NDA/BLA Clinical and Statistical Review

Application Type	sNDA
Application Number(s)/ Supplement	214876/ S-003 and S-004
Submission Received Date	September 26, 2024 (S-003), December 20, 2024 (S-004)
PDUFA Goal Date	July 26, 2025 (S-3), June 20, 2025 (S-4)
Review Completion Date	Electronic Stamp Date
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Product: **Established Name (Trade name)**	Niraparib, ZEJULA®
Established Pharmacologic Class (EPC)	PARP inhibitor
Applicant	GlaxoSmithKline LLC (GSK)
Recommended Dosage	• For patients weighing <77kg (<170 lbs) OR with a platelet count < 150,000/mcL, 200 mg orally once daily • For patients weighing ≥ 77 kg (≥170 lbs) AND who have platelet count ≥ 150,000/mcL, 300 mg orally once daily
Applicant Proposed Indication	Niraparib is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy
Recommended Regulatory Action	Regular Approval
Recommended Indication	Niraparib is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either • a deleterious or suspected deleterious BRCA mutation, and/or • genomic instability

1. Executive Summary

Niraparib is an oral poly(ADP-ribose) polymerase inhibitor (PARPi). Niraparib is currently approved for two indications: the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum based chemotherapy; and for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

Under Supplement 3, the final OS results from PRIMA were submitted, and the FDA Clinical and Statistics team's assessment of these results is discussed further in this review. Under Supplement 4, updated pharmacokinetic (PK) information across studies and a physiologically based pharmacokinetic (PBPK) model assessment of drug-drug interaction (DDI) risks were submitted to support updated PK and DDI information in the labeling. For details regarding Supplement 4, refer to the Clinical Pharmacology review (uploaded to DARRTS on June 17, 2025).

In this sNDA (S-003), the FDA review team recommends narrowing the indication for the first-line maintenance treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer to the following:

> Niraparib is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either
>
> - a deleterious or suspected deleterious BRCA mutation, and/or
> - genomic instability

The FDA review team's recommendation is based upon review of the final overall survival (OS) results from PRIMA (Study PR-30-5017-C), a Phase 3, double-blind, placebo-controlled, randomized (2:1) multicenter trial of niraparib compared to placebo maintenance in adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in a complete response (CR) or partial response (PR) to first-line platinum-based chemotherapy. Seven hundred thirty-three (733) patients were randomized 2:1 to either niraparib (n=487) or placebo (n=246). Patients who received primary debulking surgery, intraperitoneal chemotherapy and/or neoadjuvant chemotherapy were all eligible. Stratification factors at randomization included best response to platinum therapy (CR or PR),

neoadjuvant therapy (yes or no), and tumor HRD status as assessed by the Myriad Genetics myChoice® homologous recombination deficiency test (positive or negative/not determined[nd]). The HRD-positive population (n=373) contained patients with documented gBRCA1/2 or sBRCA1/2 mutation, as well as patients with a positive tumor genomic instability score (GIS), which was defined as a score ≥ 42.

In PRIMA, the primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR) according to RECIST v1.1. PFS analysis was conducted first in the HRD-positive population using a one-sided alpha level of 0.025, followed by PFS analysis in the overall population using a one-sided alpha level of 0.025 if the result was statistically significant in the HRD-positive subgroup. Overall survival (OS) was a key secondary endpoint and would be tested if PFS was statistically significant in both the HRD-positive population and the overall population. OS would be tested first in the overall population, and then in the HRD-positive population.

On April 29, 2020, niraparib was granted regular approval for all patients based upon the primary analysis of PFS by BICR results from PRIMA. The trial showed a statistically significant effect on PFS in the HRD-positive population and the overall population. In the HRD-positive population, results showed a stratified PFS HR of 0.43 (95% CI: 0.31, 0.59) and stratified log-rank p-value <0.0001. In the overall population, results showed stratified PFS HR was 0.62 (0.50, 0.76) and stratified log-rank p-value < 0.0001. At the time of approval, the review team felt that although the PFS benefit was greatest in patients with HRD-positive tumors the Benefit:Risk was favorable for the overall population. OS results were immature at the time of the approval, with only 18% of events needed for the final analysis observed; however, there was no indication of a potential OS detriment in any group. At the time of the primary PFS analysis, the interim analysis of OS was not statistically significant in the overall population (stratified log-rank p-value = 0.1238) and the stratified OS HR was 0.70 (95% CI: 0.44, 1.11). In the HRD-positive subgroup, the stratified OS HR was 0.61 (95% CI: 0.27, 1.39). Note that because the interim OS analysis in the overall population did not cross the pre-specified efficacy boundary, no alpha was available for further testing, so all subgroup analyses (including in the HRD-positive subgroup) for OS were exploratory.

Following approval of niraparib in the first-line maintenance setting, FDA became aware of a classwide safety issue for PARPi in advanced ovarian cancer. Multiple randomized trials showed potential OS detriments in the late-line treatment setting, and indications for all three PARPis were voluntarily withdrawn from the market. Potential OS detriments were also observed in multiple randomized trials in the 2L+ maintenance setting for patients without a BRCAm. Indications for all three PARPi were narrowed to only include patients with underlying BRCAm.

Specifically, the indication for niraparib was voluntarily narrowed to patients with a gBRCAm by the Applicant on December 8, 2022. In the 1L maintenance setting, the currently approved indications for the other PARPi include olaparib for patients with a g/sBRCA mutation who are in a CR or PR to platinum-based chemotherapy based on SOLO-1 and olaparib plus bevacizumab for patients with HRD-positive tumors who are in a CR or PR to platinum-based chemotherapy based on PAOLA-1. Of note, PAOLA-1 enrolled all patients, regardless of BRCAm or tumor HRD, and the trial met its PFS endpoint in the entire trial population. However, an indication was granted only for patients with HRD-positive tumors because based on PFS and OS results, clinical benefit was only observed for this population.

