patients, and up to 310 patients randomized to the non-gBRCAmut cohort. Sample size increase, including statistical assumptions, was explained in the Sample Size Considerations section of the protocol.
- Amendment 5 (date amendment final: 11 Sep 2015)
  - Guidance on monitoring patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML was added to the protocol.
- Amendment 6 (date amendment final: 09 Mar 2016)
  - Changes were made to ensure that the gBRCAmut cohort would not be overpowered to detect a small PFS difference and to provide evidence needed to determine whether there might have been a differential response to niraparib in the patient population with

gBRCAmut tumours vs HRDpos/ sBRCAmut tumours vs HRDpos/BRCAwt. Thus, the power of the gBRCAmut cohort from >95% to 90% allowed for analysis for both of the cohorts simultaneously. The new sample size for this test was determined to be approximately 100 PFS events in the gBRCAmut cohort, to maintain 90% power.

- Secondary objectives were added: TFST and TSST.
- An interim analysis of the gBRCAmut cohort, planned to follow approximately 85 PFS events, was deleted from the protocol, since the timing of these events would approximately coincide with the current planned analysis of data.

Protocol deviation

Overall, 36 (7%) of the 553 patients had a major protocol deviation.

Table 17 Major Protocol Deviations by Cohort (ITT Population) - NOVA study

Deviation	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort (N=350)	
	Niraparib (N=138) n (%)	Placebo (N=65) n (%)	Niraparib (N=234) n (%)	Placebo (N=116) n (%)
Patients with at least 1 major protocol deviation	11 (8.0)	1 (1.5)	16 (6.8)	8 (6.9)
Failed to meet eligibility criteria	9 (6.5)	0	15 (6.4)	5 (4.3)
Inclusion 5a or 5b[a]	6 (4.3)	0	11 (4.7)	4 (3.4)
Inclusion 9a[b]	2 (1.4)	0	3 (1.3)	1 (0.9)
Exclusion 7[c]	1 (0.7)	0	0	0
Exclusion 9[d]	0	0	1 (0.4)	0
Dispensed incorrect study medication kit	1 (0.7)	0	0	2 (1.7)
Non-compliant (<80%) with study drug	1 (0.7)	0	1 (0.4)	1 (0.9)
Misallocated to cohort[e]	0	1 (1.5)	0	0

Abbreviations: ANC=absolute neutrophil count; BRCA=breast cancer susceptibility gene; gBRCAmut=germline BRCA mutation; ITT=intent-to-treat; non-gBRCAmut=without a germline BRCA mutation

[a] Inclusion criteria 5a: platinum-sensitive disease or 5b: no measurable lesion >2 cm at study entry not met (see Section 9.7.1.4 for any windows applied to the evaluation).

[b] Inclusion criterion 9a: ANC ≥1500/µL not met

[c] Exclusion criterion 7: other malignancy met

[d] Exclusion criterion 9: blood transfusion within 4 weeks met

[e] Randomized to gBRCAmut cohort; central analysis not mutation positive.

Minor protocol violations

42 out of 553 (7.6%) patients had tumors with at least one dimension that measured more than 2 cm by Independent Radiology Review (IRC).

Baseline data

Demographic and Baseline characteristics

The tables below shows demographics features for all subjects, g-BRCAmut cohort, non-gBRCAmut cohort, non-gBRCAmut cohort HRD+ and non-gBRCAmut cohort HRD-.

Table 18. Study population demographic and baseline characteristic by cohort (ITT population)

Demographic/Baseline Characteristic	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort (N=350)	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
Age (years), n	138	65	234	116
Mean (StD)	56.9 (9.25)	57.2 (9.24)	62.3 (9.25)	61.3 (9.52)
Median	57.0	58.0	63.0	60.5
Min, Max	36, 83	38, 73	33, 84	34, 82
Age (years), n (%)				
18-64	110 (79.7)	49 (75.4)	130 (55.6)	69 (59.5)
65-74	24 (17.4)	16 (24.6)	85 (36.3)	39 (33.6)
≥65	28 (20.3)	16 (24.6)	104 (44.4)	47 (40.5)
≥75	4 (2.9)	0	19 (8.1)	8 (6.9)
Race, n (%)				
White	123 (89.1)	55 (84.6)	201 (85.9)	101 (87.1)
Black	1 (0.7)	1 (1.5)	4 (1.7)	1 (0.9)
Asian	2 (1.4)	3 (4.6)	10 (4.3)	4 (3.4)
American Indian/Alaska Native	1 (0.7)	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0
Unknown	11 (8.0)	6 (9.2)	19 (8.1)	10 (8.6)
BMI (kg/m^2), n	138	64	229	114
Mean (StD)	26.06 (5.749)	26.78 (6.003)	26.29 (5.606)	26.31 (4.859)
Median	24.70	25.50	25.48	25.71
Min, Max	14.0, 44.6	19.0, 50.4	16.8, 45.6	18.1, 45.7
ECOG PS, n (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
2	0	0	0	0
Geographic Region, n (%)				
US and Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe and Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)

Abbreviations: BMI=body mass index; BRCA=breast cancer susceptibility gene; ECOG=Eastern Cooperative Oncology Group; gBRCAmut=germline BRCA mutation; ITT=intent-to-treat; non-gBRCAmut=without a germline BRCA mutation; PS=performance status; StD=standard deviation

Table 19. Baseline Disease Characteristics by Cohort (ITT Population)

Baseline Disease Characteristic	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort (N=350)	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
Primary tumor site, n (%)				
Ovarian	122 (88.4)	53 (81.5)	192 (82.1)	96 (82.8)
Primary peritoneal	7 (5.1)	6 (9.2)	24 (10.3)	8 (6.9)
Fallopian Tube	9 (6.5)	6 (9.2)	18 (7.7)	11 (9.5)
Histologic subtype[a]				
Serous	117 (88.6)	59 (90.8)	215 (96.4)	110 (99.1)
Endometrioid	8 (6.1)	3 (4.6)	1 (0.4)	1 (0.9)
Mucinous	0	0	0	0
Other	13 (9.8)	3 (4.6)	11 (4.9)	3 (2.7)
gBRCA variant, n (%)[b]				
BRCA1	85 (61.6)	43 (66.2)	NA	NA
BRCA2	51 (37.0)	18 (27.7)	NA	NA
BRCA1/2 rearrangement	9 (6.5)	4 (6.2)	NA	NA
Duration since diagnosis (yrs), n	135	61	225	109
Mean (StD)	4.37 (2.564)	4.07 (2.999)	3.33 (2.210)	3.59 (1.991)
Median	3.66	3.02	2.69	2.99
Min, Max	0.3, 13.6	1.8, 19.5	0.1, 19.2	0.1, 9.3
Number of metastatic sites, n (%)				
<3	89 (64.5)	40 (61.5)	157 (67.1)	79 (68.1)
≥3	49 (35.5)	25 (38.5)	77 (32.9)	36 (31.0)

Abbreviations: BRCA=breast cancer susceptibility gene; gBRCAmut=germline BRCA mutation; ITT=intent-to-treat; NA=not applicable; non-gBRCAmut=without a germline BRCA mutation; StD=standard deviation

[a]Some patients had only cytology results available for confirmation of histologic subtype. Patients can be included in more than 1 category. Denominators for percent calculations are based on patients with data available.

[b]Based on centralized (Myriad) laboratory test; patients can report BRCA1/2 rearrangement and BRCA1 and BRCA2.

Table 20 Randomization Stratification Factors by Cohort (All Randomized Patients) –NOVA study

Stratification Factor	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort (N=350)	
	Niraparib (N=138) n (%)	Placebo (N=65) n (%)	Niraparib (N=234) n (%)	Placebo (N=116) n (%)
Time to progression after penultimate platinum regimen				
6 to <12 month	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥12 months	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Use of bevacizumab with the penultimate or last platinum regimen				
Yes	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
No	105 (76.1)	48 (73.8)	172 (73.5)	86 (74.1)

Abbreviations: BRCA=breast cancer susceptibility gene; CR=complete response; gBRCAmut=germline BRCA mutation; non gBRCAmut=without a germline BRCA mutation; PR=partial response

Prior treatments

Table 21 Prior chemotherapies for Ovarian Cancer by Cohort (ITT Population) - NOVA study

Prior Treatment Parameter	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort (N=350)	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
Number of lines of chemotherapy, n (%)				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
3	40 (29.0)	20 (30.8)	55 (23.5)	17 (14.7)
4	13 (9.4)	10 (15.4)	11 (4.7)	12 (10.3)
≥5	14 (10.1)	5 (7.7)	13 (5.6)	9 (7.8)
Missing	0	0	0	1 (0.9)
Number of lines of platinum therapy, n (%)				
1	1 (0.7)	0	0	0
2	79 (57.2)	37 (56.9)	174 (74.4)	87 (75.0)
>2	58 (42.0)	28 (43.1)	60 (25.6)	28 (24.1)
Missing	0	0	0	1 (0.9)

Abbreviations: BRCA=breast cancer susceptibility gene; gBRCAmut=germline BRCA mutation; ITT=intent-to-treat; non-gBRCAmut=without a germline BRCA mutation

Numbers analysed

The intent-to-treat (ITT) population was defined as all randomized patients in the main study with patients analysed according to the study drug assigned via randomization even if no study drug was ingested.

The per protocol (PP) population was defined as all patients randomized in the main study that did not have major protocol deviations that might have significantly impacted the interpretation of efficacy results.

The safety (SAF) population was defined as all patients who ingested any amount of study drug. The safety population was to be the primary analysis population for the safety and drug exposure analyses.

Table 22: Analysis Datasets by Cohort

	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort			
			HRDpos (N=162)		Overall (N=350)	
Analysis Set	Niraparib (N=138) n (%)	Placebo (N=65) n (%)	Niraparib (N=106) n (%)	Placebo (N=56) n (%)	Niraparib (N=234) n (%)	Placebo (N=116) n (%)
ITT Population	138 (100.0)	65 (100.0)	106 (100.0)	56 (100.0)	234 (100.0)	116 (100.0)
Safety Population	136 (98.6)	65 (100.0)	106 (100.0)	56 (100.0)	231 (98.7)	114 (98.3)
PP Population	125 (90.6)	64 (98.5)	101 (95.3)	50 (89.3)	217 (92.7)	106 (91.4)

Abbreviations: BRCA=breast cancer susceptibility gene; gBRCAmut=germline BRCA mutation; HRDpos=homologous recombination deficiency positive; ITT=intent-to-treat; non-gBRCAmut=without a germline BRCA mutation; PP=per protocol

Outcomes and estimation

gBRCAmut cohort

- **Primary endpoint-Progression-free survival (PFS)**

Maintenance treatment with niraparib prolonged PFS by 15.5 months compared to placebo in patients with gBRCAmut platinum-sensitive recurrent ovarian cancer. Median PFS as determined by the IRC was 21.0 months in the niraparib arm and 5.5 months in the placebo arm with a HR of 0.27 (95% CI: 0.173, 0.410) (p<0.0001).

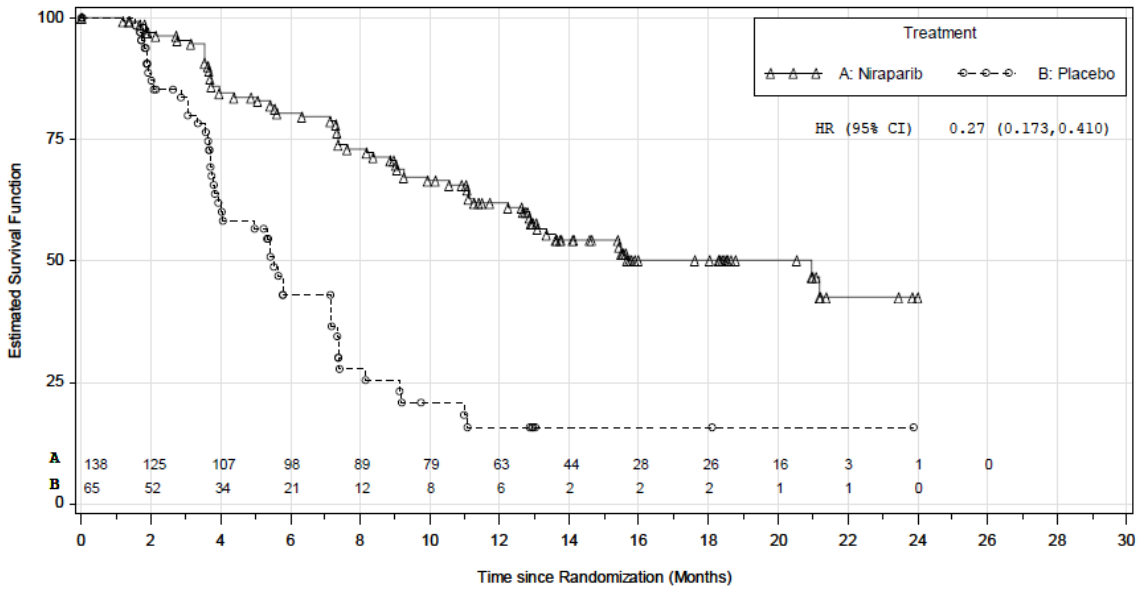


Figure 10 Kaplan-Meier Plot for Progression-Free Survival in the gBRCAmut Cohort. (Based on IRC Assessment) –NOVA study

- **Sensitivity analysis for the progression free survival**

In each of the analysis, maintenance treatment with niraparib prolonged PFS compared to placebo (p <0.0001) with HRs all ≤0.35.

Table 23 Results of the Sensitivity Analyses for Progression-free Survival in the gBRCAmut Cohort (ITT Population) –NOVA study

Sensitivity Analysis Statistic	gBRCAmut Cohort (N=203)	
	Niraparib (N=138)	Placebo (N=65)
Unstratified log-rank test and Cox proportional hazards model using treatment only as covariate		
Median PFS (months (95% CI)[a,b]	21.0 (12.9, NE)	5.5 (3.8, 7.2)
p-value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.30 (0.197, 0.445)	
Central radiological (RECIST) review only		
Median PFS (months) (95% CI)[a,b]	21.0 (12.9, NE)	5.5 (3.9, 7.4)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.26 (0.169, 0.407)	
Investigator assessment		
Median PFS (months) (95% CI)[a,b]	14.8 (12.0, 16.6)	5.5 (4.9, 7.2)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.27 (0.182, 0.401)	
Limited censoring (include subsequent anti-cancer treatment, discontinuation due to any reason, and missed tumour assessments as events)		
Median PFS (months) (95% CI)[a,b]	11.2 (9.0, 13.6)	5.4 (3.8, 6.1)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.35 (0.243, 0.496)	
Use of scheduled assessment dates (if the actual assessment showing PD was conducted after the scheduled date)		
Median PFS (months) (95% CI)[a,b]	21.0 (12.9, NE)	5.5 (3.8, 7.2)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.26 (0.172, 0.407)	

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; gBRCAmut=germline BRCA mutation; ITT=intent-to-treat; NE=not estimated; PD=progressive disease; PFS=progression-free-survival; RECIST=response evaluation criteria in solid tumours

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

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

[c]Based on the unstratified log-rank test

[d]Niraparib:Placebo, based on Cox Proportional Hazards Model using treatment only.

[e]Based on the stratified log-rank test using randomization stratification factors.

[f]Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.

- **Secondary endpoints**

Time to first subsequent therapy (TFST)

Table 24 Time to first subsequent therapy Based on IRC Assessment in the gBRCAmut Cohort (ITT Population) –NOVA study

Parameter[a] Statistic	gBRCAmut Cohort (N=203)	
	Niraparib (N=138)	Placebo (N=65)
TFST		
Median (95% CI) (months)[b]	21.0 (17.5, NE)	8.4 (6.6, 10.6)
Censored observations, n (%)	80 (58.0)	22 (33.8)
Event rate, n (%)	58 (42.0)	43 (66.2)
p-value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.31 (0.205, 0.481)	

Abbreviations: BRCA=breast cancer susceptibility gene; CFI=chemotherapy-free interval; CI=confidence interval;
gBRCAmut=germline BRCA mutation; IRC=Independent Review Committee; ITT=intent-to-treat;
NE=not estimated; TFST=time to first subsequent therapy
[a]For parameter definitions, see Table 6 in CSR.
[b]Estimates from product-limit (Kaplan-Meier) method. Confidence intervals are from Brookmeyer and Crowley method with log-log transformation.
[c]Based on stratified log-rank test using randomization stratification factors.
[d]Niraparib:Placebo, based on stratified Cox Proportional Hazards Model using randomization stratification factor.

Chemotherapy-free interval (CFI)

Table 25 chemotherapy-free interval therapy results Based on IRC Assessment in the gBRCAmut Cohort (ITT Population) –NOVA study

Parameter[a] Statistic	gBRCAmut Cohort (N=203)	
	Niraparib (N=138)	Placebo (N=65)
CFI		
Median, months (95% CI)[b]	22.8 (17.9, NE)	9.4 (7.9, 10.6)
Censored observations, n (%)	84 (60.9)	23 (35.4)
Event rate, n (%)	54 (39.1)	42 (64.6)
p-value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.26 (0.166, 0.409)	

Abbreviations: BRCA=breast cancer susceptibility gene; CFI=chemotherapy-free interval; CI=confidence interval;
gBRCAmut=germline BRCA mutation; IRC=Independent Review Committee; ITT=intent-to-treat;
NE=not estimated;
[a]For parameter definitions, see Table 6 in CSR.
[b]Estimates from product-limit (Kaplan-Meier) method. Confidence intervals are from Brookmeyer and Crowley method with log-log transformation.
[c]Based on stratified log-rank test using randomization stratification factors.
[d]Niraparib:Placebo, based on stratified Cox Proportional Hazards Model using randomization stratification factor.

Progression-free survival 2 (PFS2)

Table 26 progression-free survival 2 Based on IRC Assessment in the gBRCAmut Cohort (ITT Population) –NOVA study

Parameter[a] Statistic	gBRCAmut Cohort (N=203)	
	Niraparib (N=138)	Placebo (N=65)
PFS2		
Median, months (95% CI)[b]	25.8 (20.3, NE)	19.5 (13.3, NE)
Censored observations, n (%)	99 (71.7)	40 (61.5)
Event rate, n (%)	39 (28.3)	25 (38.5)
p-value[c]	0.0062	
Hazard ratio (95% CI)[d]	0.48 (0.280, 0.821)	

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; gBRCAmut=germline BRCA mutation; IRC=Independent Review Committee; ITT=intent-to-treat; NE=not estimated; PFS2=progression-free survival 2

[a]For parameter definitions, see Table 6 in CSR.

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

[c]Based on stratified log-rank test using randomization stratification factors.

[d]Niraparib:Placebo, based on stratified Cox Proportional Hazards Model using randomization stratification factor.

- **Overall Survival**

As of the data cut-off for the primary analysis of PFS, the OS data were immature. At that time, a total of 24 patients in the g*BRCA*mut cohort had died, including 16 (12%) of the 138 patients randomized to niraparib and 8 (12%) of the 65 patients randomized to placebo; thus, median OS was not reached for the ITT population in either randomized treatment arm with an HR of 0.91 (95% CI: 0.360, 2.282). Patients continue to be followed for OS and updated information will be provided in the final CSR.

- **Patient related outcomes**

Symptoms of ovarian cancer were assessed using the FOSI and QOL was assessed using the EQ-5D-5L health utility index and the visual analogue scale. Baseline symptoms and QOL were equivalent between placebo and niraparib patients in the cohort. Similar results were observed throughout the study for the g*BRCA*mut cohort with no significant differences observed during the maintenance (treatment) period or at post progression (p>0.05 for each assessment and each treatment arm on each patient outcome). Further, KM analysis for FOSI time to symptom worsening found no statistically significant difference between niraparib and placebo (log rank p>0.05).

non-gBRCAmut cohort

- **Primary endpoint-Progression-free survival (PFS)**

A hierarchical testing method was used: The results from the HRDpos group of the non-gBRCAmut cohort were significant and the overall cohort was therefore evaluated by the same method.

HRDpos group / non-g*BRCA*mut cohort

For the HRDpos group, the study met its primary efficacy objective; maintenance treatment with niraparib prolonged PFS by 9.1 months compared to placebo. Median PFS as determined by the IRC

was 12.9 months in the niraparib arm and 3.8 months in the placebo arm with a HR of 0.38 (95% CI: 0.243, 0.586) (p<0.0001).

