ZEJULA

Version GDSv08-IPIv08

ZEJULA

Niraparib

Qualitative and Quantitative Composition

Hard Capsule

ZEJULA 100 mg hard capsules have a white opaque body and a purple opaque cap. The white opaque capsule body is printed with "100 mg" in black ink, and the purple capsule cap is printed with "Niraparib" in white ink. The capsules contain a white to off white powder.

Each hard capsule contains niraparib tosylate monohydrate equivalent to 100 mg niraparib.

Film-coated tablet

ZEJULA 100 mg tablet is gray, oval-shaped, film-coated tablet debossed with "100" on one side and "Zejula" on the other.

ZEJULA 200 mg tablet is blue, oval-shaped, film-coated tablet debossed with "200" on one side and "Zejula" on the other.

ZEJULA 300 mg tablet is green, oval-shaped, film-coated tablet debossed with "300" on one side and "Zejula" on the other.

Each film-coated tablet contains niraparib tosylate monohydrate equivalent to 100 mg, 200 mg or 300 mg niraparib.

Clinical Information

Indications

ZEJULA is indicated:

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

Dosage and Administration

Pharmaceutical Form

Hard capsule and Tablet.

Posology

First-line Ovarian Cancer Maintenance Treatment

The recommended starting dose of *ZEJULA* is 200 mg taken once daily. However, for those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL, the recommended starting dose of *ZEJULA* is 300 mg taken once daily.

Recurrent Ovarian Cancer Maintenance Treatment

The dose is 300 mg once daily. For patients who weigh < 77 kg or have baseline platelet count <150,000/µL, the recommended starting dose of *ZEJULA* is 200 mg taken orally once daily.

Patients should be encouraged to take their dose at approximately the same time each day. Bedtime administration may be a potential method for managing nausea.

Treatment should be continued until disease progression or unacceptable toxicity.

Missing Dose

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

Dose Adjustments for Adverse Reactions

Recommendations for dose modifications for adverse reactions are provided in Tables 1, 2 and 3.

Table 1: Recommended dose modifications for adverse reactions

Starting dose	200 mg/day	300 mg/day
First dose reduction	100 mg/day	200 mg/day
Second dose reduction	Discontinue medication.	100 mg/day[a]
[a]If further dose reduction below 100 mg/day is required, discontinue *ZEJULA*.		

Table 2: Dose modifications for non-haematological adverse reactions

Non-haematological CTCAE ≥ Grade 3 treatment-related adverse reaction that persists despite treatment/prophylaxis[a]	First occurrence: Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction. Resume ZEJULA at a reduced dose level per Table 1.
	Second occurrence: Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction. Resume ZEJULA at a reduced dose or discontinue per Table 1.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered ZEJULA 100 mg/day	Discontinue treatment.
a Prophylaxis includes, but is not limited to, medications to prevent nausea, vomiting, diarrhoea, constipation, headache, back pain, myalgia, arthralgia, insomnia, decreased appetite, or dry mouth.	

Table 3: Dose modifications for haematological adverse reactions

Haematological 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 Warnings and Precautions*). Based on individual laboratory values, weekly monitoring for the second month may be warranted.	
Haematological 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 per Table 1.
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 per Table 1 based on clinical evaluation. • If platelet count is < 75,000/µL at any time, resume at a reduced dose per Table 1.
	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 per Table 1. • 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 once daily.
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 per Table 1. • 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 once daily.
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	• Permanently discontinue *ZEJULA*.

Method of Administration

Swallow capsules or tablets whole with water. Do not chew or crush capsules or tablets.

ZEJULA can be taken without regard to meals (*see Pharmacokinetics*).

Children and Adolescents

The safety and efficacy of ZEJULA in children and adolescents below 18 years of age have not yet been established.

Elderly

No dose adjustment is necessary for elderly patients (≥ 65 years).

Renal Impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. There are no data in patients with severe renal impairment or end stage renal disease undergoing haemodialysis; use with caution in these patients (*see Pharmacokinetics*).

Hepatic Impairment

No dose adjustment is needed in patients with mild hepatic impairment.

For patients with moderate hepatic impairment, the recommended starting dose of *ZEJULA* is 200 mg once daily (*see Pharmacokinetics*).

There are no data in patients with severe hepatic impairment; use with caution in these patients (*see Pharmacokinetics*).

Contraindications

Hypersensitivity to the niraparib or to any of the excipients listed in Excipients.

Breast-feeding (*see Pregnancy and Lactation*).

Warnings and Precautions

Haematological Adverse Reactions

Haematological adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with *ZEJULA*. In the PRIMA and NOVA studies, patients eligible for *ZEJULA* therapy had the following baseline haematological parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/µL; platelets ≥ 100,000 cells/µL and haemoglobin ≥ 10 g/dL (PRIMA) or ≥9 g/dL (NOVA) prior to therapy.

In the PRIMA study, the overall incidence of Grade ≥3 thrombocytopenia, anaemia and neutropenia in clinical and/or laboratory findings were reported in 39%, 31%, and 21% of patients receiving *ZEJULA,* respectively. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred in 4%, 2%, and 2% of patients, respectively.

In patients who were administered a starting dose of *ZEJULA* based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anaemia and neutropenia were reported, in 22%, 23%, and 15% of patients receiving *ZEJULA,* respectively. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred in 3%, 3%, and 2% of patients, respectively.

In the NOVA study, grade ≥3 thrombocytopenia, anaemia and neutropenia were reported in 29%, 25%, and 20% of patients receiving *ZEJULA,* respectively. Discontinuation due to thrombo-cytopenia, anaemia, and neutropenia occurred in 3%, 1%, and 2% of patients, respectively.

If a patient develops severe persistent haematological toxicity including pancytopenia that does not resolve within 28 days following interruption, *ZEJULA* should be discontinued.

Test complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time to monitor for clinically significant changes in any haematological parameter during treatment (*see Posology*).

Due to the risk of thrombocytopenia, anticoagulants and medicinal products known to reduce the thrombocyte count should be used with caution (*see Adverse Reactions*).

Myelodysplastic Syndrome/Acute Myeloid Leukaemia

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received *ZEJULA (see Adverse Reactions)*.

In clinical trials, the duration of *ZEJULA* treatment in patients prior to developing MDS/AML varied from 1 month to > 4 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow suppression.