On September 26, 2024, the Applicant submitted the current efficacy supplement with the results of the final OS analysis from PRIMA, along with updated niraparib labeling which included a proposal to maintain the all-comers indication in the first-line ovarian cancer maintenance setting and (b) (4) The final OS results from PRIMA were based on a data cutoff (DCO) date of April 8, 2024. There was no statistically significant effect on OS in the overall population with a stratified OS HR of 1.01 (95% CI: 0.84, 1.23) and stratified log-rank p-value of 0.8834. Given the result in the overall population, OS was not able to be formally tested in the HRD-positive subgroup. The descriptive OS result in the HRD-positive subgroup showed a stratified OS HR of 0.95 (0.71, 1.29). FDA conducted additional exploratory subgroup analyses of OS in important biomarker subgroups. Results showed the unstratified OS HRs were 1.07 (95% CI: 0.83, 1.38) for the grouped HRD-negative/not determined subgroup, 0.93 (95% CI: 0.69, 1.26) for the HRD-negative subgroup, and 1.39 (95% CI: 0.88, 2.19) for the HRD-not determined subgroup.

The updated final OS results from PRIMA, the small magnitude of PFS benefit in biomarker negative subgroup, and the class-wide observation of potential OS detriments in biomarker negative subgroups for PARPis in maintenance settings, changed the overall benefit-risk assessment for patients whose tumors were not HRD-positive. The exploratory PFS results in the combined HRD-negative/not determined subgroup had shown a small PFS improvement of < 2 mos with no OS improvement, and moreover, even a potential trend towards harm in OS. The team also considered that niraparib maintenance therapy was associated with hematologic, cardiovascular, and neuropsychiatric toxicities to which patients could be subjected for potentially long durations. The review team determined that the overall risk-benefit analysis for niraparib was no longer favorable for all patients. FDA recommended that the Applicant narrow the indication to patients with HRD-positive tumors only and the Applicant ultimately agreed with this recommendation.

Given the narrowing of the indication to patients with HRD-positive tumors only, a companion diagnostic is now essential for the safe and effective use of niraparib in the approved indication. FDA issued the following PMC at the time of approval of this sNDA:

4865-1 Conduct an appropriate clinical validation study using clinical trial data to support the availability of an in vitro diagnostic device that is essential for the safe and effective use of niraparib for adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation, and/or
- genomic instability.

2. Regulatory History

Key events in the regulatory history for niraparib, rucaparib, and olaparib relevant to the indication for maintenance treatment of first-line ovarian cancer in response to platinum chemotherapy:

Date	Event
April 29, 2020	FDA granted regular approval for maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy based upon PFS results from PRIMA.
December 2022-Sept 2023	FDA narrowed second-line maintenance indications for niraparib, rucaparib, and olaparib to BRCAm only due to potential OS detriments in non-BRCAm cohorts.
April 19, 2024	FDA requested an update from the Applicant on status of final OS results from PRIMA.
May 29, 2024	Applicant provided email communication with topline final OS results from PRIMA and described intention to submit efficacy supplement to update product labeling with results in Q4 2024.
September 26, 2024	Applicant submitted current supplement, providing final OS results from PRIMA.

February 25, 2025	FDA and the Applicant had a teleconference where FDA advised the Applicant that the final OS results from PRIMA were not supportive of maintaining the indication in all patients and advised the Applicant to narrow the indication to include patients with HRD-positive tumors only. FDA followed up with updated labeling to narrow indication.
April 10, 2025	Applicant submitted a rebuttal document which outlined their justification to maintain the first-line maintenance indication for niraparib in all patients (discussed below). FDA responded in writing that the indication should be narrowed to patients with HRD-positive tumors only.
April 28, 2025	Applicant agreed in writing with the narrowed indication.

3. Review of Clinical Data

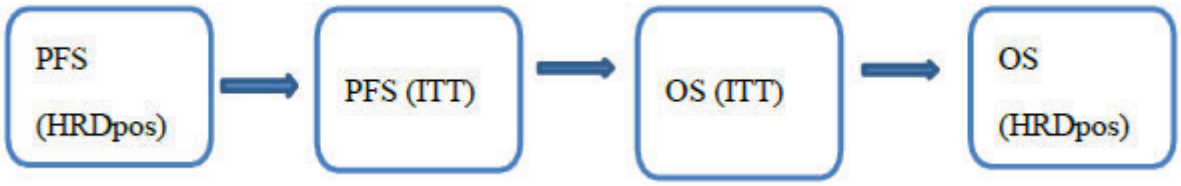
3.1 PRIMA Trial Design

PRIMA (PR-30-5017-C) was a Phase 3, double-blind, randomized (2:1), placebo-controlled trial evaluating the efficacy and safety of niraparib as maintenance treatment for patients with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in complete or partial response to first-line platinum-based chemotherapy. The trial was designed to enroll all patients, regardless of biomarker status, but randomization was stratified by three factors including 1) tumor homologous recombination deficiency (HRD) status (positive or negative/not determined; 2) neoadjuvant chemotherapy (yes or no); and 3) response to platinum therapy (complete response [CR] or partial response [PR]).

The primary endpoint for PRIMA was PFS to be tested in the HRD-positive and the overall populations, based on the Blinded Independent Central Review (BICR). OS was the key secondary endpoint to be tested in the HRD-positive and overall populations. For the primary endpoint of PFS in the HRD positive population, 99 PFS events were required to detect a HR of 0.5 with 90% power, and ~270 PFS events were expected in the overall population to provide ≥90% power to detect a HR of 0.65. For OS, the final analysis of OS was planned to occur when ~440 deaths occurred in the overall population to provide ≥80% power if true HR is ≤0.75, and it was estimated that there would be ~150 deaths in the HRD positive population to provide ≥70% power if true HR is ≤0.65.