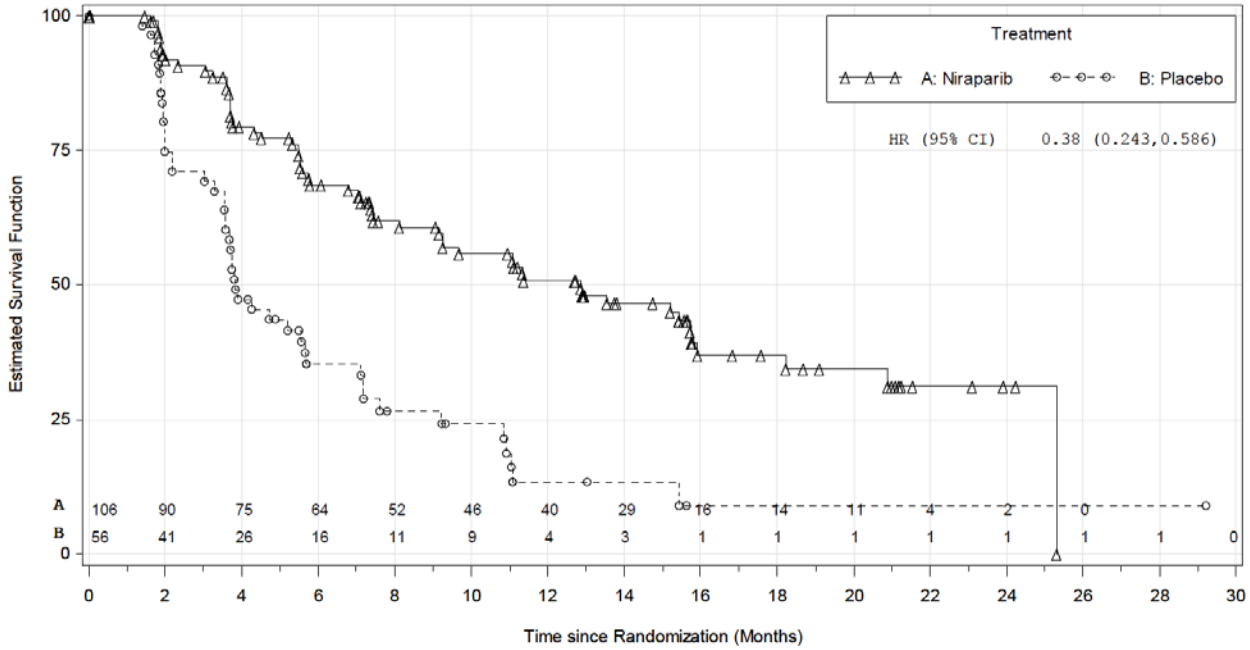
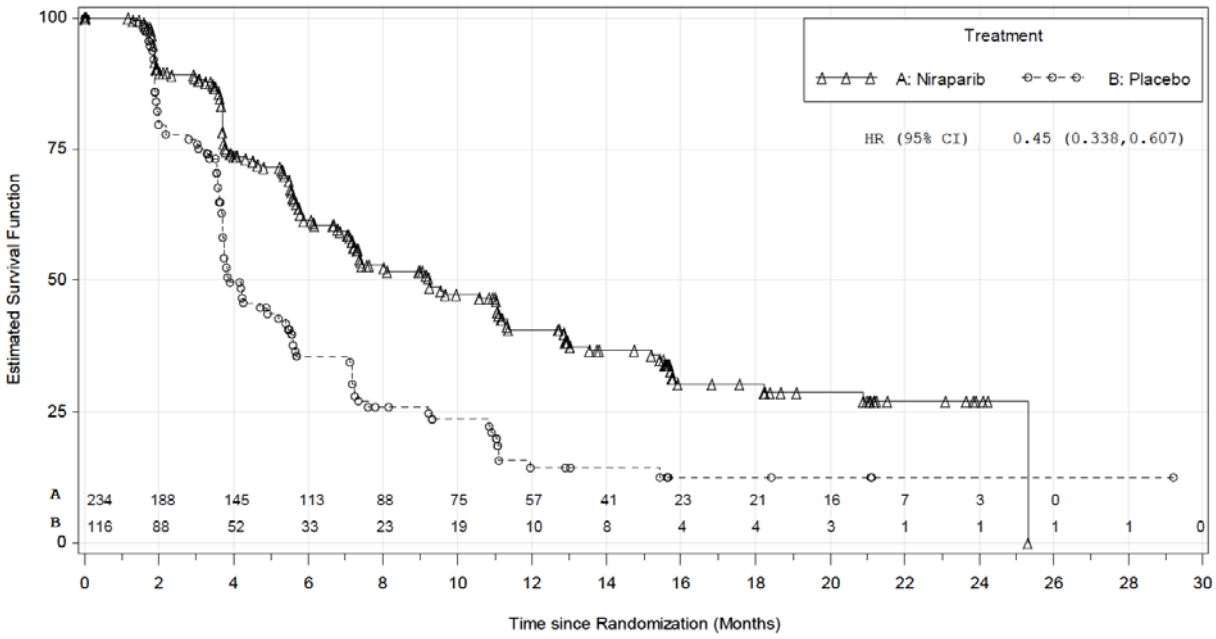


Figure 11 Kaplan-Meier Plot for Progression-Free Survival in the HRDpos Group of the Non-gBRCAmut Cohort, Based on IRC Assessment (ITT population) –NOVA study

Non-gBRCAmut Cohort Overall

For the non-gBRCAmut cohort overall, the study met its primary efficacy objective; maintenance treatment with niraparib prolonged PFS by 5.4 months compared to placebo in patients with platinum-sensitive recurrent ovarian cancer. Median PFS as determined by the IRC was 9.3 months in the niraparib arm and 3.9 months in the placebo arm with a HR of 0.45 (95% CI: 0.338, 0.607) (p<0.0001).

Figure 12 Kaplan-Meier Plot for Progression-Free Survival in the Non-gBRCAmut Cohort Overall Based on IRC Assessment (ITT Population) –NOVA study



- **Sensitivity analysis**

Results of the sensitivity analyses for the non-gBRCAmut cohort (HRDpos and overall groups) were consistent with the primary efficacy results for these groups. In each analysis, maintenance treatment with niraparib prolonged PFS compared to placebo with HRs all ≤0.66.

Table 27 Results for the Sensitivity Analyses for Progression-free Survival in HRDpos Group of the Non-gBRCAmut Cohort (ITT Population) –NOVA study

Sensitivity Analysis Statistic	HRDpos/non-gBRCAmut Cohort (N=162)	
	Niraparib (N=106)	Placebo (N=56)
Unstratified log-rank test and Cox proportional hazards model using treatment only as covariate		
Median PFS (months (95% CI)[a,b]	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.37 (0.247, 0.558)	
Central radiological (RECIST) review only		
Median PFS (months) (95% CI)[a,b]	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.39 (0.248, 0.602)	
Investigator assessment		
Median PFS (months) (95% CI)[a,b]	11.4 (9.1, 15.6)	4.0 (3.7, 5.5)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.34 (0.226, 0.524)	
Limited censoring (include subsequent anti-cancer treatment, discontinuation due to any reason, and missed tumor assessments as events)		
Median PFS (months) (95% CI)[a,b]	9.3 (6.8, 12.9)	3.8 (3.5, 5.2)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.42 (0.283, 0.626)	
Use of scheduled assessment dates (if the actual assessment showing PD was conducted after the scheduled date)		
Median PFS (months) (95% CI)[a,b]	12.9 (9.2, 15.8)	3.8 (3.5, 5.7)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.38 (0.244, 0.588)	

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; HRDpos=homologous recombination deficiency positive; ITT=intent-to-treat; non-gBRCAmut=without a germline BRCA mutation; PD=progressive disease; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours

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

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

[c]Based on the unstratified log-rank test

[d]Niraparib:Placebo, based on Cox Proportional Hazards Model using treatment only.

[e]Based on the stratified log-rank test using randomization stratification factors.

[f]Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.

Table 28 Sensitivity Analyses for Progression-free Survival in the Non-gBRCAmut Cohort Overall (ITT Population) –NOVA study

Sensitivity Analysis Statistic	Non-gBRCAmut Cohort (N=350)	
	Niraparib (N=234)	Placebo (N=116)
Unstratified log-rank test and Cox proportional hazards model using treatment only as covariate		
Median PFS (months (95% CI)[a,b]	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)
p-value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.50 (0.376, 0.653)	
Central radiological (RECIST) review only		
Median PFS (months) (95% CI)[a,b]	9.3 (7.2, 11.3)	3.9 (3.7, 5.6)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.46 (0.339, 0.615)	
Investigator assessment		
Median PFS (months) (95% CI)[a,b]	8.7 (7.3, 10.0)	4.3 (3.7, 5.5)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.53 (0.405, 0.683)	
Limited censoring (include subsequent anti-cancer treatment, discontinuation due to any reason, and missed tumor assessments as events)		
Median PFS (months) (95% CI)[a,b]	5.9 (5.5, 7.2)	3.8 (3.7, 5.4)
p-value[e]	0.0013	
Hazard ratio (95% CI)[f]	0.66 (0.512, 0.850)	
Use of scheduled assessment dates (if the actual assessment showing PD was conducted after the scheduled date)		
Median PFS (months) (95% CI)[a,b]	9.2 (7.2, 11.2)	3.8 (3.7, 5.6)
p-value[e]	<0.0001	
Hazard ratio (95% CI)[f]	0.45 (0.338, 0.609)	

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; ITT=intent-to-treat; non-gBRCAmut=without a germline BRCA mutation; PFS=progression-free survival; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumours

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

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

[c]Based on the unstratified log-rank test

[d]Niraparib:Placebo, based on Cox Proportional Hazards Model using treatment only.

[e]Based on the stratified log-rank test using randomization stratification factors.

[f]Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.

- **Secondary endpoints**

HRDpos/non-gBRCAmut cohort

Results for the secondary efficacy endpoints in the HRDpos group of the non-gBRCAmut cohort are summarized in the following tables.

Table 29 Time to First Subsequent Therapy (TFST) in non-gBRCAmut / HRD+ Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=106)	Placebo (N=56)
non-gBRCAmut HRD+	Time to First Subsequent Therapy (months) [1] [2]	75th Percentile (95% CI)	NE (22.7,NE)	13.8 (8.7,24.6)
		Median (95% CI)	15.9 (12.4,NE)	6.0 (4.7,9.8)
		25th Percentile (95% CI)	8.9 (6.7,10.9)	4.4 (4.0,5.0)
	Censored Observations	N (%)	53 (50.0)	13 (23.2)
	Event Rate, Overall	N (%)	53 (50.0)	43 (76.8)
	p-value [3]		<0.0001	
	Hazard Ratio, Niraparib:Placebo [4]	HR (95% CI)	0.36 (0.233,0.568)	

[1] TFST is defined as the date of randomization to the earlier of the start date of first follow-up anti-cancer treatment (FUACT) or death. Patients alive and not starting a first FUACT will be censored at the date last known to be alive.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] Based on stratified log-rank test using randomization stratification factors.
[4] Based on stratified Cox Proportional Hazards Model using randomization factors.

Table 30 Chemotherapy-free interval (CFI) in non-gBRCAmut / HRD+ Cohort (ITT Population)

Cohort	Parameter	Statistic	Niraparib (N=106)	Placebo (N=56)
non-gBRCAmut HRD+	CFI (months) [1] [2]	75th Percentile (95% CI)	NE (24.3,NE)	14.6 (10.4,25.9)
		Median (95% CI)	18.2 (14.2,24.3)	7.7 (6.3,10.6)
		25th Percentile (95% CI)	10.2 (7.7,12.7)	5.8 (5.4,6.3)
	Censored Observations	N (%)	58 (54.7)	15 (26.8)
	Event Rate, Overall	N (%)	48 (45.3)	41 (73.2)
	p-value [3]		<0.0001	
	Hazard Ratio, Niraparib:Placebo [4]	HR (95% CI)	0.31 (0.190,0.493)	

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

Table 31 Progression Free Survival 2 (PFS2) in non-gBRCAmut / HRD+ Cohort (ITT Population)

Cohort Subset [1]	Parameter	Statistic	Niraparib (N=106)	Placebo (N=56)
non-gBRCAmut HRD+	PFS2 (months) [1] [2]	75th Percentile (95% CI)	NE (NE,NE)	NE (22.5,NE)
		Median (95% CI)	22.3 (18.6,NE)	17.6 (12.9,NE)
		25th Percentile (95% CI)	13.4 (11.2,17.1)	10.3 (7.4,13.2)
	Survival Distribution Function (SDF) [3]	SDF (95% CI)		
	6-month		0.97 (0.91,0.99)	0.92 (0.81,0.97)
	12-month		0.81 (0.72,0.88)	0.68 (0.53,0.79)
	18-month		0.64 (0.52,0.73)	0.48 (0.30,0.64)
	24-month		0.48 (0.34,0.61)	0.36 (0.14,0.59)
	30-month		0.48 (0.34,0.61)	0.36 (0.14,0.59)
	Censored Observations	N (%)	68 (64.2)	33 (58.9)
	Event Rate, Overall	N (%)	38 (35.8)	23 (41.1)
	p-value [4]		0.1200	
	Hazard Ratio, Niraparib:Placebo [5]	HR (95% CI)	0.65 (0.372,1.124)	

[1] PFS2 is defined as the date of randomization in the current study to the earlier date of assessment of progression on the next anti cancer therapy following study treatment or death by any cause. See Section 5.1.2.1 of the SAP for details.
[2] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[3] SDF estimates from product-limit method. Confidence intervals constructed using log-log transformation.
[4] Based on stratified log-rank test using randomization stratification factors.
[5] Based on stratified Cox Proportional Hazards Model using randomization stratification factors.

Non-gBRCAmut overall

Table 32 Secondary Efficacy Analyses Based on IRC Assessment in the Non-gBRCAmut Cohort Overall–NOVA study

Parameter statistic	Non-gBRCAmut Cohort (N=350)	
	Niraparib (N=234)	Placebo (N=116)
TFST		
Median (95% CI) (months)[b]	11.8 (9.7, 13.1)	7.2 (5.7, 8.5)
Censored observations, n (%)	96 (41.0)	29 (25.0)
Event rate, n (%)	138 (59.0)	87 (75.0)
p-value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.55 (0.412, 0.721)	
CFI		
Median, months (95% CI)[b]	12.7 (11.0, 14.7)	8.6 (6.9, 10.0)
Censored observations, n (%)	104 (44.4)	35 (30.2)
Event rate, n (%)	130 (55.6)	81 (69.8)
p-value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.50 (0.370, 0.666)	
PFS2		
Median, months (95% CI)[b]	18.6 (16.2, 21.7)	15.6 (13.2, 20.9)
Censored observations, n (%)	132 (56.4)	60 (51.7)
Event rate, n (%)	102 (43.6)	56 (48.3)
p-value[c]	0.0293	
Hazard ratio (95% CI)[d]	0.69 (0.494, 0.964)	

Abbreviations: BRCA=breast cancer susceptibility gene; CFI=chemotherapy-free interval; CI=confidence interval; gBRCAmut=germline BRCA mutation; IRC=Independent Review Committee; ITT=intent-to-treat; PFS2=progression-free survival 2; TFST=time to first subsequent therapy

[a]For parameter definitions, see Table 6.

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

[c]Based on stratified log-rank test using randomization stratification factors.

[d]Niraparib:Placebo, based on stratified Cox Proportional Hazards Model using randomization stratification factor.

Overall Survival

As of the data cutoff for the primary analysis of PFS, the OS data were immature in the non-gBRCAmut cohort. At that time, a total of 71 patients in the cohort had died, including 44 (19%) of 234 patients randomized to niraparib and 27 (23%) of 116 patients randomized to placebo. Data were censored for over 75% of patients in both treatment arms. Median OS was not estimated for the ITT population in either randomized treatment arm; HR was 0.74 (95% CI: 0.452, 1.200). Follow-up continues for all patients who were ongoing on study at the time of the data cut.

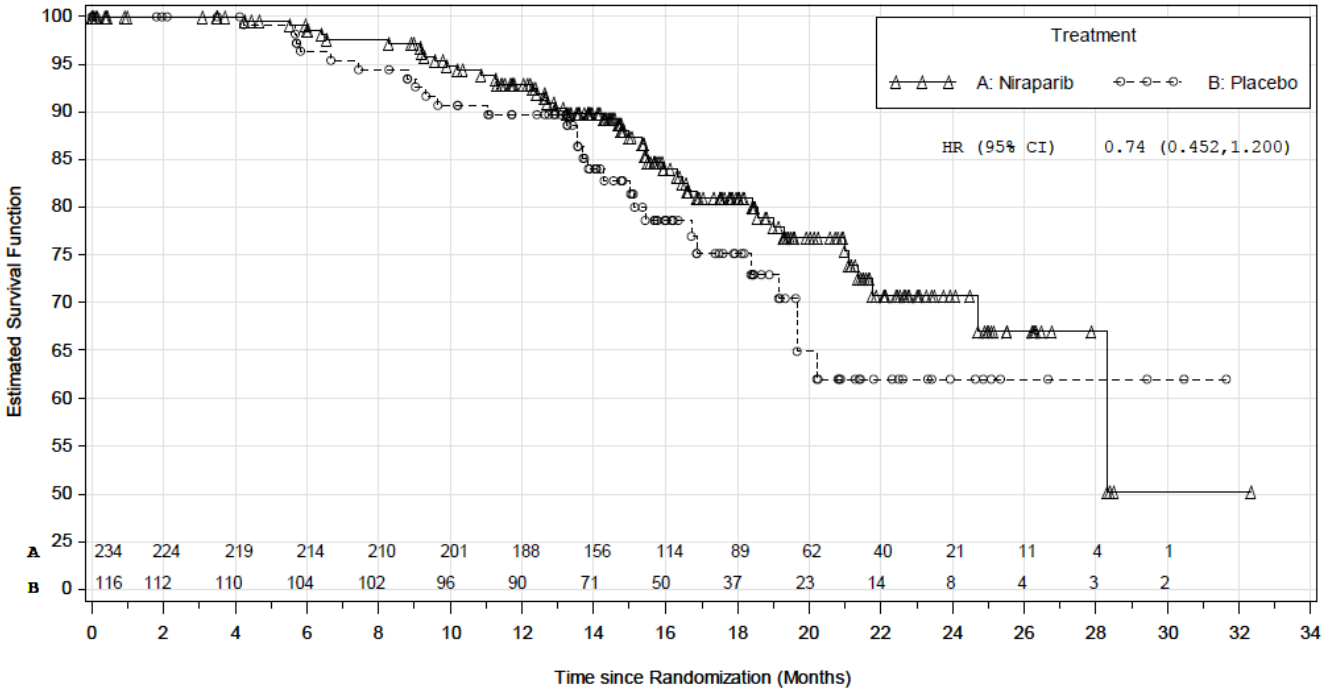
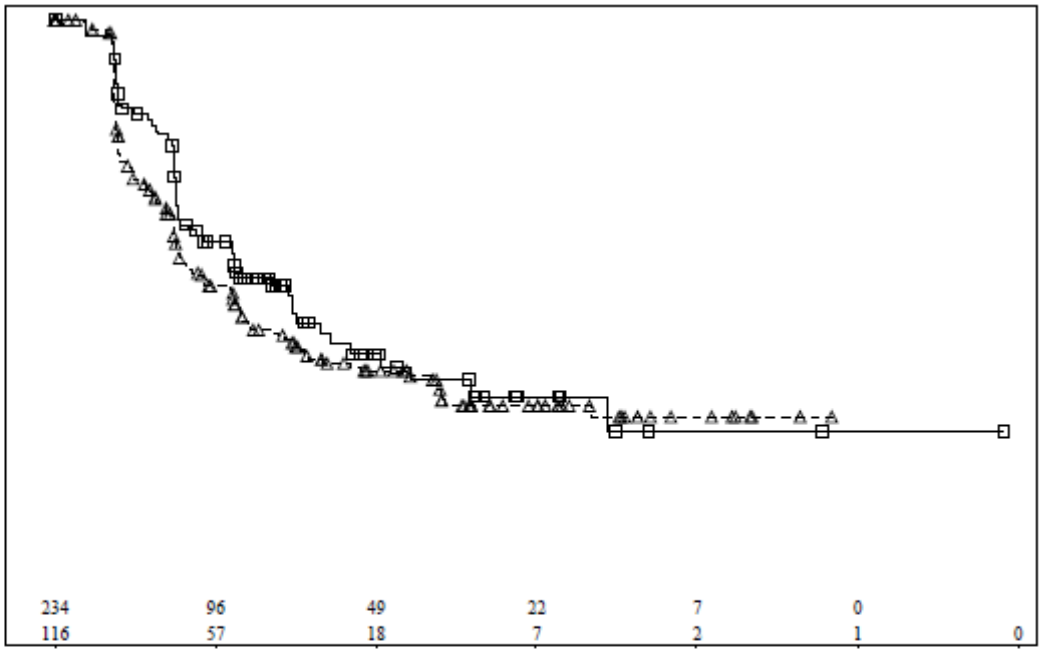


Figure 13 Overall Survival (ITT Population)COHORT=non-gBRCA Overall

- **Patient reported outcomes**

Baseline symptoms and QOL (FOSI, EQ-5D-5L) were similar between placebo and niraparib patients in the non-gBRCAmut cohort. Similar results were observed throughout the study for the non-gBRCAmut cohort with no significant differences observed during the maintenance (treatment) period or at post-progression ($p>0.05$ for each assessment and each treatment arm on each patient outcome).

Further, KM analysis for FOSI time to symptom worsening found no statistically significant difference between niraparib and placebo (log rank $p>0.05$).



Abbreviations: BRCA=breast cancer susceptibility gene; FOSI=Functional Assessment of Cancer Therapy – Ovarian Symptom Index; non-gBRCAmut=without a germline BRCA mutation; ITT=intent-to-treat

Figure 14 Kaplan-Meier Curve for FOSI Time to Symptom Worsening in the Non-gBRCAmut Cohort (ITT Population)

Exploratory endpoint

- **HRDpos/s*BRCA*mut**

Among patients in the HRDpos subgroup that had a somatic BRCA mutation (sBRCAmut, N = 47), median PFS was longer in the niraparib arm (20.9 months) compared to the placebo arm (11.0 months) with an HR of 0.27 (95% CI: 0.081, 0.903) (p=0.0248).