For suspected MDS/AML or prolonged haematological toxicities, the patient should be referred to a haematologist for further evaluation. If MDS/AML is confirmed, treatment with *ZEJULA* should be discontinued.

Hypertension, Including Hypertensive Crisis

Hypertension, including hypertensive crisis, has been reported with the use of *ZEJULA* (*see Adverse Reactions*). Pre-existing hypertension should be adequately controlled before starting *ZEJULA* treatment. Blood pressure and heart rate should be monitored at least weekly for the first two months, then monthly for the first year and periodically thereafter during treatment with *ZEJULA*.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the *ZEJULA* dose (*see Posology*), 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 (*see Posology*). *ZEJULA* should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports (0.09% of clinical trial patients) of *ZEJULA*-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES) (*see Adverse Reactions*). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of *ZEJULA*. The safety of reinitiating *ZEJULA* therapy in patients previously experiencing PRES is not known.

Pregnancy/Contraception

ZEJULA should not be used during pregnancy or in women of childbearing potential not willing to use highly effective contraception during therapy and for 6 months after receiving the last dose of *ZEJULA* (*see Pregnancy*). A pregnancy test should be performed on all women of childbearing potential prior to treatment.

Excipients

ZEJULA capsules contain tartrazine (FD&C Yellow No 5), which may cause allergic-type reactions.

Interactions

Pharmacodynamic Interactions

The combination of *ZEJULA* with vaccines or immunosuppressant agents has not been studied.

The data on *ZEJULA* in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with vaccines, immunosuppressant agents or with other cytotoxic medicinal products.

Pharmacokinetic Interactions

No clinical drug interaction studies have been performed with *ZEJULA*.

Effect of Niraparib on Other Medicinal Products

Inhibition of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5)

In vitro, neither niraparib nor its inactive major metabolite M1 is a clinically relevant inhibitor of any active substance-metabolising CYP enzymes, namely CYP1A1/2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5

Induction of CYPs (CYP1A2 and CYP3A4/5)

Neither niraparib nor M1 is a clinically relevant CYP3A4/5 inducer *in vitro*. *In vitro*, niraparib weakly induces CYP1A2 at concentrations greater than 10-fold of steady-state concentrations at 300 mg daily. This induction of CYP1A2 is not considered clinically relevant. M1 is not a CYP1A2 inducer.

Inhibition of Efflux Transporters (P-gp, BCRP, BSEP, MRO", and MATE1/2K)

Neither niraparib nor M1 is a clinically relevant inhibitor of P-gp, BCRP, BSEP or MRP2 based on *in vitro* data and physiologically based pharmacokinetic (PBPK) modeling.

Niraparib is an inhibitor of MATE1 and -2 with IC_{50} of 0.18 µM and ≤ 0.14 µM, respectively. M1 does not inhibit MATE1/2K. Simulations using PBPK modeling indicate an expected >2-fold increase in exposure of metformin when administered with niraparib at 200 mg or 300 mg daily. Close monitoring of glycaemia is recommended when starting or stopping niraparib in patients receiving metformin. A dose adjustment of metformin may be necessary.

Inhibition of Uptake Transporters (OATP1B1, OATP1B3, OCT1 *, OAT1, OAT3, and OCT2)*

Neither niraparib nor M1 is an inhibitor of hepatic uptake transporters OATP1B1 or OATP1B3 and renal uptake transporters OAT1, OAT3, or OCT2 *in vitro*. *In vitro,* niraparib inhibits hepatic uptake transporter OCT1 at concentrations greater than 7-fold of steady-state concentrations at 300 mg daily. This inhibition of OCT1 is not considered clinically relevant.

Pregnancy and Lactation

Fertility

There are no clinical data on the effects of niraparib on fertility. A reversible reduction of spermatogenesis was observed in rats and dogs (*see Animal toxicology and/or pharmacology*).

Pregnancy

Women of childbearing potential should not become pregnant while on treatment and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment. Women of childbearing potential must use highly effective contraception during therapy and for 6 months after receiving the last dose of *ZEJULA*.

There are no or limited amount of data from the use of niraparib in pregnant women. Animal reproductive and developmental toxicity studies have not been conducted. However, based on its mechanism of action, niraparib could cause embryonic or foetal harm, including embryo-lethal and teratogenic effects, when administered to a pregnant woman. *ZEJULA* should not be used during pregnancy.

Lactation

It is unknown whether niraparib or its metabolites are excreted in human milk. Breast-feeding is contraindicated during administration of *ZEJULA* and for 1 month after receiving the last dose (*see Contraindications*).

Effects on Ability to Drive and Use Machines

ZEJULA may influence the ability to drive or use machines. Patients who take *ZEJULA* may experience asthenia, fatigue, difficulty concentrating, and dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

Adverse Reactions

Clinical Trial Data

Tabulated List of Adverse Reactions

The following adverse reactions have been identified based on pooled data generated from the PRIMA and NOVA clinical trials in patients receiving *ZEJULA* monotherapy and during post-marketing experience (*see Table 4*).

Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Tabulated list of adverse reactions[a]

System Organ Class	Frequency of all CTCAE[b] grades	Frequency of CTCAE[b] grade 3 or 4
Infections and infestations	**Very common** Urinary tract infection **Common** Bronchitis, conjunctivitis	**Uncommon** Urinary tract infection, bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**Common** Myelodysplastic syndrome/ acute myeloid leukaemia	**Common** Myelodysplastic syndrome/ acute myeloid leukaemia
Blood and lymphatic system disorders	**Very common** Thrombocytopenia, anaemia, neutropenia, leukopenia **Common** Neutropenic infection **Uncommon** Febrile neutropenia, pancytopenia, neutropenic sepsis	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Neutropenic infection, febrile neutropenia, neutropenic sepsis, pancytopenia
Immune system disorders	**Common** Hypersensitivity (including anaphylaxis)	**Uncommon** Hypersensitivity (including anaphylaxis)
Metabolism and nutrition disorders	**Very common** Decreased appetite **Common** Hypokalemia	**Common** Hypokalemia **Uncommon** Decreased appetite
Psychiatric disorders	**Very common** Insomnia **Common** Anxiety, depression, cognitive impairment (memory impairment, concentration impairment) **Uncommon** Confusional state/disorientation, hallucination	**Uncommon** Insomnia, anxiety, depression, confusional state/disorientation, hallucination
Nervous system disorders	**Very common** Headache, dizziness **Common** Dysgeusia **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)	**Uncommon** Headache **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)
Cardiac disorders	**Very common** Palpitations **Common** Tachycardia	
Vascular disorders	**Very common** Hypertension **Rare** Hypertensive crisis	**Common** Hypertension **Rare** Hypertensive crisis
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnoea, cough, nasopharyngitis **Common** Epistaxis **Uncommon** Non-infectious pneumonitis	**Uncommon** Dyspnoea, epistaxis, non-infectious pneumonitis
Gastrointestinal disorders	**Very common** Nausea, constipation, vomiting, abdominal pain, diarrhoea, dyspepsia **Common** Dry mouth, mucositis, stomatitis	**Common** Nausea, vomiting, abdominal pain **Uncommon** Diarrhoea, constipation, mucositis, stomatitis, dry mouth
Skin and subcutaneous tissue disorders	**Common** Photosensitivity, rash	**Uncommon** Photosensitivity, rash

