CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
208558Orig1s025

Trade Name:	LYNPARZA tablets
Generic or Proper Name:	(olaparib)
Sponsor:	AstraZeneca Pharmaceuticals LP
Approval Date:	May 31, 2023
Indication:	In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration resistant prostate cancer (mCRPC).

CENTER FOR DRUG EVALUATION AND RESEARCH

208558Orig1s025

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology** • **Clinical Microbiology/Virology**	**X**
Product Quality Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s025

APPROVAL LETTER

NDA 208558/S-025

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals LP
Attention: Yuchao Xie, PhD
Regulatory Affairs Director
430 East, 29th Street, 16th Floor
New York, NY 10016

Dear Dr. Xie:

Please refer to your supplemental new drug application (sNDA) dated June 16, 2022, received June 16, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lynparza (olaparib) tablets.

We acknowledge receipt of your major amendment dated December 13, 2022, which extended the goal date by three months.

This Prior Approval sNDA provides for a new indication for Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (Prescribing Information and Medication Guide), with the addition of any labeling changes in pending

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

"Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which the FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application as necessary studies are impossible or highly impracticable to conduct in the pediatric population since the indication rarely if ever exists in children and an adequate study population does not exist.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4459-1 Conduct an analytical and clinical validation study using clinical trial data, adequate to support the availability of an in vitro diagnostic device using tissue samples that is essential to the safe and effective use of olaparib plus abiraterone for patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC), whose tumors harbor *BRCA1* or *BRCA2* mutations.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on May 26, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2025

4459-2 Conduct an analytical and clinical validation study using clinical trial data, adequate to support the availability of an in vitro diagnostic device using ctDNA samples from plasma that is essential to the safe and effective use of olaparib plus abiraterone for patients diagnosed with mCRPC, whose ctDNA samples harbor *BRCA1* or *BRCA2* mutations.

The timetable you submitted on May 26, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2025

Submit clinical protocols to your IND 121413 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to the FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to the FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Christal Lee, Regulatory Project Manager, at 240-402-2711 or Christal.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Daniel Suzman, MD
Acting Deputy Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DANIEL L SUZMAN
05/31/2023 02:44:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s025

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LYNPARZA safely and effectively. See full prescribing information for LYNPARZA.

LYNPARZA® (olaparib) tablets, for oral use
Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Indications and Usage, Advanced Germline BRCA-mutated (gBRCAm) Ovarian Cancer After > 3 Lines of Chemotherapy (1.4) Removed	8/2022
Indications and Usage (1.8)	05/2023
Dosage and Administration (2)	05/2023
Dosage and Administration, Advanced gBRCAm Ovarian Cancer (2.1, 2.2) Removed	8/2022
Warnings and Precautions, Venous Thromboembolism (5.3)	10/2022

INDICATIONS AND USAGE

Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

Ovarian cancer

- for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.1, 2.1)
- in combination with bevacizumab 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.

  Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza (1.2, 2.1).
- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. (1.3)

Breast cancer

- for the adjuvant treatment of adult patients with deleterious or suspected deleterious g*BRCA*m human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.4, 2.1).
- for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.5, 2.1)

Pancreatic cancer

- for the maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.6, 2.1)

Prostate cancer

- for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.7, 2.1)
- in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.8, 2.1)

DOSAGE AND ADMINISTRATION

- Recommended dosage is 300 mg taken orally twice daily with or without food. See Full Prescribing Information for the recommended duration. (2.2)
- Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.2)
- For moderate renal impairment (CLcr 31-50 mL/min), reduce Lynparza dosage to 200 mg orally twice daily. (2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: 150 mg, 100 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in approximately 1.5% of patients exposed to Lynparza monotherapy and the majority of events had a fatal outcome. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed. (5.1)
- Pneumonitis: Occurred in 0.8% of patients exposed to Lynparza, and some cases were fatal. Interrupt treatment if pneumonitis is suspected. Discontinue if pneumonitis is confirmed. (5.2)
- Venous thromboembolism (VTE), including severe or fatal pulmonary embolism (PE), occurred in patients treated with Lynparza. VTE occurred in 8% of patients with mCRPC. Monitor patients for signs and symptoms of VTE and PE and treat as medically appropriate. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (≥10%) in clinical trials:

- as a single agent were nausea, fatigue (including asthenia), anemia, vomiting, diarrhea, decreased appetite, headache, dysgeusia, cough, neutropenia, dyspnea, dizziness, dyspepsia, leukopenia, and thrombocytopenia. (6.1)
- in combination with bevacizumab were nausea, fatigue (including asthenia), anemia, lymphopenia, vomiting, diarrhea, neutropenia, leukopenia, urinary tract infection, and headache. (6.1)
- in combination with abiraterone and prednisone or prednisolone were anemia, fatigue, nausea, diarrhea, decreased appetite, lymphopenia, dizziness, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong or moderate CYP3A inhibitors: Avoid concomitant use. If concomitant use cannot be avoided, reduce Lynparza dosage. (2.4, 7.2, 12.3)
- Strong or moderate CYP3A inducers: Avoid concomitant use. (7.2, 12.3)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Lynparza is indicated in combination with bevacizumab 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.

Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.3 Maintenance Treatment of Recurrent Ovarian Cancer

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

1.4 Adjuvant Treatment of Germline *BRCA*-mutated HER2-negative High Risk Early Breast Cancer

Lynparza is indicated for the adjuvant treatment of adult patients with deleterious or suspected deleterious g*BRCA*m human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.5 Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.6 First-Line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.8 Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCAm*) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics.

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including *BRCA* mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection*

Indication	Biomarker	Sample type		
		Tumor	Blood	Plasma (ctDNA)
First-line maintenance treatment of germline or somatic *BRCA*m advanced ovarian cancer	*BRCA1*m, *BRCA2*m	X	X	
First-line maintenance treatment of HRD-positive advanced ovarian cancer in	*BRCA1*m, *BRCA2*m and/or genomic instability	X		

Indication	Biomarker	Sample type		
		Tumor	Blood	Plasma (ctDNA)
combination with bevacizumab				
Adjuvant treatment of g*BRCA*m HER2-negative high risk early breast cancer	g*BRCA1*m, g*BRCA2*m		X	
g*BRCA*m HER2-negative metastatic breast cancer	g*BRCA1*m, g*BRCA2*m		X	
First-line maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma	g*BRCA1*m, g*BRCA2*m		X	
Germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer	*ATM*m, *BRCA1*m, *BRCA2*m, *BARD1*m, *BRIP1*m, *CDK12*m, *CHEK1*m, *CHEK2*m, *FANCL*m, *PALB2*m, *RAD51B*m, *RAD51C*m, *RAD51D*m, *RAD54L*m	X		
	g*BRCA1*m, g*BRCA2*m		X	
	*ATM*m, *BRCA1*m, *BRCA2*m			X
BRCA-mutated metastatic castration-resistant prostate cancer in combination with abiraterone and prednisone or prednisolone	*BRCA1*m, *BRCA2*m	X	X	X

* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test, if available.

2.2 Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

Continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous treatment, can be treated beyond 2 years.

First-Line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Continue Lynparza treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years.

When used with Lynparza, the recommended dose of bevacizumab is 15 mg/kg every three weeks. Bevacizumab should be given for a total of 15 months including the period given with chemotherapy and given as maintenance. Refer to the Prescribing Information for bevacizumab when used in combination with Lynparza for more information.

Adjuvant Treatment of Germline *BRCA*-mutated HER2-negative High Risk Early Breast Cancer

Continue treatment for a total of 1 year, or until disease recurrence, or unacceptable toxicity, whichever occurs first. Patients receiving Lynparza for hormone receptor positive HER2-negative breast cancer should continue concurrent treatment with endocrine therapy as per current clinical practice guidelines.

Recurrent Ovarian Cancer, HER2-negative Metastatic Breast Cancer, Metastatic Pancreatic Adenocarcinoma, and HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- Maintenance treatment of recurrent ovarian cancer
- Germline *BRCA*-mutated HER-2 negative metastatic breast cancer
- First-line maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma
- HRR gene-mutated metastatic castration-resistant prostate cancer

BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Continue treatment until disease progression or unacceptable toxicity.

When used with Lynparza, the recommended dose of abiraterone is 1000 mg taken orally once daily. Abiraterone should be given in combination with prednisone or prednisolone 5 mg orally twice daily. Refer to the Prescribing Information for abiraterone for dosing information.

Patients with mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

2.3 Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

If a further dose reduction is required, then reduce to 200 mg taken twice daily.

2.4 Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors with Lynparza.

If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor.
- 150 mg twice daily when used concomitantly with a moderate CYP3A inhibitor.

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

2.5 Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 150 mg: green to green/grey, oval, bi-convex, film-coated, with debossment ‘OP150’ on one side and plain on the reverse side.
- 100 mg: yellow to dark yellow, oval, bi-convex, film-coated, with debossment ‘OP100’ on one side and plain on the reverse side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) has occurred in patients treated with Lynparza and some cases were fatal.

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1)]*, the cumulative incidence of MDS/AML was approximately 1.5% (43/2901). Of these, 51% (22/43) had a fatal outcome. The median duration of therapy with Lynparza in patients who developed MDS/AML was 2 years (range: < 6 months to > 10 years). All of these patients

had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Do not start Lynparza until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt Lynparza and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Lynparza.

5.2 Pneumonitis

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1)]*, the incidence of pneumonitis, including fatal cases, was 0.8% (24/2901). If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Lynparza treatment and treat the patient appropriately.

5.3 Venous Thromboembolism

Venous thromboembolism (VTE), including severe or fatal pulmonary embolism (PE), occurred in patients treated with Lynparza *[see Adverse Reactions (6.1)]*.

In the combined data of two randomized, placebo-controlled clinical studies (PROfound and PROpel) in patients with metastatic castration-resistant prostate cancer (N=1180), VTE occurred in 8% of patients who received Lynparza, including pulmonary embolism in 6%. In the control arms, VTE occurred in 2.5% including pulmonary embolism in 1.5%.

Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

5.4 Embryo-Fetal Toxicity

Lynparza can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Lynparza. Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1)]*
- Pneumonitis *[see Warnings and Precautions (5.2)]*
- Venous Thromboembolism *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Unless otherwise specified, the data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2901 patients; 2135 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In addition to the 2901 patients, certain subsections in the WARNINGS AND PRECAUTIONS include adverse reactions observed with exposure to Lynparza with abiraterone (n=398) in PROpel. All patients with metastatic castration resistant prostate cancer received concomitant ADT or previous bilateral orchiectomy.

In the pooled safety population, 56% of patients were exposed for 6 months or longer and 28% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anemia (36%), vomiting (32%), diarrhea (24%), decreased appetite (22%), headache (16%), dysgeusia (15%), cough (15%), neutropenia (14%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), and thrombocytopenia (10%).

First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

SOLO-1

The safety of Lynparza for the maintenance treatment of patients with *BRCA*-mutated advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was investigated in SOLO-1 *[see Clinical Studies (14.1)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=260) or placebo (n=130) until disease progression or unacceptable toxicity. The median duration of study treatment was 25 months for patients who received Lynparza and 14 months for patients who received placebo.
Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 52% and dose reductions due to an adverse reaction occurred in 28%. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anemia (23%), nausea (14%), and vomiting (10%). Discontinuation due to adverse reactions occurred in 12% of patients receiving Lynparza. The most frequent adverse reactions that led to discontinuation of Lynparza were fatigue (3.1%), anemia (2.3%), and nausea (2.3%).

Tables 2 and 3 summarize adverse reactions and laboratory abnormalities in SOLO-1.

Table 2 Adverse Reactions* in SOLO-1 (≥10% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=260		Placebo n=130	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
Gastrointestinal Disorders				
Nausea	77	1	38	0
Abdominal pain†	45	2	35	1
Vomiting	40	0	15	1
Diarrhea‡	37	3	26	0
Constipation	28	0	19	0
Dyspepsia	17	0	12	0
Stomatitis§	11	0	2	0
General Disorders and Administration Site Conditions				
Fatigue¶	67	4	42	2
Blood and Lymphatic System Disorders				
Anemia	38	21	9	2
Neutropenia#	17	6	7	3
Leukopenia♭	13	3	8	0
Thrombocytopenia♂	11	1	4	2
Infections and Infestations				
Upper respiratory tract infection/ influenza/nasopharyngitis/bronchitis	28	0	23	0
UTIª	13	1	7	0
Nervous System Disorders				
Dysgeusia	26	0	4	0
Dizziness	20	0	15	1
Metabolism and Nutrition Disorders				
Decreased appetite	20	0	10	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspneaè	15	0	6	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.
† Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal distension, abdominal discomfort, and abdominal tenderness.
‡ Includes colitis, diarrhea, and gastroenteritis.
§ Includes stomatitis, aphthous ulcer, and mouth ulceration.
¶ Includes asthenia, fatigue, lethargy, and malaise.
# Includes neutropenia and febrile neutropenia.
♭ Includes leukopenia and white blood cell count decreased.

ß Includes platelet count decreased and thrombocytopenia.
à Includes urosepsis, urinary tract infection, urinary tract pain, and pyuria.
è Includes dyspnea and dyspnea exertional.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were increased blood creatinine (8%), lymphopenia (6%), VTE (3%), hypersensitivity (2%), MDS/AML (1%), dermatitis (1%), and increased mean cell volume (0.4%).

Table 3 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-1

Laboratory Parameter*	Lynparza tablets n†=260		Placebo n†=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	87	19	63	2
Increase in mean corpuscular volume	87	-	43	-
Decrease in leukocytes	70	7	52	1
Decrease in lymphocytes	67	14	29	5
Decrease in absolute neutrophil count	51	9	38	6
Decrease in platelets	35	1	20	2
Increase in serum creatinine	34	0	18	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

PAOLA-1

The safety of Lynparza in combination with bevacizumab for the maintenance treatment of patients with advanced ovarian cancer following first-line treatment containing platinum-based chemotherapy and bevacizumab was investigated in PAOLA-1 *[see Clinical Studies (14.2)]*. This study was a placebo-controlled, double-blind study in which 802 patients received either Lynparza 300 mg BID in combination with bevacizumab (n=535) or placebo in combination with bevacizumab (n=267) until disease progression or unacceptable toxicity. The median duration of treatment with Lynparza was 17.3 months and 11 months for bevacizumab post-randomization on the Lynparza/bevacizumab arm.

Fatal adverse reactions occurred in 1 patient due to concurrent pneumonia and aplastic anemia. Serious adverse reactions occurred in 31% of patients who received Lynparza/bevacizumab. Serious adverse reactions in >5% of patients included hypertension (19%) and anemia (17%).

Dose interruptions due to an adverse reaction of any grade occurred in 54% of patients receiving Lynparza/bevacizumab and dose reductions due to an adverse reaction occurred in 41% of patients who received Lynparza/bevacizumab.

The most frequent adverse reactions leading to dose interruption in the Lynparza/bevacizumab arm were anemia (21%), nausea (7%), vomiting (3%), and fatigue (3%), and the most frequent adverse reactions leading to reduction in the Lynparza/bevacizumab arm were anemia (19%), nausea (7%), and fatigue (4%).

Discontinuation due to adverse reactions occurred in 20% of patients receiving Lynparza/bevacizumab. Specific adverse reactions that most frequently led to discontinuation in patients treated with Lynparza/bevacizumab were anemia (4%) and nausea (3%).

The most common adverse reactions (≥ 10%) for patients receiving Lynparza/bevacizumab irrespective of the frequency compared with the placebo/bevacizumab arm were nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%), diarrhea (18%), neutropenia (18%), leukopenia (18%), urinary tract infection (15%), and headache (14%).

Tables 4 and 5 summarize adverse reactions and laboratory abnormalities in PAOLA-1, respectively.

Table 4 Adverse Reactions* Occurring in ≥10% of Patients Treated with Lynparza/bevacizumab in PAOLA-1 and at ≥5% Frequency Compared to the Placebo/bevacizumab Arm

Adverse Reactions	Lynparza/bevacizumab n=535		Placebo/bevacizumab n=267	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)†	53	5	32	1.5
Gastrointestinal Disorders				
Nausea	53	2.4	22	0.7
Vomiting	22	1.7	11	1.9
Blood and Lymphatic Disorders				
Anemia‡	41	17	10	0.4
Lymphopenia§	24	7	9	1.1
Leukopenia¶	18	1.9	10	1.5

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.
† Includes asthenia and fatigue.
‡ Includes anemia, anemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anemia, normochromic normocytic anemia, normocytic anemia, and red blood cell count decreased.
§ Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.
¶ Includes leukopenia and white blood cell count decreased.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza/bevacizumab were dysgeusia (8%), dyspnea (8%), stomatitis (5%), dyspepsia (4.3%), erythema (3%), dizziness (2.6%), hypersensitivity (1.7%), and MDS/AML (0.7%).

Venous thromboembolism occurred more commonly in patients receiving Lynparza/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).

Table 5 Laboratory Abnormalities Reported in ≥25% of Patients in PAOLA-1*

Laboratory Parameter†	Lynparza/bevacizumab n†=535		Placebo/bevacizumab n‡=267	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	79	13	55	0.4
Decrease in lymphocytes	63	10	42	3.0
Increase in serum creatinine	61	0.4	36	0.4
Decrease in leukocytes	59	3.4	45	2.2
Decrease in absolute neutrophil count	35	7	30	3.7
Decrease in platelets	35	2.4	28	0.4

* Reported within 30 days of the last dose.

† Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

‡ This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Maintenance Treatment of Recurrent Ovarian Cancer

SOLO-2

The safety of Lynparza for the maintenance treatment of patients with platinum sensitive g*BRCA*m ovarian cancer was investigated in SOLO-2 *[see Clinical Studies (14.3)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=195) or placebo (n=99) until disease progression or unacceptable toxicity. The median duration of study treatment was 19.4 months for patients who received Lynparza and 5.6 months for patients who received placebo.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 45% and dose reductions due to an adverse reaction occurred in 27%. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anemia (22%), neutropenia (9%), and fatigue/asthenia (8%). Discontinuation due to an adverse reaction occurred in 11% of patients receiving Lynparza.

Tables 6 and 7 summarize adverse reactions and laboratory abnormalities in SOLO-2.