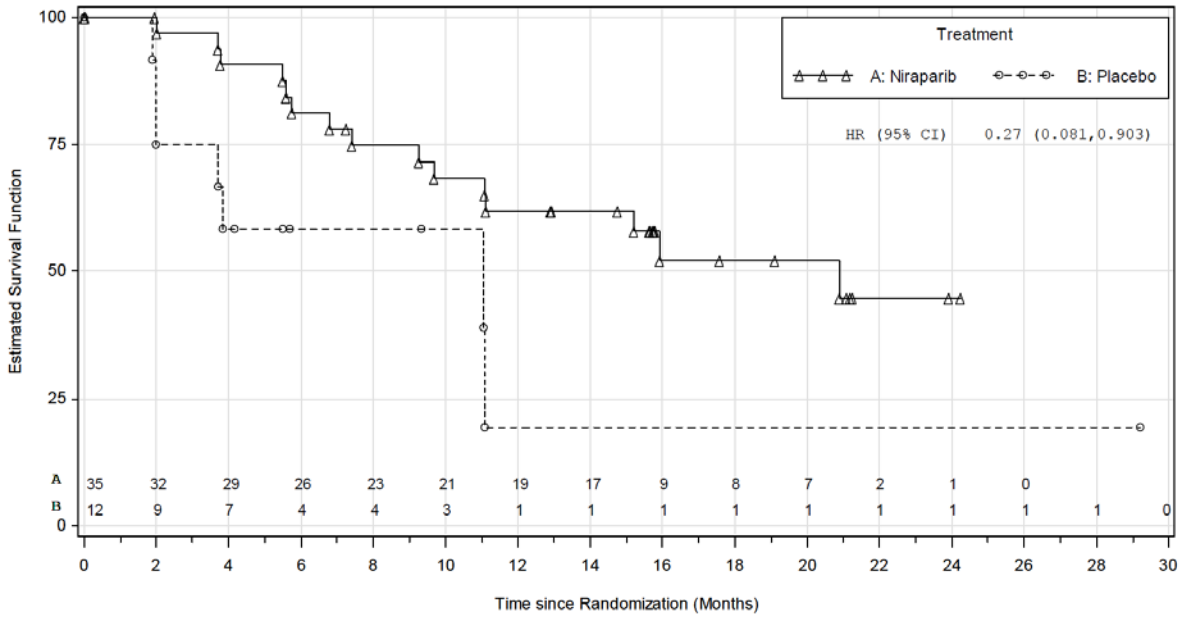


Figure 15 Kaplan-Meier Plot for Progression-Free Survival in the HRDpos/sBRCA Subgroup of the Non-gBRCAmut Cohort Based on IRC Assessment (ITT Population) –NOVA study

- **HRDpos/BRCAwt group**

In patients with HRDpos/BRCAwt tumours (N=115), treatment with niraparib also showed prolonged PFS with median PFS of 9.3 months in the niraparib arm compared to 3.7 months in the placebo arm with an HR of 0.38 (95% CI: 0.231, 0.628) (p=0.0001).

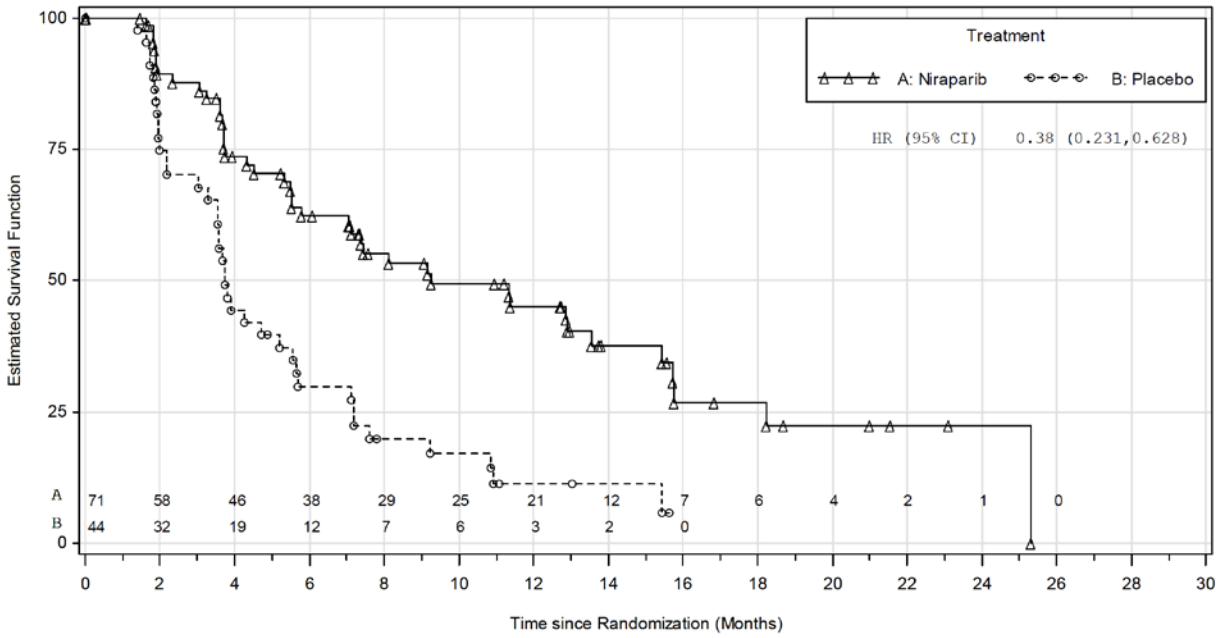


Figure 16 Kaplan-Meier Plot for Progression-Free Survival in the HRDpos/BRCAwt Subgroup of the Non-gBRCAmut Cohort Based on IRC Assessment (ITT Population) –NOVA study

- **HRDneg group**

The median PFS in the niraparib arm of the HRDneg group (N=162) was 6.9 months compared to 3.8 months in the placebo arm with an HR of 0.58 (95% CI: 0.361, 0.922) (p=0.0226). Review of the KM curves for the 2 treatment arms in the HRDneg group shows divergence of the curves after approximately 4 months with the niraparib arm above that of the placebo arm. The estimated proportion of patients in the HRDneg group who had not progressed or died at 6 months was 54% in the niraparib arm compared to 31% in the placebo arm and at 12 months was 27% compared to 7%.

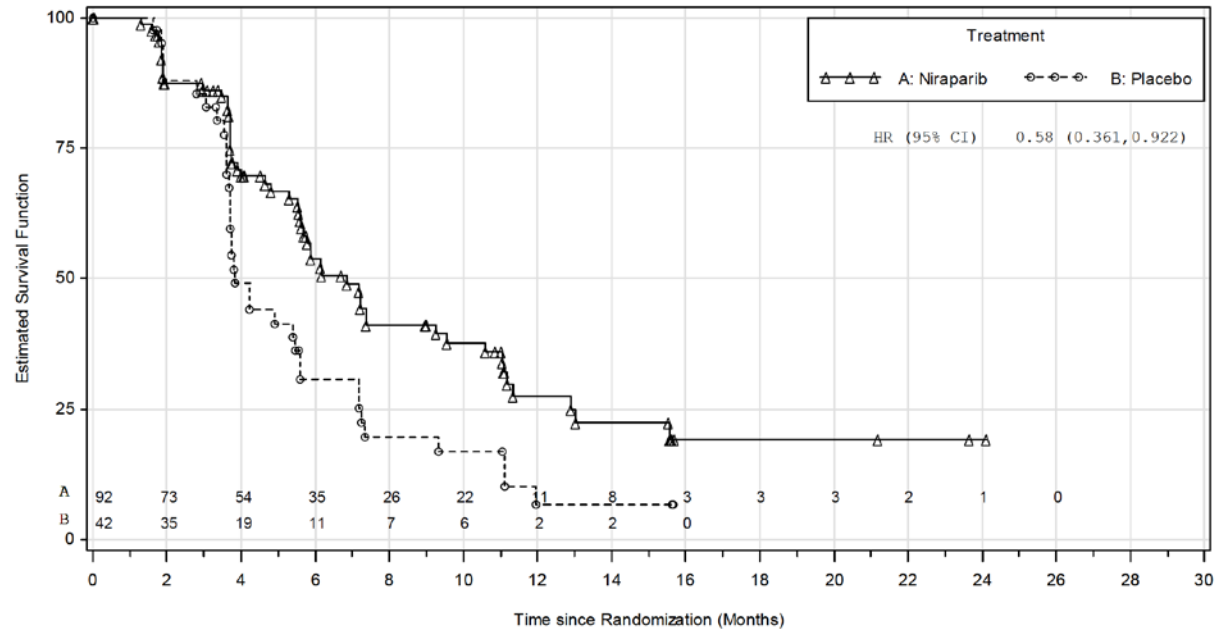


Figure 17 Kaplan-Meier Plot for Progression-Free Survival in the HRDneg Group of the Non-gBRCAmut Cohort, Based on IRC Assessment (ITT Population) –NOVA study

Ancillary analyses

Pooled efficacy analysis across the gBRCAmut and non-gBRCAmut cohorts

Given the positive outcome for niraparib maintenance treatment in both cohorts of the NOVA study, the data were pooled for analysis to allow for an evaluation of the treatment effect in a population of patients regardless of BRCA biomarker status. In addition, pooling of the data across cohorts allows for a larger and more robust dataset for the assessment of the secondary endpoints, including PFS2 and OS.

- *Progression free survival*

Median PFS as determined by the IRC for the pooled cohorts was 11.3 months among the 372 patients in the niraparib arm compared to 4.7 months among the 181 patients in the placebo arm and with a HR of 0.38 (95% CI: 0.303, 0.488), (p<0.0001).

Table 33 Progression-free Survival in the Pooled gBRCAmut and Non-gBRCAmut Cohorts Based on IRC Assessment (ITT Population) –NOVA study

Parameter Statistic	All Subjects: gBRCAmut and Non-gBRCAmut Cohorts (N=553)	
	Niraparib (N=372)	Placebo (N=181)
PFS (months)[a,b]		
75th percentile (95% CI)	25.3 (NE, NE)	9.2 (7.3, 11.1)
Median (95% CI)	11.3 (9.6, 13.5)	4.7 (3.8, 5.6)
25th percentile (95% CI)	5.4 (3.8, 5.7)	3.4 (2.1, 3.6)
Survival distribution function (95% CI)[c]		
6-month	0.69 (0.64, 0.74)	0.38 (0.31, 0.46)
12-month	0.49 (0.43, 0.55)	0.15 (0.09, 0.21)
18-month	0.38 (0.32, 0.44)	0.13 (0.08, 0.20)
24-month	0.33 (0.27, 0.40)	0.13 (0.08, 0.20)
Censored observations, n (%)	188 (50.5)	49 (27.1)
Event rate, n (%)	184 (49.5)	132 (72.9)
p-value[d]	<0.0001	
Hazard ratio (95% CI)[e]	0.38 (0.303, 0.488)	

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; gBRCAmut=germline BRCA mutation; IRC=Independent Review Committee; ITT=intent-to-treat; NE=not estimated; non gBRCAmut=without a germline BRCA mutation; 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 are from Brookmeyer and Crowley method with log-log transformation

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

[d]Based on stratified log-rank test using randomization stratification factors.

[e]Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.

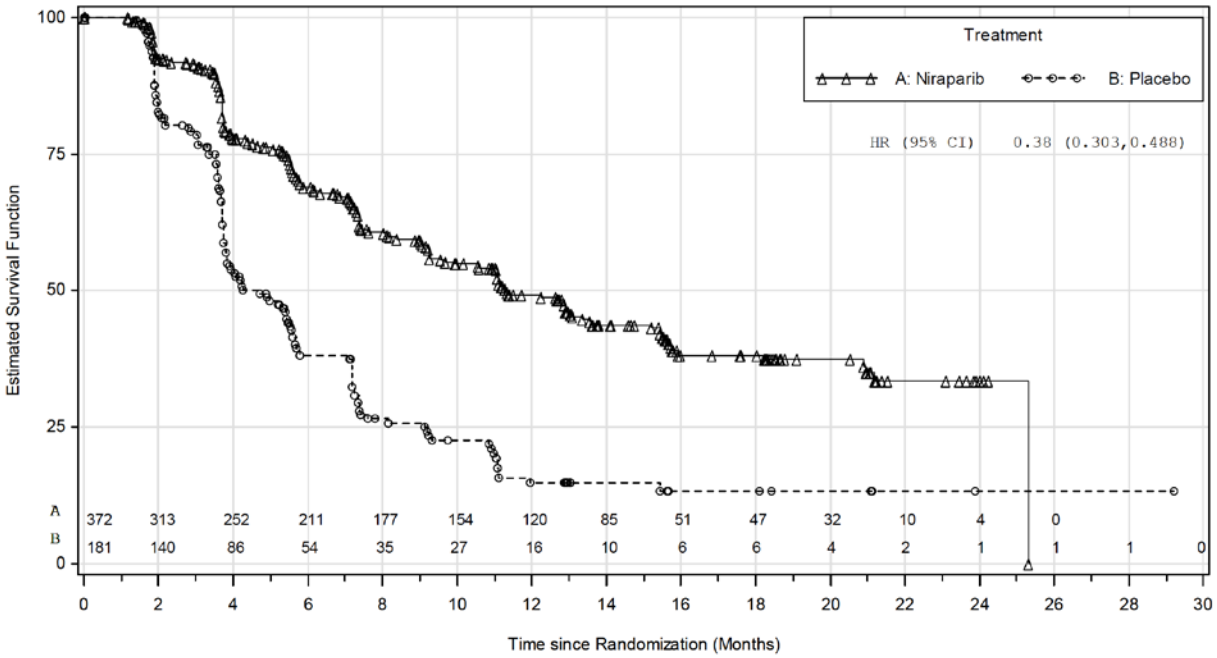


Figure 18 Kaplan-Meier Plot for Progression-Free Survival in the Pooled gBRCAmut and Non-gBRCAmut Cohorts Based on IRC Assessment (ITT Population) –NOVA study

- *TFST, CFI and PFS2*

Table 34 Secondary Efficacy Analyses in the Pooled gBRCAmut and Non-gBRCAmut Cohorts Based on IRC Assessment (ITT Population) –NOVA study

Parameter[a] Statistic	All Patients: gBRCAmut and Non-gBRCAmut Cohorts (N=553)	
	Niraparib (N=372)	Placebo (N=181)
TFST		
Median, months (95% CI)[b]	14.6 (12.5, 17.4)	7.5 (6.6, 8.7)
Censored observations, n (%)	176 (47.3)	51 (28.2)
Event rate, n (%)	196 (52.7)	130 (71.8)
p-value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.46 (0.368, 0.583)	
CFI		
Median, months (95% CI)	15.2 (13.7, 18.3)	9.0 (7.7, 10.1)
Censored observations, n (%)	188 (50.5)	58 (32.0)
Event rate, n (%)	184 (49.5)	123 (68.0)
p-value	<0.0001	
Hazard ratio (95% CI)	0.40 (0.317, 0.513)	
PFS2		
Median, months (95% CI)	21.0 (19.3, 25.9)	16.1 (14.2, 20.5)
Censored observations, n (%)	231 (62.1)	100 (55.2)
Event rate, n (%)	141 (37.9)	81 (44.8)
p-value	0.0004	
Hazard ratio (95% CI)	0.61 (0.457, 0.802)	

Abbreviations: BRCA=breast cancer susceptibility gene; CFI=chemotherapy-free interval; CI=confidence interval;
IRC=Independent Review Committee; ITT=intent-to-treat; NE=not estimated; non-gBRCAmut=without a germline BRCA mutation; PFS2=progression-free survival 2; TFST=time to first subsequent therapy

[a]For parameter definitions, see Table 6 in CSR.

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

[c]Based on stratified log-rank test using randomization stratification factors.

[d]Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.

- *PFS2-PFS interval in the pooled cohorts*

At data cutoff 62% and 55% of the data for the PFS2 analysis were censored in both cohorts for patients in the niraparib and placebo arms, respectively. Hence, an analysis was performed to evaluate the difference between PFS2 and PFS (PFS2-PFS) in all randomized patients. The median difference between PFS2 and PFS was 9.0 months for the niraparib arm and 10.3 months for the placebo arm with hazard ratio – 1.02 (95% cI: 0765 , 1.349; (p=0.9183).

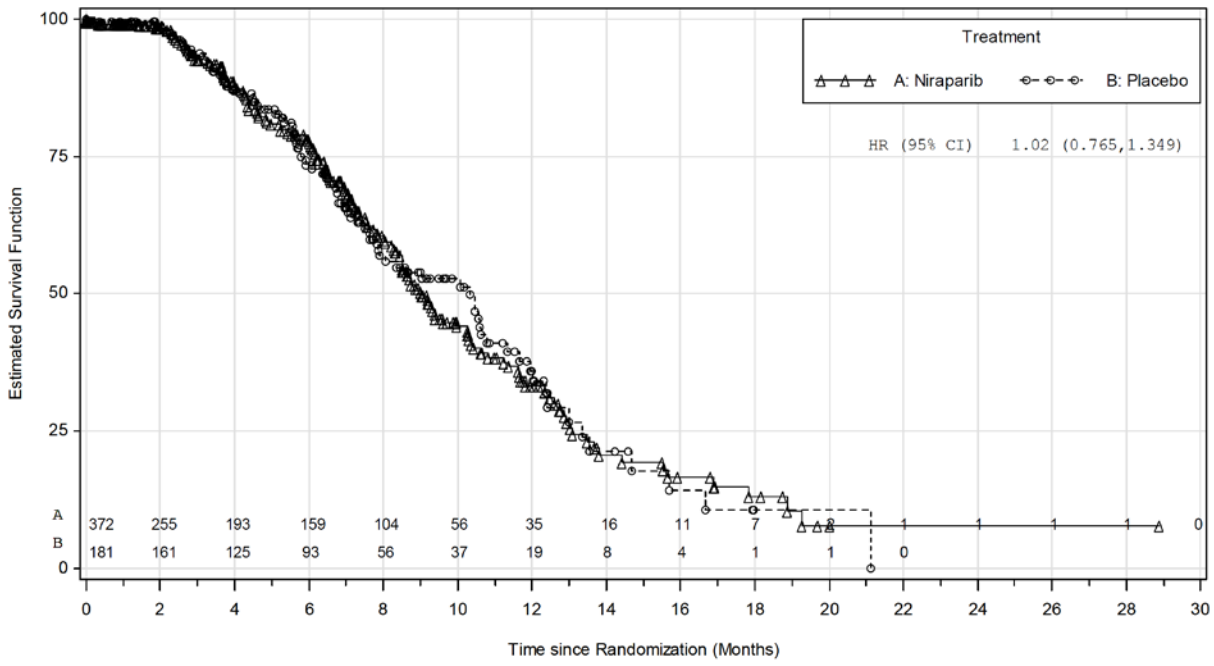


Figure 19 Kaplan-Meier Plot for PFS2-PFS in the Pooled gBRCAmut and Non-gBRCAmut Cohorts (ITT Population, N=553) –NOVA study

- *Overall survival*

Overall survival data were immature at the time of the data cutoff with >80% of patients in both treatment arms alive and therefore censored in the analysis. Median OS for the pooled analysis had not been reached in either treatment arm; the HR (95% CI) was 0.73 (0.480, 1.125) (p=0.1545). Updated analysis will be provided in the final CSR.

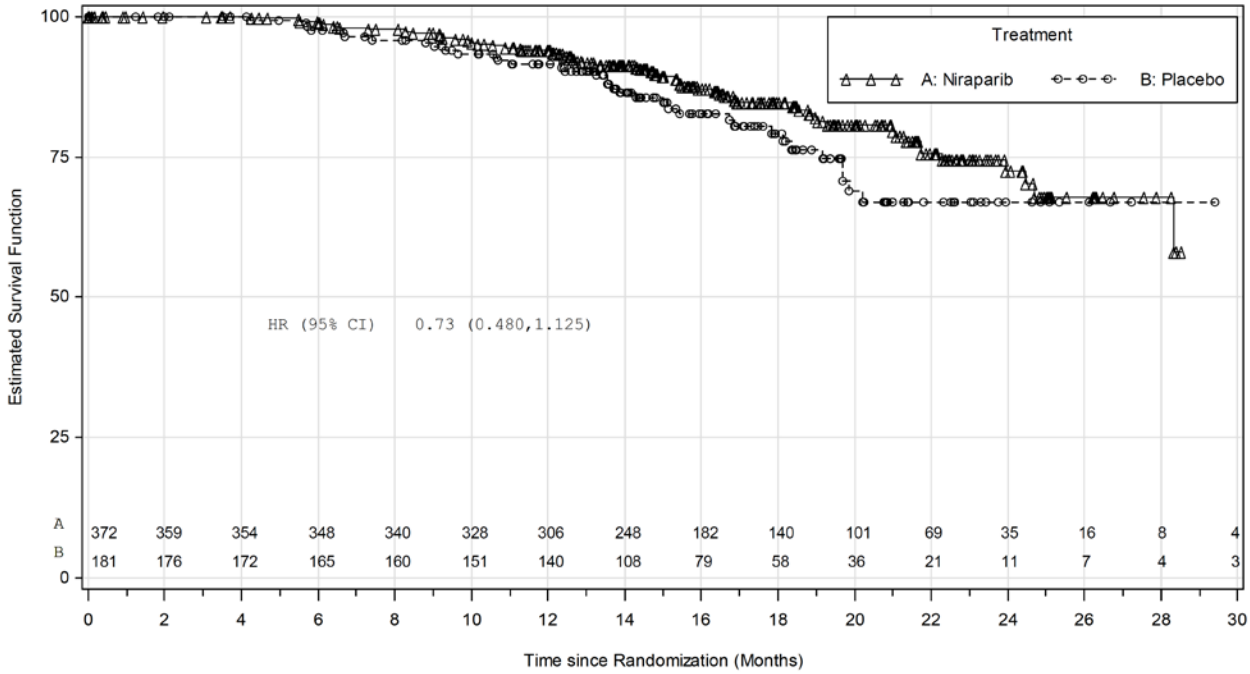


Figure 20 Kaplan-Meier Plot for Overall Survival in the Pooled gBRCAmut and Non-gBRCAmut Cohorts (ITT Population) –NOVA study

Analysis for patients with tumour BRCA in the pooled cohorts

An additional analysis was performed in the NOVA study to assess the treatment effect on PFS for patients from both study cohorts with tumour BRCA mutations; germline and somatic. In this group of patients, niraparib prolonged PFS by 15.2 months compared to placebo.

Table 35 Progression-Free Survival in Patients with Tumour BRCA Mutations from the gBRCAmut and non-gBRCAmut Cohorts Based on IRC Assessment (ITT Population) –NOVA study

Treatment	Median PFS[a] (95% CI) (Months)	Hazard Ratio[b] (95% CI) p-value[c]	% of Patients without Progression or Death at:[d]		
			6 Months	12 Months	18 Months
Niraparib (N=173)	20.9 (13.1, NE)	0.26 (0.177, 0.393) p=0.0003	81%	62%	51%
Placebo (N=77)	5.7 (3.9, 7.4)		45%	16%	16%

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; gBRCAmut=germline BRCA mutation; IRC=Independent Review Committee; NE=not estimated; non-gBRCAmut=without a germline BRCA mutation; 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]Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors. [c]Based on stratified log-rank test using randomization stratification factors. Estimates from product-limit method. Confidence intervals constructed using log-log transformation.