System Organ Class	Frequency of all CTCAE[b] grades	Frequency of CTCAE[b] grade 3 or 4
Musculoskeletal and connective tissue disorders	**Very common** Back pain, arthralgia **Common** Myalgia	**Uncommon** Back pain, arthralgia, myalgia
General disorders and administration site conditions	**Very common** Fatigue, asthenia **Common** Oedema peripheral	**Common** Fatigue, asthenia
Investigations	**Common** Gamma-glutamyl transferase increased, AST increased, blood creatinine increased, ALT increased, blood alkaline phosphatase increased, weight decreased	**Common** Gamma-glutamyl transferase increased, ALT increased **Uncommon** AST increased, blood alkaline phosphatase increased

a.- Frequency based on niraparib clinical trial data not limited to pivotal PRIMA or NOVA monotherapy studies.
b. CTCAE=Common Terminology Criteria for Adverse Events version 4.02

The adverse reactions noted in the group of patients who were administered a 200-mg starting dose of *ZEJULA* based on baseline weight or platelet count were of similar or lesser frequency compared to the group administered 300 mg (Table 4). See Warnings and Precautions for specific information regarding frequency of thrombocytopenia, anaemia, and neutropenia.

The most common serious adverse reactions >1% (treatment-emergent frequencies) were thrombocytopenia and anaemia.

Description of Selected Adverse Reactions

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

In the clinical programme, haematological adverse reactions were managed with laboratory monitoring and dose modifications (*see Posology*).

Thrombocytopenia

In the PRIMA study overall, 39% of *ZEJULA*-treated patients experienced Grade 3-4 thrombocytopenia compared to 0.4% of placebo-treated patients with a median time from first dose to first onset in the *ZEJULA* arm of 22 days (range: 15 to 335 days) and with a median duration of 6 days (range: 1 to 374 days). Discontinuation due to thrombocytopenia occurred in 4% of patients.

In the NOVA study, approximately 60% of patients receiving *ZEJULA* experienced thrombocytopenia of any grade, and 34% of patients experienced Grade 3/4 thrombocytopenia. In patients with baseline platelet count less than 180,000 cells/µL, thrombocytopenia of any grade and Grade 3/4 occurred in 76% and 45% of the patients, respectively. The median time to onset of thrombocytopenia regardless of grade and Grade 3/4 thrombocytopenia was 22 and 23 days, respectively. 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%. The median duration of thrombocytopenia events of any grade was 23 days, and the median duration of Grade 3/4 thrombocytopenia was 10 days. Patients treated with *ZEJULA* who develop thrombocytopenia might have an increased risk of haemorrhage. Discontinuation due to thrombocytopenia events (thrombocytopenia and platelet count decreased) occurred in approximately 3% of the patients.

In the NOVA study, 48 of 367 (13%) patients experienced bleeding with concurrent thrombocytopenia; all bleeding events concurrent with thrombocytopenia were Grade 1 or 2 in severity except for one event of Grade 3 petechiae and haematoma observed concurrently with a serious adverse event of pancytopenia. Thrombocytopenia occurred more commonly in patients whose baseline platelet count was less than 180,000 cells/µL. Approximately 76% of patients with lower baseline platelets (< 180,000 cells/µL) who received *ZEJULA* experienced thrombocytopenia of any grade, and 45% of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in < 1% of patients receiving *ZEJULA*.

Anaemia

In the PRIMA study overall, 31% of *ZEJULA*-treated patients experienced Grade 3-4 anaemia compared to 2% of placebo-treated patients with a median time from first dose to first onset in the *ZEJULA* arm of 80 days (range: 15 to 533 days) and with a median duration of 7 days (range: 1 to 119 days). Discontinuation due to anaemia occurred in 2% of patients.

In the NOVA study, approximately 50% of patients experienced anaemia of any grade, and 25% experienced Grade 3/4 anaemia. 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. In the clinical programme, anaemia was managed with laboratory monitoring, dose modification (*see Posology*), and where appropriate with red blood cell transfusions. Discontinuation due to anaemia occurred in 1% of patients.

Neutropenia

In the PRIMA study overall, 21% of *ZEJULA*-treated patients experienced Grade 3-4 neutropenia compared to 1% of placebo-treated patients with a median time from first dose to first onset in the *ZEJULA* arm of 29 days (range: 15 to 421 days) and with a median duration of 8 days (range: 1 to 42 days). Discontinuation due to neutropenia occurred in 2% of patients.

In the NOVA staudy, approximately 30% of patients receiving *ZEJULA* experienced neutropenia of any grade, and 20% of patients experienced Grade 3/4 neutropenia. 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 addition, Granulocyte-Colony Stimulating Factor (G-CSF) was administered to approximately 6% of patients treated with *ZEJULA* as concomitant therapy for neutropenia. Discontinuation due to neutropenia events occurred in 2% of patients.

Myelodysplastic Syndrome/Acute Myeloid Leukaemia

In clinical studies, MDS/AML occurred in 1% patients treated with *ZEJULA*, with 41% of cases having a fatal outcome. The incidence was higher in patients with relapsed ovarian cancer who had received 2 or more lines of prior platinum chemotherapy and with g*BRCA*mut following 5.6 years survival follow-up. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in g*BRCA*mut carriers. Some of the patients had a history of previous cancer or of bone marrow suppression.