The endpoints were planned to be tested in a hierarchical testing strategy to control the overall Type I error at the 1-sided alpha level of 0.025 (or 2-sided 0.05). At the primary analysis, PFS analysis in the HRD-positive population would be conducted. If the result was significant, it would be followed by analysis PFS in the ITT population, and analysis of OS in the ITT and HRD-positive population, sequentially, as shown in Figure 1. If one analysis reached a negative result, the rest of the analyses would become exploratory.

Figure 1: Hierarchical Testing Procedure



Source: SAP

3.2 PRIMA Trial Results: Efficacy

Results for Initial Approval

In the overall population, 733 patients were randomized to receive either Niraparib (n = 487) or placebo (n = 246). The overall population included 373 patients in the HRD-positive population, randomized to receive either Niraparib (n = 247) or placebo (n = 126). Table 1 shows the breakdown of the patient population by biomarker status on PRIMA.

Table 1: PRIMA Baseline HRD and BRCA Status

	Overall population N=733	
	Niraparib N=487 (%)	**Placebo N= 246 (%)**
HRD-positive	247 (51)	126 (51)
BRCAm	152 (31)	71 (29)
BRCAwt	94 (19)	55 (22)
BRCAnd	1 (0.2%)	0
HRD-negative/not determined (nd)	240 (49)	120 (49)
HRD-negative	169 (35)	80 (32)
HRD-nd	71 (15)	40 (16)

Since HRD status was a randomization stratification factor, HRD status was collected from an interactive web response system (IWRS) at randomization and was also collected in the eCRF. The concordance and discordance between HRD status collected per IWRS and eCRF are summarized in Table 2. A total of 9 patients (6 on the niraparib arm and 3 on the placebo arm) were stratified to the HRD-positive group when their tumors were categorized as HRD-negative/not-determined per eCRF. FDA notes that in this review, HRD subgroup analyses were conducted based on HRD status from eCRF rather from the values at randomization as collected per IWRS. Given the limited discordance between HRD status per IWRS and eCRF, any loss of randomization as a result should be minimal, and FDA still considered the HRD subgroups defined based on the strata of HRD-positive and HRD-negative/not determined to be interpretable.

Table 2: Concordance and Discordance for HRD status per IWRS and eCRF

	Niraparib (n=487)		Placebo (n=246)		All patients (n=733)	
	HRD -pos per IWRS	HRD-neg/nd per IWRS	HRD-pos per IWRS	HRD-neg/nd per IWRS	HRD-pos per IWRS	HRD-neg/nd per IWRS
HRD-pos per eCRF	247	0	126	0	373	0
HRD-neg/nd per eCRF	6	234	3	117	9	351

[Source: ADSL.xpt]

The results for the primary endpoint of PFS from the overall population and the HRD-positive population are shown below in Table 3 . PFS was statistically significant in both analysis populations, and these results supported regular approval for all patients on April 29, 2020.

Table 3: PRIMA Progression-Free Survival Results (DCO: May 17, 2019)

	Overall		**HRD-positive**	
	Niraparib N = 487	**Placebo N = 246**	**Niraparib N = 247**	**Placebo N = 126**
PFS Events, n (%)	232 (47.6)	155 (63.0)	81 (32.8)	73 (57.9)
Median PFS (months) (95% CI)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)	21.9 (19.3, NE)	10.4 (8.1, 12.1)
Hazard Ratio* (95% CI)	0.62 (0.50, 0.76)		0.43 (0.31, 0.59)	
p-value**	<0.0001		<0.0001	

* Based on stratified Cox proportional hazards model using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy, and homologous recombination deficiency test status (for overall population only)

** Based on stratified log-rank test
[Source: ADTTE.xpt, ADSL.xpt]

At the time of the final analysis of PFS, OS was immature with 18% of events needed for the final analysis observed, but results did not indicate potential OS detriment. The interim analysis of OS in the overall population was not statistically significant (stratified log-rank p-value = 0.1238) with a stratified OS HR of 0.70 (95% CI: 0.44, 1.11). OS in the HRD positive population was not able to be formally tested per the testing hierarchy, however the observed stratified OS HR in the HRD positive population was 0.61 (95% CI: 0.27, 1.39).

Exploratory subgroup results for PFS in important biomarker subgroups are shown in Table 4.

Table 4 Exploratory Subgroup Analyses of PFS by BICR by Biomarker Status

	Sample size Events		**Median PFS (95% CI)**		**Stratified HR* (95% CI)**	**Unstratified HR (95% CI)**
	Niraparib	**Placebo**	**Niraparib**	**Placebo**		
Overall (ITT)	487 232 (47.6)	246 155 (63.0)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)	0.62 (0.50, 0.76)	0.61 (0.50, 0.75)
HRD-positive	247 81 (32.8)	126 73 (57.9)	21.9 (19.3, NE)	10.4 (8.1, 12.1)	0.43 (0.31, 0.59)	0.43 (0.31, 0.58)
BRCAm	152 49 (32.2)	71 40 (56.3)	22.1 (19.3, NE)	10.9 (8.0, 19.4)	0.40 (0.27, 0.62)	0.40 (0.26, 0.61)
BRCAwt	94 32 (34)	55 33 (60)	19.6 (13.6, NE)	8.2 (6.7, 16.8)	0.51 (0.31, 0.85)	0.49 (0.30, 0.80)
HRD-negative/nd	240 151 (62.9)	120 82 (68.3)	8.3 (7.3, 10.2)	6.4 (5.4, 8.2)	0.78 (0.60, 1.03)	0.79 (0.60, 1.03)
HRD-negative	169 111 (65.7)	80 56 (70.0)	8.1 (5.7, 9.4)	5.4 (4.0, 7.3)	0.68 (0.49, 0.94)	0.74 (0.54, 1.02)
HRD-not determined	71 40 (56.3)	40 26 (65.0)	11.0 (7.4, 13.9)	8.3 (5.7, 12.5)	0.85 (0.51, 1.43)	0.81 (0.49, 1.33)

* Based on stratified Cox proportional hazards model using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy, and homologous recombination deficiency test status (for overall population only)
[Source: ADTTE.xpt, ADSL.xpt]

Overall, there was a larger magnitude of PFS effect observed for patients with HRD-positive tumors relative to patients with HRD-negative/not determined tumors. In the HRD-positive population, the largest magnitude of effect was observed in patients with BRCAm. In the HRD-negative and/or HRD-not determined subgroups, the differences in median PFS between arms were relatively small (all less than 3 months).