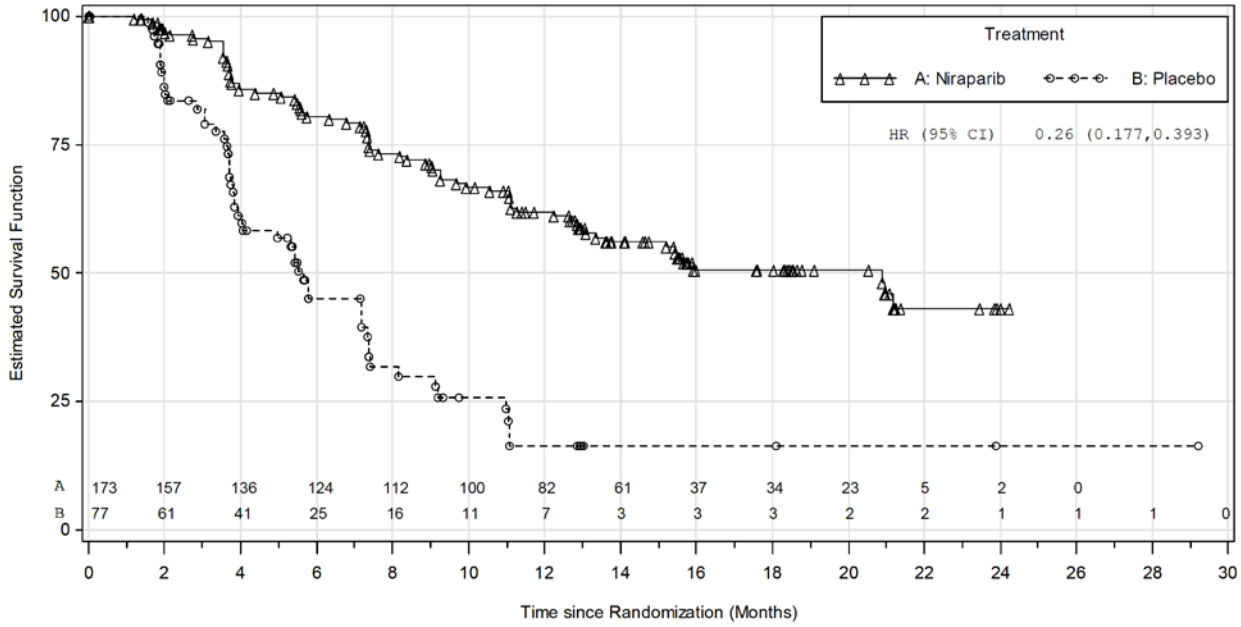


Figure 21 Kaplan-Meier Plot for Progression-Free Survival in Patients with Tumour BRCA Mutations in the gBRCAmut and Non-gBRCAmut Cohorts Based on IRC Assessment (ITT Population) –NOVA study

Subgroup analysis

Subgroup analysis of PFS were performed on data from the NOVA study for each cohort. The patient subpopulations are defined in Table 44.

Table 36 Definition of subgroups –NOVA study

Parameter	Categories
Age	<65, ≥65 years of age
Race	White, non-white
Geographic region	North America, Rest of World (Europe, Israel)
TTP after the penultimate platinum therapy before study enrollment	6 to <12 months, ≥12 months
Use of bevacizumab in conjunction with the penultimate or last platinum regimen	Yes/no
Best response during the last platinum regimen	CR and PR
Number of prior platinum regimens	2 and >2

Number of prior chemotherapy regimens	2 and >2
BRCA status (gBRCAmut cohort)	BRCA1 and BRCA2

Abbreviations: BRCA=breast cancer resistance gene; gBRCAmut=germline BRCA mutation; R=complete response; PR=partial response; TTP=time to progression

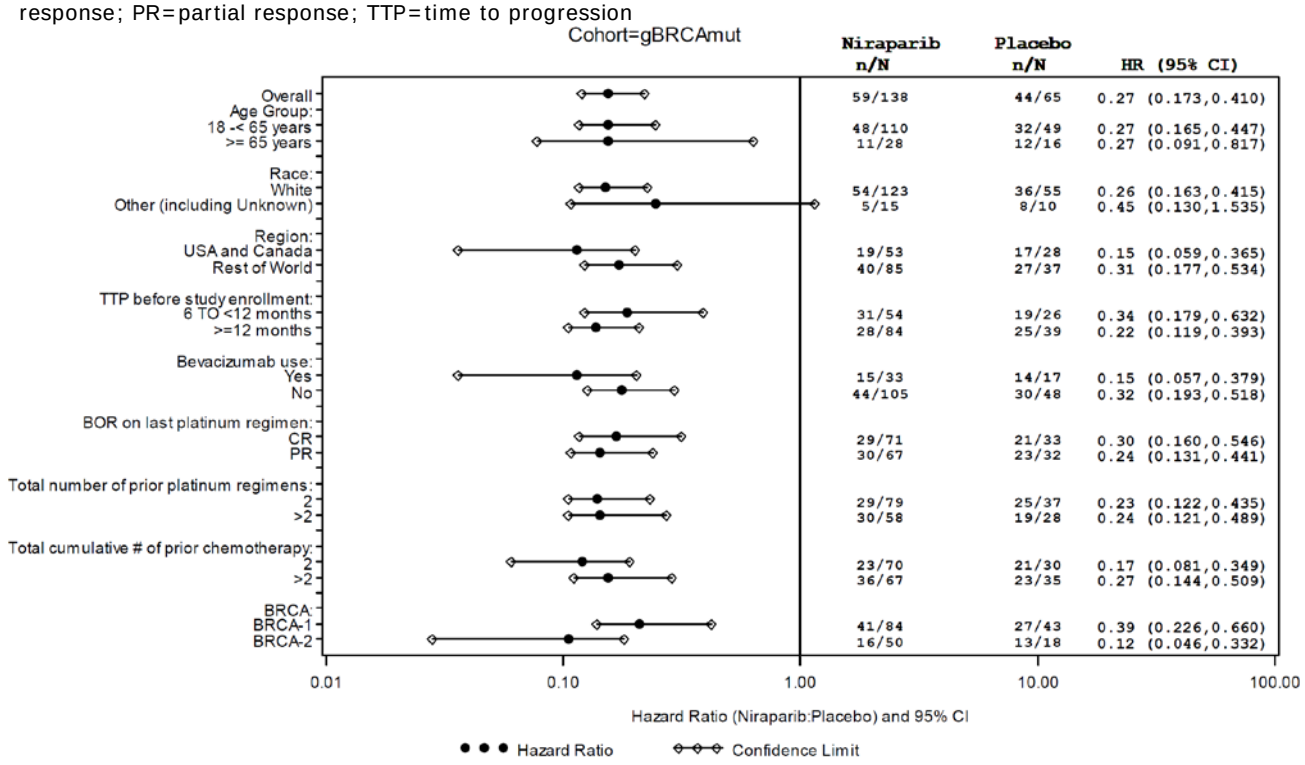


Figure 22 Forest Plot of Hazard Ratio (95% CI) for PFS by Patient Subgroups for the gBRCAmut Cohort (ITT Population) –NOVA study

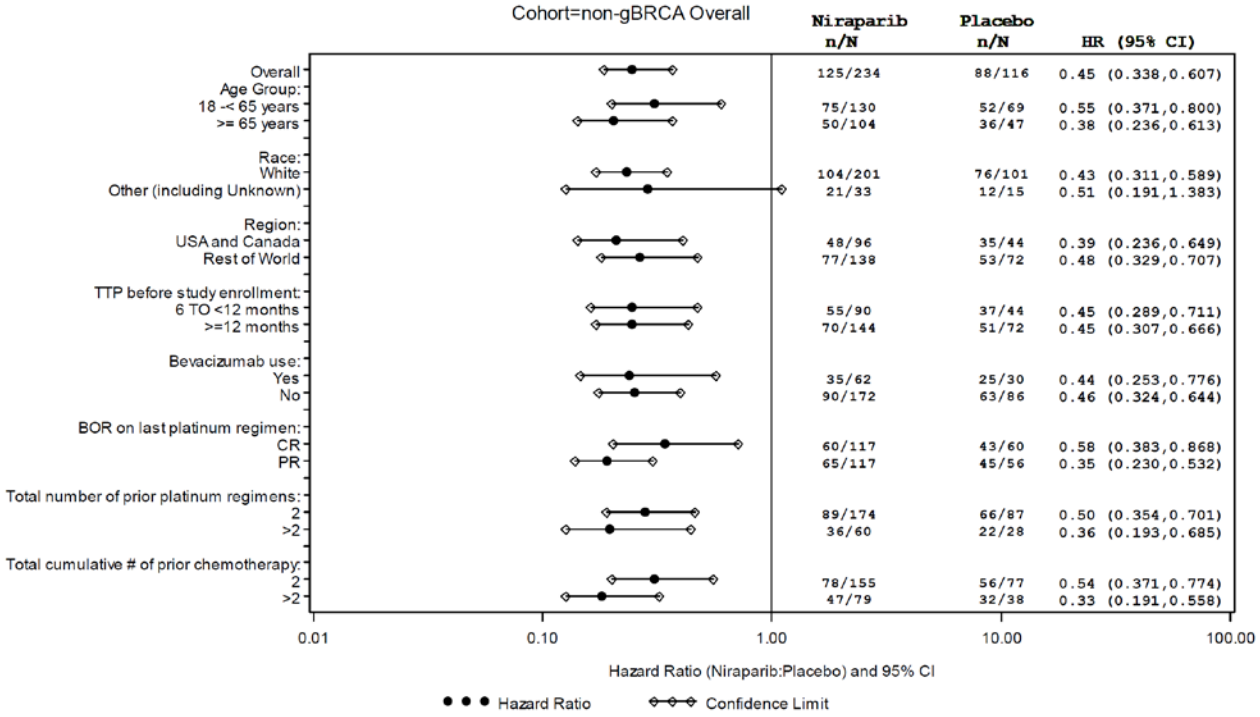


Figure 23 Forest Plot of Hazard Ratio (95% CI) for PFS by Patient Subgroups for the Non-gBRCAmut Cohort (ITT Population, N=350)

Summary of main study

Table 37 Summary of efficacy for the NOVA trial

Title:A Phase 3, Randomized, Double-Blind Trial of Maintenance with Niraparib versus Placebo in Patients with Platinum-Sensitive Ovarian Cancer			
Study identifier	Protocol Number: PR-30-5011-C IND Number: 100,996 EudraCT Number: 2013-000685-11		
Design	• double-blind, 2:1 randomized, placebo-controlled,multicenter, global clinical trial • two arms • maintenance treatment for patients with platinum-sensitive, recurrent, ovarian cancer who had received at least 2 platinum-based regimens and were in response to their last platinum-based chemotherapy.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Date first patient enrolled (signed informed consent): 26 Aug 2013 Data cutoff date: 30 May 2016 Database lock date: 20 Jun 2016 Study is ongoing Not applicable Not applicable
Hypothesis	Superiority		
Treatment groups	g*BRCA*mut cohort: Patients with a deleterious or suspected deleterious germline *BRCA* mutation.		Treatment: niraparib or placebo (2:1 randomization) Duration: Patients received their assigned treatment until disease progression Number randomized:138 assigned to niraparib; 65 assigned to placebo
	HRDpos: Patients without a germline *BRCA* mutation (non-g*BRCA*mut) that have tested positive for homologous recombination deficiency (HRD; a biomarker classifier used to enrich for niraparib sensitivity)		Treatment: niraparib or placebo (2:1) Number randomized: 106 assigned to niraparib; 56 assigned to placebo
	Overall non-g*BRCA*mut: Patients without a germline *BRCA* mutation (regardless of HRD status)		Treatment: niraparib or placebo (2:1) Number randomized: 234 assigned to niraparib; 116 assigned to placebo
Endpoints and definitions	Primary endpoint	Progression free survival (PFS)	Date of randomization to the earlier of either date of progressive disease (PD) or death by any cause (determined using Response Evaluation Criteria in Solid Tumours [RECIST] v.1.1 and clinical criteria).
	Secondary endpoint	Time to First Subsequent Treatment (TFST)	Date of randomization in the current study to the start date of the first subsequent anti-cancer therapy after maintenance treatment
	Secondary endpoint	Chemotherapy-Free Interval (CFI)	The time from the last platinum therapy dose until initiation of the next anti-cancer therapy (excluding maintenance therapy).

	Secondary endpoint	Overall Survival (OS)	Time from study randomization to the date of death by any cause.
	Secondary endpoint	Patient Reported Outcomes (PRO): Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI)	Validated, 8-item measure of symptom response to treatment for ovarian cancer[1]
	Secondary endpoint	Patient Reported Outcomes (PRO): EuroQol-5 dimensions 5-level (EQ-5D-5L)	Validated general preference-based health-related quality of life (QOL) instrument in oncology, as well as other conditions, and is intended to compliment other QOL instruments[2]
Database lock	Database lock date: 20 Jun 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description for all cohorts	The primary analysis was conducted on the Intent-to-Treat (ITT) population. The primary analysis of PFS was prospectively planned to occur when 98 events had been reported in both the g*BRCA*mut cohort and in the HRDpos non-g*BRCA*mut group.		
A	**Primary Analysis – g*BRCA*mut cohort**		
Descriptive statistics and estimate variability: g*BRCA*mut cohort	Treatment group g*BRCA*mut	Niraparib	Placebo
	Number of subject	138	65
	PFS (median [months])	21.0	5.5
	95% Confidence Interval (CI)	(12.9, not evaluable [NE])	(3.8, 7.2)

Effect estimate per comparison	Primary endpoint: PFS	Comparison groups g*BRCA*mut	Niraparib vs. Placebo
		Hazard Ratio (HR)	0.27
		95% CI	(0.173, 0.410)
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint TFST (months)	Comparison groups g*BRCA*mut	Niraparib vs. Placebo
		HR	0.31
		95% CI	(0.205, 0.481)
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint: CFI	Comparison groups g*BRCA*mut	Niraparib vs. Placebo
		HR	0.26
		95% CI	(0.166, 0.409)
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint: OS Note: At the time of data cut-off, OS	Comparison groups g*BRCA*mut	Niraparib vs. Placebo
		HR	0.91
		95% CI	(0.360, 2.282)

	data were immature and highly censored.	p-value (stratified log-rank test)	0.8346
	Secondary endpoint: FOSI (PRO)	Comparison groups g*BRCA*mut	Niraparib vs. Placebo
		FOSI (mean)	Niraparib: 25.1 Placebo: 25.6
		Standard Deviation (StD)	Niraparib: 4.18 Placebo: 3.84
		p-value (log-rank)	p>0.05
	Secondary endpoint: EQ-5D-5L (PRO) Health Utility Index (HUI)	Comparison groups g*BRCA*mut	Niraparib vs. placebo
		HUI (mean)	Niraparib: 0.850 Placebo: 0.847
		StD	Niraparib: 0.121 Placebo: 0.131
		p-value (log-rank)	p>0.05
B	**Primary Analysis – HRD-Positive (HRDpos) Cohort**		
Descriptive statistics and estimate variability: HRDpos cohort	Treatment group HRDpos	Niraparib	Placebo
	Number of subject	106	56
	PFS (Median [months])	12.9	3.8
	95% CI	(8.1, 15.9)	(3.5, 5.7)
Effect estimate per comparison	Primary endpoint PFS	Comparison groups HRDpos	Niraparib vs. placebo
		HR	0.38
		95% CI	(0.243, 0.586)
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint: TFST	Comparison groups: HRDpos	Niraparib vs. Placebo
		HR	0.36
		95% CI	(0.233, 0.568)
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint: CFI	Comparison groups: HRDpos	Niraparib vs. Placebo
		HR	0.31
		95% CI	(0.190, 0.493)
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint: OS Note: At the time of data cut-off, OS data were immature and highly censored.	Comparison groups: HRDpos	Niraparib vs. Placebo
		HR	1.39
		95% CI	(0.568, 3.416)
		p-value (stratified log-rank test)	0.4665
	Secondary endpoint: FOSI (PRO)	Comparison groups HRDpos	Niraparib vs. placebo
		FOSI (mean)	Niraparib: 26.0 Placebo: 25.3
		StD	Niraparib: 3.64 Placebo: 3.45
		p-value (log-rank)	p>0.05
	Secondary endpoint: EQ-5D-5L (PRO) Health Utility Index (HUI)	Comparison groups HRDpos	Niraparib vs. placebo
		HUI (mean)	Niraparib: 0.843 Placebo: 0.819
		StD	Niraparib: 0.118 Placebo: 0.112

		p-value (log-rank)	p>0.05
C	**Primary Analysis – Overall non-g*BRCA*mut Cohort**		
Descriptive statistics and estimate variability: Overall non- g*BRCA*mut cohort	Treatment group Overall non-g*BRCA*mut	Niraparib	Placebo
	Number of subject	234	116
	PFS (Median [months])	9.3	3.9
	95% CI	(7.2, 11.2)	(3.7, 5.5)

Effect estimate per comparison	Primary endpoint: PFS	Comparison groups	Niraparib vs. placebo
		HR	0.45
		95% CI	(0.338, 0.607)
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint: TFST	Comparison groups Non-g*BRCA*mut	Niraparib vs. Placebo
		HR	0.55
		95% CI	(0.412, 0.721)
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint: CFI	Comparison groups Non-g*BRCA*mut	Niraparib vs. Placebo
		HR	0.50
		95% CI	(0.370, 0.666)
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint: OS Note: At the time of data cut-off, OS data were immature and highly censored.	Comparison groups Non-g*BRCA*mut	Niraparib vs. Placebo
		HR	0.74
		95% CI	(0.452, 1.200)
		p-value (stratified log-rank test)	0.2181
	Secondary endpoint: FOSI (PRO)	Comparison groups Non-g*BRCA*mut	Niraparib vs. placebo
		FOSI (mean)	Niraparib: 25.4 Placebo: 25.0
		StD	Niraparib: 3.92 Placebo: 4.07
		p-value (log-rank)	p>0.05
	Secondary endpoint: EQ-5D-5L (PRO) Health Utility Index (HUI)	Comparison groups Non-g*BRCA*mut	Niraparib vs. placebo
		HUI (mean)	Niraparib: 0.837 Placebo: 0.824
		StD	Niraparib: 0.118 Placebo: 0.135
		p-value (log-rank)	p>0.05

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

No such analyses have been carried out.

Clinical studies in special populations

No specific studies were carried out, however the applicant has submitted data for efficacy in the elderly population.

Table 38: Distribution of Age by study for non-controlled and controlled studies

Cohort	*Age 65-74 n (%)*	*Age 75-84 n (%)*	*Age 85+ n (%)*
Non-controlled studies			
QUADRA (N=291)	104 (35.7)	42 (14.4)	1 (0.3%)
PN001 (N=50)[a]	9 (18.0)	0	0
FE Study (N=17)	7 (41.2)	0	0
QTc Study (N=26)	8 (30.5)	2 (7.7)	0
Total (N=384)	128 (33.3)	44 (11.6)	1 (0.3)
Controlled study			
PR-30-5011C (N=553)	164 (29.7)	31 (5.6)	0
• gBRCAmut (N=203)	40 (19.7)	4 (2.0)	0
• non-gBRCAmut (N=350)	124 (35.4)	27 (7.7)	0

[a] only patients with ovarian cancer are included

The analysis of PFS based on IRC assessment for age group 65-74 for gBRCAmut cohort and non-gBRCAmut cohort was submitted by the applicant (data not shown). The results were consistent with observations in the overall population, indicating longer PFS for patients who received maintenance therapy with niraparib compared to those who received placebo in the older patient population.

Supportive study(ies)

No supportive studies are included.

2.5.3. Discussion on clinical efficacy

No formal Phase II dose-ranging studies were conducted. The selection of the 300 mg starting dose of niraparib for the NOVA study was based on data from the phase I dose-escalating study PN001. Niraparib is a non-cytotoxic compound and the traditional dose-finding approach through the determination of the MTD may not be appropriate. Despite absence of DLT conventionally defined by grade (3)4-5 events, there was a need to reduce the initial starting dose in a very high percentage of patients in both phase I and pivotal studies.

Design and conduct of clinical studies

The applicant has submitted data from a single pivotal trial. The NOVA study is a phase III, double-blinded, randomized, placebo controlled, multicenter, global clinical trial. The primary objective was to evaluate the efficacy and safety of niraparib as maintenance treatment for patients with platinum-sensitive recurrent ovarian cancer who had received at least 2 platinum-based regimens and were in response to their last platinum-based chemotherapy. The NOVA trial was designed to show superiority using 2:1 allocation of niraparib to placebo in two different cohorts; germline BRCA cohort and non-germline BRCA cohort. This is an acceptable patient distribution between the two treatment arms and use of placebo was acceptable at the time of study start.

The germline BRCA cohort includes patients with a germline BRCA mutation only. The non-germline BRCA cohort contains patients which are HRD positive with somatic BRCA mutation (N=47), HRD positive with wild type BRCA (N=115) and HRD negative (N=134).

According to the inclusion criteria of the NOVA study, patients were considered to be platinum sensitive if they had achieved a CR or PR for more than 6 months. These patients are not considered platinum-sensitive according to NCCN criteria.

The patients were randomized separately in each cohort based on stratification by time to progression after the penultimate platinum therapy before study enrolment (6 to < 12 months and >12 months), use of bevacizumab in the penultimate or last platinum regimen and best response during last platinum treatment (CR or PR). These are clinically relevant stratification factors, but based on scientific advice by CHMP bevacizumab, was not to be used as prior maintenance treatment as platinum sensitivity was characterized prior to the introduction of maintenance therapy. Nevertheless, subgroup analysis showed no difference between patients pretreated and patients not pretreated with bevacizumab.