In the PRIMA study, the overall incidence of MDS/AML was 2.3% in patients receiving *ZEJULA* and 1.6% in patients receiving placebo with a follow-up of 6.2 years..

In the NOVA study in patients with relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy, the overall incidence of MDS/AML was 3.5% in patients receiving *ZEJULA* and 1.7% in patients receiving placebo with a follow-up of 5.6 years. In g*BRCA*mut and non-g*BRCA*mut cohorts, the incidence of MDS/AML was 6.6% and 1.7% in patients receiving *ZEJULA* and 3.1% and 0.9% in patients receiving placebo, respectively.

Hypertension

In the PRIMA study, Grade 3-4 hypertension occurred in 6% of *ZEJULA*-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset in the *ZEJULA* arm of 50 days (range: 1 to 589 days) and with a median duration of 12 days (range: 1 to 61 days). No patients discontinued due to hypertension.

In the NOVA study, hypertension of any grade occurred in 19.3% of patients treated with *ZEJULA*. Grade 3/4 hypertension occurred in 8.2% of patients. Discontinuation due to hypertension occurred in <1% of patients.

Overdose

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 provide general supportive measures and should treat symptomatically.

Pharmacological Properties

Pharmacodynamics

ATC Code

L01XK02

Mechanism of Action

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.

Pharmacodynamic Effects

Cardiac Electrophysiology

Niraparib demonstrated no clinically significant QTc prolongation in clinical trials. The potential for QTc prolongation with niraparib was evaluated in a randomised, placebo-controlled trial in patients with ovarian cancer (NOVA). QTcF analysis was conducted on 58 subjects in total (53 on niraparib, 5 on placebo) derived from the main NOVA study and two sub-studies (open label Food Effect and open label QTc). No patient who underwent intensive ECG monitoring in the NOVA main or QTc sub-study had QTcF >480 ms or QTcF change from baseline >30 ms at any post-dose time point.

The study assessed the effects of niraparib on cardiac repolarisation following a single dose of *niraparib* (300 mg orally), and correlated changes from baseline in QTc with plasma concentrations of niraparib. In patients who underwent intensive ECG monitoring in the NOVA main or QTc sub-study, the largest increase observed in QTcF from baseline (ΔQTcF) was 4.3±8.8 ms (mean±SD) at 3 hours post-dose. The upper bound of the one-sided 95% CI of the ΔQTcF was 6.7 ms at 3 hours post-dose. The largest upper bound of the one-sided 95% CI of the mean change from baseline and placebo in QTcF interval (ΔΔQTcF) was 6.3 ms at 4 hours post-dose.

Pharmacokinetics

Absorption

Following a single-dose administration of *niraparib* 300 mg under fasting conditions, niraparib was measurable in plasma within 30 minutes and the mean peak plasma concentration (C_{max}) for niraparib was reached within 5 hours [ranged 508-875 ng/mL across studies]. Following multiple oral doses of niraparib from 30 mg to 400 mg once daily, accumulation of niraparib was approximately 2 to 3-fold.

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.

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

Following a high-fat meal in patients with solid tumours, the C_{max} and AUC_{inf} of niraparib tablets increased by 11% and 28%, respectively, as compared with fasting conditions. These changes in exposure were not clinically meaningful. The tablet and capsule formulations have been demonstrated to be bioequivalent. Following administration of either one 300 mg tablet or three 100 mg capsules of niraparib in 108 patients with solid tumours under fasting conditions, the 90% confidence intervals of the geometric mean ratios for tablet compared to capsules for C_{max}, AUC_{last} and AUC_{∞} fell within the limits of bioequivalence (0.80 and 1.25).

Distribution

Niraparib was moderately protein bound in human plasma (83%), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the V_d/F was 1,074 L in cancer patients, indicating extensive tissue distribution of niraparib.

Metabolism

Niraparib is metabolised primarily by carboxylesterases to form a major inactive metabolite, M1. In a mass balance study, M1 and M10 (the subsequently formed M1 glucuronides) were the major circulating metabolites.

Elimination

Following a single oral 300-mg dose of *niraparib*, the mean terminal half-life ($t_{½}$) of niraparib ranged from 44 to 54 hours (approximately 2 days) across studies. In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of niraparib was 15.9 L/h in cancer patients.

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following 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 faeces over 21 days. Radioactive recovery in the urine accounted for 47.5% (range 33.4% to 60.2%) and in the faeces 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 faeces primarily as unchanged niraparib.

Special Patient Populations

Children

No studies have been conducted to investigate the pharmacokinetics of niraparib in paediatric patients.

Renal Impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild (CLCr < 90 to ≥ 60 mL/min) and moderate (CLCr < 60 to ≥ 30 mL/min) renal impairment did not influence the clearance of niraparib.

No patients with pre-existing severe renal impairment or end-stage renal disease undergoing hemodialysis were identified in clinical studies (*see Posology*).

Hepatic Impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild hepatic impairment did not influence the clearance of niraparib.

In a clinical study of cancer patients using NCI-ODWG criteria to classify the degree of hepatic impairment, niraparib AUC_{inf} in patients with moderate hepatic impairment (n=8) was 1.56 (90% CI: 1.06 to 2.30) times the niraparib AUC_{inf} in patients with normal hepatic function (n=9) following administration of a single 300 mg dose. *ZEJULA* dose adjustment is recommended for patients with moderate hepatic impairment (see Posology). Moderate hepatic impairment did not have an effect on niraparib C_{max} or on niraparib protein binding.

The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment (*see Posology*).

Age, Weight, and Race

Population pharmacokinetic analyses indicated that age, weight, and race had no significant impact on the pharmacokinetics of niraparib.

Clinical Studies

First-Line Ovarian Cancer Maintenance Treatment

PRIMA was a double-blind, placebo-controlled trial in which patients (n=733) in complete or partial response to first-line platinum-based chemotherapy were randomised 2:1 to *ZEJULA* or matched placebo. The study included a starting dose of 200 mg or 300 mg depending on baseline body weight or platelet count. The study also included patients receiving a starting dose of 300 mg once daily, regardless of body weight or platelet count.

