Summary Report of Benefit-Risk Assessment

ZEJULA FILM-COATED TABLET 100MG, 200MG, 300MG

NEW DRUG APPLICATION

Active Ingredient(s)	Niraparib
Product Registrant	GlaxoSmithKline Pte Ltd
Product Registration Number	SIN16459P, SIN16460P, SIN16461P
Application Route	Full evaluation
Date of Approval	01 April 2022

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A INTRODUCTION

Zejula is indicated:

- as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy; and
- 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 overall survival benefit in patients without germline breast cancer gene (BRCA) mutation ovarian cancer has not been demonstrated.

The active substance, niraparib, inhibits poly (ADP-ribose) polymerase enzymes (PARP-1 and PARP-2) and increases the formation of PARP-DNA complexes resulting in DNA damage and apoptosis of tumour cells.

Zejula film coated tablets contain 100 mg, 200 mg or 300 mg of niraparib (as niraparib tosylate monohydrate). The excipients used are crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and silicon dioxide. Components of the film coat include polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, ferrosferric oxide, FD&C Blue #2 (for 200 mg), FD&C Blue #1 (for 300 mg) and yellow iron oxide (for 300 mg).

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, niraparib as niraparib tosylate monohydrate, is manufactured at Changzhou SynTheAll Pharmaceutical Co., Ltd, Changzhou, China. The drug products, Zejula Film-coated Tablet 100 mg, 200 mg and 300 mg, are manufactured at Mayne Pharma, Inc., Greenville, United States of America.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented was adequate to support the approved storage condition and re-test period. The drug substance was packed in low-density polyethylene (LDPE) continuous liner sealed with a clamp, followed by packaging into another LDPE bag and sealed with a cable tie, thereafter, packaging into a high-density polyethylene (HDPE) drum which is sealed

with a clamp and locking ring. The drug substance is approved for storage at or below 25°C with a re-test period of 48 months.

Drug product:
The tablet is manufactured using a dry granulation approach, followed by film-coating. The process is considered a standard process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30 ºC. The container closure system is a OPA/aluminium/PVC/aluminium/vinyl/acrylic blister pack containing 7 tablets per blister.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of niraparib was supported by two pivotal clinical studies, Study PR-30-5011-C (NOVA) for the maintenance treatment of recurrent ovarian cancer, and Study PR-30-5017C (PRIMA) for the maintenance treatment of advanced ovarian cancer.

During the clinical development, the capsule formulation was used in the clinical studies. Bioequivalence between niraparib capsule and the commercial tablet formulation was demonstrated in Study 3000-01-004, which was a Phase 1, open-label, two-stage, randomised, single-dose, crossover, fasted, bioequivalence study in patients with advanced solid tumours. The calculated 90% confidence interval (CI) of the geometric means ratios for ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max} between niraparib capsule and niraparib tablet were within the bioequivalence prespecified acceptance range of 0.800 and 1.250.

<u>Recurrent ovarian cancer</u>

The NOVA study was a Phase 3, randomised, double-blind, placebo-controlled study that compared niraparib with placebo as maintenance treatment in female adult patients with recurrent, high-grade serous epithelial ovarian cancer who were in complete or partial response for more than 6 months after their penultimate platinum-based chemotherapy. All patients were to have completed at least two previous courses of platinum-containing therapy, not have any measurable lesion >2 cm at study entry and have CA-125 levels that were normal following their last platinum regimen or had decreased by >90% during their last regimen and stable (no increase by >15%) for at least 7 days. Patients were enrolled into two cohorts based on the presence (gBRCAmut) or absence (non-gBRCAmut) of germline BRCA mutation.

Patients were randomised within 8 weeks after completion of their last dose of platinum-based chemotherapy in a 2:1 ratio to receive either oral niraparib 300 mg (three capsules of 100 mg

capsule) or placebo (three matching capsules) once daily in continuous 28-day cycles. The randomisation in each cohort was stratified by time to progression after the penultimate platinum therapy before enrolment (6 to <12 months and ≥12 months), use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no), and best response during the last platinum regimen (CR or PR). The dose of niraparib could be interrupted and/or reduced to a minimum dose of 100 mg once daily during the study if the patient experienced adverse reactions. Treatment with study drug was continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Patients who were randomised to the placebo arm were not allowed to cross over to receive niraparib treatment at any time during the study.

The primary efficacy endpoint was progression-free survival (PFS), defined as the time from randomisation to first documentation of progression or death due to any cause as determined by the blinded independent central review (BICR). The secondary efficacy endpoints were the time to first subsequent treatment (TFST), time to second subsequent treatment (TSST), chemotherapy-free interval (CFI), progression-free survival 2 (PFS2), overall survival (OS), time to CA-125 progression, and patient-reported outcomes.

The primary hypothesis on PFS was independently tested for each of the gBRCAmut and non-gBRCAmut cohort to control the type I error rate. Within the non-gBRCAmut cohort, the primary hypothesis was first tested in patients with homologous recombinant (HR) deficient tumour. If the study rejected the primary hypothesis in the HR deficient tumour patient population within the non-gBRCAmut cohort, the non-gBRCAmut cohort regardless of HR tumour status would then be tested for the primary hypothesis. Otherwise, PFS was to be analysed as exploratory endpoint in the overall non-gBRCAmut cohort. The secondary efficacy endpoints were to be analysed in the same manner as that for the primary efficacy endpoint.