Table 6 Adverse Reactions* in SOLO-2 (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=195		Placebo n=99	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	76	3	33	0
Vomiting	37	3	19	1
Diarrhea	33	2	22	0
Stomatitis†	20	1	16	0
General Disorders and Administration Site Conditions				
Fatigue including asthenia	66	4	39	2
Blood and Lymphatic Disorders				
Anemia‡	44	20	9	2
Infections and Infestations				
Nasopharyngitis/URI/sinusitis/ rhinitis/influenza	36	0	29	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/myalgia	30	0	28	0
Nervous System Disorders				
Dysgeusia	27	0	7	0
Headache	26	1	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	22	0	11	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

† Represents grouped term consisting of abscess oral, aphthous ulcer, gingival abscess, gingival disorder, gingival pain, gingivitis, mouth ulceration, mucosal infection, mucosal inflammation, oral candidiasis, oral discomfort, oral herpes, oral infection, oral mucosal erythema, oral pain, oropharyngeal discomfort, and oropharyngeal pain.

‡ Represents grouped term consisting of anemia, hematocrit decreased, hemoglobin decreased, iron deficiency, mean cell volume increased, and red blood cell count decreased.

Clinically relevant adverse reactions that occurred in <20% of patients receiving Lynparza were neutropenia (19%), cough (18%), leukopenia (16%), hypomagnesemia (14%), thrombocytopenia (14%), dizziness (13%), dyspepsia (11%), increased creatinine (11%), MDS/AML (8%), edema (8%), rash (6%), VTE (5%), and lymphopenia (1%).

Table 7 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-2

Laboratory Parameter*	Lynparza tablets n†=195		Placebo n†=99	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increase in mean corpuscular volume‡	89	-	52	-
Decrease in hemoglobin	83	17	69	0
Decrease in leukocytes	69	5	48	1
Decrease in lymphocytes	67	11	37	1
Decrease in absolute neutrophil count	51	7	34	3
Increase in serum creatinine	44	0	29	0
Decrease in platelets	42	2	22	1

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > upper limit of normal (ULN).

Study 19

The safety of Lynparza as maintenance monotherapy was evaluated in patients with platinum sensitive ovarian cancer who had received 2 or more previous platinum-containing regimens in Study 19 *[see Clinical Studies (14.3)]*. Patients received Lynparza capsules 400 mg orally twice daily (n=136) or placebo (n=128). At the time of final analysis, the median duration of exposure was 8.7 months in patients who received Lynparza and 4.6 months in patients who received placebo.

Adverse reactions led to dose interruptions in 35% of patients receiving Lynparza; dose reductions in 26% and discontinuation in 6% of patients receiving Lynparza.

Tables 8 and 9 summarize adverse reactions and laboratory abnormalities in Study 19.

Table 8 Adverse Reactions* in Study 19 (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza capsules n=136		Placebo n=128	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	71	2	36	0
Vomiting	35	2	14	1
Diarrhea	28	2	25	2
Constipation	22	1	12	0
Dyspepsia	20	0	9	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	63	9	46	3
Blood and Lymphatic Disorders				
Anemia†	23	7	7	1
Infections and Infestations				

Adverse Reaction	Lynparza capsules n=136		Placebo n=128	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Respiratory tract infection	22	2	11	0
Metabolism and Nutrition Disorders				
Decreased appetite	21	0	13	0
Nervous System Disorders				
Headache	21	0	13	1

* Graded according to NCI CTCAE v4.0.
† Represents grouped terms of related terms that reflect the medical concept of the adverse reaction.

Clinically relevant adverse reactions that occurred in <20% of patients receiving Lynparza were dysgeusia (16%), dizziness (15%), dyspnea (13%), pyrexia (10%), stomatitis (9%), edema (9%), increase in creatinine (7%), neutropenia (5%), thrombocytopenia (4%), leukopenia (2%), MDS/AML (1%), VTE (1%), and lymphopenia (1%).

Table 9 Laboratory Abnormalities Reported in ≥25% of Patients in Study 19

Laboratory Parameter*	Lynparza capsules n†=136		Placebo n†=129	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	82	8	58	1
Increase in mean corpuscular volume‡	82	-	51	-
Decrease in leukocytes	58	4	37	2
Decrease in lymphocytes	52	10	32	3
Decrease in absolute neutrophil count	47	7	40	2
Increase in serum creatinine	45	0	14	0
Decrease in platelets	36	4	18	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

Adjuvant Treatment of germline *BRCA*-mutated HER2-negative High Risk Early Breast Cancer

OlympiA

The safety of Lynparza as monotherapy for the adjuvant treatment of patients with g*BRCA*-mutated HER2-negative high risk early breast cancer was investigated in OlympiA *[see Clinical Studies (14.4)]*. This study was a randomized, double-blind, multi-center study in which patients received either Lynparza tablets 300 mg orally twice daily (n=911) or placebo (n=904) for a total of 1 year, or until disease recurrence, or unacceptable toxicity. The median duration of treatment was 1 year in both arms.

Dose interruptions due to an adverse reaction of any grade occurred in 31% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 23% of patients receiving Lynparza. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (11%), neutropenia (6%), nausea (5%), leukopenia (3.5%), fatigue (3%), and vomiting (2.9%) and the most frequent adverse reactions leading to dose reduction of Lynparza were anemia (8%), nausea (4.7%), neutropenia (4.2%), fatigue (3.3%), leukopenia (1.8%), and vomiting (1.5%). Discontinuation due to adverse reactions occurred in 10% of patients receiving Lynparza. The adverse reactions that most frequently led to discontinuation of Lynparza were nausea (2%), anemia (1.8%), and fatigue (1.3%).

Tables 10 and 11 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in OlympiA.

Table 10 Adverse Reactions* in OlympiA (≥ 10% of Patients Who Received Lynparza)

Adverse Reactions	Lynparza tablets n=911		Placebo n=904	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	57	0.8	23	0
Vomiting	23	0.7	8	0
Diarrhea	18	0.3	14	0.3
Stomatitis†	10	0.1	4.5	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	42	1.8	28	0.7
Blood and Lymphatic Disorders				
Anemia‡	24	9	3.9	0.3
Leukopenia§	17	3	6	0.3
Neutropenia¶	16	5	7	0.8
Nervous System Disorders				
Headache	20	0.2	17	0.1
Dysgeusia#	12	0	4.8	0
Dizziness	11	0.1	7	0.1
Metabolism and Nutrition Disorders				
Decreased appetite	13	0.2	6	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03
† Includes aphthous ulcer, mouth ulceration, and stomatitis.
‡ Includes anemia, anemia macrocytic, erythropenia, hematocrit decreased, hemoglobin decreased, normochromic anemia, normochromic normocytic anemia, normocytic anemia, and red blood cell count decreased.
§ Includes leukopenia and white blood cell count decreased.
¶ Includes agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased.
# Includes dysgeusia and taste disorder.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were cough (9.2%), lymphopenia (7%), dyspepsia (6%), upper abdominal pain (4.9%), rash (4.9%), dyspnea (4.2%),

thrombocytopenia (4.2%), increase in creatinine (2%), hypersensitivity (0.9%), VTE (0.5%), dermatitis (0.5%), increase in mean corpuscular volume (0.2%), and MDS/AML (0.2%).

Table 11 Laboratory Abnormalities Reported in ≥25% of Patients in OlympiA

Laboratory Parameter*	Lynparza tablets n†= 911		Placebo n†=904	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in lymphocytes	77	13	59	3.7
Increase in mean corpuscular volume‡	67	0	4.8	0
Decrease in hemoglobin	65	8	31	0.9
Decrease in leukocytes	64	5	42	0.7
Decrease in absolute neutrophil count	39	7	27	1.1

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

Germline BRCA-mutated HER2-negative Metastatic Breast Cancer

OlympiAD

The safety of Lynparza was evaluated in g*BRCA*m patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD *[see Clinical Studies (14.5)]*. Patients received either Lynparza tablets 300 mg orally twice daily (n=205) or a chemotherapy (capecitabine, eribulin, or vinorelbine) of the healthcare provider's choice (n=91) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.2 months in patients who received Lynparza and 3.4 months in patients who received chemotherapy.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 35% and dose reductions due to an adverse reaction occurred in 25%. Discontinuation due to an adverse reaction occurred in 5% of patients receiving Lynparza.

Tables 12 and 13 summarize the adverse reactions and laboratory abnormalities in OlympiAD.

Table 12 Adverse Reactions* in OlympiAD (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=205		Chemotherapy n=91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	58	0	35	1
Vomiting	30	0	15	1

Adverse Reaction	Lynparza tablets n=205		Chemotherapy n=91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Diarrhea	21	1	22	0
Blood and Lymphatic Disorders				
Anemia†	40	16	26	4
Neutropenia‡	27	9	50	26
Leukopenia§	25	5	31	13
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	37	4	36	1
Infections and Infestations				
Respiratory tract infection¶	27	1	22	0
Nervous System Disorders				
Headache	20	1	15	2

* Graded according to NCI CTCAE v4.0.
† Represents grouped terms consisting of anemia (anemia erythropenia, hematocrit decreased, hemoglobin decreased, and red blood cell count decreased).
‡ Represents grouped terms consisting of neutropenia (febrile neutropenia, granulocyte count decreased, granulocytopenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased).
§ Represents grouped terms consisting of leukopenia (leukopenia and white blood cell count decreased).
¶ Represents grouped terms consisting of bronchitis, influenza, lower respiratory tract infection, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

Clinically relevant adverse reactions that occurred in <20% of patients receiving Lynparza were cough (18%), decreased appetite (16%), thrombocytopenia (11%), dysgeusia (9%), lymphopenia (8%), dyspepsia (8%), dizziness (7%), stomatitis (7%), upper abdominal pain (7%), rash (5%), increase in serum creatinine (3%), dermatitis (1%), and VTE (1%).

Table 13 Laboratory Abnormalities Reported in ≥25% of Patients in OlympiAD

Laboratory Parameter*	Lynparza tablets n†= 205		Chemotherapy n†= 91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	82	17	66	3
Decrease in lymphocytes	73	21	63	3
Decrease in leukocytes	71	8	70	23
Increase in mean corpuscular volume‡	71	-	33	-
Decrease in absolute neutrophil count	46	11	65	38
Decrease in platelets	33	3	28	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

First-line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

POLO

The safety of Lynparza as maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma following first-line treatment with platinum-based chemotherapy was evaluated in POLO *[see Clinical Studies (14.6)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=90) or placebo (n=61) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 34% were exposed for 6 months or longer and 25% were exposed for greater than one year.

Among patients who received Lynparza, dosage interruptions due to an adverse reaction of any grade occurred in 35% and dosage reductions due to an adverse reaction occurred in 17%. The most frequent adverse reactions leading to dosage interruption or reduction in patients who received Lynparza were anemia (11%), vomiting (5%), abdominal pain (4%), asthenia (3%), and fatigue (2%). Discontinuation due to adverse reactions occurred in 6% of patients receiving Lynparza. The most frequent adverse reaction that led to discontinuation of Lynparza was fatigue (2.2%).

Tables 14 and 15 summarize the adverse reactions and laboratory abnormalities in patients in POLO.

Table 14 Adverse Reactions[*] in POLO (Occurring in ≥10% of Patients who Received Lynparza)

Adverse Reaction	Lynparza tablets (n=91)[†]		Placebo (n=60)[†]	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
General Disorders and Administration Site Conditions				
Fatigue[‡]	60	5	35	2
Gastrointestinal Disorders				
Nausea	45	0	23	2
Abdominal pain[§]	34	2	37	5
Diarrhea	29	0	15	0
Constipation	23	0	10	0
Vomiting	20	1	15	2
Stomatitis[¶]	10	0	5	0
Blood and Lymphatic System Disorders				
Anemia	27	11	17	3
Thrombocytopenia[#]	14	3	7	0
Neutropenia[Þ]	12	4	8	3
Metabolism and Nutrition Disorders				
Decreased appetite	25	3	7	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	19	0	17	2
Arthralgia	15	1	10	0
Skin and Subcutaneous Tissue Disorder				
Rash[ß]	15	0	5	0

Adverse Reaction	Lynparza tablets (n=91)†		Placebo (n=60)†	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[à]	13	0	5	2
Infections and Infestations				
Nasopharyngitis	12	0	3	0
Nervous System Disorders				
Dysgeusia	11	0	5	0

* Graded according to NCI CTCAE, version 4.0
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Includes asthenia and fatigue.
§ Includes abdominal pain, abdominal pain upper, and abdominal pain lower.
¶ Includes stomatitis and mouth ulceration.
# Includes platelets count decreased and thrombocytopenia.
Þ Includes neutropenia, febrile neutropenia, and neutrophil count decreased.
ß Includes rash erythematous, rash macular, and rash maculo-papular.
à Includes dyspnea and dyspnea exertional.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were cough (9%), abdominal pain upper (7%), blood creatinine increased (7%), dizziness (7%), headache (7%), dyspepsia (5%), leukopenia (5%), VTE (3%), hypersensitivity (2%), and lymphopenia (2%).

Table 15 Laboratory Abnormalities Reported in ≥25% of Patients in POLO

Laboratory Parameter*	Lynparza tablets n†=91		Placebo n†=60	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increase in serum creatinine	99	2	85	0
Decrease in hemoglobin	86	11	65	0
Increase in mean corpuscular volume‡	71	-	30	-
Decrease in lymphocytes	61	9	27	0
Decrease in platelets	56	2	39	0
Decrease in leukocytes	50	3	23	0
Decrease in absolute neutrophil count	25	3	10	0

* Patients were allowed to enter POLO with hemoglobin ≥9 g/dL (CTCAE Grade 2) and other laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound *[see Clinical Studies (14.7)]*. This study was a randomized, open-label, multi-center study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Fatal adverse reactions occurred in 4% of patients treated with Lynparza. These included pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%).

Serious adverse reactions occurred in 36% of patients receiving Lynparza. The most frequent serious adverse reactions (≥2%) were anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%).

Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 22% of Lynparza patients. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (25%) and thrombocytopenia (6%) and the most frequent adverse reaction leading to reduction of Lynparza was anemia (16%). Discontinuation due to adverse reactions occurred in 18% of Lynparza. The adverse reaction that most frequently led to discontinuation of Lynparza was anemia (7%).

Tables 16 and 17 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 16 Adverse Reactions* Reported in ≥10% of Patients in PROfound

Adverse Reactions	Lynparza tablets n=256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and lymphatic disorders				
Anemia†	46	21	15	5
Thrombocytopenia‡	12	4	3	0
Gastrointestinal disorders				
Nausea	41	1	19	0
Diarrhea	21	1	7	0
Vomiting	18	2	12	1

Adverse Reactions	Lynparza tablets n=256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General disorders and administration site conditions				
Fatigue (including asthenia)	41	3	32	5
Metabolism and nutrition disorders				
Decreased appetite	30	1	18	1
Respiratory, thoracic, and mediastinal disorders				
Cough	11	0	2	0
Dyspnea	10	2	3	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
† Includes anemia and hemoglobin decreased.
‡ Includes platelet count decreased and thrombocytopenia.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were neutropenia (9%), VTE (7%), dizziness (7%), dysgeusia (7%), dyspepsia (7%), headache (6%), pneumonia (5%), stomatitis (5%), rash (4%), blood creatinine increase (4%), pneumonitis (2%), upper abdominal pain (2%), and hypersensitivity (1%).

Table 17 Laboratory Abnormalities Reported in ≥25% of Patients in PROfound

Laboratory Parameter*	Lynparza tablets n†= 256		Enzalutamide or abiraterone n†=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	98	13	73	4
Decrease in lymphocytes	62	23	34	13
Decrease in leukocytes	53	4	21	0
Decrease in absolute neutrophil count	34	3	9	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

PROpel

The safety of Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of patients in the first-line mCRPC setting was investigated in PROpel *[see Clinical Studies (14.8)]*. Patients were randomized to receive either Lynparza tablets 300 mg orally twice daily plus abiraterone tablets 1000 mg once daily (Lynparza/abiraterone) (n=398), or placebo plus abiraterone 1000 mg once

daily (placebo/abiraterone) (n=396) until disease progression or unacceptable toxicity. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily.

Fatal adverse reactions occurred in 6% of patients, including COVID-19 (3%) and pneumonias (0.5%).

Serious adverse reactions occurred in 39% of patients. Serious adverse reactions reported in > 2% of patients included anemia (6%), COVID-19 (6%), pneumonia (4.5%), pulmonary embolism (3.5%), and urinary tract infection (3%).

Permanent discontinuation of Lynparza due to adverse reactions occurred in 16% of patients treated in the Lynparza with abiraterone arm. The most common adverse reactions which resulted in permanent discontinuation of Lynparza were anemia (4.3%) and pneumonia (1.5%).

Dosage interruption of Lynparza due to adverse reactions occurred in 48% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage interruption of Lynparza were anemia (16%), COVID-19 (6%) fatigue (3.5%), nausea (2.8%), pulmonary embolism (2.3%), and diarrhea (2.3%).

Dose reduction of Lynparza due to adverse reactions occurred in 21% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage reductions of Lynparza were anemia (11%) and fatigue (2.5%).

The most common adverse reactions (≥10%) in patients who received Lynparza/abiraterone were anemia (48%), fatigue (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), abdominal pain (13%), and dizziness (14%).

Tables 18 and 19 summarize adverse reactions and laboratory abnormalities in PROpel, respectively.

Table 18 Adverse Reactions (≥10%) in Patients Who Received Lynparza (with a Difference of ≥5% Compared to Placebo) in PROpel

Adverse Reactions*	Lynparza/abiraterone n=398		Placebo/abiraterone n=396	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and Lymphatic Disorders				
Anemia†	48	16	18	3.3
Lymphopenia‡	14	5	6	1.8
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	38	2.3	30	1.5
Gastrointestinal Disorders				
Nausea	30	0.3	14	0.3
Diarrhea	19	1	10	0.3
Abdominal pain$^{\alpha}$	13	0	7	0.5
Metabolism and nutrition disorders				
Decreased appetite	16	1	7	0
Nervous System Disorders				
Dizziness$^{\beta}$	14	0.3	7	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
† Includes anemia, anemia macrocytic, and red blood cell count decreased
‡ Includes lymphocyte count decreased and lymphopenia
α Includes abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal pain lower
β Includes dizziness and vertigo.

Clinically relevant adverse reactions that occurred in <10% for patients receiving Lynparza plus abiraterone were headache (9%), VTE (8%), rash (7%), dysgeusia (6%), acute kidney injury (3%), and stomatitis (2.5%).

Table 19 Selected Laboratory Abnormalities Reported in ≥20% of Patients in PROpel

Laboratory Parameter	Lynparza/abiraterone n=398†		Placebo/abiraterone n=396†	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	97	12	81	1.3
Decrease in lymphocytes	70	23	49	11
Decrease in platelets	23	1.2	20	0.3
Decrease in absolute neutrophil count	23	5	6	0

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Lynparza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity including angioedema.

Skin and subcutaneous tissue disorders: Erythema nodosum, rash, dermatitis.