Patients were randomised post-completion of first-line platinum-based chemotherapy plus/minus surgery. Bevacizumab was allowed with chemotherapy. Patients who had neoadjuvant chemotherapy followed by interval debulking surgery could have visible residual or no residual disease. Randomisation was stratified by best response during the front-line platinum regimen (complete response vs partial response), neoadjuvant chemotherapy (NACT) (Yes vs No), and homologous recombination deficiency (HRD) status [positive vs negative or not determined]. Testing for HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis.

Patients began treatment on Cycle 1/Day 1 (C1/D1) with *ZEJULA* 200 or 300 mg or matched placebo administered once daily in continuous 28-day cycles. Clinic visits occurred each cycle (4 weeks ± 3 days). In the PRIMA study, 52% of patients had a dose interruption in Cycle 1, 9% of patients in Cycle 1 and 47% of patients in Cycle 2 had a dose reduction.

PRIMA was initiated with a starting dose of 300 mg once daily in continuous 28-day cycles (henceforth referred to as a fixed starting dose or FSD). Based on retrospective analyses of the NOVA trial, the starting dose in PRIMA was changed with Amendment 2 of the Protocol. From that point forward, patients with a baseline body weight ≥77 kg and baseline platelet count ≥150,000/µL were administered *ZEJULA* 300 mg (3×100 mg capsules) or placebo (3 capsules) daily and patients with a baseline body weight <77 kg or baseline platelet count <150,000/µL were administered *ZEJULA* 200 mg (2×100 mg capsules) or placebo (2 capsules) daily (henceforth referred to as an individualised starting dose or ISD).

Overall, the median dose intensity in subjects who received *ZEJULA* was 181.3 mg/day and the median relative dose intensity was 63% in subjects who received *ZEJULA*. In patients who received the individualised starting dose, the median dose intensity was 178.6 mg/day and the median relative dose intensity was 66%. In patients who received the fixed starting dose, the median dose intensity was 181.8 mg/day and the median relative dose intensity was 61%.

The major efficacy outcome measure, progression-free survival (PFS), was determined by blinded independent central review (BICR) per RECIST, version 1.1. PFS testing was performed hierarchically: first in the HR-deficient (HRd) population, then in the overall population. Overall survival (OS) was a key secondary endpoint. Time to first subsequent therapy (TFST), PFS after the first subsequent therapy (PFS2) were additional secondary endpoints. The median age was 62 and ranged from 32 to 85 years among patients randomised to *ZEJULA* and 33 to 88 years among patients randomised to placebo. Eighty-nine percent of all patients were white. Sixty-nine percent of patients randomised with *ZEJULA* and 71% of patients randomised with placebo had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 at study baseline. In the overall population, 65% of patients had stage III disease and 35% had stage IV disease. Sixty-seven percent of the patients received NACT. Sixty-nine percent of the patients had a complete response to the first-line platinum-based chemotherapy.

PRIMA demonstrated a statistically significant improvement in PFS for patients randomised to *ZEJULA* as compared with placebo in the HR deficient and overall population (Table 5 and Figures 1 and 2).

Table 5: Progression-free survival efficacy results – PRIMA[a]

	HR deficient population		Overall population	
	ZEJULA **(N=247)**	**placebo (N=126)**	***ZEJULA*** **(N=487)**	**placebo (N=246)**
PFS median months (95% CI)[b]	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)
P value[b]	<0.0001		<0.0001	
Hazard ratio (HR)[c] (95% CI)	0.43 (0.31, 0.59)		0.62 (0.50, 0.76)	

CI = confidence interval, PFS = progression-free survival, NE=not evaluable
a Efficacy analysis was based on blinded independent central review (BICR).
b Based on a stratified log-rank test
c Based on a stratified Cox proportional hazards model

In patients who were administered 200 or 300 mg dose of *ZEJULA* based on baseline weight or platelet count, comparable efficacy was observed with a hazard ratio of 0.39 (95% CI: 0.22, 0.72) in the HR deficient population, and with a hazard ratio of 0.69 (95% CI: 0.48, 0.98) in the overall population.

Figure 1.- Figure 1. Progression-free survival in the HR-deficient population - PRIMA (ITT population, N=373)

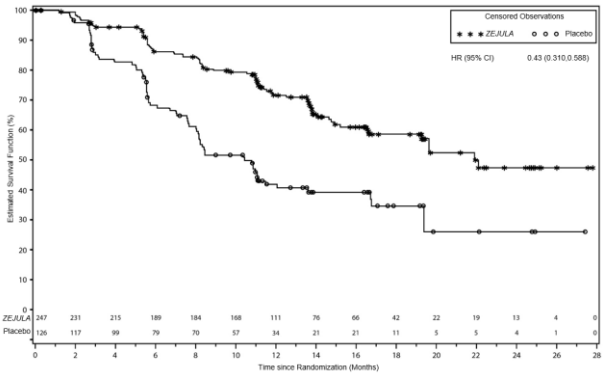
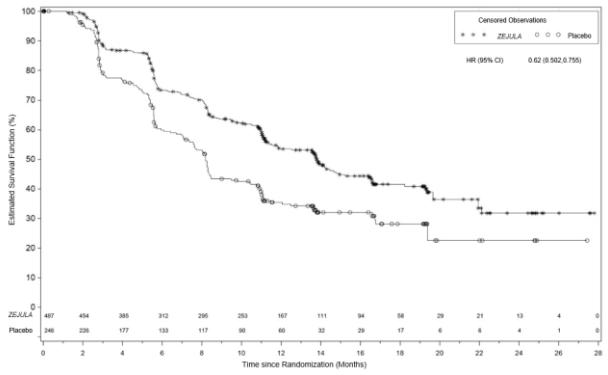


Figure 2.- Progression-free survival in the overall population - PRIMA (ITT population, N=733)



Within the HR-deficient population, a PFS hazard ratio of 0.40 (95% CI: 0.27, 0.62) was observed in the subgroup of patients with *BRCA*mut ovarian cancer (n=223). In the subgroup of HR-deficient patients without a *BRCA* mutation (n=150), a hazard ratio of 0.50 (95% CI: 0.31, 0.83) was observed. In the HR-proficient (HRD negative) population (n=249), a hazard ratio of 0.68 (95% CI: 0.49, 0.94) was observed.