A total of 553 patients were randomised into the study, comprising 372 patients in the niraparib arm and 181 patients in the placebo arm. Of these, 36.7% were enrolled into the gBRCAmut cohort and 63.3% of patients were enrolled into the non-gBRCAmut cohort. Among those in the non-gBRCAmut cohort, 46.3% of patients had HR deficient tumour, 38.3% of patients had HR proficient tumour, while the HR tumour status was not available for 15.4% of patients. The median treatment duration was 8.2 months (range: 0 - 61 months) in the niraparib arm and 5.4 months (range: 0 - 65 months) in the placebo arm.

The patient demographics and baseline characteristics were well-balanced between the treatment arms and patient cohorts. The median age was 60.0 years (range: 33 – 84 years), and 35.3% of patients were ≥65 years of age. The majority of patients were White (86.8%), had ovary as the primary tumour site (83.7%) and had serous histology tumours (94.4%). Within the gBRCAmut cohort, 63% of patients had gBRCA1 mutation variant and 34.0% had gBRCA2 mutation variant. Most of the patients (68.2%) had received 2 prior lines of platinum therapy, including 57.1% of patients in gBRCAmut cohort and 74.6% of patients in the non-gBRCAmut cohorts.

The results showed that maintenance treatment with niraparib demonstrated statistically significantly improved PFS compared with placebo in the gBRCAmut cohort (hazard ratio 0.27; 95% CI: 0.173 – 0.410; p<0.0001) and the non-gBRCAmut cohort (hazard ratio 0.45; 95% CI: 0.338 – 0.607; p<0.0001). Within the non-gBRCAmut cohort, statistically significantly improvement in PFS was similarly observed with niraparib compared with placebo in patients with HR deficient tumour (hazard ratio 0.38; 95% CI: 0.243 – 0.586; p<0.0001). The results of the secondary endpoints (TFST, CFI, PFS2, TSST) supported the primary endpoint findings.

The final OS analysis was confounded due to high percentage of missing survival status data (49%), subsequent PARP inhibitors use after progression in the placebo arm (46%), and missing information on subsequent PARP inhibitor use during follow-up (31%). Hence, no conclusion can be drawn on the survival benefits in either the gBRCAmut cohort or the non-BRCAmut cohort.

Pre-specified subgroup analyses demonstrated consistent treatment effect for the primary endpoint across subgroups analysed in the gBRCAmut and non-gBRCAmut cohorts, including age group (18 to <65 years, ≥65 years), race (White, Other), region (USA and Canada, rest of world), time to progression before study enrolment (6 to <12 months, ≥12 months), bevacizumab use (yes, no), best overall response on last platinum regimen (CR, PR), total cumulative number of prior chemotherapy (2, >2), total number of prior platinum regimen (2, >2), and BRCA mutation variant in the gBRCAmut cohort (BRCA1, BRCA2).

Summary of Key Efficacy Results (NOVA study)

	Niraparib	**Placebo**	**Hazard ratio [c] (95% CI)**	**p-value [d]**
Primary endpoint, Progression-free survival (PFS)				
gBRCAmut cohort, n	138	65		
Median PFS (months) [a]	21.0	5.5	0.27	<0.0001
95% CI	(12.9 – NE)	(3.8 – 7.2)	(0.173 – 0.410)	
Non-gBRCAmut cohort, n	234	116		
Median PFS (months) [a]	9.3	3.9	0.45	<0.0001
95% CI	(7.2 – 11.2)	(3.7 – 5.5)	(0.338 – 0.607)	
Non-gBRCAmut/HR deficient cohort, n	106	56		
Median PFS (months) [b]	12.9	3.8	0.38	<0.0001
95% CI	(8.1 – 15.9)	(3.5 – 5.7)	(0.243 – 0.586)	
Non-gBRCAmut/HR proficient cohort, n	92	42		
Median PFS (months) [b]	6.9	3.8	0.58	0.0226
95% CI	(5.6 – 9.6)	(3.7 – 5.6)	(0.361 – 0.922)	
Secondary endpoint, Overall Survival (OS)				
gBRCAmut cohort, n	138	65		
Median OS (months) [a]	43.6	41.6	0.93	0.6934
95% CI	(35.8 – 53.0)	(29.3 – 52.9)	(0.633 – 1.355)	
Non-gBRCAmut cohort, n	234	116		
Median OS (months) [a]	31.1	36.5	1.10	0.5010
95% CI	(27.8 – 37.3)	(27.9 – 41.6)	(0.831 – 1.459)	
Secondary endpoint, Progression-free survival after the first subsequent therapy (PFS2)				
gBRCAmut cohort, n	138	65		
Median PFS2 (months) [a]	30.4	22.7	0.67	0.0224
95% CI	(25.0 – 33.4)	(17.8 – 25.6)	(0.479 – 0.948)	
Non-gBRCAmut cohort, n	234	116		
Median PFS2 (months) [a]	18.5	15.6	0.81	0.1149
95% CI	(16.8 – 21.7)	(13.2 – 22.8)	(0.632 – 1.050)	
Secondary endpoint, Time to first subsequent therapy (TFST)				
gBRCAmut cohort, n	138	65		
Median TFST (months) [a]	19.1	8.6	0.54	0.0002
95% CI	(15.0 – 21.9)	(6.7 – 11.2)	(0.384 – 0.747)	
Non-gBRCAmut cohort, n	234	116		