7 DRUG INTERACTIONS

7.1 Use with Anticancer Agents

Clinical studies of Lynparza with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

7.2 Effect of Other Drugs on Lynparza

Strong and Moderate CYP3A Inhibitors

Coadministration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of strong or moderate

CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza *[see Dosage and Administration (2.4)]*.

Strong and Moderate CYP3A Inducers

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Lynparza efficacy *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of strong or moderate CYP3A inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1)]*, Lynparza can cause fetal harm when administered to a pregnant woman. There are no available data on Lynparza use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily *(see Data)*. Apprise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to Day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure ($AUC_{0\text{-}24h}$) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs, and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

8.2 Lactation

Risk Summary

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants from Lynparza, advise a lactating woman not to breastfeed during treatment with Lynparza and for one month after receiving the last dose.

8.3 Females and Males of Reproductive Potential

Lynparza can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with Lynparza.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for 6 months following the last dose.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of Lynparza have not been established in pediatric patients.

8.5 Geriatric Use

Of the 2901 patients with advanced solid tumors who received Lynparza as a single agent, 680 (23%) patients were aged ≥65 years, and this included 206 (7%) patients who were aged ≥75 years. Thirteen (0.4%) patients were aged ≥85 years.

Of the 535 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (PAOLA-1), 204 (38%) patients were aged ≥65 years, and this included 31 (6%) patients who were aged ≥75 years.

Of the 398 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with abiraterone and prednisone or prednisolone (PROpel), 268 (67%) patients were aged ≥65 years, and this included 95 (24%) patients who were aged ≥75 years.

No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

8.6 Renal Impairment

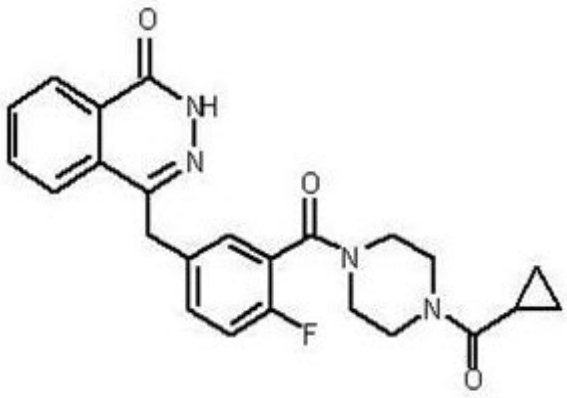
No dosage modification is recommended in patients with mild renal impairment (CLcr 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min) *[see Dosage and Administration (2.5)]*. There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C) *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. The chemical name is 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one. The empirical molecular formula for Lynparza is $C_{24}H_{23}FN_4O_3$ and the relative molecular mass is 434.46. It has the following chemical structure:



Olaparib is a crystalline solid, is non-chiral and shows pH-independent low solubility across the physiological pH range.

Lynparza (olaparib) tablets for oral use contain 100 mg or 150 mg of olaparib. Inactive ingredients in the tablet core are copovidone, mannitol, colloidal silicon dioxide, and sodium stearyl fumarate. The tablet coating consists of hypromellose, polyethylene glycol 400, titanium dioxide, ferric oxide yellow, and ferrosoferric oxide (150 mg tablet only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and

DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines in vitro and decrease tumor growth in mouse xenograft models of human cancer, both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in *BRCA1/2*, *ATM*, or other genes involved in the homologous recombination repair (HRR) of DNA damage and correlated with platinum response. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death. In prostate cancer models, PARP1 has been shown to contribute to androgen receptor (AR) activity regulation; the combination of olaparib and AR inhibition resulted in cytotoxicity in vitro and anti-tumor activity in mouse xenograft models.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of olaparib on cardiac repolarization was assessed in 119 patients following a single dose of 300 mg and in 109 patients following multiple dosing of 300 mg twice daily. No clinically relevant effect of olaparib on QT interval was observed.

12.3 Pharmacokinetics

The area under the curve (AUC) of olaparib increases approximately proportionally following administration of single doses of 25 mg to 450 mg (0.08 to 1.5 times the recommended dose) and maximal concentrations (C_{max}) increased slightly less than proportionally for the same dose range. Olaparib showed time-dependent pharmacokinetics and an AUC mean accumulation ratio of 1.8 is observed at steady state following a dose of 300 mg twice daily.

The mean (CV%) olaparib C_{max} is 5.4 µg/mL (32%) and AUC is 39.2 µg*h/mL (44%) following a single 300 mg dose. The mean steady state olaparib C_{max} and AUC is 7.6 µg/mL (35%) and 49.2 µg*h/mL (44%), following a dose of 300 mg twice daily.

Absorption

Following oral administration of olaparib, the median time to peak plasma concentration is 1.5 hours.

Effect of Food

Co-administration of a high fat and high calorie meal (800-1000 kcal, 50% of the calorie content made up from fat) with olaparib slowed the rate (t_{max} delayed by 2.5 hours) of absorption, but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 8%).

Distribution

The mean (± standard deviation) apparent volume of distribution of olaparib is 158 ± 136 L following a single 300 mg dose of Lynparza. The protein binding of olaparib is approximately 82% in vitro.

Elimination

The mean (± standard deviation) terminal plasma half-life of olaparib is 14.9 ± 8.2 hours and the apparent plasma clearance is 7.4 ± 3.9 L/h following a single 300 mg dose of Lynparza.

Metabolism

Olaparib is metabolized by cytochrome P450 (CYP) 3A in vitro.

Following an oral dose of radiolabeled olaparib to female patients, unchanged olaparib accounted for 70% of the circulating radioactivity in plasma. It was extensively metabolized with unchanged drug accounting for 15% and 6% of radioactivity in urine and feces, respectively. The majority of the metabolism is attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulfate conjugation.

Excretion

Following a single dose of radiolabeled olaparib, 86% of the dosed radioactivity was recovered within a 7-day collection period, 44% via the urine and 42% via the feces. The majority of the material was excreted as metabolites.

Specific Populations

Patients with Renal Impairment

In a renal impairment trial, the mean AUC increased by 24% and C_{max} by 15%, when olaparib was dosed in patients with mild renal impairment (CLcr=51-80 mL/min defined by the Cockcroft-Gault equation; n=13) and by 44% and 26%, respectively, when olaparib was dosed in patients with moderate renal impairment (CLcr=31-50 mL/min; n=13), compared to those with normal renal function (CLcr ≥81 mL/min; n=12). There was no evidence of a relationship between the extent of plasma protein binding of olaparib and creatinine clearance. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

Patients with Hepatic Impairment

In a hepatic impairment trial, the mean AUC increased by 15% and the mean C_{max} increased by 13% when olaparib was dosed in patients with mild hepatic impairment (Child-Pugh classification A; n=10) and the mean AUC increased by 8% and the mean C_{max} decreased by 13% when olaparib was dosed in patients with moderate hepatic impairment (Child-Pugh classification B; n=8), compared to patients with normal hepatic function (n=13). Hepatic impairment has no effect on the protein binding of olaparib and, therefore, total plasma exposure was representative of free drug. There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Drug Interaction Studies

Clinical Studies

CYP3A Inhibitors: Concomitant use of itraconazole (strong CYP3A inhibitor) increased olaparib C_{max} by 42% and AUC by 170%. Concomitant use of fluconazole (moderate CYP3A inhibitor) is predicted to increase olaparib C_{max} by 14% and AUC by 121%.

CYP3A Inducers: Concomitant use of rifampicin (strong CYP3A inducer) decreased olaparib C_{max} by 71% and AUC by 87%. Concomitant use of efavirenz (moderate CYP3A inducer) is predicted to decrease olaparib C_{max} by 31% and AUC by 60%.

In vitro Studies

CYP Enzymes: Olaparib is both an inhibitor and inducer of CYP3A and an inducer of CYP2B6. Olaparib is predicted to be a weak CYP3A inhibitor in humans.

UGT Enzymes: Olaparib is an inhibitor of UGT1A1.

Transporters: Olaparib is an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2K. Olaparib is a substrate and inhibitor of the efflux transporter P-gp. The potential for olaparib to induce P-gp has not been evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with olaparib.

Olaparib was clastogenic in an in vitro chromosomal aberration assay in mammalian Chinese hamster ovary (CHO) cells and in an in vivo rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of olaparib and indicates potential for genotoxicity in humans. Olaparib was not mutagenic in a bacterial reverse mutation (Ames) test.

In a fertility study, female rats received oral olaparib at doses of 0.05, 0.5, and 15 mg/kg/day for at least 14 days before mating through the first week of pregnancy. There were no adverse effects on mating and fertility rates at doses up to 15 mg/kg/day (maternal systemic exposures approximately 7% of the human exposure (AUC_{0-24h}) at the recommended dose).

In a male fertility study, olaparib had no effect on mating and fertility in rats at oral doses up to 40 mg/kg/day following at least 70 days of olaparib treatment (with systemic exposures of approximately 5% of the human exposure (AUC_{0-24h}) at the recommended dose).

14 CLINICAL STUDIES

14.1 First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

The efficacy of Lynparza was evaluated in SOLO-1 (NCT01844986), a randomized (2:1), double-blind, placebo-controlled, multi-center trial in patients with *BRCA*-mutated advanced ovarian, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy. Patients were randomized to receive Lynparza tablets 300 mg orally twice daily or placebo. Treatment was continued for up to 2 years

or until disease progression or unacceptable toxicity; however, patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider could derive further benefit from continuous treatment, could be treated beyond 2 years. Randomization was stratified by response to first-line platinum-based chemotherapy (complete or partial response). The major efficacy outcome was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

A total of 391 patients were randomized, 260 to Lynparza and 131 to placebo. The median age of patients treated with Lynparza was 53 years (range: 29 to 82) and 53 years (range: 31 to 84) among patients on placebo. The ECOG performance status (PS) was 0 in 77% of patients receiving Lynparza and 80% of patients receiving placebo. Of all patients, 82% were White, 36% were enrolled in the U.S. or Canada, and 82% were in complete response to their most recent platinum-based regimen. The majority of patients (n=389) had germline *BRCA* mutation (g*BRCA*m), and 2 patients had somatic *BRCA*m (s*BRCA*m).

Of the 391 patients randomized in SOLO-1, 386 were retrospectively or prospectively tested with a Myriad BRACAnalysis test and 383 patients were confirmed to have deleterious or suspected deleterious g*BRCA*m status; 253 were randomized to the Lynparza arm and 130 to the placebo arm. Two out of 391 patients randomized in SOLO-1 were confirmed to have s*BRCA*m based on an investigational Foundation Medicine tissue test.

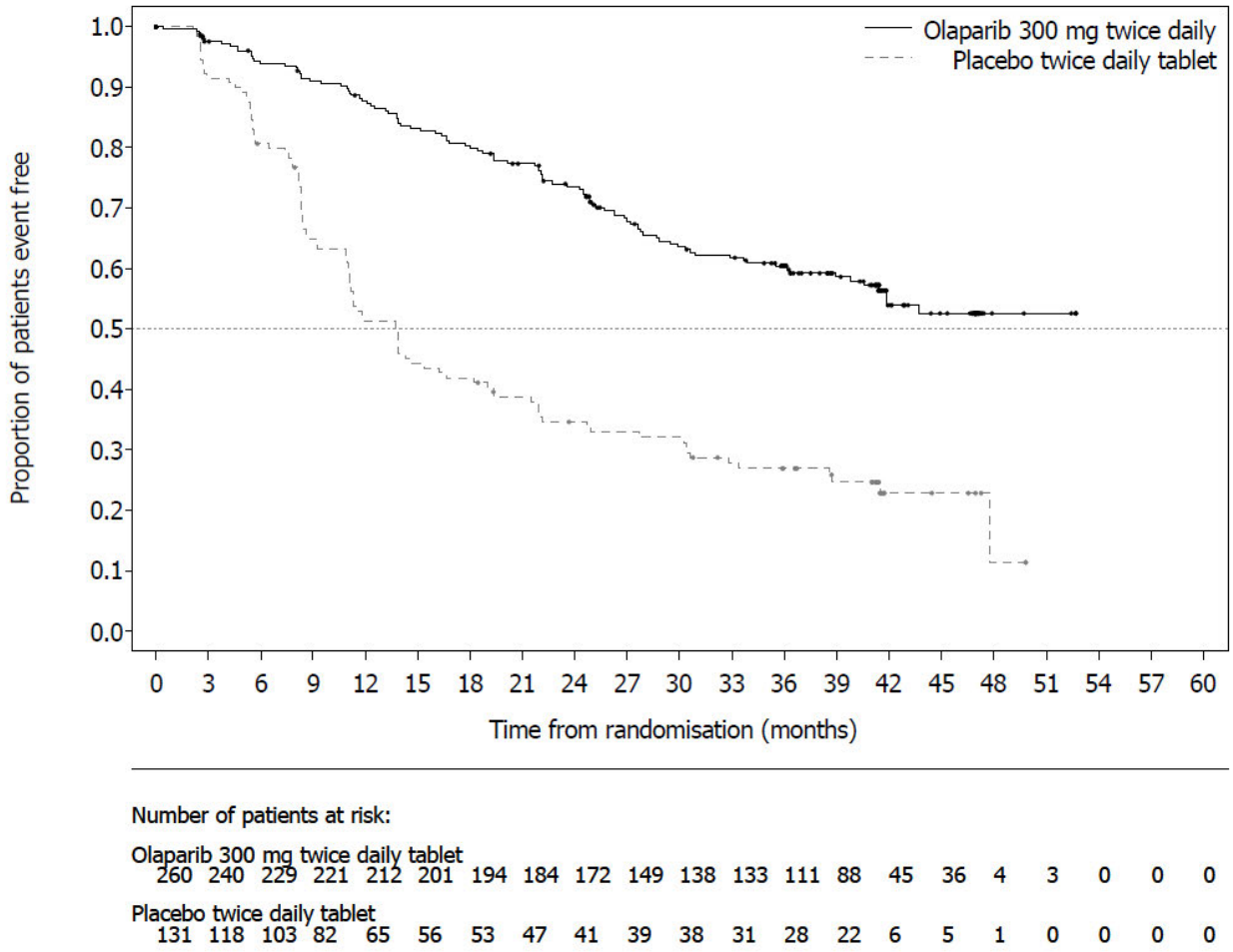
SOLO-1 demonstrated a statistically significant improvement in investigator-assessed PFS for Lynparza compared to placebo. Results from a blinded independent review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (21% of patients had died). Efficacy results are presented in Table 20 and Figure 1.

Table 20 Efficacy Results – SOLO-1 (Investigator Assessment)

	Lynparza tablets (n=260)	**Placebo (n=131)**
Progression-Free Survival*		
Number of events (%)	102 (39%)	96 (73%)
Median, months	NR	13.8
Hazard ratio† (95% CI)	0.30 (0.23, 0.41)	
p-value‡	<0.0001	

* Median follow-up of 41 months in both treatment arms.
† A value <1 favors Lynparza. Hazard ratio from a Cox proportional hazards model including response to previous platinum chemotherapy (complete response versus partial response) as a covariate.
‡ The p-value is derived from a stratified log-rank test.
NR not reached; CI Confidence Interval.

Figure 1 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival - SOLO-1



14.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

PAOLA-1 (NCT02477644) was a randomized, double-blind, placebo-controlled, multi-center trial that compared the efficacy of Lynparza in combination with bevacizumab versus placebo/bevacizumab for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab. Randomization was stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and t*BRCAm* status, determined by prospective local testing. All available clinical samples were retrospectively tested with Myriad myChoice® CDx. Patients were required to have no evidence of disease (NED) due to complete surgical resection, or who were in complete response (CR), or partial response (PR) following completion of first-line platinum-containing chemotherapy and bevacizumab. Patients were randomized (2:1) to receive Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (n=537) 15 mg/kg every three weeks or placebo/bevacizumab (n=269). Patients continued bevacizumab in the maintenance setting and started treatment with Lynparza after a minimum of 3 weeks and up to a maximum of 9 weeks following

completion of their last dose of chemotherapy. Lynparza treatment was continued for up to 2 years or until progression of the underlying disease or unacceptable toxicity. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment could be treated beyond 2 years. Treatment with bevacizumab was for a total of up to 15 months, including the period given with chemotherapy and given as maintenance.

The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST, version 1.1. An additional efficacy endpoint was overall survival (OS).

The median age of patients in both arms was 61 years overall (range 26 to 87). Ovarian cancer was the primary tumor type in 86% of patients in both arms. Ninety six percent (96%) were serous histological type. The ECOG performance score was 0 in 70% of patients and 1 in 28% of patients, overall. All patients had received first-line platinum-based therapy and bevacizumab. First-line treatment outcomes at screening indicated that patients had no evidence of disease with complete macroscopic resection at initial debulking surgery (32%, both arms), no evidence of disease/CR with complete macroscopic resection at interval debulking surgery (31%, both arms), no evidence of disease/CR in patients who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery (15%, both arms) and patients with a partial response (22%, both arms). Thirty percent (30%) of patients in both arms had a deleterious mutation. Patients were not restricted by the surgical outcome with 65% having complete cytoreduction at initial or interval debulking surgery and 35% having residual macroscopic disease. Demographics and baseline disease characteristics were balanced and comparable between the study and placebo arms in the Intention to Treat (ITT) population and also in the HRD-positive subgroup.