The rationale for selecting a platinum sensitive/responsive patient population is well argued and sensible as these patients are most likely to benefit from PARP inhibition. Sensitivity to platinum adducts indicate deficiency in HRD with reduced ability to repair DNA damage. Hence, platinum sensitivity is a clinical indicator of sensitivity to PARP inhibitors and thus, the inclusion criteria for NOVA required patients to have ovarian cancer sensitive to platinum-based treatment as demonstrated by PFS >6 months on their penultimate platinum-based regimen. In addition the platinum sensitive population was assigned to two different cohorts based on their germline BRCA mutation status to further enrich for the most potent responders. Taken together, this allows for analysis of subgroups of patients believed to have the most benefit of niraparib treatment. This pre-enrichment strategy is also supported by another clinical study where the PARP inhibitor olaparib was tested.

The myChoice HRD test has been developed in parallel with the clinical development of niraparib and was intended to be used for determination of HRD status in patients´ tumours. Thus, the protocol was amended to incorporate the MyChoice HRD test to classify the HRD status of the patients in the non-gBRCAmut cohort. Patients were, based on the test results allocated to the HRDpos or HRDneg subpopulation.

However, there are yet no other available clinical data for validation of the test except for a Receiver Operating Characteristics (ROC) analysis which concluded that the test after all cannot be used to select patients suitable for niraparib treatment. The possible reasons why the test failed to define eligible patients in the NOVA study were presented during the procedure. These relates to i) probability that the test misses some individual tumours that should have been classified as HRD positives (false HRD negative), ii) the test might not capture all genes that play a role in the HR pathway, iii) high PARP-1 expression in the tumour. Based on the totality of these arguments the HRD test is considered not to be suitable to define eligible patients for niraparib treatment. Although there are limitations about the test, the results in patients HRD positive and HRD

negative together with information about the test and its limitations have been reflected in section 5.1 of SmPC).

Selecting PFS as primary endpoint was accepted by the CHMP in scientific advice as long as there would be no signs of inferior PFS2 or OS and an overall positive benefit-risk assessment. In the NOVA study, PFS is supported by several secondary endpoints with OS and PFS2 being the most relevant for study population. PRO has been included as a secondary endpoint. A combination of favourable PRO and PFS data could support approval as long as no detrimental effect on PFS2 or OS is observed.

In general, the study is well-designed and in line with the scientific advice provided by CHMP.

Efficacy data and additional analyses

The data cutoff date for the NOVA study was 30 May 2016 with a database lock date of 20 Jun 2016. At that time, a total of 553 patients (ITT population) had been enrolled; 372 were randomized to the niraparib arm and 181 to the placebo arm. Two hundred and three (203) patients were randomized into the gBRCAmut cohort and 350 patients randomized into the non-gBRCAmut cohort. Among the 350 patients in the non-gBRCAmut cohort, 162 had tumours that were HRD positive and 134 were HRD negative. For 54 of the patients the HRD status was not determined. Reasons why HRD status could not be determined include inadequate formalin-fixed tumour samples and tumour content of samples being less than 20%.

Baseline characteristics were generally well distributed between the cohorts and the treatment arms. The age distribution in the gBRCAmut cohort was slightly lower than for the non-gBRCAmut cohort. Also, in the gBRCAmut cohort there is a slight bias between the two arms for the BRCA2 mutation with 10% more patients allocated to the niraparib arm as compared to placebo. This latter point could potentially affect the primary analysis for this cohort towards longer median PFS since these patients have been found to have better survival and therapeutic response (Guoyan et al, 2012). The treatment groups were also generally well balanced in the two cohorts with regards to the total number of previous chemotherapy regimens. gBRCAm patients were generally more exposed to platinum treatments than non-gBRCAm patients; i.e. non-gBRCA mutated patients were previously mainly treated by only 2 platinum lines (~75%) vs ~ 57% for gBRCA mutated patients.

The study demonstrated significant improvement in median PFS for the niraparib arm of both cohorts and also for the HRDpos and the overall groups in the non-gBRCAmut cohort as compared to the placebo arm. The largest effect was obtained for the gBRCA cohort with a median prolongation of 15.5 months (HR = 0.27). In the sensitivity analysis the median PFS for the niraparib arm is reduced from 21 months in the primary analysis to 14.8 months in the investigator assessment and 11.2 months in the limited censoring analysis. The difference in median PFS between the assessments likely reflects differences in censoring rules (and thus event rates). Therefore, as requested, different sensitivity analyses have been performed to evaluate the robustness of the primary efficacy results. HR data from these analyses are consistent with the primary IRC analysis, whereas median (months) PFS data are similar to the investigator assessed PFS value. To reflect this, data from the investigator assessment sensitivity analysis has been included in section 5.1 of the SmPC.

In the non-gBRCAmut cohort, the median PFS is 12.9 months in the HRDpos group and 9.3 months in the overall group for the niraparib treated patients. Also the HRDneg group shows favourable PFS with a median prolongation of 3.1 months. All three groups demonstrate beneficial HR values (<0.60). Moreover, the difference in median PFS in the primary IRC analysis and the sensitivity analysis is far less pronounced for the non-gBRCAmut cohort (HRDpos/overall), and within acceptable variation. As per today, and based on the conclusion above on the HRD test, there are

no biomarker tests that can be used to correctly separate the HRDneg patients from the HRDpos patients.

The Kaplan-Meier plots for the 2 treatment arms show early divergence of the curves, with the niraparib curve consistently above that of placebo, as well as sustained separation in the curves throughout the observation period in both the gBRCAmut cohort and the overall non-gBRCAmut cohort . The probability of remaining progression-free at 12 months was estimated to be 27% in the niraparib arm and 7% in the placebo arm. At 18 months, the probability of remaining progression-free was 19% in the niraparib arm and 7% in the placebo arm.

A positive treatment effect was observed in all subgroups indicates that all patients with relapsed platinum-sensitive ovarian cancer experienced clinical benefit from treatment. Currently there are no means of identifying patients that are not sensitive to niraparib. Thus, prior platinum sensitivity seems to be the only clinical indicator for selection of patients to niraparib (PARP) treatment as reflected in the indication. Results for the secondary efficacy endpoints were consistent with the primary efficacy endpoint in the gBRCAmut cohort showing a treatment effect for niraparib compared to placebo for TFST, CFI and PFS2.

Next-line therapies (both chemotherapy and maintenance) will affect, PFS2 and OS of both arms. In the gBRCAmut cohort, the reported difference in PFS prolongation between the niraparib and the placebo arm is 15.5 months in the primary PFS analysis and 6.3 months in the PFS2 analysis. In the non-gBRCAmut cohort, the reported difference in PFS prolongation between the niraparib and the placebo arm is 5.4 months in the primary PFS analysis and 3 months in the PFS2 analysis.

Overall, the number of patients receiving any subsequent anticancer therapy was higher in the placebo arm as compared to the niraparib arm for both the gBRCAmut cohort (64.6% vs 39.1%,respectively) and the non-gBRCAmut cohort overall (69.8% vs 55.6%, respectively) and could explain some of the differences observed for PFS and PFS2. In relation to the PFS2 endpoint, data are immature with 72 % of patients censored in the niraparib arm and 57% in the placebo arm.

Clinical data are not available in patients with ECOG performance status 2 to 4.

The efficacy of niraparib in children and adolescents below 18 years of age has not yet been established.

The applicant is recommended to submit updated PFS2 and OS data from the NOVA study when they are available.

2.5.4. Conclusions on the clinical efficacy

Positive treatment effect has been demonstrated in both the gBRCA and the non-gBRCA cohort of the NOVA study. There is some uncertainty related to the possible differences in size of the effect in non-gBRCAmut subpopulations. However, there are currently no means of identifying patients that are sensitive to platinum but not sensitive to niraparib. Based on this, efficacy of niraparib is considered demonstrated in patients with both gBRCA and non-gBRCA ovarian cancer who are in response to platinum based chemotherapy.

2.6. Clinical safety

The primary data to support the safety of treatment with niraparib in the proposed indication are derived from the NOVA main study (PR-30-5011-C) in which 546 patients with ovarian cancer received at least one dose of study treatment, including 367 who received niraparib and 179 received placebo. Key supportive safety information is available from 384 ovarian cancer patients

treated in 4 open-label, single-arm studies or sub-studies: the Phase 1 Study PN001 (104 patients total, 50 with ovarian cancer), the Phase 2 Study PR-30-5020-C (QUADRA, 291 patients), and the 2 sub-studies of NOVA, PR-30-5011-C1-QTC (26 patients) and PR-30-5011-C2-FE (17 patients); data from these studies have been pooled for analysis. This single pool of studies provides an evaluation of the safety of niraparib in women receiving treatment for recurrent ovarian cancer and is designated the Ovarian Cancer Treatment (OCT) pool. Five additional studies with niraparib in other indications contributed with safety data Table 22.

Patient exposure

Overall, the entire clinical safety programme includes an evaluation of safety across a total of 854 patients who received at least 1 dose of niraparib administered as a monotherapy dose of 3x100 mg (capsules), in line with the proposal being sought. In the entire safety population, 277 subjects (75.5%) continued treatment with niraparib for ≥6 to <12 months and 150 subjects (40.9%) for ≥12 months at the data cut-off date of 30/05/2016. In the placebo-controlled NOVA study, 367 patients were exposed to at least one dose of niraparib, 245 subjects (66.8%) for ≥6 to <12 months and 163 subjects (44.4%) for ≥12 months at the data cut-off date.

The most commonly used dose in naraprib-treated patients in the NOVA trial was 200 mg.

In the NOVA study, the mean (SD) duration of treatment in the safety analysis set (SAF Population, N=546; n=367 on niraparib, n=179 on placebo) was longer in the niraparib arm with 299.9 (210.89) days equivalent to 11.0 (7.66) 28-days cycles compared to placebo with 212.5 (163.79) days corresponding to 7.9 (5.93) cycles. The median (range) overall treatment exposure from first to last dose was 250 days (~9 cycles; 1.0, 815.0) in the niraparib arm and 163 days (~6 cycles; 12.0, 926.0) in the placebo arm. Hence, the difference in duration of exposure was approximately 3 months between the two treatment arms. The mean (SD) dose intensity (sum of the daily doses actually consumed divided by total duration) was 194.98 (69.355) mg/day in the niraparib arm and 289.54 (25.656) mg/day in the placebo arm. Consequently, the patients in the niraparib and placebo group received a mean (SD) relative dose intensity of 64.99 (23.118) and 96.51 (8.552) percentage, respectively.

In the gBRCAmut cohort, the median number of treatment cycles was higher in the niraparib arm than the placebo arm (14 and 7 cycles, respectively). More patients in the niraparib group continued treatment for more than 12 months than patients in the placebo group (54.4% and 16.9% respectively).

In the overall non-gBRCAmut cohort, the median number treatment cycles was higher in the niraparib arm than in the placebo arm (8 and 5 cycles, respectively). More patients in the niraparib group continued treatment for more than 12 months than patients in the placebo group (34.2% and 21.1%, respectively.

A high proportion of patients in both treatment arms had received 3 or more prior lines of chemotherapy, including 39% (146/372) and 41% (74/181) of the patients in the niraparib and placebo arms, respectively. In comparison, the patients across the OCT pool were more heavily pre-treated for their underlying ovarian cancer with 92% (353/384) of the patients who had received 3 or more lines of prior chemotherapy. Notably, this was an inclusion criterion in the QUADRA study and the majority of the patients in Study PN001 and the FE sub-study had received more than 4 prior lines.

Adverse events

Most patients in both treatment arms of the NOVA study experienced at least 1 AE, including all 367 patients (100%) who received niraparib and 96% (171/179) who received placebo. Overall,

the incidence of treatment-related AEs was 98% in the niraparib arm and 71% in the placebo arm. The incidence of CTCAE Grade 3/4 AEs (74% vs 23%), SAEs (30% vs 15%), any related SAEs (17% vs 1%), treatment interruption (67% vs 15%), dose reduction (69% vs 5%), and discontinuation (15% vs 2%) due to AEs was higher in the niraparib arm compared to the placebo arm. There were no on-treatment deaths reported during the study. However, three deaths due to MDS that occurred in the post-treatment period, 1 in the niraparib arm and 2 in the placebo arm, were assessed as treatment-related by the Investigators.

Common adverse events

AEs reported in ≥10% of patients in either treatment arm are summarized for the Safety Population (SAF Population) in the NOVA study in Table 47.

The pattern of AEs is similar to that observed for olaparib, a PARP inhibitor approved in EU for platinum-sensitive recurrent BRCA-mutated ovarian cancer, except that thrombocytopenia and constipation are reported more commonly, and hypertension constitute a new safety signal for niraparib.

Table 39 Treatment-Emergent Adverse Events Reported in ≥10% of Patients in Either Treatment Arm (NOVA Main Study, SAF Population, N=546)

MedDRA Preferred Term	Niraparib (N=367) n (%)	Placebo (N=179) n (%)
Any TEAE	***367 (100.0)***	***171 (95.5)***
Nausea	270 (73.6)	63 (35.2)
Anaemia	178 (48.5)	12 (6.7)
Thrombocytopenia	169 (46.0)	6 (3.4)
Fatigue	168 (45.8)	58 (32.4)
Constipation	146 (39.8)	36 (20.1)
Vomiting	126 (34.3)	29 (16.2)
Headache	95 (25.9)	17 (9.5)
Decreased appetite	93 (25.3)	26 (14.5)
Insomnia	89 (24.3)	13 (7.3)
Abdominal pain	83 (22.6)	53 (29.6)
Platelet count decreased	74 (20.2)	4 (2.2)
Dyspnoea	71 (19.3)	15 (8.4)
Hypertension	71 (19.3)	8 (4.5)
Diarrhoea	70 (19.1)	37 (20.7)
Neutropenia	66 (18.0)	6 (3.4)
Dizziness	61 (16.6)	13 (7.3)
Asthenia	58 (15.8)	16 (8.9)
Cough	55 (15.0)	8 (4.5)
Back pain	49 (13.4)	21 (11.7)
Neutrophil count decreased	49 (13.4)	5 (2.8)
Arthralgia	43 (11.7)	22 (12.3)
Dyspepsia	42 (11.4)	17 (9.5)
Nasopharyngitis	41 (11.2)	13 (7.3)
Urinary tract infection	38 (10.4)	11 (6.1)
Palpitations	38 (10.4)	3 (1.7)
Dysgeusia	37 (10.1)	7 (3.9)
Myalgia	30 (8.2)	18 (10.1)
Abdominal distension	28 (7.6)	22 (12.3)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SAF=safety; TEAE=treatment-emergent adverse event. Source: CSR PR-30-5011-C Table 14.3.1.1A and Table 14.3.1.3B

The most frequently reported AEs overall in the OCT pool were consistent with the commonly reported AEs in the niraparib-treated patients of the NOVA study, including gastrointestinal events (nausea and vomiting), fatigue, decreased appetite, and events related to hematologic laboratory abnormalities. However, hypertension did not constitute one of the most commonly reported AEs in the OCT pool, as this AE was reported in only 3 patients (0.8%) across the studies.

Treatment Related Adverse Events

In the NOVA study, 98% (358/367) of the patients who received niraparib and 71% (127/179) who received placebo experienced treatment-related AEs. Treatment-related AEs reported in >25% of patients in the niraparib arm with corresponding incidence in the placebo arm were nausea (69%;

253/367, and 25%; 45/179), anaemia (46%; 170/367, and 5%; 8/179), thrombocytopenia (45%; 164/367, and 2%; 4/179), and fatigue (37%; 137/367, and 21%; 37/179).

Treatment-related AEs reported in ≥10% of the patients in the OCT pool were consistent with the incidence of AEs across the studies in general, and included nausea (50%; 190/384), anaemia (40%; 153/384), thrombocytopenia (35%; 133/384), fatigue (34%; 132/384), vomiting (29%; 111/384), decreased appetite (19%; 71/384), neutropenia (16%; 62/384), platelet count decreased (15%; 58/384), and constipation (14%; 55/384).

CTCAE Grade 3/4 AEs

Table 40: Grade 3/4 Treatment-Emergent Adverse Events Reported in ≥5% of Patients in Either Treatment Arm (NOVA Main Study, SAF Population, N=546)

MedDRA Preferred Term	Niraparib (N=367) n (%)	Placebo (N=179) n (%)
Any CTCAE Grade 3/4 TEAE	*272 (74.1)*	*41 (22.9)*
Thrombocytopenia	104 (28.3)	1 (0.6)
Anaemia	91 (24.8)	0
Neutropenia	41 (11.2)	1 (0.6)
Neutrophil count decreased	32 (8.7)	2 (1.1)
Hypertension	30 (8.2)	4 (2.2)
Platelet count decreased	27 (7.4)	0
Fatigue	21 (5.7)	0

In the NOVA study, 65% (237/367) of the patients treated with niraparib experienced ≥Grade 3 treatment-related AEs, most commonly thrombocytopenia (28%; 103/367) and anaemia (25%; 90/367). The overall incidence of treatment-related Grade 3/4 AEs in the placebo arm was low (5%; 8 patients); no treatment-related Grade 3/4 AE was reported in more than 2 patients receiving placebo.

The incidence of all Grade ≥3 AEs were markedly decreased following dose reduction to 200 mg, except for anaemia and hypertension where the incidences were reduced first at doses of 100 mg (Table 39).

Table 41: Grade 3/4 Treatment-Emergent Adverse Events Reported in ≥5% of Patients in the Niraparib Arm Overall by Dose at Onset of the Event (SAF Population, N=367)

	Niraparib Dose		
MedDRA Preferred Term	300 mg (N=367) n (%)	200 mg (N=254) n (%)	100 mg (N=128) n (%)
Thrombocytopenia	103 (28.1)	13 (5.1)	2 (1.6)
Anaemia	55 (15.0)	40 (15.7)	8 (6.3)
Neutropenia	35 (9.5)	15 (5.9)	2 (1.6)
Neutrophil count decreased	31 (8.4)	6 (2.4)	0
Platelet count decreased	26 (7.1)	2 (0.8)	1 (0.8)
Hypertension	17 (4.6)	12 (4.7)	3 (2.3)
Fatigue	19 (5.2)	3 (1.2)	0

Adverse events of special interest

Myelosuppression Events

In the NOVA study, patients eligible for niraparib therapy had the following baseline haematologic parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/µL; platelets ≥ 100,000 cells/µL and haemoglobin ≥ 9 g/dL prior to therapy. Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with niraparib.

Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) including clinical diagnoses and/or laboratory findings generally occurred early during niraparib treatment with the incidence decreasing over time.

Table 42: Overall Summary of Treatment-emergent Myelosuppression Events by Type of Event (NOVA Main Study, SAF Population, N=546)

AESI Category Treatment Arm	Overall n (%)	Grade 3/4 n (%)	SAE n (%)	Dose Interrup-tion n (%)	Dose Reduction n (%)	Discon-tinuation n (%)
Thrombocytopenia Event						
Niraparib (N=367)	225 (61.3)	124 (33.8)	41 (11.2)	138 (37.6)	148 (40.3)	12 (3.3)
Placebo (N=179)	10 (5.6)	1 (0.6)	0	1 (0.6)	1 (0.6)	1 (0.6)
Anemia Event						
Niraparib (N=367)	184 (50.1)	93 (25.3)	14 (3.8)	74 (20.2)	68 (18.5)	5 (1.4)
Placebo (N=179)	12 (6.7)	0	0	0	0	0
Leukopenia Event[a]						
Niraparib (N=367)	129 (35.1)	79 (21.5)	4 (1.1)	60 (16.3)	35 (9.5)	7 (1.9)
Placebo (N=179)	22 (12.3)	4 (2.2)	0	2 (1.1)	2 (1.1)	0
Neutropenia Event						
Niraparib (N=367)	111 (30.2)	72 (19.6)	4 (1.1)	56 (15.3)	32 (8.7)	7 (1.9)
Placebo (N=179)	11 (6.1)	3 (1.7)	0	2 (1.1)	2 (1.1)	0
Pancytopenia Event						
Niraparib (N=367)	5 (1.4)	4 (1.1)	4 (1.1)	2 (0.5)	1 (0.3)	3 (0.8)
Placebo (N=179)	0	0	0	0	0	0

Thrombocytopenia Events

In the NOVA study, reports of AEs relating to thrombocytopenia events (thrombocytopenia and platelet count decreased) were high in the niraparib arm (approx. 60% overall (61%); 34% Grade 3/4) compared to placebo (6%;<1% Grade 3/4).

The median time to onset of thrombocytopenia regardless of grade was 22 days and 23 days for Grade 3/4 events. Thrombocytopenia occurred more commonly in patients whose baseline platelet count was less than 180 × 10^9/L. Approximately 76 % of patients with lower baseline platelets (< 180 × 10^9/L) who received niraparib experienced thrombocytopenia of any grade, and 45 % of the patients experienced Grade 3/4 thrombocytopenia.

Niraparib-treated patients with any prior history of thrombocytopenia also had a higher risk of any Grade thrombocytopenia (70%; 121/172) compared to those without a prior history (53%; 104/195). In the NOVA study, 48 of 367 (13 %) of patients experienced bleeding with concurrent thrombocytopenia; all bleeding events concurrent with thrombocytopenia were Grade 1 or 2 in

severity, except for one patient who experienced Grade 3 petechiae and hematoma concurrent with an SAE of pancytopenia.

The overall incidence of thrombocytopenia events (thrombocytopenia and platelet count decreased) was reported in a slightly lower proportion of patients in the OCT pooled dataset compared to the NOVA study (49% vs 61%). However, the incidence of Grade ≥3 events (28% vs 34%) and SAEs (8% vs 11%) was almost similar.

The median times to onset of any Grade and Grade 3/4 thrombocytopenia events among patients who received niraparib were 22 and 23 days, respectively. The median duration was 23 days, with a shorter duration of Grade 3/4 thrombocytopenia events, resolving within approximately 10 days following dose interruptions of niraparib. The same median times to onset and median durations were observed across the OCT pool.

The rate of new incidences of thrombocytopenia after intensive dose modifications were performed during the first two months of treatment from Cycle 4 was 1.2 %.

Discontinuation due to thrombocytopenia events (thrombocytopenia and platelet count decreased) occurred in approximately 3 % of the patients.

The incidence of any Grade of thrombocytopenia in the NOVA study and the OCT pool was highest during the first treatment cycle and decreased rapidly thereafter, most probably due to the intensive dose modifications (interruptions and/or reductions) performed during the first two cycles of treatment.