Secondary efficacy endpoints in PRIMA

At the final analysis, the median TFST in the overall population was 17.0 months (95% CI: 15.4, 20.1) in patients randomised to *ZEJULA* compared to 12.0 months (95% CI: 10.4, 14.1) in the placebo arm, with a hazard ratio of 0.74 (95% CI: 0.62, 0.89). In the HR-deficient population, the median TFST was 26.9 months (95% CI: 23.2, 39.0) in patients randomised to *ZEJULA* compared to 13.9 months (95% CI: 11.6, 18.1) in the placebo arm, with a hazard ratio of 0.55 (95% CI: 0.43, 0.71).

At the final analysis, the median PFS2 in the overall population was 30.1 months (95% CI: 27.1, 33.1) in patients randomised to *ZEJULA* compared to 27.6 months (95% CI: 24.2, 33.1) in the placebo arm, with a hazard ratio of 0.96 (95% CI: 0.79, 1.17). In the HR-deficient population, the median PFS2 was 43.4 months (95% CI: 37.2, 54.1) in patients randomised to niraparib compared to 39.3 months (30.3, 55.7) in the placebo arm, with a hazard ratio of 0.87 (95% CI: 0.66, 1.17).

In the overall population, 11.7% of patients randomised to *ZEJULA* and 37.8% in the placebo arm received subsequent PARPi therapy. In the HR-deficient population, 15.8% of patients randomised to niraparib and 48.4% in the placebo arm received subsequent PARPi therapy.

Overall survival analyses in PRIMA

At the final analysis of OS, the median OS in the overall population was 46.6 months (95% CI: 43.7, 52.8) for patients randomised to *ZEJULA* compared with 48.8 months (95% CI: 43.1, 61.0) in the placebo arm, with a hazard ratio of 1.01 (95% CI: 0.84, 1.23) (Figure 3). The maturity of the OS data for the overall population was 62.5%.

The median OS in the HR-deficient population was 71.9 months (95% CI: 55.5, NE) for patients randomised to *ZEJULA* compared to 69.8 months (95% CI: 51.6, NE) in the placebo arm, with a hazard ratio of 0.95 (95% CI: 0.70, 1.29) (Figure 4). The maturity of the OS data for the HR-deficient group was 49.6%.

Figure 3.- Overall survival in the overall population – PRIMA (ITT population, N = 733)

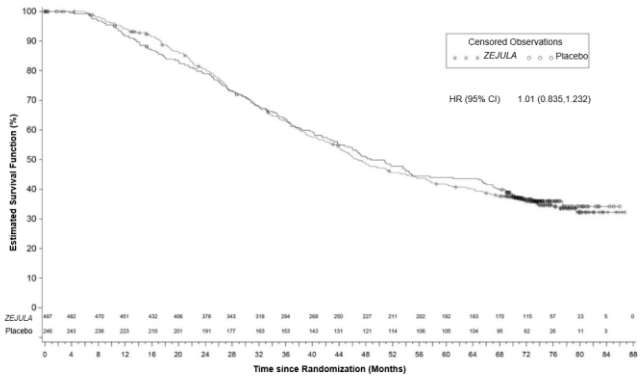
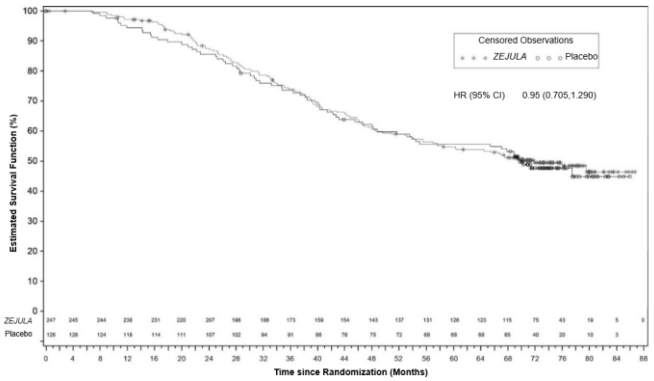


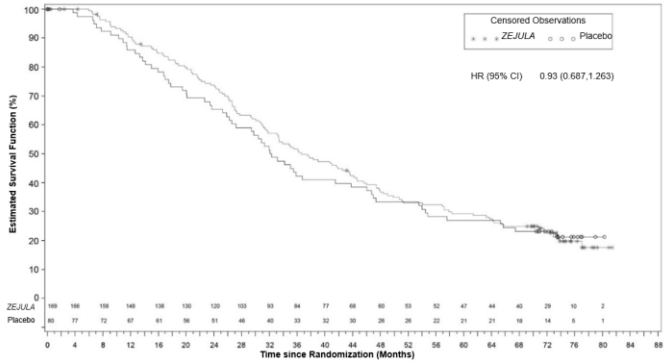
Figure 4.- Overall survival in the HR-deficient population – PRIMA (ITT population, N = 373)



Overall survival analyses – additional subgroups results in PRIMA

The median OS in the HR-proficient population (n = 249) was 36.6 months (95% CI: 31.7, 43.7) for patients randomised to *ZEJULA* compared to 32.2 months (95% CI: 26.3, 43.8) in the placebo arm, with a hazard ratio of 0.93 (95% CI: 0.69, 1.26) (Figure 5).

Figure 5. Overall survival in the HR-proficient population – PRIMA (ITT population, N = 249)



Within the HR-deficient population, the OS hazard ratio results for patients with and without a *BRCA* mutation were consistent across subgroups. An OS hazard ratio of 0.94 (95% CI: 0.63, 1.41) was observed in the subgroup of patients with a *BRCA* mutation (n = 223). In the subgroup of HR-deficient patients without a BRCA mutation (n = 149), a hazard ratio of 0.97 (95% CI: 0.62, 1.53) was observed.

Patient-Reported Outcomes

At the final analysis, no differences were observed overall between *ZEJULA* and placebo in patient reported symptoms, function (Physical, Role, Emotional, Cognitive, Social), or health-related quality of life (HRQoL) as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires, EORTC-QLQ-C30 and EORTC-QLQ-OV28.