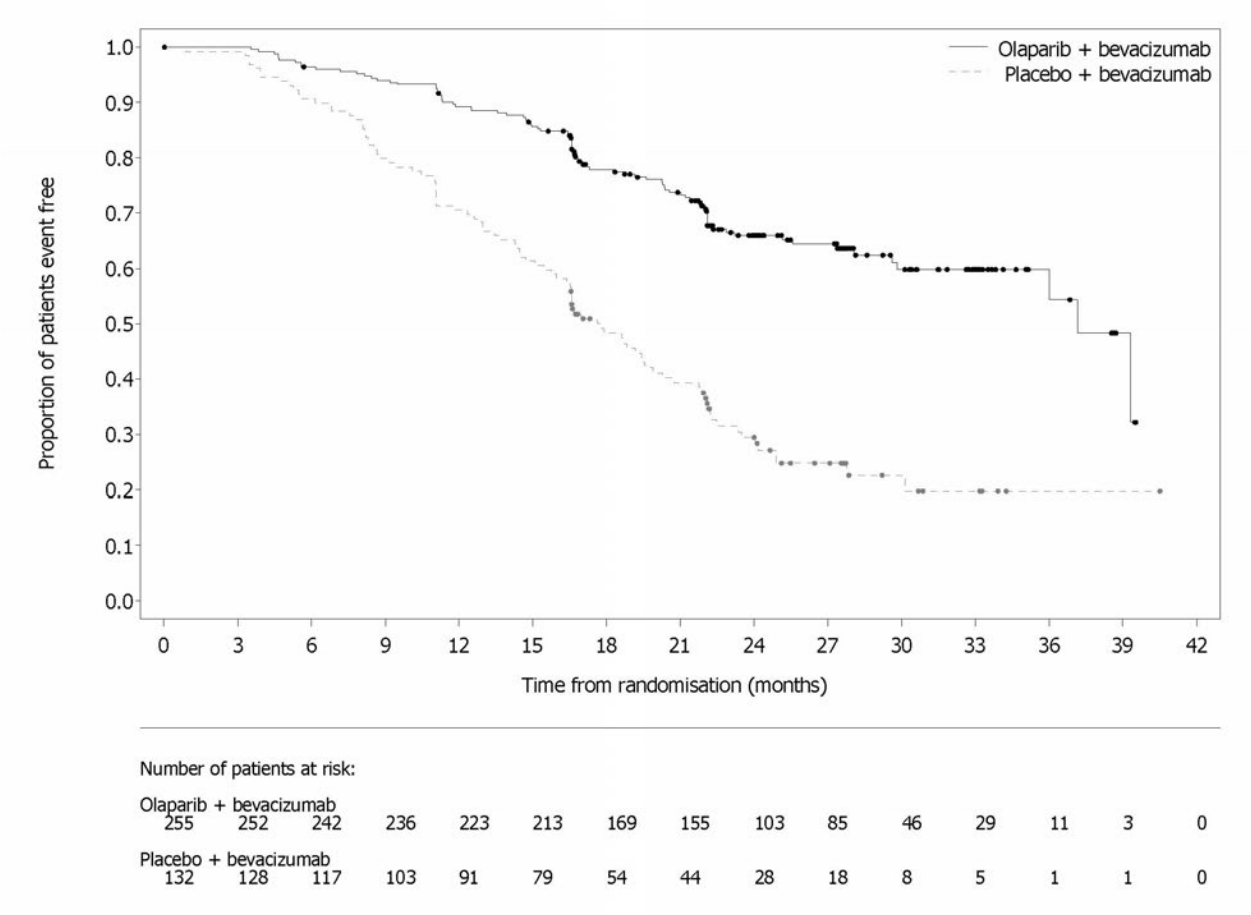
Efficacy results from a biomarker subgroup analysis of 387 patients with HRD-positive tumors, identified post-randomization using the Myriad myChoice® HRD Plus tumor test, who received Lynparza/bevacizumab (n=255) or placebo/bevacizumab (n=132), are summarized in Table 21 and Figure 2. Results from a blinded independent review of PFS were consistent. Overall survival data in this subpopulation were immature with 16% deaths.

Table 21 Efficacy Results – PAOLA-1 (HRD-positive status*, Investigator Assessment)

	Lynparza/bevacizumab (n=255)	**Placebo/bevacizumab (n=132)**
Progression-Free Survival		
Number of events (%)	87 (34%)	92 (70%)
Median, months	37.2	17.7
Hazard ratio† (95% CI)	0.33 (0.25, 0.45)	

* Median follow-up of 27.4 months in Lynparza/bevacizumab arm and 27.5 months in placebo/bevacizumab arm.
† The analysis was performed using an unstratified Cox proportional hazards model.
CI Confidence interval

Figure 2 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – PAOLA-1 (HRD-positive status)



14.3 Maintenance Treatment of Recurrent Ovarian Cancer

The efficacy of Lynparza was investigated in two randomized, placebo-controlled, double-blind, multi-center studies in patients with recurrent ovarian cancers who were in response to platinum-based therapy.

SOLO-2

The efficacy of Lynparza was evaluated in SOLO-2 (NCT01874353), a randomized (2:1) double-blind, placebo-controlled trial in patients with g*BRCA*m ovarian, fallopian tube, or primary peritoneal cancer. Patients were randomized to Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. Randomization was stratified by response to last platinum chemotherapy (complete versus partial) and time to disease progression in the penultimate platinum-based chemotherapy prior to enrollment (6-12 months versus >12 months). All patients had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-

based regimen. The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST, version 1.1. An additional efficacy outcome measure was OS.

A total of 295 patients were randomized, 196 to Lynparza and 99 to placebo. The median age of patients treated with Lynparza was 56 years (range: 28 to 83) and 56 years (range: 39 to 78) among patients treated with placebo. The ECOG PS was 0 in 83% of patients receiving Lynparza and 78% of patients receiving placebo. Of all patients, 89% were White, 17% were enrolled in the U.S. or Canada, 47% were in complete response to their most recent platinum-based regimen, and 40% had a progression-free interval of 6-12 months since their penultimate platinum regimen. Prior bevacizumab therapy was reported for 17% of those treated with Lynparza and 20% of those receiving placebo. Approximately 44% of patients on the Lynparza arm and 37% on placebo had received three or more lines of platinum-based treatment.

All patients had a deleterious or suspected deleterious germline *BRCA* mutation as detected either by a local test (n=236) or central Myriad CLIA test (n=59), subsequently confirmed by BRACAnalysis CDx® (n=286).

SOLO-2 demonstrated a statistically significant improvement in investigator-assessed PFS in patients randomized to Lynparza as compared with placebo. Results from a blinded independent review were consistent. The final analysis of OS did not reach statistical significance. Efficacy results are presented in Table 22 and Figures 3 and 4.

Table 22 Efficacy Results – SOLO-2 (Investigator Assessment)

	Lynparza tablets (n=196)	**Placebo (n=99)**
Progression-Free Survival		
Number of events (%)	107 (55%)	80 (81%)
Median, months	19.1	5.5
Hazard ratio* (95% CI)	0.30 (0.22, 0.41)	
p-value†	<0.0001	
Overall Survival		
Number of events (%)	116 (59)	65 (66)
Median, months	51.7	38.8
Hazard ratio* (95% CI)	0.74 (0.54, 1.00)	

	Lynparza tablets (n=196)	Placebo (n=99)
p-value†	0.0537	

* Hazard ratio from a Cox proportional hazards model including response to last platinum chemotherapy (complete response versus partial response) and time to disease progression in the penultimate platinum-based chemotherapy prior to enrollment (6-12 month versus >12 months) as covariates.
† The p-value is derived from a stratified log-rank test.

Figure 3 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – SOLO-2

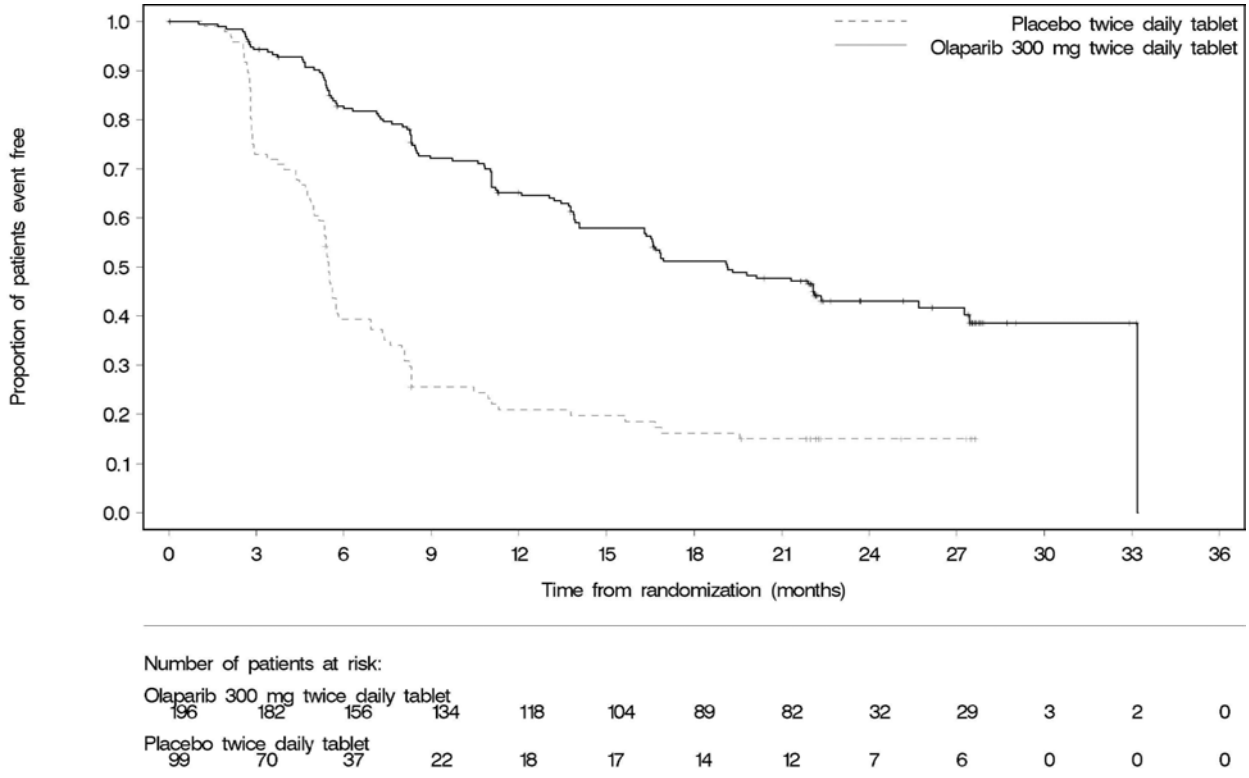
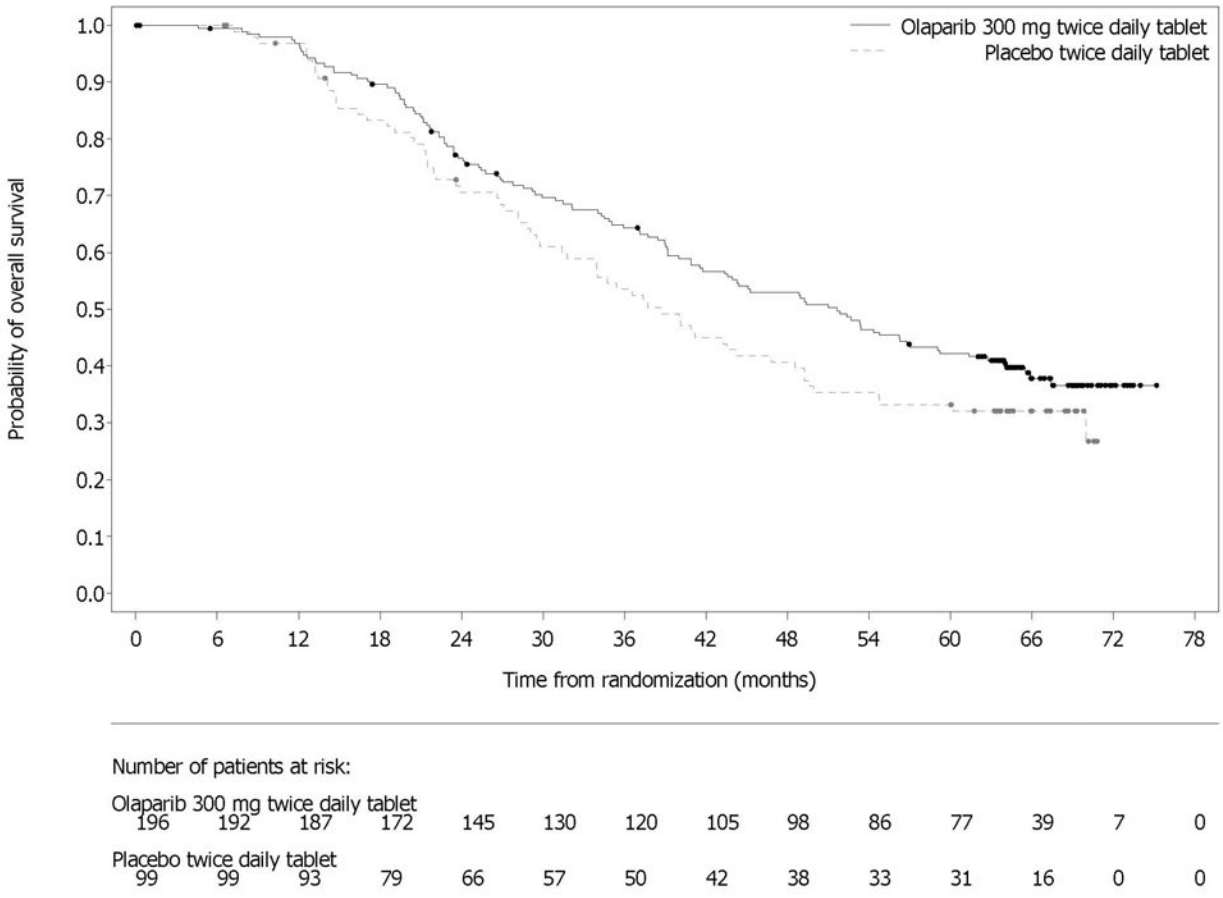


Figure 4 Kaplan-Meier Curves of Overall Survival – SOLO-2



Study 19

The efficacy of Lynparza was evaluated in Study 19 (NCT00753545), a randomized (1:1) double-blind, placebo-controlled trial in patients with platinum-sensitive ovarian cancer who had received 2 or more previous platinum-containing regimens. Patients were randomized to Lynparza capsules 400 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. Randomization was stratified by response to last platinum chemotherapy (complete response versus partial response), time to disease progression in the penultimate platinum-based chemotherapy (6-12 months versus >12 months), and descent (Jewish versus non-Jewish). The major efficacy outcome measure was investigator-assessed PFS according to RECIST, version 1.0.

A total of 265 patients were randomized, 136 to Lynparza and 129 to placebo. The median age of patients treated with Lynparza was 58 years (range: 21 to 89) and 59 years (range 33 to 84) among patients treated with placebo. ECOG PS was 0 in 81% of patients receiving Lynparza and 74% of patients receiving placebo. Of all patients, 97% were White, 19% were enrolled in the US or Canada, 45% were in complete response following their most recent platinum chemotherapy regimen, and 40% had a progression-free

interval of 6-12 months since their penultimate platinum. Prior bevacizumab therapy was reported for 13% of patients receiving Lynparza and 16% of patients receiving placebo.

A retrospective analysis for germline *BRCA* mutation status, some performed using the Myriad test, indicated that 36% (n=96) of patients from the ITT population had deleterious g*BRCA* mutation, including 39% (n=53) of patients on Lynparza and 33% (n=43) of patients on placebo.

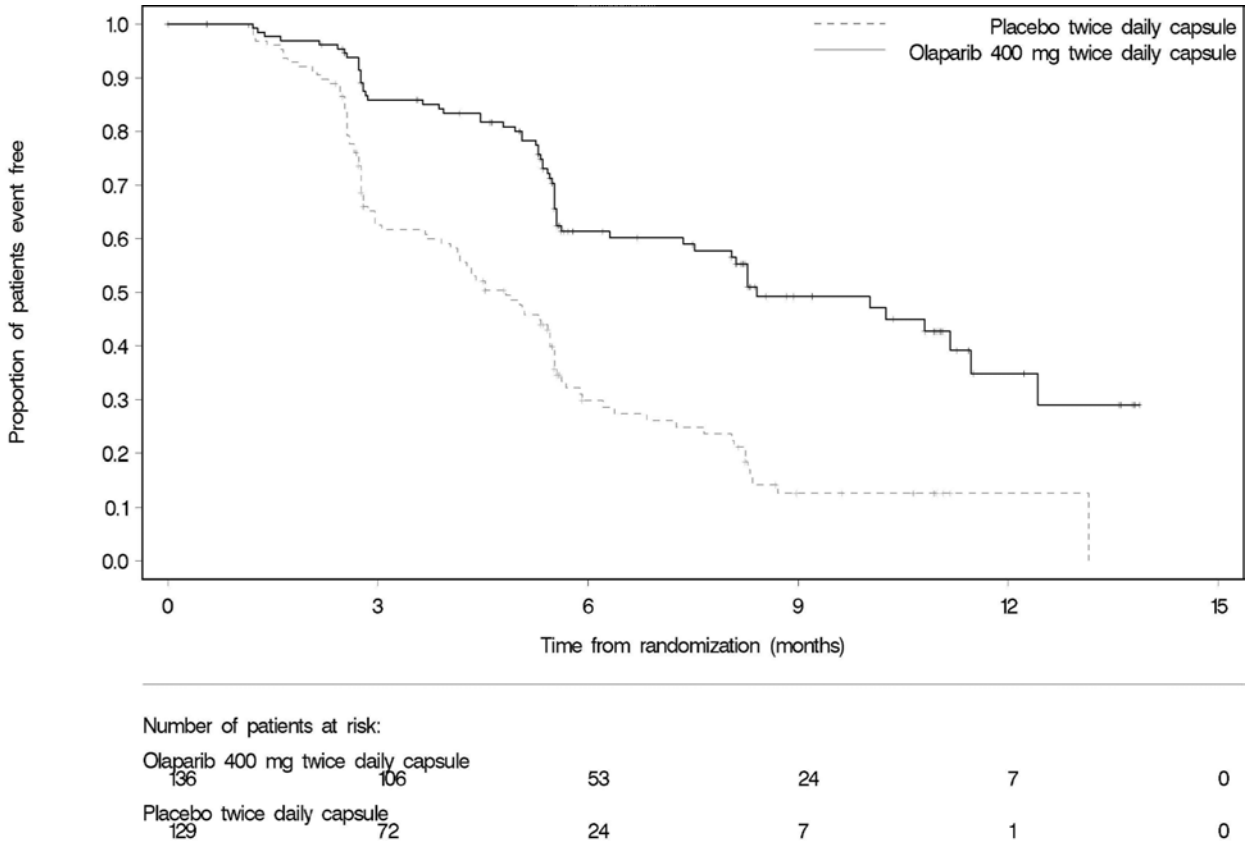
Efficacy results are presented in Table 23 and Figure 5. Study 19 demonstrated a statistically significant improvement in investigator-assessed PFS in patients treated with Lynparza versus placebo.

Table 23 Efficacy Results - Study 19 (Investigator Assessment)

	Lynparza capsules (n=136)	**Placebo (n=129)**
Progression-Free Survival		
Number of events (%)	60 (44%)	94 (73%)
Median, months	8.4	4.8
Hazard ratio* (95% CI)	0.35 (0.25, 0.49)	
p-value†	<0.0001	
Overall Survival‡		
Number of events (%)	98 (72%)	112 (87%)
Median, months	29.8	27.8
Hazard ratio (95% CI)	0.73 (0.55, 0.95)	

* Hazard ratio from a Cox proportional hazards model including response to last platinum chemotherapy (complete response versus partial response), time to disease progression in the penultimate platinum-based chemotherapy (6-12 months versus >12 months) and Jewish descent (yes versus no) as covariates.
† The p-value is derived from a Cox proportional hazards model.
‡ Without adjusting for multiple analyses.