Results in Current Submission (Final OS results)

The Final OS results (DCO April 8, 2024) for PRIMA were submitted on September 26, 2024. The final OS results for the overall population and the HRD-positive population is shown below in Table 5 and Figure 1.

Table 5: PRIMA Final Overall Survival Results (DCO: April 8, 2024)

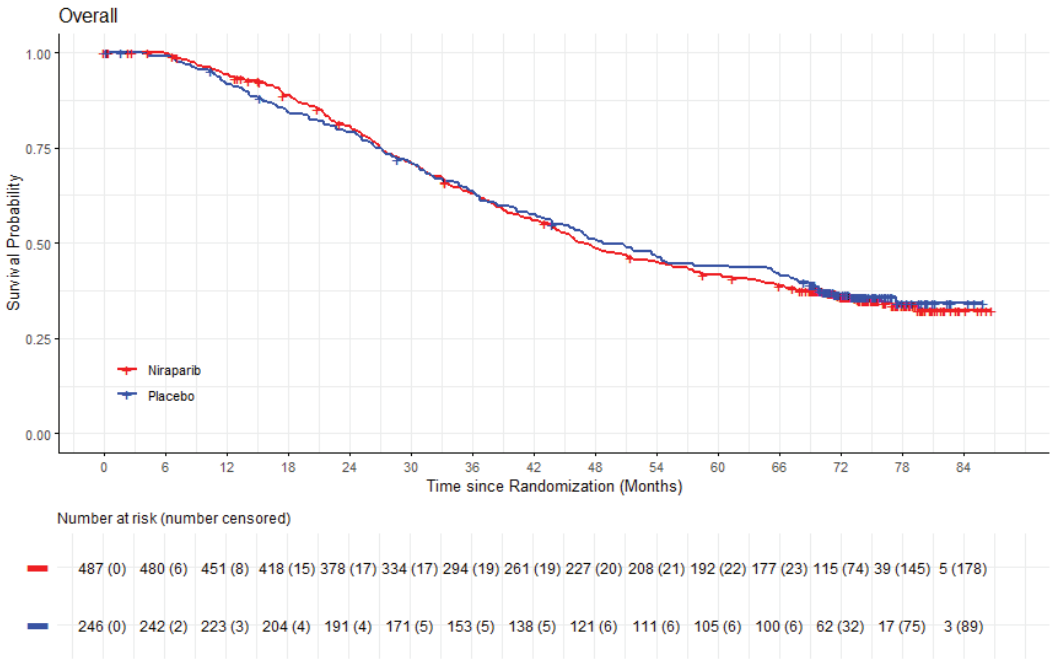
	Overall		HRD-positive	
	Niraparib N = 487	**Placebo N = 246**	**Niraparib N = 247**	**Placebo N = 126**
OS Events, n (%)	304 (62.4)	154 (62.6)	120 (48.6)	65 (51.6)
Median OS (months) (95% CI)	46.6 (43.7, 52.8)	48.8 (43.1, 61.0)	71.9 (55.5, NE)	69.8 (51.6, NE)
Hazard Ratio* (95% CI)	1.01 (0.84, 1.23)		0.95 (0.71, 1.29)	
p-value**	0.8834		NA	

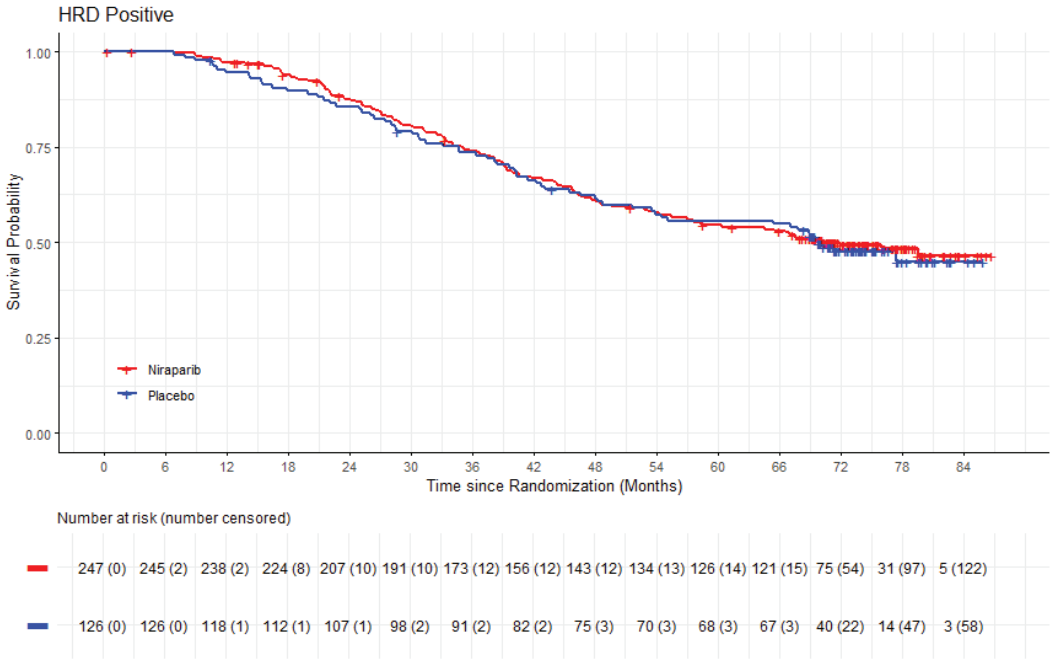
* Based on stratified Cox proportional hazards model using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy, and homologous recombination deficiency test status (for overall population only)