Recurrent Ovarian Cancer Maintenance Treatment

The safety and efficacy of *ZEJULA* as maintenance therapy was studied in a Phase 3 randomised, double-blind, placebo-controlled international trial (NOVA) in patients with relapsed predominantly high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who were platinum sensitive, 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 *ZEJULA* treatment, the patient should be in response (CR or PR) following completion of last platinum-based chemotherapy. The CA-125 levels should be normal (or a > 90% decrease in CA-125 from baseline) following their last platinum treatment and be stable for at least 7 days. Patients could not have received prior PARP inhibitor (PARPi) therapy, including *ZEJULA*. Eligible patients were assigned to one of two cohorts based on the results of a germline *BRCA* (g*BRCA*) mutation test. Within each cohort, patients were randomised using a 2:1 allocation of *ZEJULA* and placebo. Patients were assigned to the g*BRCA*mut cohort based on blood samples for g*BRCA* analysis that were taken prior to randomisation. Testing for tumour *BRCA* (t*BRCA*) mutation and HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis or at the time of recurrence.

Randomisation within each cohort was stratified by time to progression after the penultimate platinum therapy before study enrolment (6 to <12 months and ≥12 months); use or not of bevacizumab in conjunction with the penultimate or last platinum regimen; and best response during the most recent platinum regimen (complete response and partial response).

Patients began treatment on Cycle 1/Day 1 (C1/D1) with *ZEJULA* 300 mg or matched placebo administered once daily in continuous 28-day cycles. Clinic visits occurred each cycle (4 weeks ± 3 days).

In the NOVA study, 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 *ZEJULA*-treated patients in the NOVA study was 200 mg.

Progression-free survival was determined per RECIST (Response Evaluation Criteria in Solid Tumors, version 1.1) or clinical signs and symptoms and increased CA-125. PFS was measured from the time of randomisation (which occurred up to 8 weeks after completion of the chemotherapy regimen) to disease progression or death.

The primary efficacy analysis for PFS was determined by blinded central independent assessment and was prospectively defined and assessed for the g*BRCA*mut cohort and the non-g*BRCA*mut cohort separately.

Secondary efficacy endpoints included chemotherapy-free interval (CFI), time to first subsequent therapy (TFST), PFS after the first subsequent therapy (PFS2), and overall survival (OS).

Demographics, baseline disease characteristics, and prior treatment history were generally well balanced between the *ZEJULA* and placebo arms in the g*BRCA*mut (n=203) and the non-g*BRCA*mut cohorts (n=350). Median ages ranged from 57 to 63 years across treatments and cohorts. The primary tumour site in most patients (>80%) within each cohort was the ovary; most patients (>84%) had tumours with serous histology. A high proportion of patients in both treatment arms in both cohorts had received 3 or more prior lines of chemotherapy, including 49% and 34% of *ZEJULA* patients in the g*BRCA*mut and non-g*BRCA*mut cohorts, respectively. Most patients were age 18 to 64 years (78%), Caucasian (86%) and had an ECOG performance status of 0 (68%).

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

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

The study met its primary objective of statistically significantly improved PFS for *ZEJULA* maintenance monotherapy compared with placebo in the g*BRCA*mut cohort (HR 0.27; 95% CI: 0.173, 0.410; p < 0.0001) as well as in the overall non-g*BRCA*mut cohort (HR 0.45; 95% CI: 0.338, 0.607; p < 0.0001). Table 6 and Figures 3 and 4 show the results for the PFS primary endpoint for the primary efficacy populations (g*BRCA*mut cohort and the overall non-g*BRCA*mut cohort).

Table 6.- Progression-free survival efficacy results – NOVA study

	g*BRCA*mut cohort		Non-g*BRCA*mut cohort	
	ZEJULA **(N = 138)**	**placebo (N = 65)**	***ZEJULA*** **(N = 234)**	**placebo (N = 116)**
PFS median, months (95% CI)	21.0 (12.9, NE)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)
P value	< 0.0001		< 0.0001	
Hazard ratio (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)	
CI = confidence interval, PFS = progression-free survival, NE=not evaluable.				

Prior to unblinding of the study, tumours of patients were tested for the presence of HRD using an 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 the HRDpos group, the hazard ratio was 0.38 (95% CI: 0.243, 0.586; p < 0.0001). In the HRDneg group, the hazard ratio was 0.58 (95% CI: 0.361, 0.922; p = 0.0226). The experimental test was not able to discriminate which patients would or would not benefit from *ZEJULA* maintenance therapy.

Figure 6.- Progression-free survival in the gBRCAmut cohort based on IRC assessment – NOVA (ITT population, N = 203)

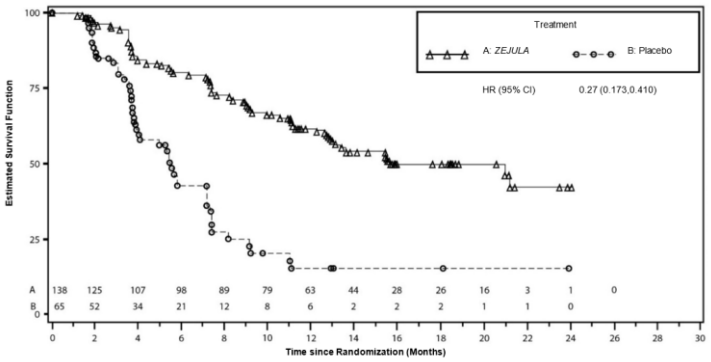
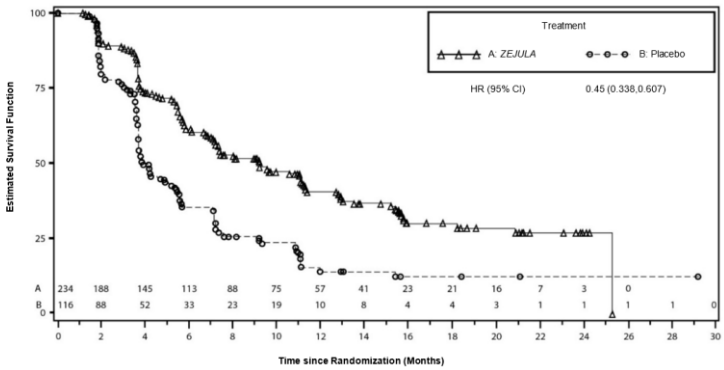


Figure 7.-Progression-free survival in the non-gBRCAmut cohort /overall based on IRC assessment – NOVA (ITT population, N = 350)



Secondary Efficacy Endpoints in NOVA

At the final analysis, the median CFI in the g*BRCA*mut cohort was 20.0 months for patients treated with *ZEJULA* compared to 9.4 months for patients on placebo (HR=0.39; 95% CI: 0.27, 0.56). The median CFI in the non-g*BRCA*mut cohort was 13.4 months for patients treated with *ZEJULA* compared to 8.7 months for patients on placebo (HR=0.56; 95% CI: 0.43, 0.73).