Median TFST (months) [a] 95% CI	11.8 (9.9 – 13.6)	7.4 (5.8 – 8.7)	0.62 (0.481 – 0.797)	0.0002
Secondary endpoint, Chemotherapy-free interval (CFI)				
gBRCAmut cohort, n Median TFST (months) [b] 95% CI	138 22.8 (17.9 – NE)	65 9.4 (7.9 – 10.6)	 0.26 (0.166 – 0.409)	 <0.0001
Non-gBRCAmut cohort, n Median TFST (months) [b] 95% CI	234 12.7 (11.0 – 14.7)	116 8.6 (6.9 – 10.0)	 0.50 (0.370 – 0.666)	 <0.0001

BICR: blinded independent central review; CI: confidence interval; CFI: chemotherapy-free interval; gBRCAmut: germline breast cancer gene mutation; HR: homologous recombination; n: number of patients; NE: not estimated; OS: overall survival; PFS: progression-free survival; PFS2: progression-free survival 2; TFST: time to first subsequent therapy

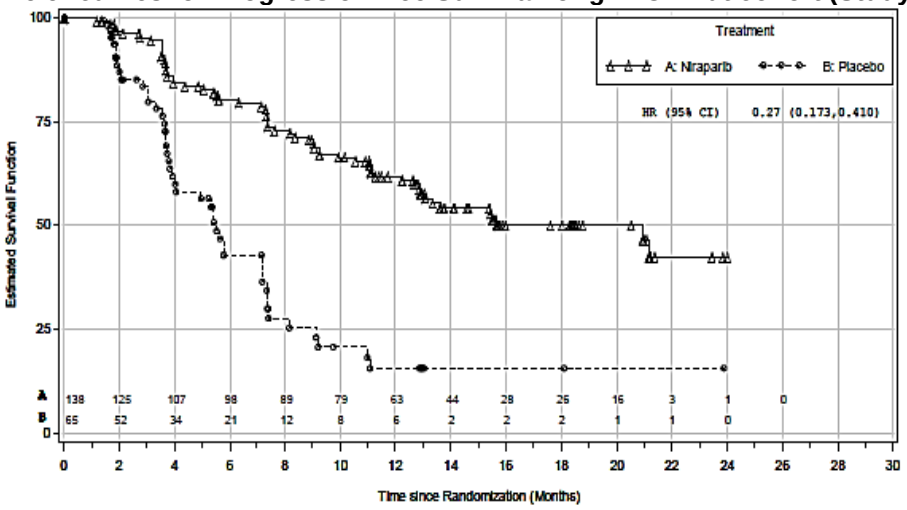
[a] Based on final analyses at data cut-off date of 1 October 2020.

[b] Based on data cut-off date of 30 May 2016.

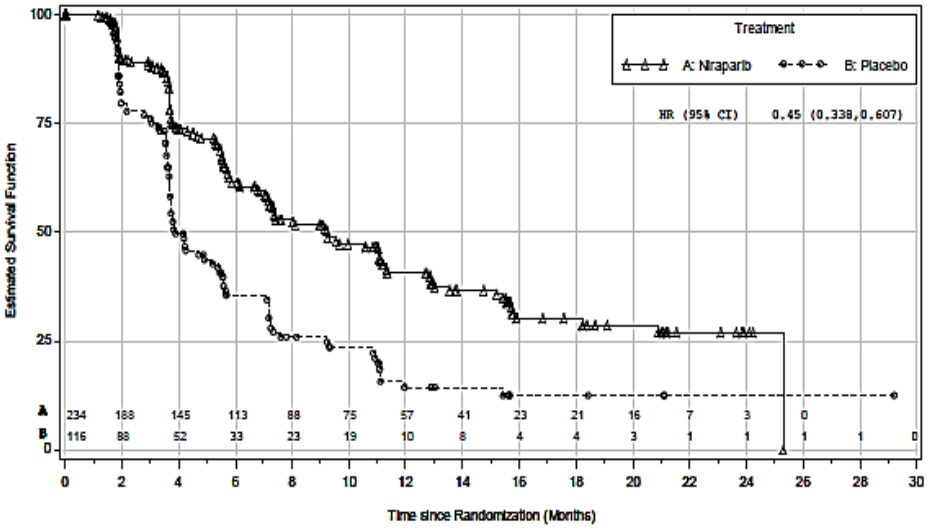
[c] Niraparib versus placebo, based on the stratified Cox proportional hazards model using randomisation stratification factors.