** Based on stratified log-rank test

[Source: ADTTE.xpt, ADSL.xpt]

Figure 1: PRIMA Kaplan-Meier Plots of OS (Overall (top), HRD-positive (bottom)





The final analysis of OS in the overall population was not statistically significant (stratified log-rank p-value =0.8834) and showed a stratified hazard ratio of 1.01 (95% CI: 0.84, 1.23). Thus, the final analysis of OS in the HRD-positive population was not formally tested per the testing hierarchy; the observed stratified HR in the HRD-positive population was 0.95 (95% CI: 0.71, 1.29). FDA conducted additional exploratory subgroup analyses for OS in important biomarker subgroups, and the results are shown in Table 6 and Figure 2.

Table 6: PRIMA Final Overall Survival Results (DCO: April 8, 2024)

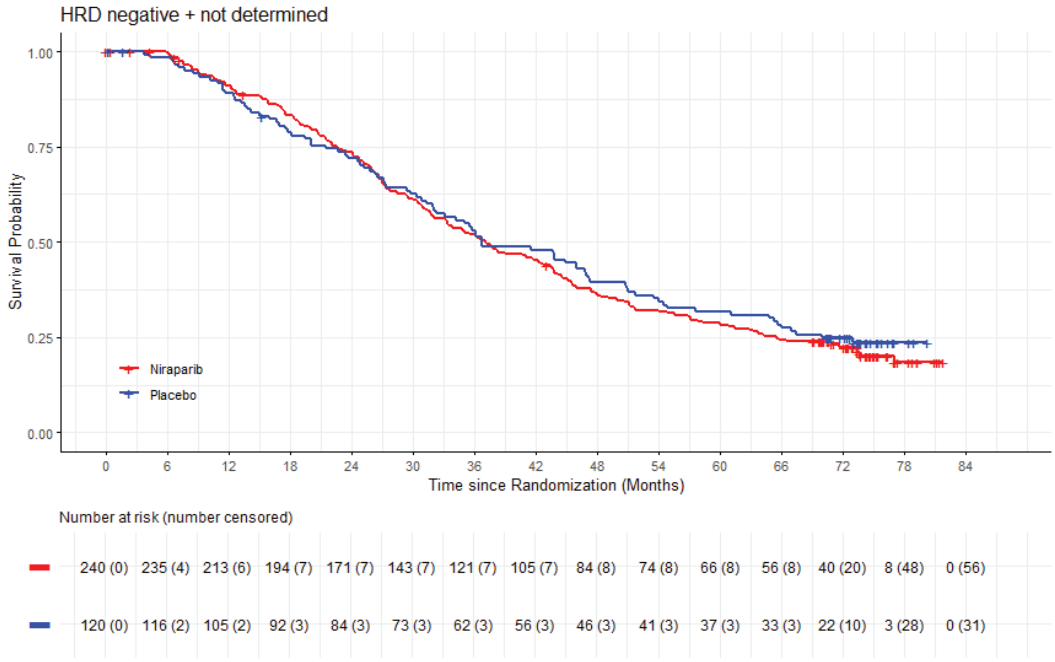
	Sample size Events		**Median OS (95% CI)**		**Stratified HR* (95% CI)**	**Unstratified HR (95% CI)**
	Niraparib	**Placebo**	**Niraparib**	**Placebo**		
Overall (ITT)	487 304 (62.4)	246 154 (62.6)	46.6 (43.7, 52.8)	48.8 (43.1, 61.0)	1.01 (0.84, 1.23)	1.02 (0.84, 1.24)
HRD-positive	247 120 (48.6)	126 65 (51.6)	71.9 (55.5, NE)	69.8 (51.6, NE)	0.95 (0.71, 1.29)	0.96 (0.71, 1.29)
BRCAm	152 71 (46.7)	71 35 (49.3)	79.5 (57.6, NE)	NE (48.2, NE)	0.94 (0.63, 1.41)	0.97 (0.65, 1.45)

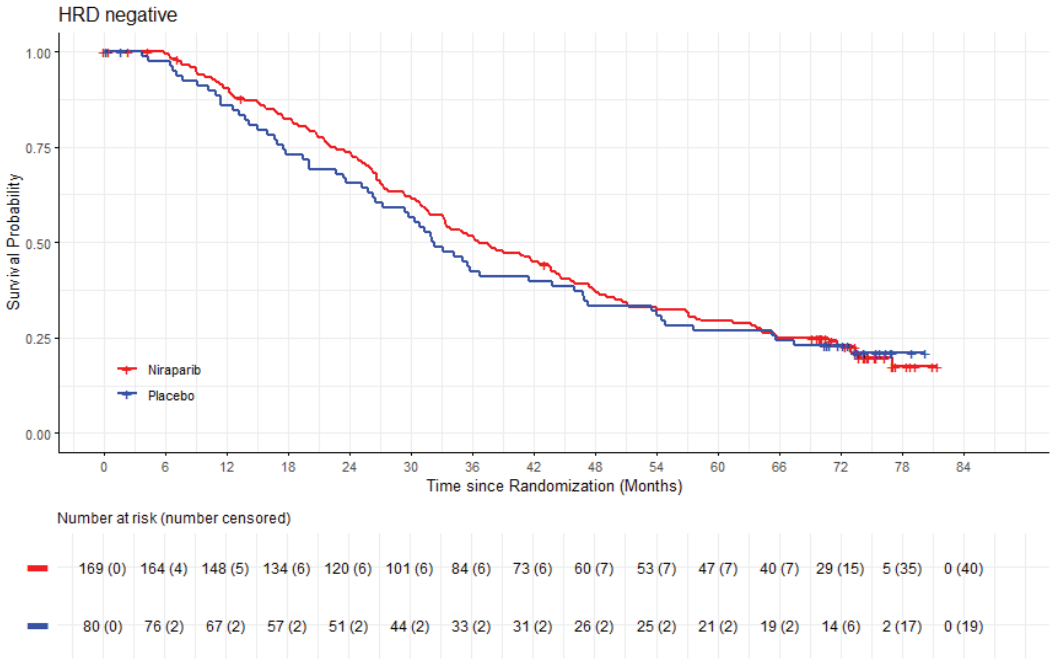
BRCAwt	94 49 (52.1)	55 30 (54.5)	58.4 (44.2, NE)	68.9 (45.5, NE)	1.01 (0.64, 1.59)	0.97 (0.62, 1.53)
HRD-negative/nd	240 184 (76.7)	120 89 (74.2)	37.1 (32.1, 43.5)	36.7 (32.0, 47.0)	1.07 (0.83, 1.38)	1.07 (0.83, 1.38)
HRD-negative	169 129 (76.3)	80 61 (76.3)	36.6 (31.7, 43.7)	32.2 (26.3, 43.8)	0.89 (0.65, 1.21)	0.93 (0.69, 1.26)
HRD-not determined	71 55 (77.5)	40 28 (70.0)	37.3 (28.5, 45.1)	50.8 (36.7, 66.0)	1.44 (0.90, 2.30)	1.39 (0.88, 2.19)