Additionally, 20% of the patients treated with niraparib in the NOVA study received 1 to 2 platelet transfusions mainly during the first cycle, without need for further transfusions after dose modification.

Anaemia Events

In the NOVA study, reports of AEs relating to anaemia events (anaemia and haemoglobin decreased) were high in the niraparib arm (50%; 25% Grade 3/4) compared to placebo (7%; none Grade 3/4).

The incidence of on-treatment anaemia of any Grade was more common among patients with lower baseline haemoglobin concentration (<10 g/dL) with 82% (18/22) developing anaemia compared to those patients in the NOVA study with higher baseline levels (≥12 g/dL). Patients with any prior history of anaemia also had a somewhat higher risk of any Grade anaemia on study (53%; 126/236) compared to those without a prior history (44%; 58/131). Among niraparib-treated patients, 28% (102/367) received a red blood cell (RBC) transfusion. In the niraparib arm, 61 patients (17%) experienced concurrent AESI of any Grade anaemia with Grade ≥2 fatigue.

The median time to onset of anaemia of any grade was 42 days, and 85 days for Grade 3/4 events. The median duration of anaemia of any grade was 63 days, and 8 days for Grade 3/4 events. Anaemia of any grade might persist during Zejula treatment. Discontinuation due to anaemia occurred in 1 % of patients.

The overall incidence of anaemia event in the OCT pool was similar to the NOVA study, 45% (173/384) vs 50%; as was the incidence of Grade ≥3 events (21% (81/384) and 25%) and SAEs (3% (10/384) and 4%).

Across the studies in the OCT pool versus the NOVA study, the median time to onset of the first anaemia event of any Grade (29 vs 42 days) and Grade 3/4 (57 vs 85 days) were shorter, as was the median durations of all-Grade (51 and 63 days). However, the median duration of Grade ≥3 events were similar in the two safety populations (7 and 8 days, respectively). Moreover, as anaemia events) can lead to fatigue, a review was conducted to assess anaemia events that

occurred concurrent with Grade ≥2 fatigue events in the NOVA study. Overall, 17% of the patients in the niraparib arm experienced concurrent (±30 days) AESI of any Grade anaemia with Grade ≥2 fatigue; no patients in the placebo arm experienced concurrent anaemia and fatigue events.

Neutropenia Events

In the NOVA study, reports of AEs relating to neutropenia events (neutropenia, neutrophil count decreased, and febrile neutropenia) were high in patients treated with niraparib (30% overall; 20% Grade 3/4) compared to patients who received placebo (6%; 2% Grade 3/4).

The incidence of on-treatment neutropenia was most common among patients with a prior history of Grade 4 neutropenia (56%; 20/36) and was also more common among patients with any prior history of neutropenia (36%; 75/206) compared to those without a prior history (22%; 36/161).

Overall, 1% (5/367) of niraparib-treated patients and none of the placebo patients experienced a Grade 4 neutropenia event concurrent (±30 days) with an infection. Infections occurring concurrently with Grade 4 neutropenia included urinary tract infection (0.5%; 2 patients), and bronchitis, clostridial infection, and eye infection (0.3%/1 patient each).

The median time to onset of neutropenia of any grade was 27 days, and 29 days for Grade 3/4 events. The median duration of neutropenia of any grade was 26 days, and 13 days for Grade 3/4 events.

In the clinical programme, neutropenia was managed with laboratory monitoring and dose modifications (see section 4.2). In addition, Granulocyte-Colony Stimulating Factor (G-CSF) was administered to approximately 6 % of patients treated with niraparib as concomitant therapy for neutropenia. Discontinuation due to neutropenia events occurred in 2 % of patients.The overall incidence of neutropenia events was reported in a slightly lower proportion of patients in the OCT pooled dataset compared to the NOVA study, 22% (83/384) vs 30%, as was the incidence of Grade ≥3 events (14% (54/384) vs 20%).

The median (range) of the total duration of exposure was 163 days in the NOVA study and 57 days across the OCT pool. The median times to onset of the first occurrence of any Grade and Grade ≥3 neutropenia event across the studies in the OCT pool (28 and 29 days, respectively) was similar to the NOVA study (27 and 29 days, respectively). The median durations of all Grade and Grade ≥3 neutropenia events were shorter in the OCT pool (15 and 8 days, respectively) compared to the niraparib arm of the NOVA study (26 and 13 days, respectively).

The overall incidence of neutropenia events in the NOVA study and OCT pool was highest during the first treatment cycle and was lower in all other cycles thereafter probably due to intensive dose modifications (interruptions and/or reductions) performed during the first two cycles of treatment.

Leukopenia Events

Leukopenia events include reports of neutropenia, neutrophil count decrease, white blood cell count decreased, leukopenia, lymphocyte count decreased, lymphopenia, febrile neutropenia, and monocyte count decreased. In accordance with the occurrence of neutropenia events in the NOVA study, reports of AEs related to leukopenia events were high in patients treated with niraparib (35%; 22% Grade 3/4) compared to patients who received placebo (12%; 2% Grade 3/4).

The incidences of both any Grade and Grade 3/4 of leukopenia events seems to mainly be affected by the occurrence of neutropenia events. The proportions of patients experiencing SAEs related to leukopenia events and withdraw study drug due to leukopenia events is identical to the incidences observed for neutropenia events in niraparib-treated patients.

Myelodysplastic Syndrome (MDS) and Acute Myelogenous Leukaemia (AML)

The overall incidence of MDS/AML across the clinical development program of niraparib was 0.9% (7/751). In the NOVA study, the incidence of MDS/AML in patients who received niraparib (1.4 %) was similar to that in patients who received placebo (1.1 %). The duration of niraparib treatment in patients prior to developing MDS/AML varied from 1 month to > 2 years. The cases were typical of secondary, cancer therapy-related MDS/AML. Of note, the majority of the patients that developed MSD/AML was heavily pre-treated (7/9) and had a prior history of myelosuppression (8/9). All patients had received multiple platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia.

Hypertension

In the NOVA study, hypertension was reported as a TEAE in 19.3% (71/367) of the patients who received niraparib and in 5% (8/179) of the patients who received placebo. Grade 3 hypertension was reported in 8.2% (30/367) in the niraparib arm and Grade 3 hypertensive crisis was reported in 2 (<1%) compared to 4 patients (2%) in the placebo arm with Grade 3 hypertension. Among the patients in the niraparib arm who developed Grade 3 hypertension, 47% (15/32) reported a medical history of hypertension. There were no reports of Grade 4 hypertension.

No patients discontinued treatment due to hypertension in the NOVA study, although hypertension led to dose reduction for 5 niraparib-treated patients (1.4%) and none in the placebo arm.

In the clinical programme, hypertension was readily managed with anti-hypertensive medicinal products. Discontinuation due to hypertension occurred in < 1 % of patients.

Fatigue

The data from the NOVA study suggest that the incidence is more common for niraparib-treated patients (59%; 218/367) compared to patients who received placebo (41%; 74/179). The events were reported to be severe in approximately 8% (30/367; Grade 3) of the patients treated with niraparib.

In addition, when accounting for duration of exposure in terms of PEY (patient-exposure years), an even higher incidence was reported across the OCT pool compared to the NOVA study (2.77 vs 0.93 PEY). In the NOVA study, the fatigue events were reported to be severe in approximately 8% (Grade 3) of the patients treated with niraparib.

Gastrointestinal Disorders

In the NOVA study, AEs of nausea, vomiting, and constipation were experienced at substantially higher incidences in the niraparib arm (74%, 34%, and 40%; 3%, 2%, and 0.5% Grade 3/4, respectively) compared to the placebo arm (35%, 16%, 20%; 1%, 0.6%, and 0.6% Grade 3/4, respectively). Both nausea and vomiting tended to occur early during niraparib treatment with the highest incidences observed within the first cycle of treatment. The incidences markedly declined after the first month of treatment, most probably due to the intensive dose modifications performed during the first two cycles of treatment. The prevalence of nausea or decreased slowly and therefore remained relatively sustained throughout the study (>42% and >8%, respectively).

Accordingly, the most common gastrointestinal AEs within the OCT pool were nausea (60%; Grade ≥3: 8%) and vomiting (40%; Grade ≥3: 8%). However, when accounting for duration of exposure in terms of PEY, an even higher incidence was reported across the OCT studies. Overall, in the NOVA study, the incidence rates of nausea and vomiting by PEY were 2.94 and 0.61, respectively, and 5.58 and 2.06, respectively, in the OCT pool. Both nausea and vomiting tended to occur early during niraparib treatment with the highest incidences observed within the first cycle of treatment,

declining markedly thereafter, most probably because of the intensive dose modifications performed during the first two cycles of treatment.

Other AESIs

Other AESIs includes pneumonitis, headache, decreased appetite, insomnia, dyspnoea, dizziness, cough, palpitations and dysgeusia.

Adverse drug reactions (ADRs)

The relative risk for common AEs and Grade 3/4 AEs in the NOVA study was assessed for patients treated with niraparib versus patients treated with placebo to determine the suspected adverse drug reactions (ADRs) for inclusion in the Summary of Product Characteristics (SmPC). Given the high frequency of treatment-related AEs in both treatment arms per the investigator assessment of relationship, relative risk for TEAEs in the niraparib treatment arm versus the placebo arm was selected as the primary method to determine ADRs.

In the pivotal NOVA study, adverse reactions (ADRs) occurring ≥ 10 % of patients receiving Zejula monotherapy were nausea, thrombocytopenia, fatigue/asthenia, anaemia, constipation, vomiting, abdominal pain, neutropenia, insomnia, headache, decreased appetite, nasopharyngitis, diarrhoea, dyspnea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dysgeusia. The most common serious adverse reactions > 1 % (treatment emergent frequencies) were thrombocytopenia and anaemia.

Table 43: Adverse Drug Reactions; frequencies based on all-causality Adverse Events NOVA study*

System Organ Class	ADR PT	Frequency of all CTCAE grades (%)	Frequency of CTCAE grade 3 or 4 (%)
Infections and infestations	Urinary tract infection	10.4	0.8
	Bronchitis	5.4	0.3
	Conjunctivitis	1.9	0.0
Blood and lymphatic system disorders	Thrombocytopenia	46.0	28.3
	Anaemia	48.5	24.8
	Neutropenia	18.0	11.2
	Leukopenia	7.4	2.7
	Pancytopenia	0.5	0.5
Metabolism and nutrition disorders	Decreased appetite	25.3	0.3
	Hypokalemia	5.7	1.4
Psychiatric disorders	Insomnia	24.3	0.3
	Anxiety	8.2	0.3
	Depression	4.9	0.3
Nervous system disorders	Dizziness	16.6	0
	Headache	25.9	0.3
	Dysgeusia	10.1	0
Cardiac disorders	Palpitations	10.4	0
	Tachycardia	6.5	0
Vascular disorders	Hypertension	19.3	8.2
Respiratory, thoracic and	Dyspnea	19.3	1.1

System Organ Class	ADR PT	Frequency of all CTCAE grades (%)	Frequency of CTCAE grade 3 or 4 (%)
mediastinal disorders	Nasopharyngitis	11.2	0
	Cough	15.0	0
	Epistaxis	4.6	0
Gastrointestinal disorders	Vomiting	34.3	1.9
	Diarrhoea	19.1	0.3
	Nausea	73.6	3.0
	Constipation	39.8	0.5
	Abdominal pain	22.6	1.1
	Abdominal distention	7.6	0
	Mucosal inflammation (includes mucositis)	7.1	0.3
	Stomatitis	3.8	0.3
	Dyspepsia	11.4	0
	dry mouth	9.3	0.3
Skin and subcutaneous tissue disorders	Rash	6.5	0.3
	Photosensitivity	8.7	0.3
Musculoskeletal and connective tissue disorders	Myalgia	8.2	0.3
	Back pain	13.4	0.5
	Arthralgia	11.7	0.3
General disorders and administration site conditions	Fatigue	45.8	5.7
	Asthenia	15.8	2.5
	Oedema peripheral	6.5	0
Investigations	AST increased	5.4	0.8
	ALT increased	4.9	0.8
	Gamma-glutamyl transferase increased	6.5	3.5
	blood creatinine increased	5.4	0
	blood alkaline phosphatase increased	4.1	0.5
	weight decreased	3.0	0

* Frequencies are based on percent of patients using all-causality adverse events.

Serious adverse event/deaths/other significant events

Serious adverse events reported in the NOVA study are shown in **Table 52**.

Table 44: Serious Adverse Events Reported in ≥1% of Patients in Either Treatment Arm: All Patients Cohort (NOVA Main Study, SAF Population, N=546)

MedDRA Preferred Term	Niraparib (N=367) n (%)	Placebo (N=179) n (%)
Any SAE	*110 (30.0)*	*27 (15.1)*
Thrombocytopenia	40 (10.9)	0
Anaemia	14 (3.8)	0
Small intestinal obstruction	5 (1.4)	4 (2.2)
Constipation	4 (1.1)	1 (0.6)
Urinary tract infection	3 (0.8)	2 (1.1)
Pleural effusion	3 (0.8)	2 (1.1)
Ascites	2 (0.5)	2 (1.1)
Nausea	1 (0.3)	3 (1.7)
Ileus	0	2 (1.1)
Metastases to central nervous system	0	2 (1.1)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SAE= serious adverse event; SAF=safety. Source: CSR PR-30-5011-C Table 14.3.1.1A and Table 14.3.1.6

In the OCT pool, treatment-emergent SAEs were reported in 39% (150/384) of the patients across the studies. The most commonly reported SAEs were thrombocytopenia (7%; 26/384), small intestinal obstruction (6%; 24/384), and vomiting (6%; 23/384).

In the NOVA study, treatment-related SAEs were reported in 17% (62/367) of the patients who received niraparib and 1% (2/179) who received placebo. All of the thrombocytopenia and anaemia AEs reported as SAEs were assessed as related to study drug. All other related SAEs were reported in <1% of niraparib-treated patients. In the OCT pool, treatment-related SAEs were reported in 18% (68/384) of the patients, most commonly thrombocytopenia (7%; 26/384), vomiting (4%; 14/384), anaemia (3%; 10/384), nausea (2%; 7/384), and neutropenia (2%; 6/384).

Deaths

No on-treatment deaths were reported in the NOVA study. Nevertheless, 95 deaths were reported during the follow-up period, including 16% (60/372) randomized to niraparib and 19% (35/181) of the patients randomized to placebo.

Three deaths were reported during the post-treatment follow-up period due to MDS/AML, including 1 patient who received niraparib and 2 who received placebo.

Across all 384 patients in the OCT pool, 5 (1%) experienced AEs that were fatal; 4 of the 5 events occurred during QUADRA and 1 occurred in the FE sub-study. Two of the deaths, including gastrointestinal haemorrhage and acute respiratory failure, both in QUADRA, were assessed as treatment related. The deaths in the other 3 patients were assessed as unrelated to study treatment and included sepsis and hyperbilirubinemia in QUADRA and disease progression in the FE sub-study.

Laboratory findings

Haematology

Details on changes from baseline in platelet count, haemoglobin concentrations, neutrophil counts, and leukocyte counts observed in the NOVA study and OCT pool can be found in the section '*Adverse events of special interest*'.

No meaningful changes or shifts from baseline were observed for other haematology parameters during the NOVA study.

Creatinine increase

In the NOVA study, reports of raised creatinine levels from baseline was higher in the niraparib arm (37%; 136/367) compared to the placebo arm (15%; 26/179). However, the majority of the reports were Grade 1 or 2 in severity, and only two patients in each treatment arm reported a shift to Grade ≥3 in creatinine levels. Of note, a dose-dependent reduction in the frequency of raised creatinine levels was observed in the NOVA study: 4.9% (18/367) at 300 mg, 2.4% (6/254) at 200 mg, and 0.8% (1/128) at 100 mg dose of niraparib.

Gamma-Glutamyltransferase GGT

Twice as many patients in the niraparib arm compared to the placebo arm (4% vs 2%), reported Grade 3/4 increases in GGT. In addition, 6 possible cases of Hy's law were reported in patients with ovarian cancer during the clinical development program of niraparib (in the NOVA study and the OCT pool). All cases was attributed to concurrent elevations in alkaline phosphatase to >2-6×ULN due to hepatic cholestasis. None of the cases was considered related to study treatment.

QTc prolongation

The low number of cases of QTc prolongation in the NOVA study precludes any firm conclusion on the association with niraparib treatment. However based on PK data, niraparib is not expected to have a significant effect on QTc.

Safety in special populations

Fertility, pregnancy and lactation

There are no data regarding the use of niraparib in pregnant and lactating women, as both pregnancy and breast feeding were exclusion criteria in the clinical studies. Moreover, animal studies have not been conducted. Still, based on the mode of action of niraparib, embryo-foetal toxicity is possible. Niraparib should not be used during pregnancy or in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose. Women of childbearing potential should not become pregnant while on niraparib. A pregnancy test should be performed on all women of childbearing potential prior to treatment. It is unknown whether niraparib or its metabolites are excreted in human milk (see sections 4.3, 4.4, 4.6 of the SmPC).

Age

In the NOVA study, 65% (n=355) of the patients were <65 years in age, whereas 29.3% (n=160) were 65-74 years old, and 5.7% (n=31) were 74-84 years old. No patients over the age of 84 were included in the main study.

Table 45: TEAEs by Patient Age (NOVA study)

MedDRA Terms	Age <65 N= 355		Age 65-74 N=160		Age 75-84 N=31	
	Niraparib N=238 (%)	Placebo N=117 (%)	Niraparib N=106 (%)	Placebo N=54 (%)	Niraparib N=23 (%)	Placebo N=8 (%)
Total AEs	238 (100.0)	111 (94.9)	106 (100.0)	52 (96.3)	23 (100.0)	8 (100.0)
Serious AEs – Total	68 (28.6)	15 (12.8)	34 (32.1)	10 (18.5)	8 (34.8)	2 (25.0)
- Fatal	3 (0.85)		1 (0.63)		0	
- Hospitalization/prolong existing	74 (20.8)		41 (25.6)		11 (35.5)	
- Life-threatening	6 (1.7)		0		0	
- Disability/incapacity	0		0		0	
- Other (medically significant)	19 (5.4)		8 (5.0)		3 (9.7)	
AE leading to drop-out	32 (13.4)	2 (1.7)	18 (17.0)	2 (3.7)	4 (17.4)	0
Psychiatric disorders	83 (34.9)	21 (17.9)	39 (36.8)	7 (13.0)	9 (39.1)	2 (25.0)
Nervous system disorders	120 (50.4)	40 (34.2)	63 (59.4)	11 (20.4)	15 (65.2)	3 (37.5)
Accidents and injuries	20 (8.4)	6 (5.1)	8 (7.5)	2 (3.7)	3 (13.0)	0
Cardiac disorders	52 (21.8)	5 (4.3)	16 (15.1)	1 (1.9)	5 (21.7)	1 (12.5)
Vascular disorders	72 (30.3)	14 (12.0)	35 (33.0)	7 (13.0)	9 (39.1)	2 (25.0)
Cerebrovascular disorders	0	0	0	0	0	0
Infections and infestations	115 (48.3)	38 (32.5)	44 (41.5)	25 (46.3)	12 (52.2)	3 (37.5)
Anticholinergic syndrome	83 (34.9)	18 (15.4)	43 (40.6)	12 (22.2)	8 (34.8)	2 (25.0)
Quality of life decreased	0	0	0	0	1 (4.3)	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	39 (16.4)	10 (8.5)	29 (27.4)	5 (9.3)	5 (21.7)	2 (25.0)

In summary, the data from the NOVA study demonstrates trends toward more AEs in patients above 65 years. While there does not appear to be much differences in the frequency of AEs between patients in the age groups 65-74 and 75-84 years, the observed differences may be owing to a very low number of patients in the 75-84 age cohort.

The AEs reported to occur more frequently in patients ≥65 vs <65 years were dizziness (21.7% versus 13.9%, respectively), paresthesias (7.8% versus 2.9%), peripheral sensory neuropathy (5.4% versus 2.1%) and sciatica (4.7% versus 1.3%). In addition, there were minimal (≤5%) to (≤10%) modest increases in the older versus youngest population for AEs of the following SOCs: psychiatric, accident and injuries, cardiac, and anti-cholinergic syndrome.

The overall frequency of AEs reported was similar between the age groups of patients between 64-74 and 75-84 years, but for nervous system AEs the frequency was higher for the older patient group (65.2% vs 59.4%) and the opposite was observed for the sum of hypotension, falls, black outs, syncope, dizziness, ataxia and fractures (27.4% vs. 21.7%). Both of these categories of AEs were reported with a lower frequency in the younger patient population < 65 years, with an incidence of 50.4% and 16.4% respectively.

Race

The majority of the patients included in the NOVA study and OCT pool were Caucasian (86%) and exposure in non-Caucasian patients is limited.

Weight

Approximately 25 % of patients in the NOVA study weighed less than 58 kg, and approximately 25 % of patients weighed more than 77 kg. The incidence of Grade 3 or 4 ADRs was greater among low body weight patients (78 %) than high body weight patients (53 %). Only 13 % of low body weight patients (< 58 kg) remained at a dose of 300 mg beyond Cycle 3 compared to 37% for patients ≥77 kg.

Hepatic and renal impairment

No studies in patients with severe hepatic or renal impairment using niraparib have been performed.

Immunological events

No specific immunological events associated with niraparib has been reported by the Applicant.

Safety related to drug-drug interactions and other interactions

No specific in vivo drug-drug interaction studies have been performed, which raises the concern that niraparib potentially could cause serious drug-drug interactions in a clinical setting. Please refer to the subsection 3.4.1 *Pharmacokinetics* of this AR for more information.

Discontinuation due to adverse events

AEs resulting in withdrawal of study drug in the NOVA study were reported in 15% (54/367) who received niraparib and in 2% (4/179) of the patients who received placebo (**Table 54**).