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

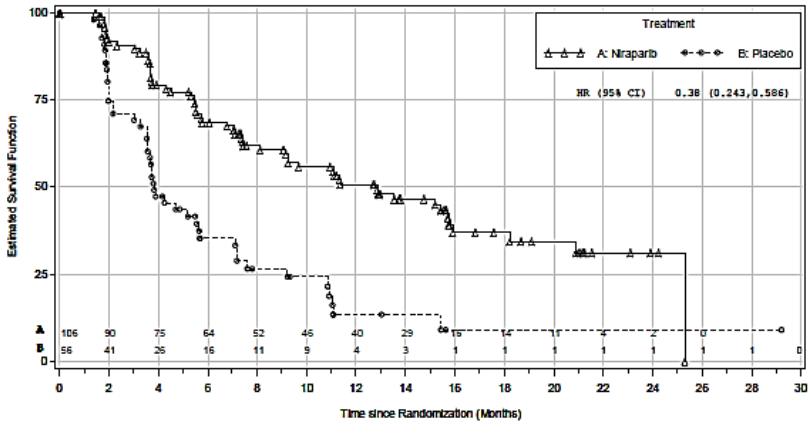
Kaplan-Meier curves for Progression-free Survival for gBRCAmut cohort (Study NOVA)



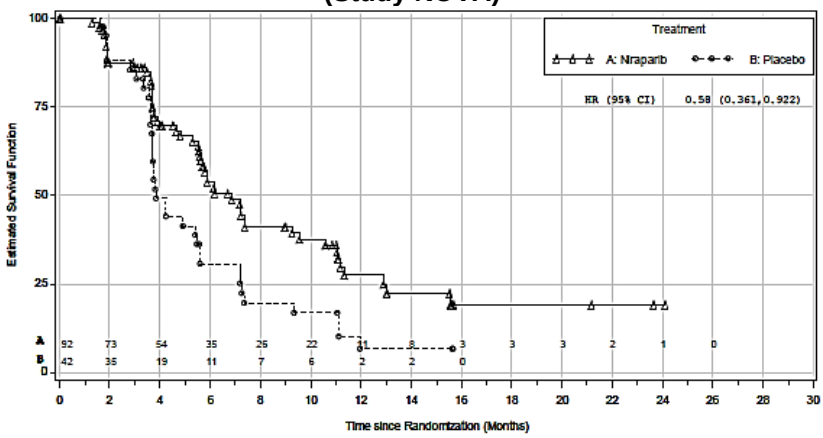
Kaplan-Meier curves for Progression-free Survival for non-gBRCAmut cohort (Study NOVA)



Kaplan-Meier curves for Progression-free Survival for non-gBRCAmut/HR deficient cohort (Study NOVA)



Kaplan-Meier curves for Progression-free Survival for non-gBRCAmut/HR proficient cohort (Study NOVA)



Overall, the results in NOVA study supported the treatment benefit of niraparib in the maintenance treatment of patients with platinum-sensitive, relapsed, and high grade serous epithelial ovarian cancer who are in response to platinum-based chemotherapy. The survival benefit in patients without germline BRCA mutation ovarian cancer has not been demonstrated.

Advanced ovarian cancer

The PRIMA study was a Phase 3, randomised, double-blind, placebo-controlled study that compared niraparib with placebo as maintenance treatment in female adult patients with advanced (FIGO Stage III or IV) epithelial high-grade ovarian cancer who are in complete or partial response following completion of their first-line platinum-containing chemotherapy.

Patients were initially randomised within 12 weeks after completion of their last chemotherapy cycle in a 2:1 ratio to receive either a fixed starting dose of niraparib 300 mg (three capsules of 100 mg capsules) or placebo (three matching capsules) once daily in continuous 28-day cycles (referred to as the fixed starting dose cohort). The randomisation was stratified by best response to first-line platinum chemotherapy, receipt of neoadjuvant chemotherapy, and HR tumour status.

At protocol amendment 2, the starting dose was modified and assigned based on individual patient's baseline body weight and/or platelet count (referred to as the individualised starting dose cohort). Patients who were randomised to niraparib arm and had a baseline body weight of ≥77kg and baseline platelet count of ≥150,000/μL were assigned to receive a starting dose of 300 mg niraparib, while patients who had a baseline body weight of <77kg or baseline platelet count of <150,000/μL were assigned to receive a starting dose of 200 mg niraparib. The dose of niraparib could be escalated to 300 mg for patients who had received a starting dose of 200 mg if there was no treatment interruption of discontinuation due to adverse reactions during the first two cycles of treatment.

For the fixed starting dose and individualised starting dose cohorts, the dose of niraparib could be interrupted and/or reduced up to a minimum dose of 100 mg once daily during the study if the patient experienced adverse reactions. Treatment with study drug was continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Patients who were randomised to the placebo arm were not allowed to cross over to receive niraparib treatment at any time during the study.

The primary efficacy endpoint was PFS assessed by BICR. The key secondary efficacy endpoint was OS. Other secondary endpoints included TFST, PFS2, time to CA-125 progression, outcomes for the next anticancer therapy following study treatment, and patient-reported outcomes. The primary hypothesis (PFS) was tested in hierarchical order to control the type I error rate. If the study rejected the primary hypothesis in the patient population with HR deficient tumour, the overall intent-to-treat (ITT) population regardless of HR tumour status would then be tested for the primary hypothesis. Otherwise, PFS was to be analysed as exploratory endpoint in the overall ITT population. The secondary efficacy endpoints were to be analysed in the same manner as for the primary efficacy endpoint. An interim analysis of OS was performed at the time of the primary PFS analysis with appropriate adjustment for multiplicity.