Figure 5 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – Study 19



14.4 Adjuvant Treatment of Germline *BRCA*-mutated HER2-negative High Risk Early Breast Cancer

The efficacy of Lynparza was evaluated in OlympiA (NCT02032823), a randomized (1:1), double-blind, placebo-controlled, international study in patients with g*BRCA*m HER2-negative high risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. Patients were randomized to receive Lynparza tablets 300 mg orally twice daily or placebo. Treatment was continued for up to 1 year, or until disease recurrence, or unacceptable toxicity. Patients were required to have completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or both. Prior platinum for previous cancer (e.g., ovarian) or as adjuvant or neoadjuvant treatment for breast cancer was allowed. Patients with high-risk early breast cancer were defined as follows:

- patients who received prior neoadjuvant chemotherapy: patients with either triple negative breast cancer (TNBC) or hormone receptor positive breast cancer must have had residual invasive cancer in the breast and/or the resected lymph nodes (non-pathologic complete response) at the time of surgery. Additionally, patients with hormone receptor positive breast cancer must have had a score of ≥3 based on pre-treatment clinical and post-treatment pathologic stage (CPS), estrogen receptor (ER) status, and histologic grade as shown in Table 24.

Table 24 Early Breast Cancer Stage, Receptor Status, and Grade Scoring Requirements for Study Enrollment*

Stage/feature		Points
Clinical Stage (pre-treatment)	I/IIA	0
	IIB/IIIA	1
	IIIB/IIIC	2
Pathologic Stage (post-treatment)	0/I	0
	IIA/IIB/IIIA/IIIB	1
	IIIC	2
Receptor status	ER positive	0
	ER negative	1
Nuclear grade	Nuclear grade 1-2	0
	Nuclear grade 3	1

* Total score of ≥3 required for patients with hormone receptor positive breast cancer.

- patients who received prior adjuvant chemotherapy: patients with TNBC must have had node positive disease or node negative disease with a ≥2cm primary tumor; patients with hormone receptor positive, HER2-negative breast cancer must have had ≥4 pathologically confirmed positive lymph nodes.

Randomization was stratified by hormone receptor status (hormone receptor positive versus triple negative), by prior neoadjuvant versus adjuvant chemotherapy, and by prior platinum use for breast cancer (yes versus no).

The major efficacy outcome measure was invasive disease free survival (IDFS), defined as the time from randomization to date of first recurrence, where recurrence is defined as invasive loco-regional, distant recurrence, contralateral invasive breast cancer, new cancer or death from any cause. An additional efficacy outcome measure was OS.

A total of 1836 patients were randomized, 921 to Lynparza and 915 to placebo. Demographic and baseline characteristics were well balanced between arms. The median age was 42 years. Sixty-seven percent (67%) of patients were White, 29% were Asian, and 3% were Black. Three percent (3%) of patients were Hispanic or Latino. Two patients (0.2%) in the Lynparza arm and four patients (0.4%) in the placebo arm were male. Sixty-one percent (61%) of patients were pre-menopausal. Eighty-nine percent (89%) of patients were ECOG performance status 0 and 11% ECOG PS 1. Eighty-two percent (82%) of patients had TNBC and 18% had hormone receptor-positive disease. Fifty percent (50%) of patients had received prior neoadjuvant and 50% received prior adjuvant chemotherapy. Ninety-four percent (94%) of patients received anthracycline and taxane chemotherapy. Twenty-six (26%) of patients overall had received prior platinum for breast cancer. Ninety percent (90%) of patients with hormone receptor positive breast cancer received concurrent endocrine therapy.

Patients enrolled based on local g*BRCA* test results provided a sample for retrospective confirmatory central testing with BRACAnalysis®. Out of 1836 patients enrolled into OlympiA, 1623 were confirmed as g*BRCAm* by Myriad BRACAnalysis®, either prospectively or retrospectively.

A statistically significant improvement in IDFS and OS was demonstrated in patients in the Lynparza arm compared with the placebo arm. Efficacy data for OlympiA (FAS) are presented in Table 25 and Figures 6 and 7.

Table 25 Efficacy Results – OlympiA

	Lynparza tablets (N=921)	Placebo (N=915)
Invasive Disease Free Survival (IDFS)*		
Number of events (%)	106 (12)	178 (20)
Hazard ratio (95% CI)†	0.58 (0.46, 0.74)	
p-value (2-sided)‡	< 0.0001	
3-year event-free rate, % (95% CI)§	86 (82.8, 88.4)	77 (73.7, 80.1)
Overall Survival¶		
Number of events (%)	75 (8)	109 (12)
Hazard ratio (95% CI)†	0.68 (0.50, 0.91)	
p-value (2-sided)‡	0.0091	
3-year event-free rate, % (95% CI)§	93 (90.8, 94.4)	89 (86.7, 91)

* Data from the pre-specified interim analysis (86% of the number of events for the planned final analysis).
† Based on the stratified Cox's Proportional Hazards Model.
‡ p-value from a stratified log-rank test. Compared with the allocated alpha of 0.005 for IDFS and 0.015 for OS.
§ Percentage are calculated using Kaplan-Meier estimates.
¶ Data from the pre-specified second interim analysis of OS (at ~330 IDFS events).
CI = confidence interval.

Figure 6 Kaplan-Meier Curves of IDFS – OlympiA

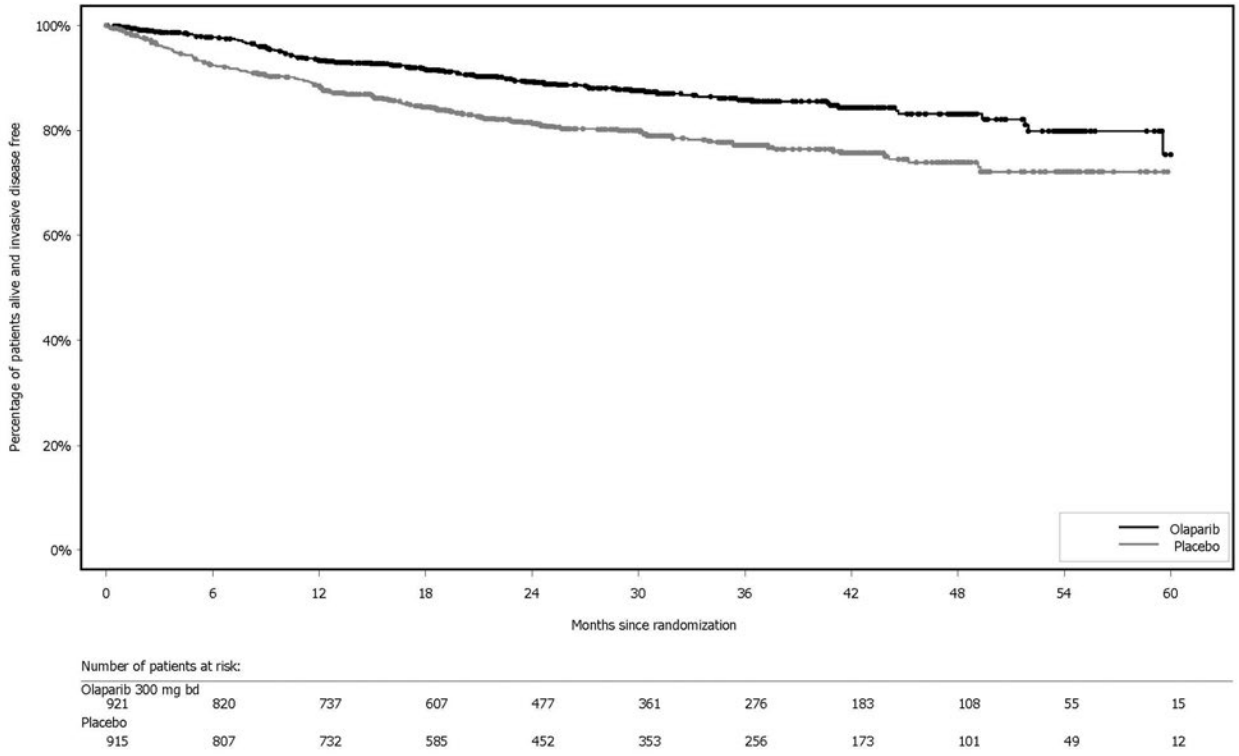
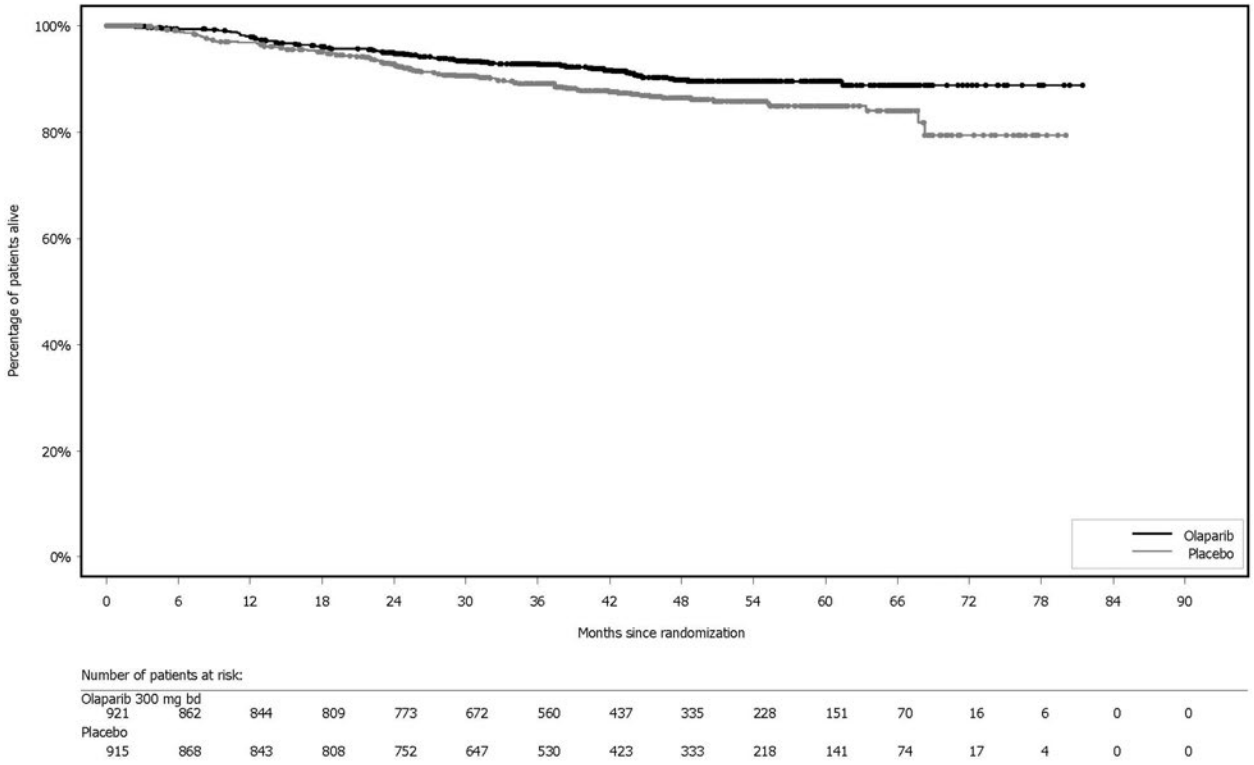


Figure 7 Kaplan-Meier Curves of OS – OlympiA



14.5 Treatment of Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer

The efficacy of Lynparza was evaluated in OlympiAD (NCT02000622), an open-label randomized (2:1) study in patients with g*BRCA*m HER2-negative metastatic breast cancer. Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have progressed on at least 1 endocrine therapy (adjuvant or metastatic), or have disease that the treating healthcare provider believed to be inappropriate for endocrine therapy. Patients with prior platinum therapy were required to have no evidence of disease progress during platinum treatment. No prior treatment with a PARP inhibitor was permitted. Patients were randomized to Lynparza tablets 300 mg orally twice daily or healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). The major efficacy outcome measure was PFS assessed by blinded independent central review (BICR) using RECIST version 1.1.

A total of 302 patients were randomized, 205 to Lynparza and 97 to chemotherapy. Among the 205 patients treated with Lynparza, the median age was 44 years (range: 22 to 76), 65% were White, 4% were males and all the patients had an ECOG PS of 0 or 1. Approximately 50% of patients had triple-negative tumors and 50% had estrogen receptor and/or progesterone receptor positive tumors and the proportions were balanced across treatment arms. Patients in each treatment arm had received a median of 1 prior chemotherapy regimen for metastatic disease; approximately 30% had not received a prior chemotherapy regimen for metastatic breast cancer. Twenty-one percent of patients in the Lynparza arm and 14% in the

chemotherapy arm had received platinum therapy for metastatic disease. Seven percent of patients in each treatment arm had received platinum therapy for localized disease.

Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx® and 297 were confirmed to have deleterious or suspected deleterious g*BRCA*m status; 202 were randomized to the Lynparza arm and 95 to the healthcare provider's choice of chemotherapy arm.

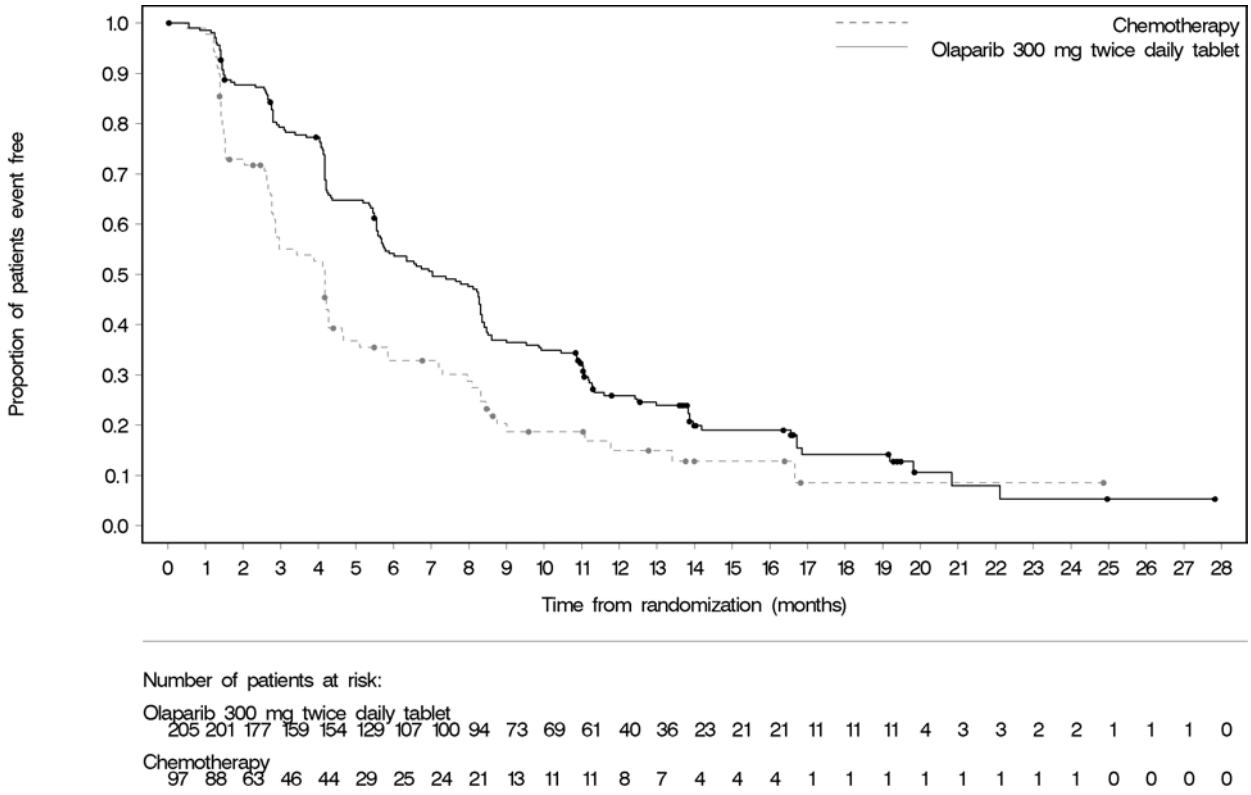
A statistically significant improvement in PFS was demonstrated for the Lynparza arm compared to the chemotherapy arm. Efficacy data for OlympiAD are displayed in Table 26 and Figure 8. Consistent results were observed across patient subgroups defined by study stratification factors. An exploratory analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results.

Table 26 Efficacy Results - OlympiAD (BICR-assessed)

	Lynparza tablets (n=205)	**Chemotherapy (n=97)**
Progression-Free Survival		
Number of events (%)	163 (80%)	71 (73%)
Median, months	7.0	4.2
Hazard ratio (95% CI)*	0.58 (0.43, 0.80)	
p-value†	0.0009	
Patients with Measurable Disease	n=167	n=66
Objective Response Rate (95% CI)‡	52% (44, 60)	23% (13, 35)
Overall Survival		
Number of events (%)	130 (63%)	62 (64%)
Median, months	19.3	17.1
Hazard ratio (95% CI)*	0.90 (0.66, 1.23)	

* Hazard ratio is derived from a stratified log-rank test, stratified by ER, PgR negative versus ER and or PgR positive and prior chemotherapy (yes versus no).
† For PFS, p-value (2-sided) was compared to 0.05.
‡ Response based on confirmed responses. The confirmed complete response rate was 7.8% for Lynparza compared to 1.5% for chemotherapy arm.

Figure 8 Kaplan-Meier Curves of Progression-Free Survival – OlympiAD



14.6 First-Line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

The efficacy of Lynparza was evaluated in POLO (NCT02184195), a randomized (3:2), double-blind placebo-controlled, multi-center trial. Patients were required to have metastatic pancreatic adenocarcinoma with a deleterious or suspected deleterious germline *BRCA* mutation (g*BRCA*m) and absence of disease progression after receipt of first-line platinum-based chemotherapy for at least 16 weeks. Patients were randomized to receive Lynparza tablets 300 mg orally twice daily or placebo until disease progression or unacceptable toxicity. The major efficacy outcome measure was PFS by BICR using RECIST, version 1.1 modified to assess patients with clinical complete response at entry who were assessed as having no evidence of disease unless they had progressed based on the appearance of new lesions. Additional efficacy outcome measures were OS and ORR.