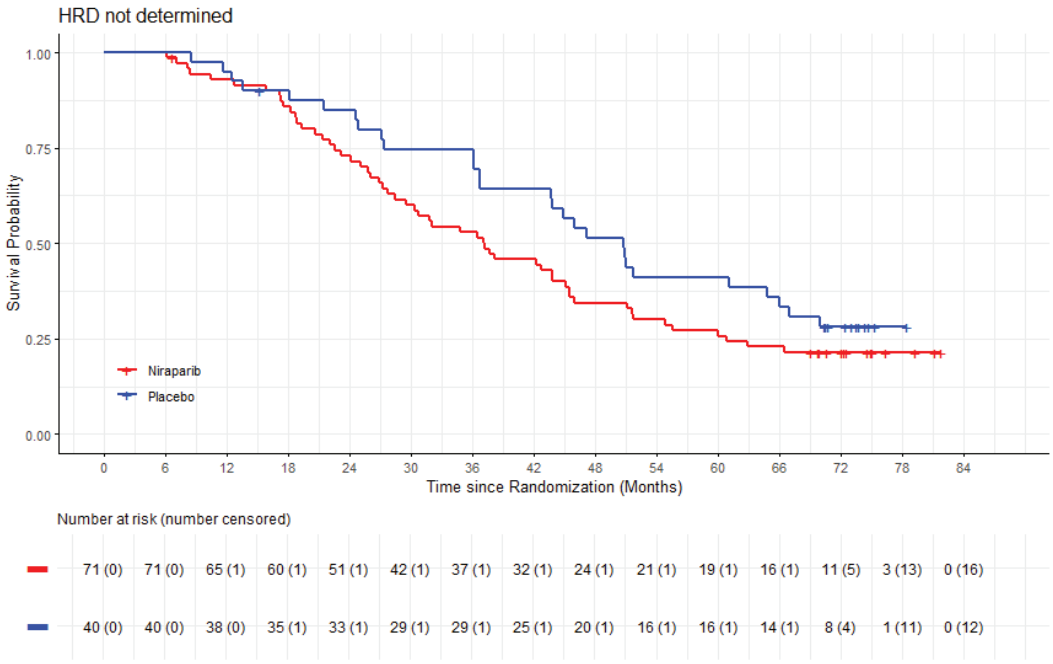
* Based on stratified Cox proportional hazards model using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy, and homologous recombination deficiency test status (for overall population only)

[Source: ADTTE.xpt, ADSL.xpt]

Figure 2 PRIMA Kaplan-Meier Plots of Final OS Results (HRD-negative + not determined (top), HRD-negative (middle), HRD-not determined (bottom)







The FDA examined the potential impact of subsequent treatment with PARPi on the final OS results. The percentage of patients receiving subsequent PARPi in the overall population and relevant biomarker subgroups (by treatment arm) is shown in Table 7.

Table 7: Use of Any Subsequent PARPi by Patients on PRIMA

	Niraparib %	**Placebo** %
Overall	11.7	37.8
HRD-positive	15.8	48.4
HRD-negative/not determined	7.5	26.7
HRD-negative	5.9	18.8
HRD-not determined	11.3	42.5

[Source: ADCM.xpt]

FDA and the Applicant conducted additional sensitivity analyses to account for use of subsequent PARPi which included analyses in which patients were censored at initiation of subsequent PARPi (with varying assumptions for the treatment arms) as well as a rank-preserving structural failure time model (RPSFTM). Results from all sensitivity analyses were fairly consistent with the primary OS findings in the overall population and biomarker subgroups and indicated a potential OS detriment for patients in the HRD-negative/not determined subgroup.

The FDA also conducted additional analyses in the HRD-not determined subgroup which had an unstratified OS HR of 1.39 (95% CI: 0.88, 2.19). Tumor HRD status was “not determined” in 111 patients (15.1% of the trial population, including 71 patients on niraparib and 40 patients on placebo). It was understood that the HRD-not determined subgroup was comprised of a combination of patients with HRD-positive and HRD-negative tumors. FDA sent an information request (IR) to the Applicant on December 9, 2024 requesting that the Applicant explain why HRD status was not determined for these patients and whether it would be possible to obtain this information. In a response received on December 20, 2024, the Applicant explained that “not determined” indicated that either tumor sample was missing for that patient or HRD test results were inconclusive or testing could not be performed. If tumor HRD could not be determined on the initial test, re-testing was attempted, and if that was unsuccessful, another sample was requested from the trial site enrolling the patient. Because a lot of tumor tissue was required for the Myriad myChoice test, sometimes sufficient tumor tissue was not available for re-testing. The Applicant concluded that definitive HRD status would remain “not determined” for 15% of the trial population.