A total of 733 patients were randomised into the study, comprising 487 patients in the niraparib arm and 246 patients in the placebo arm. A total of 30.4% of patients in the overall ITT population had BRCAmut tumour and 50.9% of patients had HR deficient tumour. The median treatment duration was 11.1 months (range: 0 to 29 months) in the niraparib arm and 8.3 months (range: 0 to 28 months) in the placebo arm.

The patient demographics and baseline characteristics were well-balanced between the treatment arms. The median age was 62.0 years (range: 32 - 88 years), and 30.0% of patients were ≥65 years of age. The majority of patients were White (89.3%), had ovary as the primary tumour site (80.4%), and had serous histology tumours (94.8%). Of the 223 patients with BRCAmut tumour, 66.4% of patients had BRCA1 mutation variant and 33.6% had BRCA2 mutation variant.

The results showed that maintenance treatment with niraparib demonstrated statistically significant improvements in PFS compared with placebo in the HR deficient tumour patient population (hazard ratio 0.43; 95% CI: 0.310 – 0.588; p<0.0001) and the overall ITT population (hazard ratio 0.62; 95% CI: 0.502 – 0.755; p<0.0001).

The key secondary endpoint of OS was immature at the data cut-off date of 17 May 2019 with only 79 death events, including 48 (9.9%) patients in the niraparib arm and 31 (12.7%) patients in the placebo arm. The hazard ratio for OS was 0.61 (95% CI: 0.265 – 1.388) in the HR deficient tumour patient population and 0.70 (95% CI: 0.442 – 1.106) in the overall ITT population. Similarly, the data for the other secondary endpoints (TFST and PFS2) were

immature as of the data cut-off date. Nonetheless, the secondary endpoint results showed a trend that favoured the niraparib arm.

The post-hoc exploratory analyses demonstrated comparable PFS benefit between the fixed starting dose cohort (hazard ratio 0.62; 95% CI: 0.465 – 0.833) and the individualised starting dose cohort (hazard ratio 0.68; 95% CI: 0.49 – 0.94) in the overall ITT population. Within the HR deficient tumour patient population, comparable PFS benefit was observed between the fixed starting dose cohort (hazard ratio 0.46; 95% CI: 0.296 – 0.706) and the individualised starting dose cohort (hazard ratio 0.54; 95% CI: 0.33 – 0.91).

Pre-specified subgroup analyses demonstrated consistent treatment effect for the primary endpoint across subgroups analysed in the overall population and HR deficient tumour patient population, including age group (<65years, ≥65 years), race (White, non-White), ECOG performance status (0, 1), stage of disease at initial diagnosis (stage III, stage IV), receipt of neoadjuvant chemotherapy (yes, no), best response to first-line platinum regimen (CR, PR), tumour BRCA status (tBRCA mutation, tBRCA wild-type), baseline CA-125 level (≤upper limit of normal [ULN], >ULN), region (North America, rest of world), and HR tumour status (HR deficient, HR proficient, HR not determined).

Summary of Key Efficacy Results (PRIMA study)

	Niraparib	**Placebo**	**Hazard ratio [b] (95% CI)**	**p-value [c]**
Primary endpoint, Progression-free survival (PFS) [a]				
HR deficient population, n	247	126		
Median PFS (months)	21.9	10.4	0.43	<0.0001
95% CI	(19.3, NE)	(8.1, 12.1)	(0.310 – 0.588)	
Overall ITT population, n	487	246		
Median PFS (months)	13.8	8.2	0.62	<0.0001
95% CI	(11.5, 14.9)	(7.3, 8.5)	(0.502 – 0.755)	
Key secondary endpoint, Overall Survival (OS) [a]				
HR deficient population, n	247	126		
Median OS (months)	30.3	NE	0.61	0.2323
95% CI	(30.3, NE)	(25.0, NE)	(0.265 – 1.388)	
Overall ITT population, n	487	246		
Median OS (months)	30.3	NE	0.70	0.1238
95% CI	(30.3, NE)	(25.0, NE)	(0.442 – 1.106)	
Secondary endpoint, Progression-free survival after the first subsequent therapy (PFS2)				
HR deficient population, n	247	126		
Median PFS2 (months)	NE	NE	0.84	0.5311
95% CI	(25.3, NE)	(NE, NE)	(0.485 – 1.453)	
Overall ITT population, n	487	246		
Median PFS2 (months)	27.2	NE	0.81	0.2242
95% CI	(25.3, NE)	(NE, NE)	(0.577 – 1.139)	
Secondary endpoint, Time to first subsequent therapy (TFST)				
HR deficient population, n	247	126		
Median TFST (months)	NE	13.7	0.46	<0.0001
95% CI	(24.7, NE)	(11.6, 19.3)	(0.330 – 0.640)	
Overall ITT population, n	487	246		
Median TFST (months)	18.6	12.0	0.65	0.0001
95% CI	(15.8, 24.7)	(10.3, 13.9)	(0.521 – 0.802)	