At the final analysis, the median TFST in the g*BRCA*mut cohort was 19.1 months for patients treated with *ZEJULA* compared to 8.6 months for patients on placebo (HR=0.57; 95% CI: 0.41, 0.78). The median TFST in the non-g*BRCA*mut cohort was 12.4 months for patients treated with *ZEJULA* compared to 7.4 months for patients on placebo (HR=0.58; 95% CI: 0.45, 0.74).

At the final analysis, the median PFS2 in the g*BRCA*mut cohort was 29.9 months for patients treated with *ZEJULA* compared to 22.7 months for patients on placebo (HR=0.70; 95% CI: 0.50, 0.97). The median PFS2 in the non-g*BRCA*mut cohort was 19.5 months for patients treated with *ZEJULA* compared to 16.1 months for patients on placebo (HR=0.80; 95% CI: 0.63, 1.02).

Overall survival analyses in NOVA

Overall survival analyses were secondary outcome measures in the NOVA study. At the final analysis of overall survival, the median OS in the g*BRCA*mut cohort (n = 203) was 40.9 months for patients treated with *ZEJULA* compared with 38.1 months for patients on placebo (HR=0.85; 95% CI: 0.61, 1.20). The cohort maturity for the g*BRCA*mut cohort was 76%. The median OS in the non-*gBRCA*mut cohort (n = 350) was 31.0 months for patients treated with *ZEJULA* compared with 34.8 months for patients on placebo (HR=1.06; 95% CI: 0.81, 1.37). The cohort maturity for the non-g*BRCA*mut cohort was 79%.

Overall survival analyses in NORA

The overall survival results of NOVA are supported by an OS analyses from a Phase 3 regional registrational study. NORA was a randomised, double-blind, placebo-controlled clinical study (n = 265) conducted in China to evaluate the efficacy and safety of *ZEJULA* as maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer.

Based on an analysis of preliminary OS events from the NORA study, a potential favourable OS trend was observed in the *ZEJULA* maintenance treatment arm, compared with placebo in ITT (44% maturity), g*BRCA*mut (36% maturity) and non-g*BRCA*mut (47% maturity), despite considerable numbers of patients in the placebo arm receiving PARPi in subsequent therapy.

Patient-Reported Outcomes

Patient-reported outcome (PRO) data from validated survey tools (FOSI and EQ-5D) indicate that *ZEJULA*-treated patients reported no difference from placebo in measures associated with quality of life (QoL).

Data to Support ISD in Recurrent Ovarian Cancer Maintenance Treatment Population

In the NORA study, after the first 16 patients were enrolled on a fixed starting dose of 300 mg, the study was amended to include an individualised starting dose of 200 mg or 300 mg depending on baseline body weight or platelet count (henceforth referred to as an individualised starting dose or ISD).

The PFS for all patients in the study (n=265) and for patients with an ISD (n=249) was 18.3 months in the *ZEJULA* group and 5.4 months in the placebo group. Comparable efficacy was observed with a hazard ratio of 0.32 (95% CI: 0.23, 0.46) for all patients in the study, and a hazard ratio of 0.30 (95% CI 0.21, 0.43) in the patients with an ISD.

Patients receiving a starting dose of *ZEJULA* 200 mg accounted for 87.5% (155 of 177 cases) of the pooled patients receiving *ZEJULA*,and had a median PFS consistent with the pooled *ZEJULA* group (18.3 months), indicating a therapeutic effect in the patients receiving an ISD regimen and no reduction in the therapeutic effect compared with the overall population of NORA or the patient population of NOVA study.

Non-Clinical Information

Carcinogenesis/Mutagenesis

Carcinogenicity studies have not been conducted with niraparib.

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.

Reproductive Toxicology

Reproductive and developmental toxicity studies have not been conducted with niraparib.

Animal Toxicology and/or Pharmacology

In vitro, niraparib inhibited the dopamine transporter DAT at concentration levels below human exposure levels. In mice, single doses of niraparib increased intracellular levels of dopamine and metabolites in cortex. Reduced locomotor activity was seen in one of two single dose studies in mice. The clinical relevance of these findings is not known. No effect on behavioural and/or neurological parameters have been observed in repeat-dose toxicity studies in rats and dogs at estimated CNS exposure levels similar to or below expected therapeutic exposure levels.

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 parameters.

Additionally, decreased spermatogenesis was seen in both species. These findings occurred at exposure levels below those seen clinically and were largely reversible within 4 weeks of cessation of dosing.

Pharmaceutical Information

List of Excipients

Hard Capsule

Capsule Content

Magnesium stearate

Lactose monohydrate

Capsule Shell

Titanium dioxide (E 171)

Gelatin

Brilliant blue FCF (E 133)

Erythrosine (E 127)

Tartrazine (E 102)

Printing Ink

Shellac (E 904)

Propylene glycol (E 1520)

Potassium hydroxide (E 525)

Black iron oxide (E 172)

Sodium hydroxide (E 524)

Povidone (E 1201)

Titanium dioxide (E 171)

Each hard capsule shell contains the colouring agent tartrazine (E 102) [0.0172 mg] (*see Warnings and Precautions*).

Film-Coated Tablets:

Tablet Core

Crospovidone,

Lactose monohydrate,

Magnesium stearate,

Microcrystalline cellulose,

Povidone,

Silicon dioxide.

Tablet Coat

Opadry II Gray (100 mg)

Opadry II Blue (200 mg)

Opadry II Green (300 mg)

Purified water.

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Nature and Contents of Container

ZEJULA Capsules are available in Aclar/PVC/aluminium foil perforated unit dose blisters.

ZEJULA film-coated tablets are available in square high-density polyethylene bottles and in oPA/aluminium/PVC/aluminium/vinyl/acrylic blisters in cartons, or oPA/aluminium/PVC/aluminium/vinyl/acrylic/paper child-resistant blisters in cartons.

Incompatibilities

Not applicable.

Use and Handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Not all presentations are available in every country.

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