FDA examined the baseline characteristics between arms for the HRD-not determined subgroup and noted a few imbalances with worse prognostic features on the niraparib arm, including more patients with Stage IV disease at diagnosis, more patients receiving neoadjuvant chemotherapy, and more patients with ECOG 1 at baseline. FDA notes that there could be additional imbalances in unknown factors in this subgroup. FDA also considered that the HRD-

not determined subgroup was an unstratified subgroup (indicating a potential loss of randomization) without a biologic basis (as it represents those with HRD-positive and HRD-negative tumors). Overall, the results in this subgroup could be a chance finding and are difficult to interpret. Following this assessment, FDA was still concerned about the potential OS detriment in the (stratified) HRD-negative/not determined subgroup.

Efficacy Conclusions

In PRIMA, niraparib demonstrated a PFS improvement in the HRD-positive and overall populations. At the time of initial NDA review, the PFS results across the different biomarker subgroups (including HRD-negative/not determined) were considered supportive of granting an indication in the overall population. However, the magnitude of PFS benefit was greatest in the HRD-positive population, and was relatively small (differences in median PFS between arms were less than 3 months for all subgroups) for patients in the HRD negative and/or HRD not determined subgroups.

The final OS results in the overall population did not reach statistical significance, so further hierarchical testing (in the HRD-positive population) was descriptive only. However, the results in the HRD-positive population were not concerning for potential detriment (stratified OS HR of 0.95 [95% CI: 0.71, 1.29]). Conversely, the results of an exploratory subgroup analysis of final OS in the HRD negative/not determined group showed an unstratified OS HR of 1.07 (95% CI: 0.83, 1.38), which were concerning for a potential detriment.

The final OS results from PRIMA were considered in the context of the classwide observation of potential OS detriments in biomarker-negative subgroups with 2L+ maintenance PARPi therapy for advanced ovarian cancer. All three maintenance PARPi indications in this setting, including niraparib, were narrowed to patients with BRCAm only following observation of potential OS detriments in those without BRCAm. Additionally, a potential OS detriment was observed in the 1L maintenance setting for patients without HRD-positive tumors who received olaparib plus bevacizumab. These previous findings of potential OS detriments among biomarker-negative populations receiving maintenance PARPi increase the likelihood that the potential OS detriment in the HRD-negative/not determined subgroup in PRIMA was not due to chance.

Based on the initial PFS findings, as well as the final OS results, the FDA review team concluded that only patients with HRD-positive tumors appeared to be deriving benefit from niraparib in the 1L maintenance ovarian cancer setting. An indication in all patients was no longer appropriate.

Safety Conclusions

The Applicant submitted updated safety data, including new information on patient deaths due to adverse drug reactions, and an updated summary of new cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), which are known safety concerns with niraparib. There were 4 deaths due to adverse reactions during or within 30 days of treatment in niraparib-treated patients with HRD-positive tumors. The causes of death were intestinal perforation in the absence of documented disease progression in one patient, cardiac death in one patient, sudden death in one patient, and AML in one patient. Product labeling was updated to describe niraparib-treated patients with HRD-positive tumors who experienced fatal adverse reactions on PRIMA.

An updated assessment of all cases of MDS/ AML on PRIMA was also conducted. In patients with HRD-positive tumors (including BRCAm and BRCAwt), there 8 patients out of 245 (3.3%) on the niraparib arm who were diagnosed with MDS or AML (3 MDS and 5 AML), 5 of which were fatal. There were also 3 patients out of 125 (2.4%) on the placebo arm diagnosed with MDS/AML. All 3 of these placebo-treated patients received PARPi therapy subsequent to trial participation and prior to diagnosis with MDS or AML.

Although it was determined that there were no new safety signals identified for niraparib based upon the updated survival data, it was recognized that niraparib is being administered in a maintenance setting in which patients would otherwise not be receiving any treatment. The toxicity profile of niraparib therapy includes risks such as MDS/ AML, other secondary malignancies, bone marrow suppression, hypertension and cardiovascular adverse reactions (e.g., tachycardia and arrhythmias), and potential for posterior reversible encephalopathy syndrome (PRES). Additionally, niraparib was associated with high frequency of dose interruptions and reductions. Niraparib was also associated with high frequency (≥ 20%) of toxicities including cytopenias (thrombocytopenia, anemia, neutropenia), gastrointestinal toxicities (nausea, vomiting, and constipation), fatigue, musculoskeletal pain, headache, dizziness, insomnia, hypertension, decreased appetite, dyspnea, and cough. Management of these toxicities requires frequent monitoring of laboratory parameters and potential use of additional medications to manage treatment-related side effects.

Due to the added toxicity in a maintenance setting and a potential OS detriment for patients without HRD-positive tumors, the FDA review team determined that the benefit-risk assessment for niraparib was unfavorable for patients with ovarian cancer (including fallopian tube and primary peritoneal cancers) patients without HRD-positive tumors.

For the HRD-positive population, including patients with tumors with BRCA mutation and/or genomic instability, although the FDA review team determined that the benefit-risk for niraparib was still favorable, the FDA requested that the Applicant update the USPI to better convey the risks of niraparib treatment. The MDS/AML section in Warnings and Precautions was updated to describe that MDS/ AML occurred in 3.3% of patients with HRD-positive tumors treated with niraparib and in 2.4% of patients treated with placebo. FDA also updated Section 6.1 of the USPI to describe the frequencies of adverse reactions (including fatal adverse reactions) and dosage modifications for patients with HRD-positive ovarian cancer treated on PRIMA, (b) (4) to reflect the patient population for whom niraparib is now indicated.