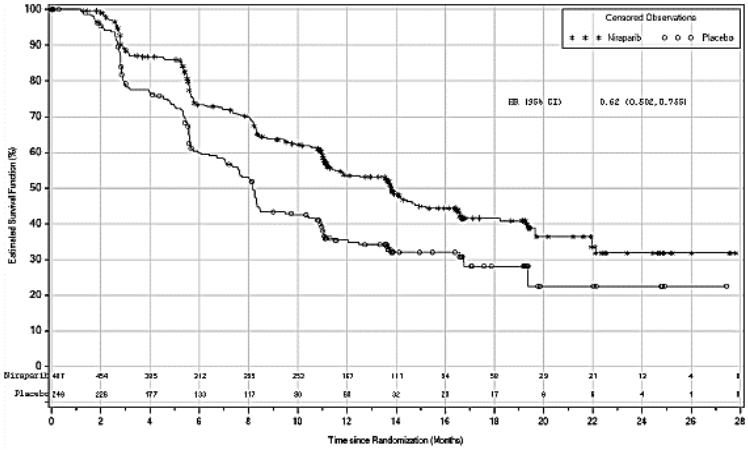
BICR: blinded independent central review; CI: confidence interval; HR: homologous recombination; ITT: intent-to-treat; n: number of patients; NE: not estimated; OS: overall survival; PFS: progression-free survival; PFS2: progression-free survival 2; TFST: time to first subsequent therapy

[a] Based on data cut-off date of 17 May 2019.

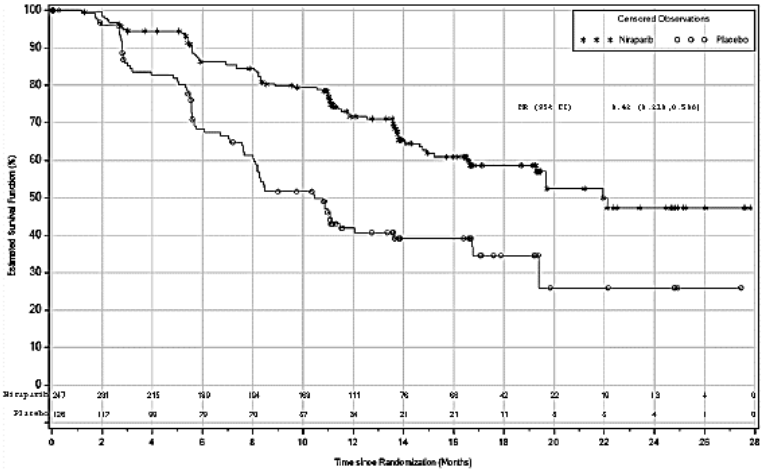
[b] Niraparib versus placebo, based on the stratified Cox proportional hazards model using randomisation stratification factors.

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

Kaplan-Meier curves for Progression-free Survival for Overall ITT population (Study PRIMA)



Kaplan-Meier curves for Progression-free Survival for HR deficient cohort (Study PRIMA)



Overall, the results in PRIMA study supported the efficacy of niraparib in the maintenance treatment of patients with advanced epithelial high-grade ovarian cancer who are in response following completion of first-line platinum-based chemotherapy.

D ASSESSMENT OF CLINICAL SAFETY

Recurrent ovarian cancer

The safety data on the use of niraparib in the maintenance treatment of recurrent ovarian cancer were mainly derived from Study NOVA, comprising a total of 546 patients (367 patients in the niraparib arm and 179 patients in the placebo arm). The median treatment duration was 8.2 months (range: 0 – 61 months) in the niraparib arm and 5.4 months (range: 0 – 65 months) in the placebo arm.

Overall of Safety Profile (Study NOVA, Safety Analysis Set)

Number (%) of patients with:	Niraparib (N=367)	Placebo (N=179)
Any TEAE	367 (100)	172 (96.1)
Any study drug-related TEAE	359 (97.8)	126 (70.4)
Any TEAE grade ≥3 in severity	280 (76.3)	42 (23.5)
Any study drug-related TEAE grade ≥3 in severity	242 (65.9)	8 (4.5)
Any serious TEAE	123 (33.5)	27 (15.1)
Any study drug-related serious TEAE	69 (18.8)	2 (1.1)
Any TEAE with outcome death	3 (0.8%)	0
Any TEAE leading to dose reduction of study drug	254 (69.2)	9 (5.0)
Any TEAE leading to dose interruption of study drug	254 (69.2)	26 (14.5)
Any TEAE leading to discontinuation of study drug	64 (17.4)	4 (2.2)

N: number of patients; TEAE: treatment-emergent adverse event

The percentage of patients who experienced study drug-related treatment-emergent adverse events (TEAEs) was higher in niraparib arm (97.8%) compared to the placebo arm (70.4%). TEAEs related to study drug that were reported more frequently in niraparib arm compared to the placebo arm included nausea (69.5% vs 25.7%), anaemia (48.0% vs 4.5%), thrombocytopenia (45.2% vs 2.2%), fatigue (38.4% vs 21.8%), vomiting (24.8% vs 6.1%), constipation (23.4% vs 9.5%), platelet count decreased (21.0% vs 1.7%), decreased appetite (20.2% vs 9.5%), neutropenia (17.7% vs 2.8%), asthenia (15.0% vs 5.0%), neutrophil count decreased (13.9% vs 1.7%), diarrhoea (12.5% vs 10.1%), headache (12.0% vs 3.9%), white blood cell count decreased (11.2% vs 2.2%), insomnia (10.6% vs 2.8%) and dizziness (10.1% vs 2.8%). Patients treated with a starting dose of 300 mg niraparib compared to 200 mg niraparib reported higher rates of TEAEs of nausea (67.8% vs 26.8%), thrombocytopenia (45.2% vs 24.8%), and fatigue (34.1% vs 26.0%).