Table 46: Treatment-Emergent Adverse Events Resulting in Withdrawal of Study Drug in ≥1% of All Patients (NOVA Main Study, SAF Population, N=546)

MedDRA Preferred Term	Niraparib (N=367) n (%)	Placebo (N=179) n (%)
Any TEAE Resulting in Study Drug Withdrawal	*54 (14.7)*	*4 (2.2)*
Fatigue	10 (2.7)	0
Thrombocytopenia	7 (1.9)	1 (0.6)
Nausea	6 (1.6)	0
Anaemia	5 (1.4)	0
Platelet count decreased	5 (1.4)	0
Neutrophil count decreased	4 (1.1)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SAF=safety; TEAE=treatment-emergent adverse event.

In the OCT pool, 18% (68/384) of the patients withdrew from niraparib treatment due to AEs. The most common reasons for withdrawal due to AEs in the OCT pool were vomiting (3.1%; 12/384), small intestinal obstruction (2.6%; 10/384), thrombocytopenia (2.6%; 10/384), and nausea (2.3%; 9/384); all other events leading to withdrawal were reported in ≤1% of the patients.

Dose interruptions and dose reductions

In the NOVA study, at least 1 study drug interruption was instituted for 244 patients (67%) who received niraparib and for 26 patients (15%) who received placebo. Per protocol, dose interruptions in the NOVA study were required for any patient with platelet count $<100\times10^9$/L, neutrophil count $<1.0\times10^9$/L, haemoglobin <8 g/dL, or any Grade 3/4 treatment-related non-hematologic toxicity.

Consistent with these dose modification requirements, the most common AEs leading to interruption of niraparib dosing were thrombocytopenia (30.8%; 113/367), anaemia (19.6%; 72/367), and neutropenia (10.1%; 37/367). These events were uncommonly reported as leading to treatment interruption in the placebo arm, with incidences of respectively 0.6%, 0 and 1.1%. Platelet count decrease (9.0%; 33/367), nausea (7.4%; 27/367), vomiting (6.0%; 22/367), neutrophil count decrease (5.2%; 19/367) and fatigue (4.6%; 17/367) all led to dose interruption in ≥4% of the patients in the niraparib arm. The incidences of these AEs in the placebo arm were considerably lower, specifically 0, 2.2%, 2.2%, 0 and 1.1%, respectively. Notably, hypertension led to treatment interruption for 5 (1.4%) patients in the niraparib arm and 1 (0.6%) patient in the placebo arm.

In the OCT pool, study drug interruption was instituted for 63% (242/384) of the patients across the studies. Consistent with the results of the NOVA study, the most commonly reported events leading to dose interruption were haematology laboratory abnormalities and gastrointestinal disturbances, including thrombocytopenia (26%; 98/384), anaemia (13%; 49/384), platelet count decreased (11%; 41/384), nausea (9%; 35/384), vomiting (8%; 32/384), and neutropenia (7%; 26/384).

Figure 24 displays the percent of patients in the overall niraparib arm of the NOVA study with dose interruptions and dose reductions reported due to AEs over time on treatment. As shown, interruptions were instituted early in treatment (Month 1) with reductions employed primarily in Month 2; decreases in the incidence of these dose modifications were observed thereafter.

In the NOVA study, at least 1 dose reduction was instituted for AEs in 253 patients (69%) who received niraparib and in 9 patients (5%) who received placebo. 48 % of patients had a dose interruption in Cycle 1. Approximately 47 % of patients restarted at a reduced dose in Cycle 2. The most commonly used dose in niraparib treated patients in the NOVA study was 200 mg.

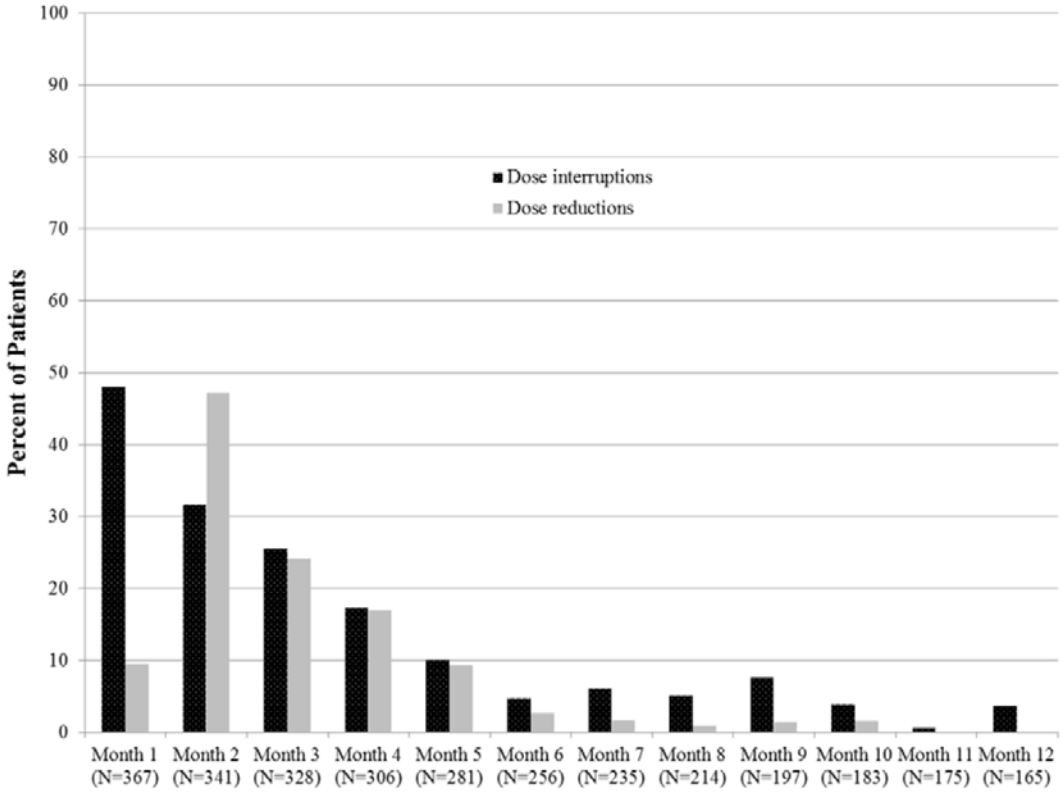


Figure 24 Niraparib Dose Interruptions and Reductions Over Time in the NOVA study (SAF Population, N=367)

The overall incidence of dose reduction reported in the OCT pool (28%; 107/384) was much lower than the incidence reported in the NOVA study. This is related to changes to the required dose modification criteria implemented in the QUADRA study which no longer mandated dose reductions for patients with platelet counts <100,000/µL; dose reductions were required for patients with platelet counts <75,000/µL and at the second occurrence of counts <100,000/µL.

Table 47: Treatment-Emergent Adverse Events Resulting in Study Drug Dose Reduction in ≥1% of Patients in Either Treatment Arm: All Patients Cohort (NOVA Main Study, SAF Population, N=546)

MedDRA Preferred Term	Niraparib (N=367) n (%)	Placebo (N=179) n (%)
Any TEAE Resulting in Study Drug Dose Reduction	***253 (68.9)***	***9 (5.0)***
Thrombocytopenia	112 (30.5)	1 (0.6)
Anaemia	65 (17.7)	0
Platelet count decreased	39 (10.6)	0
Nausea	19 (5.2)	0
Neutropenia	17 (4.6)	0
Neutrophil count decreased	15 (4.1)	2 (1.1)
Fatigue	14 (3.8)	2 (1.1)
Vomiting	8 (2.2)	0
Dyspnoea	6 (1.6)	1 (0.6)
Asthenia	6 (1.6)	0
Hypertension	5 (1.4)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SAF=safety; TEAE=treatment-emergent adverse event.

Dose reductions in the NOVA study tended to occur early with most patients reaching their individual adjusted dose level by the start of Month 4 (i.e., Cycle 4) of treatment. Overall, dose interruptions for any reason were instituted for 80% of patients on niraparib; 73% underwent a dose reduction. The rates were lower for placebo with 19% having the dose interrupted and 6% having a dose reduction.

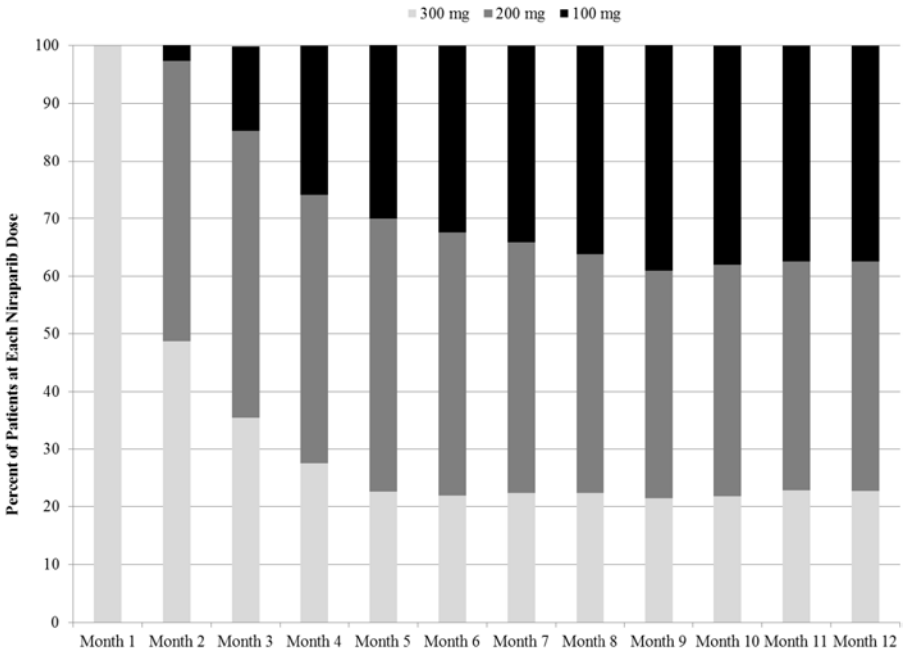


Figure 25 Niraparib Dose Level by Month on Treatment

Discontinuations due to adverse events

Fatigue (2.7%), nausea (1.6%) and myelosuppression in terms of thrombocytopenia (1.9%), anaemia (1.4%), platelet- (1.4%) and neutrophil count decrease (1.1%) were the most common AEs leading to treatment discontinuation from the niraparib arm of the NOVA study. None of the patients in the placebo arm discontinued treatment due to these AEs, with the exception of one patient who discontinued due to thrombocytopenia.

2.6.1. Discussion on clinical safety

The clinical safety programme includes an evaluation of safety across a total of 854 patients who received at least 1 dose of niraparib administered as a monotherapy dose of 3x100 mg (capsules). This includes 367 patients in the placebo-controlled NOVA study, which were exposed to at least one dose of 300 mg niraparib, and 245 subjects (66.8%) and 163 subjects (44.4%) who were treated for ≥6 to <12 months and ≥12 months, respectively, with 100-300 mg/day niraparib at the data cut-off date. However, the mean relative dose intensity of approximately 65% (195 mg/day) of the scheduled dose in the niraparib arm of the NOVA study is considered rather low compared to the placebo group (97%; 290 mg/day). The intensive dose modifications performed (>70%) in the niraparib arm of the NOVA study were consistent with a picture of severe AEs experienced by these patients, which questions the selected start dose of 300 mg/day with respect to patient's tolerability.

A lower starting dose (e.g. 200 mg/day) would require further clinical investigation in the context of a new phase III study. It is not clear whether the observed efficacy, particularly in patients without BRCA mutation, would have been experienced with a lower starting dose. It is acknowledged that tolerability to niraparib treatment was acceptable once a dose was modified to a

patient's individual profile, primarily within the first three cycles of treatment, and most patients remained on treatment long enough to experience continuing benefit from niraparib.

In spite of the convincing efficacy results, less than 30% of the patients continued on the starting dose of 300 mg during the NOVA study. In addition, most dose reductions occurred within the first 60 days of the study, reflecting excess exposure of niraparib in most of the patients that might be due to the chosen starting dose. Some of the AEs (e.g. anaemia, fatigue, nausea and vomiting) also persisted after dose reductions were performed, which further reinforces that dose reduction may not be the optimal strategy to manage toxicity. Importantly, niraparib will be used as a maintenance treatment of patients with ovarian cancer who are in complete or partial response to prior treatment when niraparib is initiated, hence tolerability of the medicine is quite crucial.

The applicant informs that they are currently testing an approach where niraparib is initiated at a lower starting dose of 200 mg daily in combination with pembrolizumab in the ongoing TOPACIO study in patients with ovarian or triple negative breast cancer. The initial dose may then be increased in a subset of patients without evidence of thrombocytopenia as this AE is the main acute concern with niraparib use in the NOVA study. However, other haematological laboratory abnormalities and treatment-related AEs observed in the first cycles of treatment with niraparib, such as fatigue, anemia and neutropenia, also constitute safety concerns related to the recommended starting dose of niraparib in the sought indication.

The most common AEs in the NOVA study were related to myelosuppression and gastrointestinal events. There were marked differences observed between the niraparib and placebo arm in the incidence of thrombocytopenia events (61%; Grade 3/4: 34%), anaemia events (50%; Grade 3/4: 25%), and nausea (74%; Grade 3/4: 3%). Other AEs commonly reported in the niraparib arm with higher incidences than the placebo arm were: constipation (40%), vomiting (34%; Grade 3/4: 2%), insomnia (24%), headache (26%), hypertension (19%; Grade 3: 8%), neutropenia events (30%; Grade 3/4: 20%), fatigue events (59%; Grade 3: 8%), dyspnoea (19%), decreased appetite (25%), and cough (15%). The most frequently reported AEs overall in the OCT pool were consistent with the commonly reported AEs in the niraparib-treated patients of the NOVA study, including gastrointestinal events (nausea and vomiting), fatigue, decreased appetite, and events related to hematologic laboratory abnormalities. However, hypertension did not constitute one of the most commonly reported AEs in the OCT pool, as this AE was reported in only 3 patients (0.8%) across the studies. The pattern of AEs is similar to that observed for olaparib, a PARP inhibitor approved in EU for platinum-sensitive recurrent BRCA-mutated ovarian cancer, except that thrombocytopenia and constipation are reported more commonly and that hypertension constitutes a new safety signal for niraparib.

In the NOVA study, a significantly higher rate of treatment-related SAEs was reported in niraparib-treated patients compared to patients who received placebo, 17% vs 1%. The treatment-related SAEs with the highest incidence, which also were increased for niraparib compared to placebo, were thrombocytopenia (10.9% vs 0) and anaemia (3.8% vs 0). Too few events for the other SAEs were reported in order to draw any conclusion on whether there is a real difference between the two treatment arms. The types and incidence of commonly reported SAEs in the OCT pool, primarily haematology laboratory abnormalities and gastrointestinal disturbances, were similar to the SAEs reported in the NOVA study. The proportion of patients reporting treatment-related SAEs was similar between patients treated with niraparib in the NOVA study and OCT pool (17% and 18%, respectively).

The safety profile of niraparib in terms of thrombocytopenia events were poor and seems to be related to the recommended daily dose of 300 mg. Patients treated with niraparib might have an increased risk of haemorrhage, especially in the setting of concurrent thrombocytopenia. In the clinical programme, thrombocytopenia was managed with laboratory monitoring, dose modification and platelet transfusion where appropriate (see SmPC, section 4.2).

Due to the risk of thrombocytopenia, anticoagulants and medicinal products known to reduce the thrombocyte count should be used with caution (see sections 4.4 and 4.8 of the SmPC).

In accordance with the incidences of thrombocytopenia events, reports of AEs relating to anaemia events (anaemia and haemoglobin decreased) were high among niraparib-treated patients in the NOVA study (50%; Grade 3/4: 25%). In the clinical programme, anaemia was also managed with laboratory monitoring, dose modification (see section 4.2), and where appropriate with red blood cell transfusions.

Although markedly lower than for thrombocytopenia and anaemia events, the incidences of neutropenia events (neutropenia, neutrophil count decreased, and febrile neutropenia) in the NOVA study were rather high among niraparib-treated patients (30%; Grade 3/4: 20%). In the clinical programme, neutropenia was managed with laboratory monitoring and dose modifications (see section 4.2). In addition, Granulocyte-Colony Stimulating Factor (G-CSF) was administered to approximately 6 % of patients treated with niraparib as concomitant therapy for neutropenia.

Pancytopenia has been observed in < 1 % of patients receiving niraparib. If a patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, Zejula should be discontinued.

Testing complete blood counts (CBC) weekly for the first month of treatment and the dose should be modified as needed. After the first month, it is recommended to monitor CBC monthly for the next 10 months of treatment and periodically after this time is recommended to monitor for clinically significant changes in any haematologic parameter during treatment (see section 4.2).

The incidence of MDS/AML in the niraparib arm of the NOVA study was slightly higher than the placebo arm (1.4% vs 1.1%). MDS diagnosis and progression may take years to develop after treatment initiation. Thus, due to the relatively short duration of exposure to niraparib and the short follow-up within the NOVA study, it cannot be excluded that development of MDS/AML is related to niraparib. If MDS and/or AML are confirmed while on treatment with niraparib, treatment should be discontinued and the patient treated appropriately.

The increased risk of MDS/AML with niraparib maintenance treatment is not well defined and the level of this risk should be better characterized, particularly in view of the duration of the exposure. The potential risk of MDS/AML will be further monitored as an Adverse Event of Special Interest in all clinical trials and in all post-marketing activities. The applicant will perform a PASS to further investigate the extent to which niraparib may contribute to the risk of MDS/AML. The applicant will submit a synopsis outlining the details of the planned analyses within 3 months of marketing approval (see RMP).

Hypertension, including hypertensive crisis, has been reported with the use of Zejula. Pre-existing hypertension should be adequately controlled before starting Zejula treatment. Blood pressure should be monitored monthly for the first year and periodically thereafter during treatment with niraparib.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the Zejula dose (see sections 4.2 and 4.4 of the SmPC), if necessary. In the clinical programme, blood pressure measurements were obtained on Day 1 of each 28-day cycle while the patient remained on Zejula. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without Zejula dose adjustment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy (see sections 4.2 and 4.4 of the SmPC).

Although occurrence of fatigue events (include fatigue, asthenia, malaise and lethargy) are symptoms associated with ovarian cancer, the data from the NOVA study suggest that the incidence is more common for niraparib-treated patients compared to patients who received

placebo (59% vs 41%). Twice as many patients in the niraparib arm compared to the placebo arm (4% vs 2%), reported Grade 3/4 increases in GGT. In addition, 6 possible cases of Hy's law were reported in patients with ovarian cancer during the clinical development program of niraparib (in the NOVA study and the OCT pool). No clear causal association was shown in the worsening of hepatic injury. In consequence, there is insufficient evidence of a risk of severe hepatic toxicity with niraparib use to warrant specific SmPC guidance.

The majority of the patients included in the NOVA study and OCT pool were Caucasian (86%) and exposure in non-Caucasian patient is thus limited. Accordingly, an assessment of safety by race is difficult. However, in the population pharmacokinetic and pharmacodynamic modelling report, no significant effect on the pharmacokinetics of niraparib related to race and ethnicity was observed. Moreover, although based on limited number of non-Caucasians, there were no clinically significant differences in the incidences of Grade 3/4 AEs based on race and ethnicity. From the information provided, it is therefore not anticipated that the safety profile will be significantly different in patients of different racial and/or ethnic origin. The lack of robust data on niraparib in non-Caucasian patients is reflected in the proposed SmPC.

In general, there were no clinically significant differences observed in the frequency of AEs between different age groups. However, data from the NOVA study demonstrates trends toward more AEs in patients ≥ 65 years old. Since the oldest age group of patients between 75-84 years is a small patient cohort (n=31), no conclusions can be drawn regarding the differences in the frequencies of AEs observed between the different age groups and a general warning in section 4.4 of the SmPC cannot be supported.

Only 13 % of low body weight patients remained at a dose of 300 mg beyond Cycle 3. A starting dose of 200 mg for patients weighing less than 58 kg may be considered (see section 4.2 of the SmPC).

There are no clinical data on fertility with niraparib .Breast feeding is contraindicated during administration of niraparib and for 1 month after receiving the last dose (see sections 4.3 and 4.6 of the SmPC).

The incidences of dose interruptions (63% vs 67%) and discontinuations (18% vs 15%) due to AEs in the OCT pool was similar to the incidence observed among niraparib-treated patients in the NOVA study; however, the incidence of dose reductions was markedly lower in the OCT pool (28% vs 69%). The applicant suggested that the lower dose reduction rate in the OCT pool might be related to changes implemented in the QUADRA study protocol that did not require mandatory dose reductions for platelet counts <100,000/µL, which seems plausible.

Although a trend towards higher incidences of haematological AEs in the gBRCAmut cohort compared to the non-gBRCAmut cohort was seen, analysis of various baseline characteristics did not reveal any clear predictors for patient subgroups that clearly required dose reductions or initiation of treatment at a lower starting dose.

There is no specific treatment in the event of Zejula overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically (see SmPC section 4.9).

Zejula has moderate influence on the ability to drive or use machines. Patients who take Zejula may experience asthenia, fatigue and dizziness. Patients who experience these symptoms should observe caution when driving or using machines (see SmPC section 4.7).

Zejula hard capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

Zejula contains tartrazine (E 102), which may cause allergic reactions.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Thrombocytopenia, anaemia, neutropenia, fatigue and nausea/vomiting are the major factors limiting the patient's tolerability to niraparib and the main reasons for one or more dose reductions. Although most of the AEs with niraparib can be handled by dose interruptions/reductions, some AEs persisted after intensive dose modifications were performed (e.g. anaemia, fatigue, nausea and vomiting). Thus, the optimal dosing of niraparib is still questioned. However, the daily dose of 300 mg niraparib should be the recommended starting dose until new relevant data are available. Accordingly, the applicant is encouraged to look into alternative dosing strategies in upcoming clinical trials with niraparib and to study PK parameters to obtain information about the plasma concentration-response relationship at different dose levels of niraparib.

The Applicant is recommended to submit updated safety data from the NOVA study when available.