A total of 154 patients were randomized, 92 to Lynparza and 62 to placebo. The median age was 57 years (range 36 to 84); 54% were male; 92% were White, 4% were Asian, and 3% were Black; baseline ECOG PS was 0 (67%) or 1 (31%). The median time from initiation of first-line platinum-based chemotherapy to randomization was 5.8 months (range 3.4 to 33.4 months). Seventy-five percent (75%) of patients received FOLFIRINOX with a median of 9 cycles (range 4-61), 8% received FOLFOX or XELOX, 4% received GEMOX, and 3% received gemcitabine plus cisplatin; 49% achieved a complete or partial response to platinum-based chemotherapy.

All patients had a deleterious or suspected deleterious germline *BRCA*-mutation as detected by the Myriad BRAC*Analysis*® or BRACAnalysis CDx® at a central laboratory only (n=106), local *BRCA* test only (n=4), or both local and central testing (n=44). Among the 150 patients with central test results, 30% had a mutation in *BRCA1;* 69% had a mutation in *BRCA2*; and 1 patient (1%) had mutations in both *BRCA1* and *BRCA2*.

POLO demonstrated a statistically significant improvement in BICR-assessed PFS in patients randomized to Lynparza as compared with placebo. The final analysis of OS did not reach statistical significance. Efficacy results of POLO are provided in Table 27 and Figure 9.

Table 27 Efficacy Results - POLO (BICR-assessed)

	Lynparza tablets (n=92)	**Placebo (n=62)**
Progression-Free Survival		
Number of events (%)*	60 (65)	44 (71)
Median, months (95% CI)	7.4 (4.1, 11.0)	3.8 (3.5, 4.9)
Hazard ratio† (95% CI)	0.53 (0.35, 0.81)	
p-value	0.0035	
Overall Survival		
Number of events (%)	61 (66)	47 (76)
Median, months (95% CI)	19.0 (15.3, 26.3)	19.2 (14.3, 26.1)
Hazard ratio† (95% CI)	0.83 (0.56, 1.22)	
p-value	0.3487	
Patients with Measurable Disease	n=78	n=52
Objective Response Rate (95% CI)	23% (14, 34)	12% (4, 23)
Complete response (%)	2 (2.6)	0
Partial response (%)	16 (21)	6 (12)
Duration of Response (DOR)		

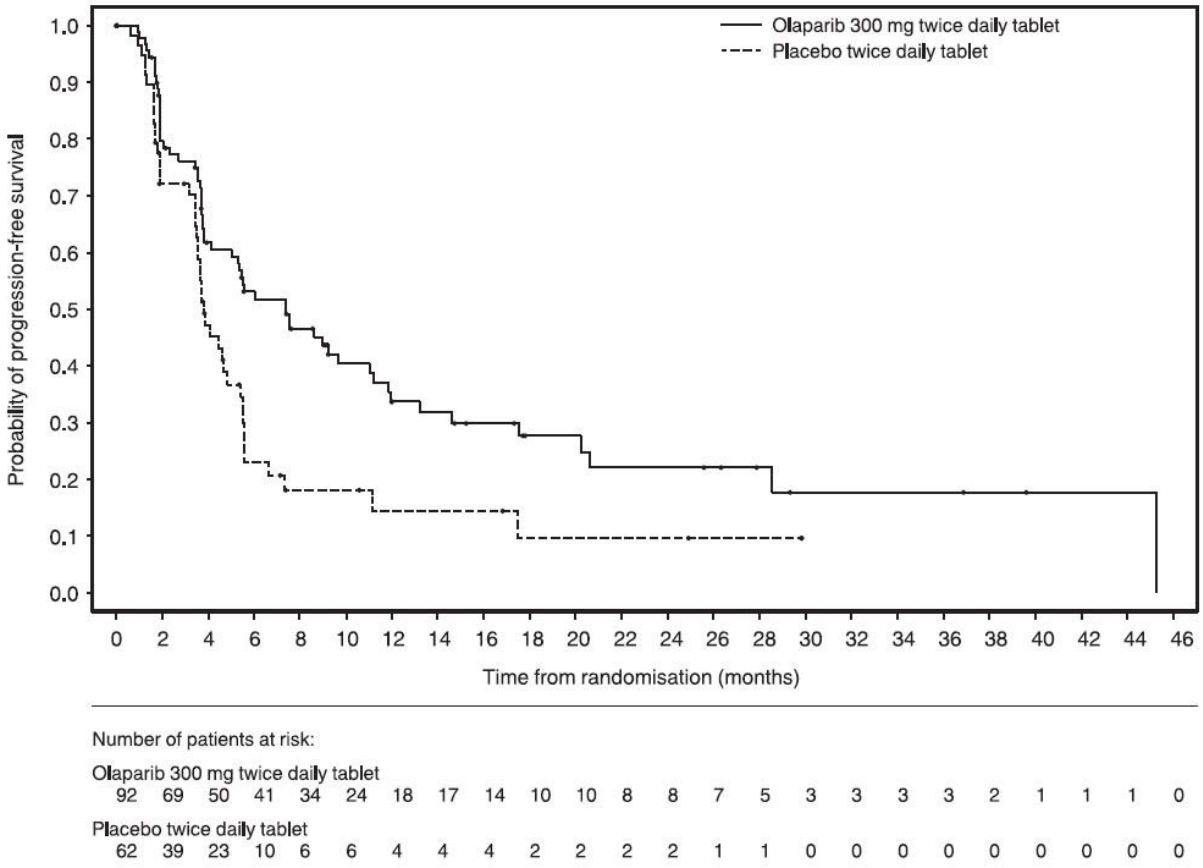
	Lynparza tablets (n=92)	Placebo (n=62)
Median time in months (95% CI)	25 (15, NC)	4 (2, NC)

* Number of events: Progression – Lynparza 55, placebo 44; death before BICR-documented progression – Lynparza 5, placebo 0

† Hazard ratio, 95% CI, and p-value calculated from a log-rank test. A hazard ratio <1 favors Lynparza.

NC Not calculable

Figure 9 Kaplan-Meier Curves of BICR-Assessed Progression-Free Survival – POLO



14.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

The efficacy of Lynparza was evaluated in PROfound (NCT02987543), randomized, open-label, multi-center trial that evaluated the efficacy of Lynparza 300 mg twice daily versus a comparator arm of investigator's choice of enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer (mCRPC). All patients received a GnRH analog or had prior bilateral orchiectomy. Patients needed to have progressed on prior enzalutamide or abiraterone for the treatment of metastatic prostate cancer and/or CRPC and have a tumor mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway.

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2*, or *ATM* were randomized in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) were randomized in Cohort B; patients with co-mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A. Although patients with *PPP2R2A* gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit. Patients were randomized (2:1), 256 to Lynparza arm and 131 to enzalutamide or abiraterone acetate arm; in Cohort A there were 245 (162 Lynparza arm and 83 in enzalutamide or abiraterone acetate arm) and in Cohort B there were 142 patients (94 in Lynparza arm and 48 in enzalutamide or abiraterone acetate arm). Randomization was stratified by prior receipt of taxane chemotherapy and presence of measurable disease by RECIST 1.1. Treatment was continued until objective radiological disease progression determined by BICR. Upon radiological progression confirmed by BICR, patients randomized to enzalutamide or abiraterone acetate were given the option to switch to Lynparza. Patients with HRR gene mutations were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRR assay performed at a central laboratory.

Determination of deleterious or suspected deleterious somatic or germline HRR mutation status in line with the FDA-approved mutation classification and testing criteria for the Foundation Medicine F1CDx tissue-based assay and assessment of the germline-*BRCA* status using the Myriad BRACAnalysis CDx blood-based assay was performed retrospectively. Representation of individual gene mutations by cohort is provided in Table 28. No patients were enrolled who had mutations in two of the 15 pre-specified HRR genes: *FANCL* and *RAD51C*.

Table 28 Frequency of Patients with HRR Mutations Enrolled in PROfound

HRR Mutation	Cohort A N=245 n (%)	Cohort B* N=142 n (%)
Single mutation	224 (91)	135 (95)
BRCA2	127 (52)	1 (<1)
ATM	84 (34)	2 (1)
BRCA1	13 (5)	0
CDK12	0	89 (63)
CHEK2	0	12 (8)
PPP2R2A†	0	10 (7)
RAD51B	0	5 (4)
RAD54L	0	5 (4)
PALB2	0	4 (3)
BRIP1	0	3 (2)
CHEK1	0	2 (1)
BARD1	0	1 (<1)
RAD51D	0	1 (<1)
Co-occurring mutation‡	21 (9)	7 (5)

* Three patients with single *BRCA2* or *ATM* gene mutations and 1 patient with co-occurring *BRCA2+CDK12* gene mutations were incorrectly assigned to Cohort B.

† Lynparza is not indicated for patients with *PPP2R2A* mutations.

‡ Patients with co-occurring mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A.

In Cohort A+B, the median age was 69 years (range: 47 to 91 years) in both arms; 69% were White, 29% were Asian, and 1% were Black. The ECOG performance score was 0 or 1 in most patients (95%) in both arms. In patients treated with Lynparza, the proportion of patients with RECIST 1.1 measurable disease at baseline was 58%, including 17% with lung and 10% with liver metastases, respectively. At randomization, 66% of patients had received prior taxane chemotherapy, 40% had received enzalutamide, 38% had received abiraterone acetate, and 20% had received both enzalutamide and abiraterone acetate. Patient characteristics were well-balanced between arms.

The major efficacy outcome of the study was radiological progression-free survival (rPFS) (Cohort A) as determined by BICR using RECIST version 1.1 and Prostate Cancer Clinical Trials Working Group 3 (PCWG3) (bone) criteria. Additional efficacy outcomes included confirmed objective response rate (ORR) (Cohort A), rPFS (combined Cohorts A+B) as assessed by BICR, and overall survival (OS) (Cohort A).

PROfound demonstrated a statistically significant improvement in BICR-assessed rPFS for Lynparza compared to investigator's choice of enzalutamide or abiraterone acetate in Cohort A and Cohort A+B. In an exploratory analysis for patients in Cohort B, the median rPFS was 4.8 months for Lynparza vs 3.3 months for comparator with a HR of 0.88 (95% CI 0.58, 1.36). The major efficacy outcome was supported by a statistically significant improvement in ORR by BICR for patients with measurable disease at baseline in Cohort A. In Cohort B, ORR by BICR was 3.7% (95% CI 0.5, 12.7) in Lynparza treated patients and 8.3% (95% CI 1.0, 27.0) in patients treated with enzalutamide or abiraterone acetate.

The final analysis of overall survival (OS) demonstrated a statistically significant improvement in OS in patients randomized to Lynparza compared to patients in the enzalutamide or abiraterone acetate arm in Cohort A.

Efficacy results of PROfound are provided in Tables 29 and 30 and Figures 10 and 11.

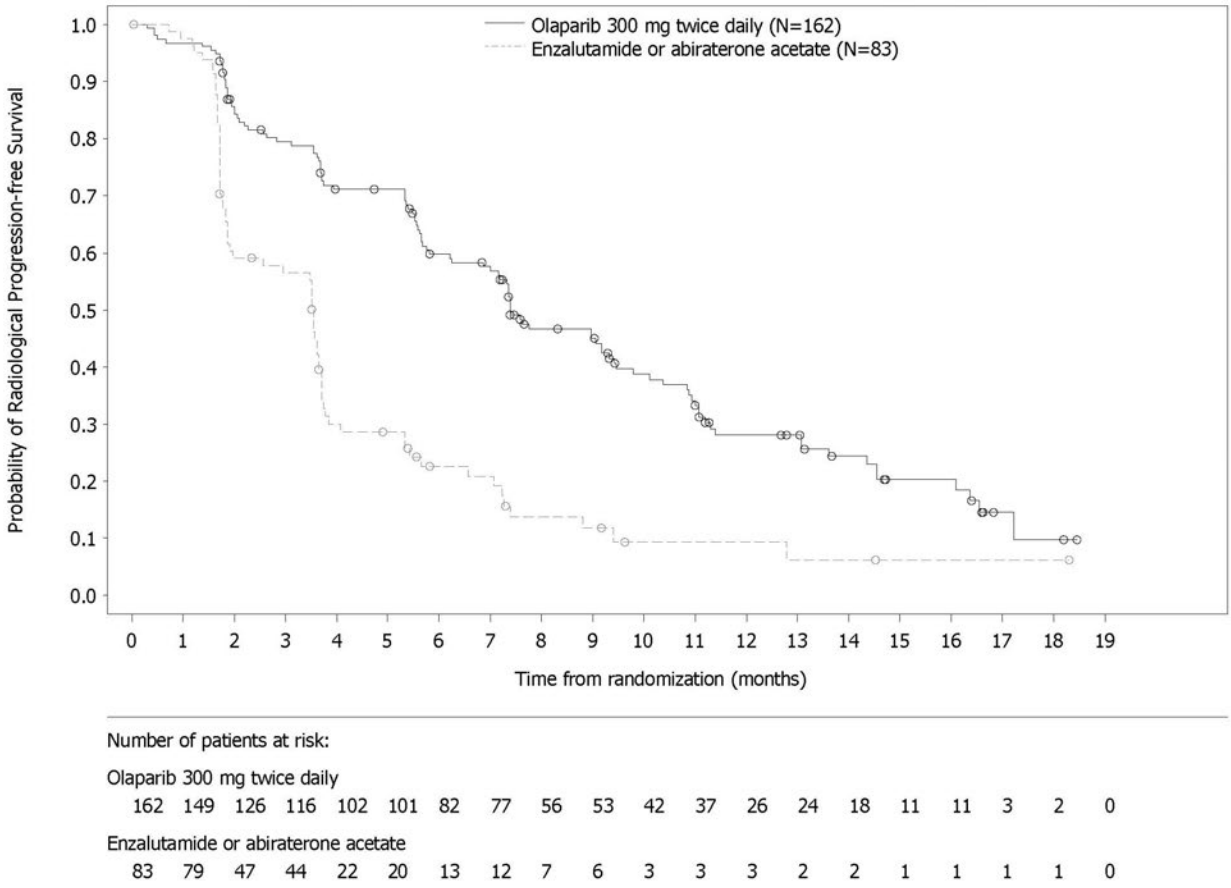
Table 29 Efficacy Results - PROfound (BICR-assessed)

	Cohort A		**Cohort A+B***	
	Lynparza tablets (n=162)	**Enzalutamide or Abiraterone acetate (n=83)**	**Lynparza tablets (n=256)**	**Enzalutamide or Abiraterone acetate (n=131)**
Radiological Progression-Free Survival (rPFS)				
Number of events (%)	106 (65)	68 (82)	180 (70)	99 (76)
Median (95% CI), in months	7.4 (6.2, 9.3)	3.6 (1.9, 3.7)	5.8 (5.5, 7.4)	3.5 (2.2, 3.7)

	Cohort A		Cohort A+B*	
	Lynparza tablets (n=162)	**Enzalutamide or Abiraterone acetate (n=83)**	**Lynparza tablets (n=256)**	**Enzalutamide or Abiraterone acetate (n=131)**
Hazard ratio (95% CI)†	0.34 (0.25, 0.47)		0.49 (0.38, 0.63)	
p-value‡	<0.0001		<0.0001	
Confirmed ORR				
Patients with measurable disease at baseline	n=84	n=43	-	-
ORR, n (%)	28 (33)	1 (2)	-	-
(95% CI)	(23, 45)	(0, 12)	-	-
p-value	<0.0001		-	
Overall Survival	n=162	n=83	-	-
Number of events (%)	91 (56)	57 (69)	-	-
Median (95% CI), in months	19.1 (17.4, 23.4)	14.7 (11.9, 18.8)	-	-
Hazard ratio (95% CI)†	0.69 (0.50, 0.97)		-	
p-value‡	0.0175		-	

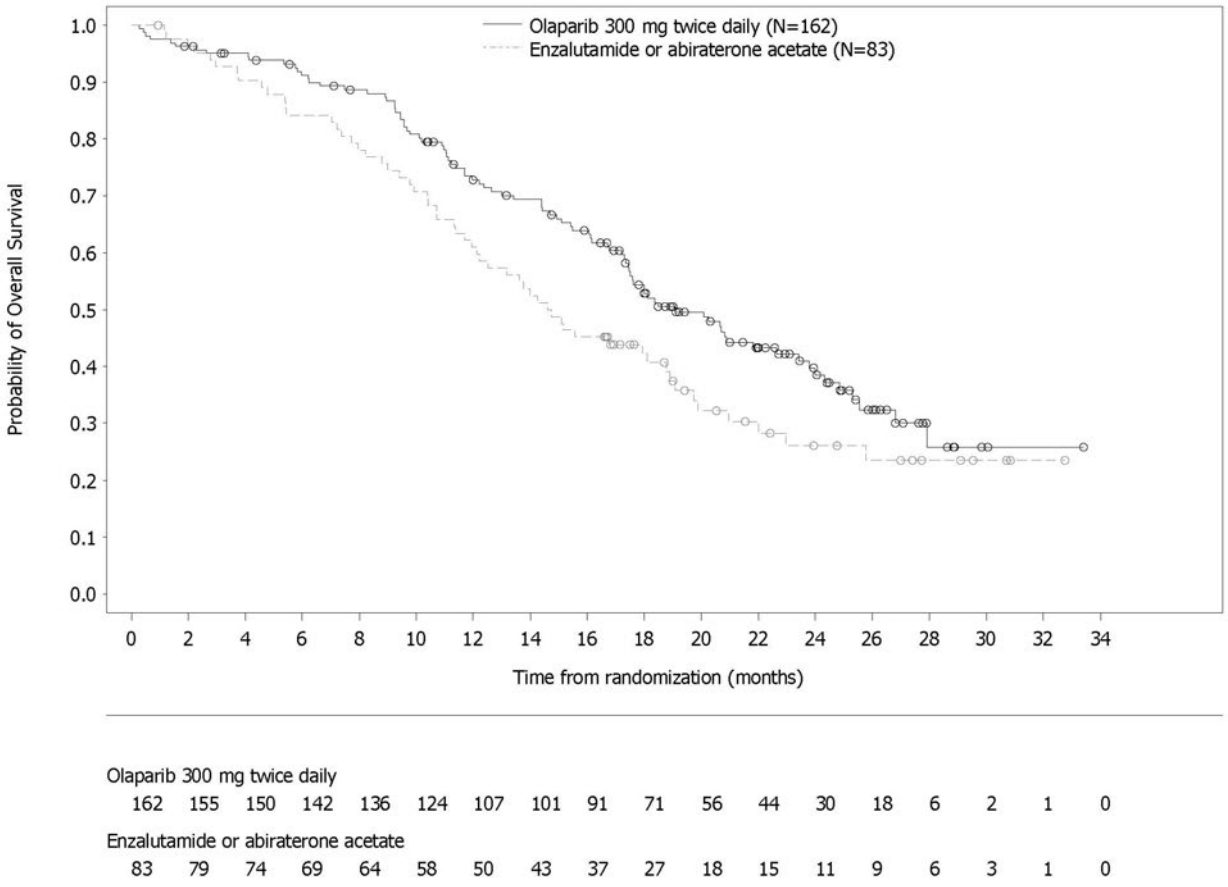
* Although 10 patients with *PPP2R2A* mutation were included in all analyses of Cohort A+B, Lynparza is not indicated for this population due to unfavorable risk-benefit.
† The HR and CI were calculated using a Cox proportional hazards model adjusted for prior taxane use and measurable disease. An HR <1 favors Lynparza 300 mg taken orally twice daily.
‡ The analysis was performed using the log-rank test stratified by prior taxane use and measurable disease.
CI Confidence interval

Figure 10 Kaplan-Meier Curves of BICR-Assessed rPFS – PROfound – Cohort A



Consistent results were observed in exploratory analyses of rPFS for patients who received or did not receive prior taxane therapy and for those with germline-*BRCA* mutations identified using the Myriad BRACAnalysis CDx assay compared with those with *BRCA* mutations identified using the Foundation Medicine F1CDx assay.