Grade 3 or 4 TEAEs related to study drug were reported in 65.9% of patients in niraparib arm and 4.5% of patients in the placebo arm. The commonly reported grade 3 or 4 TEAEs related to study drug that were reported more frequently in niraparib arm compared to the placebo arm included thrombocytopenia (28.6% vs 0.6%), anaemia (25.3% vs 0%), neutropenia (11.4% vs 0.6%), neutrophil count decreased (9.3% vs 0.6%) and platelet count decrease (7.9% vs 0%). Patients treated with a starting dose of 300 mg niraparib compared to 200 mg niraparib reported higher rates of grade 3 or 4 TEAEs of thrombocytopenia (28.1% vs 5.1%), anaemia (15.0% vs 15.7%), neutrophil count decreased (8.4% vs 2.4%), platelet count decreased (7.1% vs 0.8%), neutropenia (9.5% vs 5.9%), hypertension (4.6% vs 4.7%) and fatigue (5.2% vs 1.2%).

TEAEs that led to the permanent discontinuation of study drug were reported more frequently in niraparib arm than the placebo arm (17.4% vs 2.2%). The difference was driven by higher percentage of patients in niraparib arm compared to the placebo arm who experienced fatigue (2.5% vs 0%), thrombocytopenia (2.2% vs 0.6%), nausea (1.9% vs 0%), platelet count decreased (1.6% vs 0%), anaemia (1.4% vs 0%), and neutrophil count decreased (1.1% vs 0%). A higher percentage of patients in the niraparib arm (69.2%) had at least one dose reduction of study drug due to TEAE as compared to the placebo arm (5.0%). TEAEs that led to the dose reduction of study drug that were reported more frequently in niraparib arm than the placebo arm included thrombocytopenia (30.2% vs 0.6%), anaemia (18.0% vs 0%), platelet count decreased (10.4% vs 0%) and nausea (5.2% vs 0%).

There were 3 cases of deaths in the niraparib arm, of which, 2 deaths were due to acute myelogenous leukaemia (AML) that were assessed by the Investigator to be related to

niraparib. The other death event was due to sepsis and acute kidney injury and was assessed by the Investigator to be likely related to niraparib.

The notable safety concerns with niraparib in Study NOVA were myelosuppression, myelodysplastic syndrome (MDS)/AML, and hypertension. The incidence of MDS/AML was higher in niraparib arm (3.0%) as compared to the placebo arm (1.7%). The increased risk and causality of MDS/AML events with niraparib were not well-defined given the background medical history of these patients who had been exposed to multiple prior lines of chemotherapies and the longer duration of exposure to niraparib than placebo. There were higher proportion of patients in the niraparib arm compared to the placebo arm who experienced hypertension events (23% vs 5%), grade 3 or 4 hypertension event (9% vs 2%) and grade 3 hypertensive crisis (<1% vs 0%). These safety concerns have been described in the relevant sections of the package insert including recommendations for dose interruptions and/or modifications to manage myelosuppression, warnings and precautions. These AEs will be monitored as part of routine pharmacovigilance.

Advanced ovarian cancer

The safety data on the use of niraparib in the maintenance treatment of advanced ovarian cancer were mainly derived from Study PRIMA, comprising a total of 728 patients (484 patients in niraparib arm and 244 patients in placebo arm). The total exposure of patients to study drug was longer in niraparib arm (median 11.1 months; range 0.0 – 29.0 months) compared to the placebo arm (median 8.3 months; range 0.0 – 28.0 months).

Overall of Safety Profile (Study PRIMA, Safety Analysis Set)

Number (%) of patients with:	**Niraparib (N=484)**	**Placebo (N=244)**
Any TEAE	478 (98.8)	224 (91.8)
Any study drug-related TEAE	466 (96.3)	168 (68.9)
Any TEAE grade ≥3 in severity	341 (70.5)	46 (18.9)
Any study drug-related TEAE grade ≥3 in severity	316 (65.3)	16 (6.6)
Any serious TEAE	156 (32.2)	32 (13.1)
Any study drug-related TEAE	118 (24.4)	6 (2.5)
Any TEAE with outcome death	2 (0.4)	1 (0.4%)
Any TEAE leading to dose reduction of study drug	343 (70.9)	20 (8.2)
Any TEAE leading to dose interruption of study drug	385 (79.5)	44 (18.0)
Any TEAE leading to discontinuation of study drug	58 (12.0)	6 (2.5)

N: number of patients; TEAE: treatment-emergent adverse event

The percentage of patients who experienced study drug-related TEAEs was higher in niraparib arm (96.3%) than placebo arm (68.9%). TEAEs related to study drug that were reported more frequently in niraparib arm compared to the placebo arm included anaemia (60.5% vs 12.7%), nausea (50.6% vs 20.1%), thrombocytopenia (45.2% vs 3.3%), fatigue (29.8% vs 23.0%), platelet count decreased (26.9% vs 1.2%), neutropenia (26.0% vs 5.7%), and constipation (25.8% vs 5.7%). Patients in the individualised starting dose cohort experienced lower incidences of TEAEs compared to the fixed starting dose cohort, including TEAEs of anaemia (49.7% vs 70.8%), thrombocytopenia (33.7% vs 52.4%), constipation (31.4% vs 43.2%), vomiting (16.6% vs 25.4%), platelet count decreased (22.5% vs 30.2%), diarrhoea (13.6% vs 21.6%), neutrophil count decreased (12.4% vs 19.4%), headache (21.9% vs 28.3%), and abdominal pain (17.8% vs 24.1%).