2.7. Risk Management Plan

Safety concerns

Table 48: Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Haematological toxicity (thrombocytopenia, anaemia, neutropenia) Hypertension
Important potential risks	Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) Second primary malignancies other than MDS and AML Embryo-foetal toxicity Pneumonitis
Missing information	Exposure in patients with severe renal impairment and ESRD Exposure in patients with severe hepatic impairment

Pharmacovigilance plan

Table 49: On-going and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned)**
Meta-analysis of completed, ongoing and planned niraparib clinical	1. A comparison of the risks of MDS/AML among patients treated with niraparib and	To provide additional safety information about the important	A full protocol will be submitted	TBD

studies for MDS/AML and other second primary malignancies Category 3	suitable comparator. 2. A comparison of the risks of other second primary malignancy among patients treated with niraparib and suitable comparator.	potential risks of MDS/AML and second primary malignancies other than MDS/AML in patients treated with niraparib in clinical studies.	within 3 months of marketing approval.	
Risks of MDS/AML and Other Second Primary Malignancies in Adult Patients with Recurrent Epithelial Ovarian Cancer Receiving Maintenance Treatment with Zejula (Niraparib) Category 3	1. 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. 2. Estimate the incidence rate of other SPM among the same cohort of patients. 3. If feasible, estimate the incidence rate ratios of MDS/AML and other SPM in the Zejula-treated patients compared with a cohort of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and who have not been treated with a PARP inhibitor.	To provide additional safety information about the important potential risks of MDS/AML and second primary malignancies other than MDS/AML in patients treated in clinical practice with existing medicines for ovarian cancer and patients treated with niraparib.	A full protocol will be submitted within 3 months of marketing approval.	TBD

Risk minimisation measures

Table 50: Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Haematological toxicity	• Guidance in SmPC section 4.2 on dosing interruptions and adjustments in cases of haematological toxicity • Warning in SmPC section 4.4 that haematological toxicity is expected and to use caution with anticoagulation and antiplatelet drugs • Listed as adverse reactions in SmPC section 4.8 • Prescription only medicine • Treatment under supervision of a specialist physician	None
Hypertension	• Warning in SmPC section 4.4 that hypertension has been reported with niraparib therapy and that blood pressure should be monitored • Listed as an adverse reaction in SmPC section 4.8 • Prescription only medicine • Treatment under supervision of a specialist physician	None
Important Potential Risks		
Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML)	• Guidance in SmPC section 4.2 on dosing interruptions and adjustments in cases of haematological toxicity • Warning in SmPC section 4.4 of the possible occurrence of MDS/AML and for treatment with niraparib to be discontinued if MDS/AML are confirmed • Prescription only medicine • Treatment under supervision of a specialist physician	None
Second primary malignancies other than MDS and AML	• Prescription only medicine • Treatment under supervision of a specialist physician	None
Embryo-foetal toxicity	• Warnings advised in SmPC sections 4.4 and 4.6 that women of childbearing potential should not become pregnant while on niraparib • Prescription only medicine • Treatment under supervision of a specialist physician	None
Pneumonitis	• Prescription only medicine • Treatment under supervision of a specialist physician	None
Missing Information		
Patients with severe renal impairment and ESRD	• Warning in SmPC section 4.2 that there is no data on the effect of niraparib in patients with severe renal impairment or ESRD and should be	None

	used with caution • Prescription only medicine • Treatment under supervision of a specialist physician	
Patients with severe hepatic impairment	1. Warning in SmPC section 4.2 that there is no data on the effect of niraparib in patients with severe hepatic impairment and should be used with caution 2. Prescription only medicine 3. Treatment under supervision of a specialist physician	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4, dated 11 September 2017 is acceptable.

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 27.03.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. New Active Substance

The applicant compared the structure of niraparib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers niraparib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zejula (niraparib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that

this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for Zejula is "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."

Platinum sensitivity was defined by complete response (CR) or partial response (PR) for more than six months to their penultimate (next to last) platinum-based therapy. To be eligible for niraparib treatment the patient should be in response (CR or PR) following completion of last platinum based chemotherapy.

Deficiency in the homologous recombinant DNA repair pathway (HRD) including mutations in the BRCA1 or BRCA2 genes is expected to enhance sensitivity to PARP inhibition (niraparib). This defect is referred to as 'synthetic lethality'; and is somehow or in part linked to platinum sensitivity. In addition, there might be other, undefined genome defects (BRCA epigenetic modifications, other mutations) that could account for the sensitivity to platinum treatment, sometimes referred to as 'BRCAness' or 'HRD deficiencies'. In total, information on deficiency in these genes could potentially maximize on the output of the treatment.

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 considered of clinical relevance also without an improvement in OS.

3.1.2. Available therapies and unmet medical need

Standard drug treatment for advanced-stage ovarian cancer in the first-line setting is platinum (cisplatin or carboplatin) plus a taxane (paclitaxel or docetaxel) with or without bevacizumab. Initial chemotherapy response rate is high in the platinum sensitive population, but most patients with advanced disease will recur within 2 years.

The claimed indication of niraparib is maintenance treatment in the chemotherapy free interval in order to prolong disease control and delay progression. Treatment options today of patients with prior platinum-sensitive, recurrent ovarian cancer in the chemotherapy free interval are as per NCCN and ESMO guidelines

- surveillance; monitor until disease progression while managing the patient's symptoms but not provide active anti-cancer treatment
- bevacizumab in combination with chemotherapy followed by bevacizumab monotherapy
- olaparib maintenance treatment following response to platinum-based chemotherapy in patients with *BRCA* mutation

Despite these treatment options, relapsed disease remains inevitable. Also, repeated platinum-based chemotherapy can cause cumulative toxicities, serious side effects and patients also report a significant burden on quality of life (QOL), as well as hospital fatigue. Effective maintenance

treatment options for patients with platinum-sensitive recurrent ovarian cancer remain limited, and represent as such an unmet medical need. In particular, there is a medical need for patients that are negative in BRCA mutation, since the current olaparib indication as maintenance treatment is only approved for the BRCA mutated population.

3.1.3. Main clinical studies

A single pivotal phase III study (NOVA; PR-30-5011-C) is submitted to support the efficacy in the claimed indication. NOVA is a double-blind, 2:1 randomized, placebo-controlled, multicentre, 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) to their last platinum-based chemotherapy. The patient population is assigned to two cohorts (germline BRCA cohort and non-germline BRCA cohort) using an established and validated blood test to define the BRCA mutation status.

The applicant has performed separate analysis in the two cohorts/groups of the ITT population: those with germline BRCA mutation (gBRCAmut cohort) (N=203) and those who were not germline BRCA mutation carriers (non-gBRCAmut cohort) (N=350). However, despite allocation to and analyses in different subgroups, the proposed indication includes the whole platinum sensitive population.

The primary data to support the safety of treatment with niraparib in the proposed indication are derived from the NOVA main study including 546 ovarian cancer patients receiving at least one dose of study treatment, out of which 367 received niraparib and 179 received placebo. Key supportive safety information is available from 384 ovarian cancer patients treated in 4 open-label, single-arm studies or sub-studies: the Phase 1 Study PN001 (N=104 patients total, 50 with ovarian cancer), the Phase 2 QUADRA study (N=291 patients), and the 2 sub-studies of NOVA, PR-30-5011-C1-QTC (N=26 patients) and PR-30-5011-C2-FE (N=17 patients); data from these studies have been pooled for analysis. This single pool of studies provides an evaluation of the safety of niraparib in women receiving treatment for recurrent ovarian cancer and is designated as the Ovarian Cancer Treatment (OCT) pool.

3.2. Favourable effects

gBRCAmut cohort

The primary endpoint PFS was met in this cohort with a HR of 0.27 (95% CI: 0.173 to 0.410, p<0.0001) in favour of the niraparib arm. The median PFS was 21 (95% CI: 12.9, NE) months for the niraparib arm versus 5.5 (95% CI: 3.8, 7.2) months in the placebo arm. This represents a prolongation in PFS of 15.5 months.

For the patient related outcome, both baseline symptoms and QOL (FOSI and EQ-5D-5L) were similar between placebo and niraparib patients in the gBRCAmut cohort with no statistical significant difference between the two arms.

The superiority of the niraparib arm over the placebo arm was observed in all predefined subgroups (HR<0.45) and the highest efficacy was observed for the BRCA2 mutation with a HR of 0.12 (95% CI: 0.016, 0.332).

HRDpos/non-gBRCAmut cohort

The NOVA study met its primary endpoint for the HRDpos group of the non-g*BRCA*mut cohort with a HR of 0.38 (95% CI: 0.243 to 0.586, p<0.001). The median PFS was 12.9 (95% CI: 8.1, 15.9)

months for the niraparib arm versus 3.8 (95% CI: 3.5, 5.7) months in the placebo arm. This represents a prolongation in PFS of 9.1 months.

Overall / non-gBRCAmut cohort

The primary endpoint was also met in the overall non-g*BRCA*mut cohort with a HR of 0.45 (95% CI: 0.338 to 0.607) (p<0.0001). The median PFS was 9.3 (95% CI: 7.2, 11.2) months for the niraparib arm versus 3.9 (95% CI: 3.7, 5.5) months in the placebo arm. This represents a prolongation in PFS of 5.4 months.

For the sensitivity analysis data are consistent in the various analysis groups of both HRDpos and overall, with similar HR values as reported for the primary endpoint.

Baseline symptoms and QOL (FOSI and EQ-5D-5L) were equivalent between placebo and niraparib patients in the non-gBRCAmut cohort.

The superiority of the niraparib arm over the placebo arm was observed in all predefined subgroups of the non-gBRCAmut cohort.

3.3. Uncertainties and limitations about favourable effects

There is some uncertainty about the precise size of the PFS effect for niraparib in the germline BRCA cohort, due to conflicting data between the primary (IRC-based) analysis with HR=0.27 (95% CI: 0.173, 0.410) and sensitivity analyses which showed a HR= 0.35 (0.243, 0.496) when applying IRC limited censoring (considering start of subsequent anti-cancer treatment, discontinuation due to any reason, or missed tumour assessments as events), and investigator assessment of PFS with HR=0.27 (0.182, 0.401). Similarly, there is some uncertainty about the precise size of the PFS effect for niraparib in the non-germline BRCA cohort due to conflicting data between the primary (IRC-based) analysis with HR=0.45 (0.338, 0.607) vs HR=0.53 (95 % CI, 0.405, 0.683) as adjudicated by the investigator. However, the differences are small and overall there are no concerns about the statistical significance or the consistency of the effect, and the issue has not been pursued further. Results based on investigator assessed PFS have been reflected in the SmPC to acknowledge this uncertainty (section 5.1).

Over 50% of the data for patients in both treatment arms in both cohorts were censored for PFS2 and median OS was not reached for the ITT population in either randomized treatment arm. Updated PFS2 and OS data will be provided (see letter of Recommendation).

In an exploratory analysis the median PFS in the niraparib arm of the HRDneg group (N=134) was 6.9 months (95% CI: 5.6, 9.6) compared to 3.8 months (95% CI: 3.7, 5.6) in the placebo arm with a HR of 0.58 (95% CI: 0.361, 0.922) (p=0.0226). Based on the underlying molecular mechanism this group is not expected to respond to PARP inhibition. Whether this positive response of 3.1 months prolongation is, among other hypothesis, due to HRD positive patients being incorrectly allocated to the HRDneg group (false negative) by the HRD test has not been possible to assess based on current methods and knowledge. Still, the effect was overall qualitatively consistent so that this did not warrant a restriction in the indication and testing for HRD negativity is not recommended based on the available data. Results in this subpopulation have been adequately described in section 5.1 of the SmPC to acknowledge uncertainties about the magnitude of the effect in this subpopulation.

3.4. Unfavourable effects

The most common AEs in the NOVA study were related to myelosuppression and gastrointestinal events. These were reported more commonly for niraparib compared to placebo: thrombocytopenia

events (61%; Grade 3/4: 34%), anaemia events (50%; Grade 3/4: 25%), and nausea (74%; Grade 3/4: 3%) (see effects table below for incidence rates).

Other notable AEs reported more commonly for niraparib than placebo were constipation (40%), vomiting (34%; Grade 3/4: 2%), insomnia (24%), headache (26%), hypertension (19%; Grade 3: 8%), neutropenia events (30%; 20% Grade 3/4), fatigue events (59%; Grade 3: 8%), dyspnoea (19%), decreased appetite (25%), and cough (15%). The most frequently reported AEs overall in the OCT pool were consistent with the commonly reported AEs in the niraparib-treated patients of the NOVA study, including gastrointestinal events (nausea and vomiting), fatigue, decreased appetite, and events related to hematologic laboratory abnormalities.

The incidences of most of the treatment-related AEs, including thrombocytopenia-, anaemia-, and neutropenia events, nausea and vomiting, were highest during the first month of treatment. The incidences were, however, markedly reduced after intensive dose modifications were performed during the first two cycles of treatment, from cycle 4 through the remainder of treatment.

Reported SAEs in the NOVA study were predominantly thrombocytopenia (10.9%) and anaemia (3.8%). Consistently, commonly reported SAEs across the OCT studies were primarily haematology laboratory abnormalities and gastrointestinal disturbances. The proportion of patients reporting treatment-related SAEs was similar between patients treated with niraparib in the NOVA study and OCT pool (17% and 18%, respectively).

The incidence of fatal AEs was low in both the NOVA study and OCT pool. Three deaths were reported during the post-treatment follow-up period in the NOVA study due to MDS/AML. In the OCT pool, two of the 5 patients with fatal AEs were causally related to niraparib according to the investigator.

Overall, 9 cases of MDS/AML were observed among patients in the NOVA study and OCT pool. The incidence of MDS/AML was marginally higher in niraparib-treated patients, 1.4% vs 1.1% in the placebo group. In addition, two cases were identified in the FE and QTc sub-studies of the OCT pool. Thus, the overall incidence of MDS/AML across the clinical development program of niraparib was 0.9%, similar to that reported for another PARP inhibitor, olaparib.

A causal relationship was found between lower baseline body weight and increased incidences of ≥ Grade 3 AEs, SAEs, and AEs leading to dose modification or treatment discontinuation, which occurred more commonly in patients with a baseline weight <58 kg compared to patients ≥77 kg. Approximately 80% of the patients with a body weight of less than 58 kg had a dose reduction compared to 59% of the patients with a weight greater than or equal to 77 kg. A 200 mg dose may be considered as an alternative starting dose for patients with a body weight less than 58 kg (see SmPC section 4.2).

3.5. Uncertainties and limitations about unfavourable effects

The mean dose of niraparib administered in the NOVA study was approximately 195 mg/day, corresponding to a dose that is 105 mg lower than the proposed dose of 300 mg once daily. The intensive dose modifications performed (>70%) in the niraparib arm of the NOVA study were consistent with the severe AEs experienced by these patients, which questions the selected dose of 300 mg/day with respect to patient's tolerability. Moreover, the majority of the interruptions occurred during the first month after treatment initiation, while dose reductions occurred primarily during the second month.

PARP-inhibitors could potentially predispose patients to development of MDS/AML, based on genotoxicity results and mode of action. Therefore, as MDS diagnosis and progression may take years to develop after treatment initiation and the incidence in the niraparib arm of the NOVA

study was slightly higher than the placebo arm (1.4% vs 1.1%), it cannot be ruled out that development of MDS/AML are related to niraparib. Due to the lack of long-term follow-up, the long-term safety concerning increased risk of MDS/AML with niraparib maintenance treatment is not well defined. The level of this risk will be better characterized in a post authorisation safety study, particularly in view of the duration of the exposure (see RMP).

3.6. Effects Table

Table 51: Effects Table for Zejula in the treatment of platinum sensitive, recurrent ovarian cancer (NOVA; PR-30-5011-C data cut-off: 30 May 2016)

Effect	Short Description	Unit	Niraparib	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
			gBRCAmut cohort			
Primary endpoint:						
PFS Progression-free survival (HR)	From randomisation to progression or death (blinded independent review)		0.27 (p<0.0001)	1.00	OS and PFS2 data are immature.	
PFS (median)		Months	21.0	5.5	Sensitivity analyses indicate that the median in the niraparib arm may be overestimated.	
			Overall / non-gBRCAmut cohort			
PFS (HR)			0.45 (p<0.0001)	1.00	The efficacy in the overall population may be driven by the HRDpos population. Some improvement in PFS has been observed also in an exploratory analysis of the HRDneg subpopulation. However, there are concerns regarding the allocation of patients to this population.	
PFS (median)		Months	9.3	3.9	Sensitivity analyses support the primary analysis.	
Unfavourable Effects						
Thrombocytopenia events*	Incidence all grades	%	61	6		
	Grade3/4		34	<1		
	SAEs		10.9	0		
	Incidence of discontinuation		3.3	0		
Anaemia events**	Incidence all grades	%	50	7		
	Grade 3/4		25	0		
	SAEs		3.8	0		
	Incidence of discontinuation		1.4	0		

Effect	Short Description	Unit	Niraparib	Placebo	Uncertainties/ Strength of evidence	References
Nausea	Incidence all grades	%	74	35		
	Incidence of discontinuation		1.6	0		
Vomiting	Incidence all grades	%	34	16		
Neutropenia events***	Incidence all grades	%	30	6		
	Grade 3/4		20	2		
	Incidence of discontinuation		7	0		
Fatigue events****	Incidence all grades	%	59	41		
	Grade 3/4		8	<1		
	Incidence of discontinuation		2.7	0		

Notes: *Thrombocytopenia events include thrombocytopenia and platelet count decreased; **Anaemia events includes anaemia and haemoglobin decreased; ***Neutropenia events includes neutropenia, neutrophil count decreased, and febrile neutropenia; ****Fatigue events includes fatigue, asthenia, malaise and lethargy.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The main clinical objective of the study is to show that niraparib can delay cancer progression after a chemotherapy regimen in a population of patients that are platinum sensitive. The use of PFS as primary endpoint for maintenance therapy in ovarian cancer is supported when there is no detrimental effect on OS. This has also been agreed upon with CHMP in scientific advice and is in line with the guideline on the evaluation of anticancer medical product in man (EMA/CHMP/205/95/Rev. 4) stating that PFS is a valid surrogate endpoint for OS. For the germline cohort the reported gain in PFS from the primary IRC analysis was 15.5 months, which is a clinically relevant effect. The PFS data are supported by several sensitivity analyses all showing PFS benefit when compared to placebo. The QoL results did not show any detrimental effect of niraparib compared to placebo throughout the study period.

A positive PFS effect is seen also for the non-gBRCAmut cohort, both in the HRDpos population (including somatic BRCA mutations and BRCA wild type patients) and the cohort overall, which includes the HRDneg population. The statistically significant PFS prolongations are 9.1 months and 5.4 months, respectively. These analyses are further substantiated by similar outcome in the sensitivity analyses for this cohort. In conclusion, as for the germline cohort, these effects are considered clinically relevant for the patient in a maintenance setting between two chemotherapy intervals.

Women with relapsed ovarian cancer that are not BRCA mutated have limited treatment options in the surveillance period between two chemotherapy regimens, and there is plausible reason to treat patients in the maintenance phase with the purpose to postpone the next chemotherapy regimen. Positive treatment effect has been demonstrated in both cohorts, including the HRDneg group and currently there are no means of identifying patients that that are sensitive to platinum but not sensitive to niraparib.

The primary IRC efficacy analyses are in concordance with the statistically convincing IRC analysis for the secondary endpoint TFST (time to first subsequent therapy) for both cohorts. This results in a postponement of the next therapy of 12.6 months for the germline cohort and 4.6 months for the non-germline cohort, both being relevant in a clinical setting.

Importance of unfavourable effects

In the NOVA study, a significantly higher rate of treatment-related SAEs was reported in niraparib-treated patients compared to patients who received placebo, 17% vs 1%. Overall, the pattern of AEs is similar to that observed for olaparib, another PARP inhibitor recently approved in the EU for platinum-sensitive recurrent BRCA-mutated ovarian cancer, except that thrombocytopenia and constipation are reported more commonly, and that hypertension constitutes a new safety signal for niraparib. Thrombocytopenia, anaemia, neutropenia, fatigue and nausea/vomiting are the major factors limiting the tolerability of niraparib in patients and the main reason for one or more dose reductions. The majority of the dose interruptions occurred early in treatment during the first month after treatment initiation, while dose reductions occurred primarily during the second month. Particularly, the mean dose of niraparib administered in the NOVA study was approximately 195 mg/day, corresponding to a dose that is 105 mg lower than the proposed (starting) dose of 300 mg once daily.

Strength of evidence / Impact of uncertainties

With reference to the importance of favourable effects in the section discussed above, the reported median PFS benefit in the germline cohort is not fully supported by the sensitivity analyses where large differences are reported between the different analyses. The median PFS estimate of niraparib is also uncertain, since the analysis is based on immature data. Still, it can be assumed that the PFS estimate lies somewhere in the range of 14.8 and 21 months, i.e. a gain in PFS of between 5.8 and 15.5 months as compared with the placebo arm. Even in the lower range of this interval, the effect is considered to be of clinical relevance.

Of note, OS data for olaparib have recently been published and demonstrate a positive outcome in the gBRCAmut cohort (Ledermann et al, 2016). Niraparib OS data are still immature.

The large amount of dose modifications due to AEs (i.e. >70%) observed in the NOVA study is indicative of poor patient tolerability to the 300 mg daily dose of niraparib. Although most of the AEs with niraparib can be handled by dose interruptions/reductions, some AEs persisted after intensive dose modifications were performed (e.g. anaemia, fatigue, nausea and vomiting). Thus, the optimal dosing of niraparib is still uncertain. However, the daily dose of 300 mg niraparib should be the recommended starting dose until new relevant data are available. The applicant is encouraged to further investigate alternative dosing strategies in upcoming clinical trials with niraparib.

3.7.2. Balance of benefits and risks

Efficacy has been demonstrated in all patients independent of BRCA/HRD status and the safety profile is manageable with dose reductions. Hence, the benefit risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Zejula is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Zejula is not similar to Lynparza and Yondelis within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zejula is favourable in the following indication:

Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum based chemotherapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that niraparib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.