Applicant Rebuttal

During review of this sNDA, rather than narrowing the indication to patients with HRD-positive tumors only as FDA requested, the Applicant initially proposed maintaining an indication in all patients (b) (4) (b) (4) The FDA disagreed with this proposal for several reasons. (b) (4) Finally, as described in the FDA Draft Guidance "Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products," information that narrows an indication should be incorporated directly into the indication whenever possible. Therefore, using (b) (4) would be inappropriate. The FDA re-stated that the indication should be narrowed to patients with HRD-positive tumors only and the Applicant agreed with FDA's proposed revised product labeling.

4. Labeling Considerations

Under Supplement 3, the niraparib indication was narrowed to patients with HRD-positive tumors only, and final OS results for this population was added to labeling.
Under Supplement 4, pharmacokinetic (PK) information and drug-drug interaction (DDI) information were updated. Labeling changes made under both supplements are described in the table below.

Section of Approved USPI	Labeling Change Implemented
Highlights of Prescribing Information	Modified the wording for the first-line advanced epithelial ovarian, fallopian tube, or primary peritoneal maintenance indication to insert "whose cancer is associated with HRD positive, defined by either deleterious BRCA mutation and/or genomic instability" as follows: • for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy and **whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either** ○ **a deleterious or suspected deleterious *BRCA* mutation, and/or** ○ **genomic instability.** Clarified recommended dosage information for patients with moderate hepatic impairment.
Section 1	Revised Section 1.1 to reflect the narrowed indication: "First-line maintenance treatment of **HRD-positive** advanced ovarian cancer" "ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy and **whose cancer is associated with homologous recombination deficiency (HRD)positive status defined by either** ○ **a deleterious or suspected deleterious *BRCA* mutation, and/or** ○ **genomic instability."**
Section 2	Revised Section 2.1 to convey that prescribers should select patients for first-line maintenance treatment with niraparib based upon HRD defined by either

	deleterious or suspected deleterious BRCA mutation and/or genomic instability. Noted that an FDA-approved test for detection of HRD-positive status is not currently available. Revised Section 2.4 to clarify dosage modification for patients with moderate hepatic impairment.
Section 5	Revised Section 5.1 to describe the frequency of MDS/AML for patients enrolled to PRIMA who had HRD-positive tumors. The duration of follow-up and duration of therapy for patients who developed secondary MDS/AML was also updated.
Section 6	Modified the Section 6.1 Clinical Trials Experience subheading from (b) (4) to "First-Line Maintenance Treatment of **HRD-Positive** Advanced Ovarian Cancer" Revised section 6.1 to include the frequencies of dosage modifications, adverse reactions (including deaths), and laboratory abnormalities for patients with **HRD-positive** ovarian cancer enrolled to PRIMA, (b) (4)
Section 8	Section 8.6 Renal Impairment was removed from labeling as there were no specific dosing recommendations. Section 8.6 Hepatic Impairment was modified to clarify recommendations for niraparib dosing in patients with moderate hepatic impairment.
Section 12	Section 12.2 Cardiac Electrophysiology information was revised based on QT labeling guidance. Section 12.3 Pharmacokinetics information on was updated based on data provided in Supplement 4. Additional edits were also made for clarity.
Section 14	Section 14.1 First-Line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer • "HRD-positive" inserted into heading to reflect narrowed indication • The test used to determine HRD status was described as an investigational HRD assay as there is currently no CDx for the narrowed indication. • The clinical study results description for PRIMA were updated to (b) (4) describe the results in the HRD-positive population treated with either niraparib or placebo.

	• The text was revised to remove (b) (4) [redacted] • Table 10 was modified to describe PFS results in the HRD-positive population (b) (4) • Final OS results in the HRD-positive population were described in text.
Patient Information	The "What is ZEJULA?" section was updated to describe the narrowed indication for first-line maintenance treatment as only patients with a certain type of abnormal BRCA gene or a positive laboratory tumor test for genomic instability.

5. Summary and Conclusion

Approval of niraparib for the first-line maintenance treatment of ovarian cancer in all patients was based on demonstration of a statistically significant PFS improvement in the HRD-positive and overall populations. Although PFS was not formally tested in the BRCAm, BRCAwt, HRD-negative, and HRD-not determined subgroups, exploratory sensitivity analyses in all of these subgroups showed trends toward PFS improvement favoring niraparib. However, the magnitude of PFS improvement in the stratified HRD-negative/not determined subgroup was small (< 2 months). At the time of initial approval, OS data were immature with only 18% of events needed, but there was no indication of OS detriment in any subgroup. These results, along with the safety profile, were considered to represent a favorable benefit-risk profile and supported the decision to grant regular approval for niraparib maintenance for the overall population in April 2020.

Final OS results did not reach statistical significance in the overall population, HR 1.01 (95% CI: 0.84, 1.23), and subsequent testing in the HRD-positive population was exploratory. The results in the HRD-positive population did not indicate a potential OS detriment. However, exploratory final OS results in the HRD-negative/not determined subgroup indicated a potential OS detriment (unstratified HR 1.07 (95% CI: 0.83, 1.38)). The previous classwide findings of potential OS detriments associated with PARPi maintenance treatment in biomarker-negative (non-BRCAm or non-HRD-positive) populations heightened the FDA's concern that patients in the HRD-negative/not determined subgroup of PRIMA were not experiencing OS benefit and furthermore, were potentially subject to harm.

Given the modest PFS improvement, potential OS detriment, and added toxicity of niraparib in a maintenance treatment setting when patients also have the option of being under observation only, the review team concluded that the benefit-risk assessment for patients without HRD-positive tumors was no longer favorable. The benefit-risk assessment remained

favorable for those with HRD-positive tumors. The review team advised the Applicant to narrow the indication for niraparib maintenance in the frontline ovarian cancer setting to patients with HRD-positive disease only. The Applicant agreed with FDA's recommendation.

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