Grade 3 or 4 TEAEs related to study drug were reported in higher percentage of patients in the niraparib arm (65.3%) as compared to the placebo arm (6.6%). The commonly reported grade 3 or 4 TEAEs related to study drug included anaemia (30.2% vs 0.4%), thrombocytopenia (28.7% vs 0%), neutropenia (12.4% vs 0.8%), platelet count decreased (13.0% vs 0%) and neutrophil count decreased (7.6% vs 0%). The individualised starting dose cohort experienced lower incidences of grade 3 or 4 TEAEs as compared to the fixed starting dose cohort (60.4% vs 75.9%).

TEAEs that led to the permanent discontinuation of study drug were reported more frequently in niraparib arm than the placebo arm (12.0% vs 3.0%). The difference was driven by higher percentage of patients who experienced thrombocytopenia (3.7% vs 0%), anaemia (1.9% vs 0%), neutropenia (1.2% vs 0%), nausea (1.2% vs 0%), platelet count decreased (0.6% vs 0%), neutrophil count decreased (0.6% vs 0%), fatigue (0.8% vs 0%) and dizziness (0.6% vs 0%). A higher percentage of patients experienced at least one dose reduction of study drug due to TEAEs in niraparib arm (70.9%) compared to the placebo arm (8.2%). TEAEs leading to dose reduction of study drug that were reported more frequently in niraparib arm compared to the placebo arm included thrombocytopenia (50.8% vs 2.0%), anaemia (27.1% vs 0.8%), neutropenia (8.1% vs 1.2%), platelet count decreased (18.6% vs 0%), neutrophil count decreased (5.0% vs 1.6%) and nausea (2.9% vs 0%).

There were 2 cases of deaths in the niraparib arm and 1 case of death in the placebo arm. The death events were assessed by the Investigator as not related to study drug.

Similar to Study NOVA, the major safety concerns with niraparib in Study PRIMA were myelosuppression, MDS/AML, and hypertension. MDS/AML was reported in 1 patient (0.2%) in niraparib arm and none in the placebo arm. A higher percentage of patients in niraparib arm experienced hypertension event (18% vs 7%) and grade 3 or 4 hypertension event (6% vs 1%) as compared to the placebo arm. There was no hypertensive crisis event reported in Study PRIMA. These safety concerns have been described in the dosing regimen, warnings and precaution, and/or adverse drug reaction section of the package insert and will be monitored as part of routine pharmacovigilance.

Overall, the safety profile of niraparib was considered acceptable for the intended population given the poor prognosis of the disease. The individualised starting dose regimen of niraparib presented a more tolerable safety profile compared to the fixed starting dose regimen. Appropriate warnings and precautions have been put in place in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Advanced and recurrent ovarian cancer are serious, life-threatening and incurable diseases. The majority of patients experienced disease recurrence despite good response to first-line standard of care and may eventually become resistant or refractory to repeated rounds of platinum-containing chemotherapy.

The NOVA study demonstrated that niraparib as maintenance treatment for platinum-sensitive recurrent ovarian cancer showed statistically significantly improvement in median PFS of 21 months compared to 5.5 months in the placebo arm in patients with gBRCAmut tumours (hazard ratio 0.27; 95% CI: 0.173 – 0.410). Consistent results were observed in the non-gBRCAmut and HR deficient recurrent ovarian tumour cohort with a median PFS of 9.3 months

in the niraparib arm vs 3.9 months in the placebo arm (hazard ratio 0.38; 95% CI: 0.243 – 0.586). The OS benefit in patients without gBRCAmut tumours has not been demonstrated.

The PRIMA study demonstrated that niraparib as maintenance treatment for advanced ovarian cancer in patients who were in response to first-line platinum-based chemotherapy showed statistically significantly improvement in median PFS of 21.9 months compared to 10.4 months in the placebo arm in patients with HR deficient tumour (hazard ratio 0.43; 95% CI: 0.310 – 0.588).

The safety profile of niraparib was considered acceptable relative to its treatment benefit considering the poor prognosis of the disease. Niraparib-related myelosuppression and hypertension could be managed through dose interruption, dose reduction and/or treatment discontinuation. These safety concerns have been adequately addressed in the package insert with relevant warnings and precautions as well as dose adjustment recommendations. The potential risk of MDS/AML with niraparib will be monitored as part of routine pharmacovigilance.

Overall, the benefit-risk profile of niraparib in the maintenance treatment of adult patients with advanced or relapsed high-grade ovarian cancer who are in response to platinum-based chemotherapy was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of niraparib outweighed the risks in the maintenance treatment of:

- Patients with platinum-sensitive relapsed high grade ovarian cancer who are in response to platinum-based chemotherapy; and
- Patients with advanced high-grade ovarian cancer who are in response following completion of first-line platinum-based chemotherapy.

Approval of the product registration was granted on 01 April 2022.

APPROVED PACKAGE INSERT AT REGISTRATION