Figure 11 Kaplan-Meier Curves of Overall Survival – PROfound – Cohort A



Response data by HRR mutations for patients in the Lynparza arm are presented in Table 30. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an *ATM* mutation alone and 2 patients with co-occurring mutations (one with *PALB2+PPP2R2A* and one with *CDK12+PALB2*).

Table 30 Response Rate and Duration of Response by HRR Mutation in Patients with Measurable Disease at Baseline on the Lynparza Arm – PROfound (BICR-assessed)

HRR mutation*	Patients (N=138)	Confirmed ORR†	
		n (%)	95% CI
Single mutation			
BRCA2	43	24 (56)	(40, 71)
ATM	30	3 (10)	(2, 27)
CDK12	34	2 (6)	(1, 20)
BRCA1	6	SD, PD (4), NE	NA
CHEK2	4	SD (2), PD (2)	NA
BRIP1	2	SD, PD	NA
PALB2	2	SD, PD	NA

HRR mutation*	Patients (N=138)	Confirmed ORR†	
		n (%)	95% CI
CHEK1	1	PD	NA
RAD51B	1	SD	NA
RAD51D	1	PD	NA
RAD54L	1	SD	NA
Co-occurring mutations			
BRCA2/CDK12	2	PR, SD	NA
BRCA2/ATM	2	SD, SD	NA
BRCA2/BARD1	1	PD	NA
BRCA2/CHEK2	1	SD	NA
CDK12/CHEK1	1	SD	NA
CDK12/PALB2	1	PD	NA
BRCA2/CDK12/CHEK2	1	PD	NA
BRCA2/CHEK2/RAD51D	1	SD	NA

* No patients with *FANCL* or *RAD51C* enrolled. Three patients with *PPP2R2A* mutations had measurable disease, however, Lynparza is not indicated for patients with *PPP2R2A* mutation.
† In patients with a single *BRCA2* mutation the median duration of response in the Lynparza arm (n=24) was 5.6 months (95% C.I: 5.5, 9.2). In the 3 responders with a single *ATM* mutation in the Lynparza arm, the duration of response ranged from 5.8+ to 9.0 months. In the 2 responders with a single *CDK12* mutation in the Lynparza arm, the duration of response was 3.7 and 7.2 months. + denotes ongoing response.
PR Partial response; SD Stable disease; PD Progressive disease; NE Not evaluable; NA Not applicable due to small numbers or lack of response.

14.8 Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

The efficacy of Lynparza in the treatment of patients with mCRPC was investigated in PROpel (NCT03732820), a randomized, double-blind, placebo-controlled, multi-center study that compared the efficacy of Lynparza in combination with abiraterone with placebo plus abiraterone for patients with mCRPC. Patients (n=796) were randomized (1:1) to receive Lynparza tablets 300 mg orally twice daily in combination with abiraterone 1000 mg daily (n=399) compared with placebo plus abiraterone (n=397). All patients received either prednisone or prednisolone 5 mg twice daily, and a GnRH analog or prior bilateral orchiectomy. Patients with prior treatment with abiraterone were excluded. Prior docetaxel for localized or metastatic hormone-sensitive prostate cancer (mHSPC) was allowed. Randomization was stratified by metastases (bone only, visceral, or other) and docetaxel treatment at mHSPC stage (yes or no). Lynparza treatment was continued until objective radiological disease progression determined by investigator or unacceptable toxicity.

BRCA gene mutation (*BRCA*m) status was assessed after randomization and before primary analysis by both NGS-based tumor tissue and ctDNA tests. *BRCA*m classification criteria in line with the FDA approved assays were used to determine the deleterious and suspected deleterious somatic or germline mutation status of patients.

The major efficacy outcome measure was investigator-assessed rPFS evaluated according to RECIST, version 1.1 and Prostate Cancer Working Group (PCWG3) (bone) criteria. Overall survival (OS) was an additional efficacy outcome measure.

Of the 796 patients tested, 85 (11%) had *BRCAm* determined by either a positive ctDNA test (9%) or a tumor tissue test (6%). Among these 85 patients, the median age was 68 years (range 43 to 85), and 67%

were 65 years or older; 72% were White, 22% Asian, and 2% Black or African American; 66% had ECOG performance status (PS) 0 and 34% had ECOG PS 1; 25% had prior docetaxel treatment for mHSPC; 53% had bone-only metastases, 15% had visceral metastases, and 32% had other metastases.

A statistically significant improvement in rPFS for Lynparza/abiraterone compared to placebo/abiraterone was observed in the intention to treat (ITT) population. In an exploratory analysis in the subgroup of 711 patients without an identified *BRCA*m, the rPFS hazard ratio was 0.77 (95% CI: 0.63, 0.96) and the OS hazard ratio was 0.92 (95% CI: 0.74, 1.14), indicating that the improvement in the ITT population was primarily attributed to the results seen in the subgroup of patients with *BRCA*m.

Results of an exploratory analysis in the subgroup of 85 patients on PROpel with *BRCA*m are summarized in Table 31 and Figure 12.

Results from the BICR assessment were consistent with the investigator-assessed rPFS results.

Table 31 Efficacy Results – PROpel (Patients with *BRCA*m)

	Lynparza/abiraterone N = 47	**Placebo/abiraterone** N = 38
Radiological Progression-Free Survival (rPFS)[§]		
Events, n (%)	14 (30)	28 (74)
Median (95% CI), months	NR (NR, NR)	8 (6, 15)
Hazard ratio (95% CI)*	0.24 (0.12, 0.45)	
Overall Survival (OS)		
Events, n (%)	13 (28)	25 (66)
Median (95% CI), months	NR (NR, NR)	23 (18, 34)
Hazard ratio (95% CI)*	0.30 (0.15, 0.59)	

[§] Investigator-assessed
NR: Not reached
* Calculated using an unstratified univariable Cox proportional hazards model.

Figure 12 Kaplan-Meier Curves of rPFS – PROpel (Patients with *BRCA*m, Investigator Assessment)

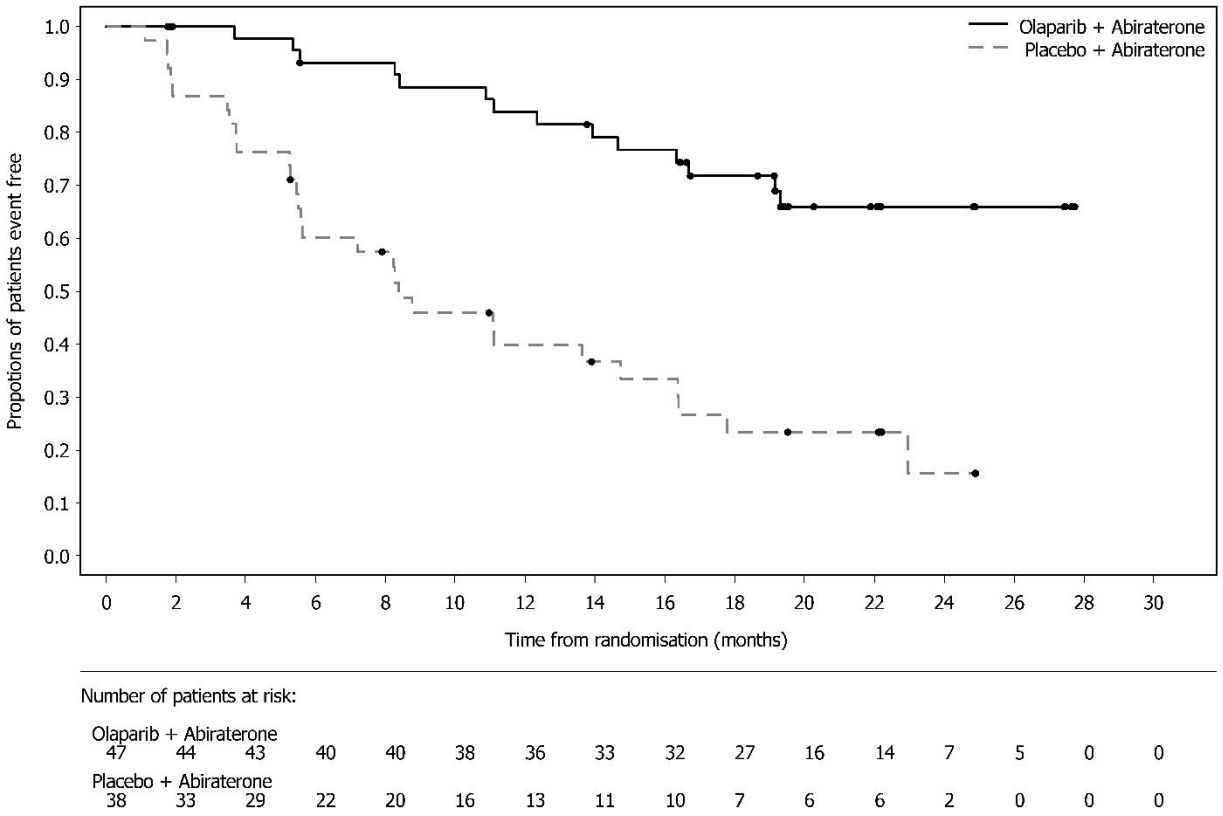
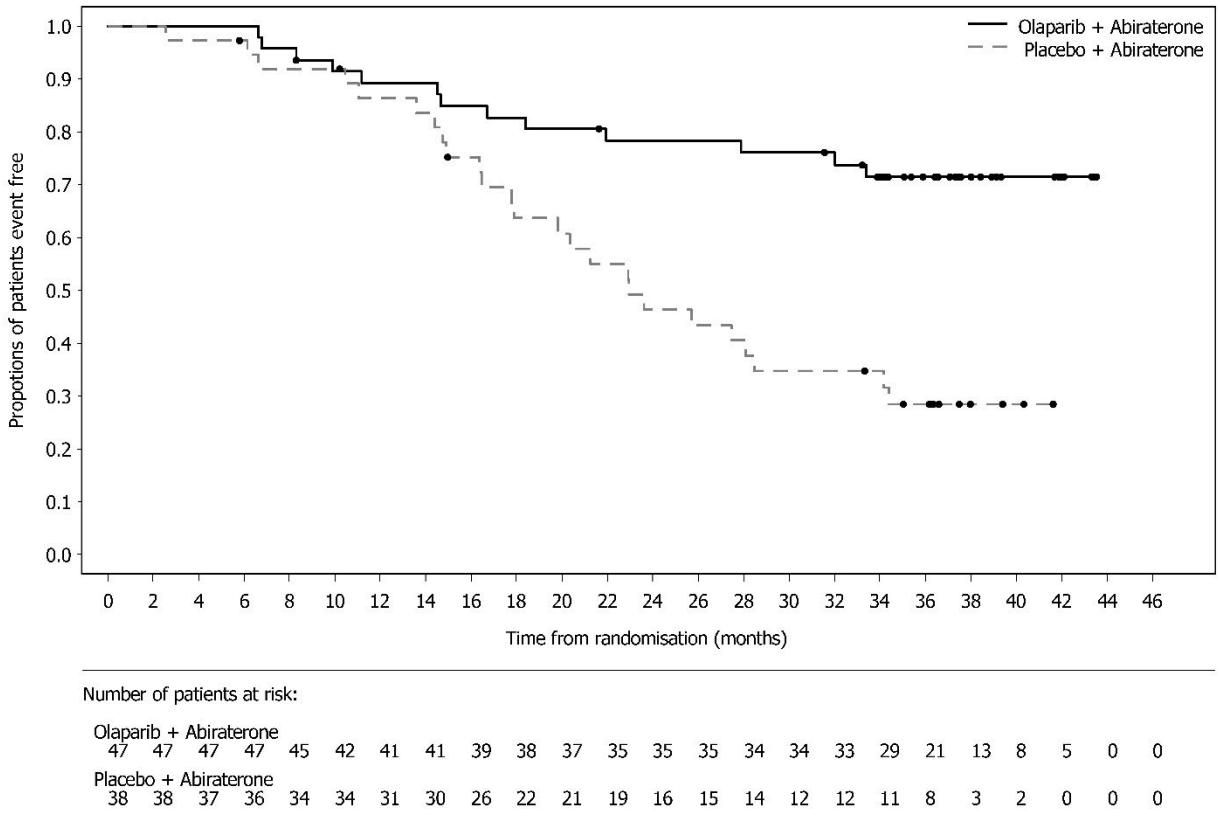


Figure 13 Kaplan-Meier Curves of OS – PROpel (Patients with *BRCA*m)



16 HOW SUPPLIED/STORAGE AND HANDLING

Lynparza is available as 150 mg and 100 mg tablets.

- 150 mg tablets: green to green/grey, oval, bi-convex, film-coated tablet, with debossment ‘OP150’ on one side and plain on the reverse, are available in:
    - Bottles of 60 tablets (NDC 0310-0679-60) and
    - Bottles of 120 tablets (NDC 0310-0679-12).
- 100 mg tablets: yellow to dark yellow, oval, bi-convex, film-coated tablet, with debossment ‘OP100’ on one side and plain on the reverse, are available in:
    - Bottles of 60 tablets (NDC 0310-0668-60) and
    - Bottles of 120 tablets (NDC 0310-0668-12).

Store at 20ºC to 25ºC (68ºF to 77ºF), excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. Store in original bottle to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

MDS/AML

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematological toxicity or a more serious uncommon bone marrow problem called 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukemia' (AML) which have been reported in patients treated with Lynparza *[see Warnings and Precautions (5.1)]*.

Pneumonitis

Advise patients to contact their healthcare provider if they experience any new or worsening respiratory symptoms including shortness of breath, fever, cough, or wheezing *[see Warnings and Precautions (5.2)]*.

Venous Thromboembolism

Advise patients to immediately report any signs or symptoms of thromboembolism such as pain or swelling in an extremity, shortness of breath, chest pain, tachypnea, and tachycardia *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

Inform pregnant women of the risk to a fetus and potential loss of the pregnancy. Advise females to inform their healthcare provider of known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months after receiving the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.3)]*.

Lactation

Advise patients not to breastfeed while taking Lynparza and for one month after receiving the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice while taking Lynparza *[see Drug Interactions (7.2)]*.

Nausea/Vomiting

Advise patients that mild or moderate nausea and/or vomiting is very common in patients receiving Lynparza and that they should contact their healthcare provider who will advise on available antiemetic treatment options *[see Adverse Reactions (6.1)]*.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Medication Guide
Lynparza® (Lin-par-zah)
(olaparib)
tablets

What is the most important information I should know about Lynparza?

Lynparza may cause serious side effects, including:

Bone marrow problems called Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML). Some people who have received previous treatment with chemotherapy, radiotherapy or certain other medicines for their cancer have developed MDS or AML during treatment with Lynparza. MDS or AML may lead to death. If you develop MDS or AML, your healthcare provider will stop treatment with Lynparza.

Symptoms of low blood cell counts are common during treatment with Lynparza, but can be a sign of serious bone marrow problems, including MDS or AML. Symptoms may include:

- weakness
- weight loss
- fever
- frequent infections
- blood in urine or stool
- shortness of breath
- feeling very tired
- bruising or bleeding more easily

Your healthcare provider will do blood tests to check your blood cell counts:

- before treatment with Lynparza
- every month during treatment with Lynparza
- weekly if you have low blood cell counts that last a long time. Your healthcare provider may stop treatment with Lynparza until your blood cell counts improve.

Lung problems (pneumonitis). Tell your healthcare provider if you have any new or worsening symptoms of lung problems, including shortness of breath, fever, cough, or wheezing. Your healthcare provider may do a chest x-ray if you have any of these symptoms. Your healthcare provider may temporarily or completely stop treatment if you develop pneumonitis. Pneumonitis may lead to death.

Blood clots (Venous Thromboembolism). Some people may develop a blood clot in a deep vein, usually in the leg (venous thrombosis), or a clot in the lungs (pulmonary embolism) which may be severe or lead to death. Tell your healthcare provider right away if you have any symptoms such as pain or swelling in an extremity, shortness of breath, chest pain, breathing that is more rapid than normal (tachypnea), or heart beats faster than normal (tachycardia). Your healthcare provider will monitor you for these symptoms and may prescribe blood thinner medicine.

What is Lynparza?

Lynparza is a prescription medicine used to treat adults who have:

- advanced ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with a certain type of inherited (germline) or acquired (somatic) abnormal *BRCA* gene. Lynparza is used alone as maintenance treatment after the cancer has responded to your first treatment with platinum-based chemotherapy. Your healthcare provider will perform a test to make sure that Lynparza is right for you.
- advanced ovarian cancer, fallopian tube cancer or primary peritoneal cancer with a certain type of abnormal *BRCA* gene or a positive laboratory tumor test for genomic instability called HRD. Lynparza is used in combination with another anti-cancer medicine, bevacizumab, as maintenance treatment after the cancer has responded to your first treatment with platinum-based chemotherapy. Your healthcare provider will perform a test to make sure that Lynparza is right for you.

- ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, as maintenance treatment, when the cancer has come back. Lynparza is used after the cancer has responded to treatment with platinum-based chemotherapy.
- human epidermal growth factor receptor 2 (HER2)-negative early breast cancer with a certain type of inherited (germline) abnormal *BRCA* gene. Lynparza is given after surgery (treatment after surgery is called adjuvant therapy). You should have received chemotherapy medicines before or after surgery to remove the tumor. Your healthcare provider will perform a test to make sure that Lynparza is right for you.
- a certain type of abnormal inherited *BRCA* gene, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has spread to other parts of the body (metastatic). You should have received chemotherapy medicines, either before or after your cancer has spread. If you have hormone receptor (HR)-positive disease, you should have been treated with hormonal therapy. Your healthcare provider will perform a test to make sure that Lynparza is right for you.
- metastatic pancreatic cancer with a certain type of abnormal inherited *BRCA* gene. Lynparza is used as maintenance treatment after your cancer has not progressed on at least 16 weeks of treatment with platinum-based chemotherapy. Your healthcare provider will perform a test to make sure that Lynparza is right for you.
- prostate cancer with certain inherited or acquired abnormal genes called homologous recombination repair (HRR genes). Lynparza is used when the cancer has spread to other parts of the body (metastatic), and no longer responds to a medical or surgical treatment that lowers testosterone, and has progressed after treatment with enzalutamide or abiraterone. Your healthcare provider will perform a test to make sure Lynparza is right for you.
- prostate cancer with a certain type of abnormal inherited or acquired *BRCA* gene that has spread to other parts of the body (metastatic) and no longer responds to a medical or surgical treatment that lowers testosterone. Lynparza is used in combination with another anti-cancer medicine, abiraterone, together with the steroid medicine, prednisone or prednisolone.

It is not known if Lynparza is safe and effective in children.

Before taking Lynparza, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems
- have kidney problems
- are pregnant, become pregnant, or plan to become pregnant. Lynparza can harm your unborn baby and may cause loss of pregnancy (miscarriage).
  - If you are able to become pregnant, your healthcare provider may do a pregnancy test before you start treatment with Lynparza.
  - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with Lynparza and for 6 months after the last dose of Lynparza. Talk to your healthcare provider about birth control methods that may be right for you. Tell your healthcare provider right away if you become pregnant or think you might be pregnant following treatment with Lynparza.
  - **Males** with female partners who are pregnant or able to become pregnant should use effective birth control (contraception) during treatment with Lynparza and for 3 months after the last dose of Lynparza.
  - Do not donate sperm during treatment with Lynparza and for 3 months after your last dose.

- are breastfeeding or plan to breastfeed. It is not known if Lynparza passes into your breast milk. Do not breastfeed during treatment with Lynparza and for 1 month after receiving the last dose of Lynparza. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking Lynparza and certain other medicines may affect how Lynparza works and may cause side effects.

How should I take Lynparza?

- Take Lynparza tablets exactly as your healthcare provider tells you.
- Do not change your dose or stop taking Lynparza unless your healthcare provider tells you to. Your healthcare provider may temporarily stop treatment with Lynparza or change your dose of Lynparza if you experience side effects.
- Your healthcare provider will decide how long you stay on treatment.
- **Do not** take more than 4 Lynparza tablets in 1 day. If you have any questions about Lynparza, please talk to your healthcare provider or pharmacist.
- Take Lynparza by mouth 2 times a day.
- Each dose should be taken about 12 hours apart.
- Swallow Lynparza tablets whole. Do not chew, crush, dissolve, or divide the tablets.
- Take Lynparza with or without food.
- If you are taking Lynparza for early breast cancer and you have hormone receptor-positive disease, you should continue to take hormonal therapy during your treatment with Lynparza.
- If you are taking Lynparza for prostate cancer and you are receiving gonadotropin-releasing hormone (GnRH) analog therapy, you should continue with this treatment during your treatment with Lynparza unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you miss a dose of Lynparza, take your next dose at your usual scheduled time. Do not take an extra dose to make up for a missed dose.
- If you take too much Lynparza, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking Lynparza?

Avoid grapefruit, grapefruit juice, Seville oranges and Seville orange juice during treatment with Lynparza since they may increase the level of Lynparza in your blood.

What are the possible side effects of Lynparza?

Lynparza may cause serious side effects.

See "What is the most important information I should know about Lynparza?"

The most common side effects of Lynparza when used alone are:

- nausea or vomiting. Tell your healthcare provider if you get nausea or vomiting. Your healthcare provider may prescribe medicines to treat these symptoms.
- tiredness or weakness
- low red blood cell counts
- diarrhea
- loss of appetite
- headache
- low white blood cell counts
- changes in the way food tastes
- cough
- dizziness
- shortness of breath
- indigestion or heartburn

The most common side effects of Lynparza when used in combination with abiraterone are:

- low red blood cell counts
- tiredness or weakness
- nausea or vomiting. Tell your healthcare provider if you get nausea or vomiting. Your healthcare provider may prescribe medicines to treat these symptoms.
- diarrhea
- loss of appetite
- low white blood cell counts
- dizziness
- abdominal pain

These are not all of the possible side effects of Lynparza.
Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Lynparza?

- Store Lynparza at room temperature, between 68°F to 77°F (20°C to 25°C).
- Store Lynparza in the original bottle to protect it from moisture.

Keep Lynparza and all medicines out of reach of children.

General information about the safe and effective use of Lynparza.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Lynparza for a condition for which it was not prescribed. Do not give Lynparza to other people, even if they have the same symptoms you have. It may **harm** them.

You can ask your healthcare provider or pharmacist for information about Lynparza that is written for health professionals.

What are the ingredients in Lynparza?
Active ingredient: olaparib

Inactive ingredients:
Tablet contains: copovidone, mannitol, colloidal silicon dioxide and sodium stearyl fumarate
Tablet coating contains: hypromellose, polyethylene glycol 400, titanium dioxide, ferric oxide yellow and ferrosoferric oxide (150 mg tablet only)

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
For more information, call 1-800-236-9933 or go to www.Lynparza.com.
This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 05/2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s025

MULTI-DISCIPLINE REVIEW

Summary Review
Cross Discipline Team Leader Review Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Supplement
Application Number(s)	NDA 208558/S-025
Priority or Standard	Priority
Submit Date(s)	June 16, 2022
Received Date(s)	June 16, 2022
PDUFA Goal Date	December 16, 2022
Division/Office	DO1
Review Completion Date	May 31, 2023
Established Name	Olaparib
(Proposed) Trade Name	LYNPARZA
Pharmacologic Class	Poly (ADP-ribose) polymerase (PARP) inhibitor
Code name	N/A
Applicant	AstraZeneca Pharmaceuticals LP
Formulation(s)	Tablet
Dosing Regimen	300 mg taken orally twice daily with or without food
Applicant Proposed Indication(s)/Population(s)	Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated • in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated • in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC).

Table of Contents

Table of Tables

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

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OSE/DMEPA	Janine Stewart
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CDRH Medical Officer	Anand Pathak
CDRH Diagnostic Devices Team Lead	Abdelrahmman Abukhdeir
CDRH Deputy Branch Chief	Shyam Kalavar
Other	

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

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OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADR	adverse drug reaction
ADT	androgen-deprivation therapy
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AR	androgen receptor
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
BICR	blinded independent central review
bid	twice daily
BLA	biologics license application
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer susceptibility gene
COA	clinical outcome assessment
CFR	Code of Federal Regulations
CI	confidence interval
ClinRO	Clinician-reported outcome
COVID-19	coronavirus disease 2019
CRPC	castration resistant prostate cancer
CSP	clinical study protocol
CSR	clinical study report

CTC	circulating tumor cell
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCO	data cut-off
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
ESMO	European Society for Medical Oncology
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy – Prostate Cancer
FAS	full analysis set
FDA	Food and Drug Administration
*gBRCA*m	germline *BRCA* mutated
GCP	Good Clinical Practice
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRD	homologous recombination deficiency
HRQoL	health related quality of life
HRR	homologous recombination repair
HRRm	homologous recombination repair mutated
HRRm unknown	patients without a sample or who failed testing
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
ITT	intent to treat

IV	intravenous
mCRPC	metastatic castration resistant prostate cancer
mHSPC	metastatic hormone sensitive prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	metastatic hormone sensitive prostate cancer
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCT	National Clinical Trial
NDA	new drug application
NHA	new hormonal agents
NME	new molecular entity
Non-HRRm	patients without loss of function mutations detected in HRR
NPM	new primary malignancy
ObsRO	observer-reported outcome
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PARP	polyadenosine 5'diphosphoribose polymerase
PCWG	Prostate Cancer Working Groups
PerfO	performance outcome
PFS	progression-free survival
PFS2	time from randomization to second progression or death
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PSA	prostate specific antigen

PSP	pediatric study plan
qd	once daily
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
rPFS	radiological progression-free survival
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
sNDA	supplemental new drug application
SOC	system organ class
SSRE	symptomatic skeletal related event
TFST	time from randomization to start of first subsequent therapy or death
TSST	time to second subsequent therapy or death
TTPP	time from randomization to pain progression
US	United States
USPI	United States Prescribing Information
vs	versus
VTE	venous thromboembolism
WRO	written responses only

1 Executive Summary

1.1. Product Introduction

Olaparib (LYNPARZA) is an inhibitor of poly (ADP-ribose) polymerase enzymes. Olaparib was previously approved for the treatment of patients with deleterious or suspected deleterious germline or somatic homologous HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone, in addition to approvals in other solid tumors.

Abiraterone is an androgen biosynthesis inhibitor that inhibits 17 α-hydroxylase/ C17,20-lyase (CYP17). Abiraterone was previously approved for the treatment of patients with mCRPC in combination with prednisone.

The proposed indication for olaparib is: in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC.

The proposed dosage for olaparib is 300 mg taken orally twice daily. The proposed dosage of abiraterone is 1000 mg taken orally once in combination with prednisone or prednisolone 5 mg orally twice daily. Patients should also receive a GnRH analog concurrently or should have bilateral orchiectomy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends traditional approval of olaparib in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) mCRPC. This is a narrower indication than that initially proposed by the Applicant, which included patients unselected for the presence of a mutation in *BRCA* or other HRR genes.

Olaparib is administered at a dose of 300 mg orally twice daily. The recommended dose of abiraterone is 1000 mg taken orally once in combination with prednisone or prednisolone 5 mg orally twice daily. Patients should also receive a GnRH analog concurrently or should have had bilateral orchiectomy.

The recommended indication is supported by clinical data from PROpel, a randomized, double-blind, placebo-controlled, multi-center trial of olaparib + abiraterone (henceforth referred to as the olaparib arm in this section) vs placebo plus abiraterone (henceforth referred to as the placebo arm in this section) in patients with mCRPC, with both arms receiving prednisone or prednisolone and ADT. Patients were stratified by metastases (bone only, visceral, or other) and docetaxel treatment at mHSPC stage (yes or no). In total, 796 patients were randomized 1:1 to the olaparib arm (N = 399) or to the placebo arm (N = 397). The primary efficacy outcome measure was rPFS per investigator in the intent-to-treat (ITT) population, evaluated according to RECIST version 1.1 and PCWG3 (bone) criteria. A blinded independent central review (BICR) sensitivity analysis of rPFS was also performed. Imaging frequency was every 2 months for the first 6 months and then every 3 months. The key secondary endpoint was overall survival (OS).

At the time of the first interim analysis, PROpel demonstrated a statistically significant improvement in investigator-assessed rPFS for olaparib vs. placebo in the ITT population (HR 0.66 [95% CI 0.54, 0.81] $p<0.0001$) and an 8-month improvement in median rPFS (25 months vs. 17 months). At the time of the prespecified final OS analysis there was no statistically significant OS difference between arms in the ITT population, however, the point estimate of HR for OS favored the olaparib arm (HR 0.81 [95% CI 0.67, 1.00]) in the heterogeneous ITT population.

PROpel was not stratified by *HRR*m or *BRCA*m status, which were assessed retrospectively by both NGS-based tissue and ctDNA tests. Results of at least one assay were available for 98% of patients. Due to the known predictive effect of *BRCA* mutation status for PARP inhibitors (PARPi), FDA analyzed PROpel data with subgroups based on likelihood of *BRCA* mutation. Due to high test specificity, FDA considered patients positive for *BRCA*m by either tumor tissue or ctDNA testing to have a *BRCA* mutation (11% of ITT). FDA considered those with negative results by both tests to not have a mutation (54% of ITT) and those with negative results by only one test and/or unknown results to have undetermined *BRCA* status (35% of ITT). Using the above grouping, the improved rPFS in PROpel appeared heavily attributable to efficacy in the subgroup of patients with *BRCA* mutation, in whom median rPFS was not reached (NR) vs. 8 months in the olaparib vs. placebo arms (HR 0.24 [95% CI 0.12, 0.46]). OS results were consistent, with median OS NR vs. 23 months in the olaparib vs. placebo arms (HR 0.30 [95% CI 0.15, 0.60]). In contrast, for the non-*BRCA*m subgroup, comprised of patients confirmed to be tumor *BRCA* negative by both ctDNA and tissue assays, the HR for rPFS was 0.85 (95% CI 0.66, 1.11) with median rPFS of 22 vs. 17 months in the olaparib vs. placebo arms; the HR for OS was 1.06 (95% CI 0.81, 1.39) with median OS of 37 vs. 38 months in the olaparib vs. placebo arms. The subgroup of patients with undetermined *BRCA* status had results

intermediate between patients with *BRCA* mutation and those with *BRCA* negative status confirmed by two tests, with a HR for rPFS of 0.66 (95% CI 0.46, 0.94) and a HR for OS of 0.73 (95% CI 0.52,1.03) for the olaparib vs. placebo arms.

The FDA also analyzed PROpel in terms of those with *BRCA* mutations (11% of the ITT population) vs all those without a demonstrated *BRCA* mutation (89% of the ITT population). For the subgroup of all those without a demonstrated *BRCA* mutation, the HR of rPFS was 0.77 (95% CI 0.63, 0.96) with a 5-month improvement in median rPFS (24 vs 19 months) and the HR for OS was 0.92 (95% CI 0.74, 1.14) for the olaparib vs placebo arms. The FDA considered a 5-month improvement in median rPFS in this early disease setting with no improvement in OS to constitute only modest efficacy for an add-on therapy.

The review team did not consider there to be a clear demonstration of efficacy in patients with identified *HRR* mutations other than *BRCA*m. In this population, the HR for rPFS per investigator was 0.8 (95% CI 0.5, 1.27) and the HR for OS was 1.02 (95% CI 0.65, 1.59).

The overall safety profiles of olaparib and abiraterone in PROpel were consistent with their known toxicities with no new safety signals emerging. However, the combination of olaparib and abiraterone was more toxic than abiraterone and placebo, with a higher incidence of ≥ Grade 3 adverse reactions (56% vs 43%), nausea/vomiting (35% vs 21%), myelosuppression (57% vs 26%), blood transfusion (18% vs 4%), and venous thromboembolism (VTE) (9 vs 3.5%). Exploratory analyses of patient-reported outcomes (PROs) showed that a higher proportion of patients in the olaparib arm reported bothersome side effects from treatment compared to placebo. The FDA review team was especially concerned about the added toxicity in patients without *BRCA* mutations, particularly in an add-on treatment setting where the median duration of rPFS with abiraterone as a single agent is approximately 16 months. This differs from a monotherapy where there may be early progression if the drug is ineffective and the drug may be stopped, avoiding unnecessary toxicity. Further, patients with previously untreated mCRPC are generally asymptomatic or minimally symptomatic at baseline (70% of patients on PROpel) and thus the risk/benefit of prolonged treatment with a drug that adds toxicity in the absence of clear efficacy is less favorable than in a later-line setting with fewer available treatment options.

The Sponsor also submitted results of Study 8, which was similar in design to PROpel, but smaller in size and conducted in a later line of therapy. Study 8 randomized 142 patients with mCRPC 1:1 to the combination of olaparib plus abiraterone vs. placebo plus abiraterone, with both arms receiving prednisone/prednisolone and ADT. While Study 8 met its primary endpoint of improvement in rPFS by investigator assessment in the ITT, with an rPFS HR of 0.65 (95% CI 0.44, 0.97, p-value = 0.034) for olaparib vs. placebo (median rPFS for olaparib vs. placebo of 13.8 months vs 8.2 months), there was no OS benefit [HR for OS in of 0.91 (95% CI 0.60,

1.38)]. A sensitivity analysis of rPFS by BICR assessment demonstrated no rPFS benefit, with HR of 0.95 (95% CI 0.62, 1.44). Additionally, exploratory subgroup analysis showed that in the 16% of patients with *BRCA*-negative status determined by two tests, the rPFS HR was 1.72 (95% CI 0.56, 5.76) and the OS HR was 2.77 (95% CI 1.06, 8.06). There were an insufficient number of patients with *BRCA*m (5%) to estimate a HR for rPFS or OS. Overall, results of Study 8 were consistent with those of PROpel in the demonstration of no OS benefit of the combination of olaparib + abiraterone compared to abiraterone alone in the overall ITT population and diminished efficacy and potential harm from the addition of olaparib in the subgroup of patients with non-*BRCA*m.

The review team considered the rPFS improvement demonstrated in the ITT population to be primarily attributable to the 11% of patients with identified *BRCA* mutations. Exploratory analyses adjusting the efficacy results for baseline risk as determined by a validated prognostic model did not change the overall conclusion that there was minimal added efficacy from the addition of olaparib to abiraterone in patients without a *BRCA* mutation, indicating that this conclusion was robust despite the lack of stratification by *BRCA* status. In addition to PROpel and Study 8 results, minimal efficacy from PARPi in patients without *BRCA* mutations has been demonstrated in studies of other PARPi in mCRPC publicly available during this review (1,2). Lack of efficacy in non-*BRCA*m populations was also demonstrated in studies of PARPi in patients with other cancers, including advanced ovarian cancer, leading to restricted indications excluding patients negative for *BRCA*m due to concerns for potential OS detriments (3,4). *BRCA*m status thus consistently appears to be a strong predictive biomarker for PARPi efficacy based on PROpel and other results.

The FDA review team therefore presented this sNDA to the Oncologic Drugs Advisory Committee (ODAC) on April 28, 2023, asking the committee to answer the following question:

> *"As FDA reviews the proposed indication for olaparib in combination with abiraterone for initial treatment of mCRPC, should the indication be restricted to patients whose tumors have a BRCA mutation?*
>
> *If you feel the combination should not be approved at all, please abstain from voting and explain your thinking regarding approvability during the post-voting discussion period."*

In an 11-1 vote with one abstention, the ODAC members voted in favor of restricting the indication to patients with *BRCA*m tumors, generally opining that the Applicant had not demonstrated overall clinical benefit in patients without *BRCA*m.

Consistent with the ODAC vote, the FDA review team concluded that substantial evidence of efficacy for the combination of olaparib and abiraterone was demonstrated only in patients with BRCAm mCRPC and that the risk/benefit for patients without an identified BRCA mutation was unfavorable in light of the add-on design, modest rPFS improvement, lack of OS improvement, and potential for prolonged exposure without evidence of lack of olaparib activity, putting patients at risk for toxicities that included a substantial transfusion requirement and increased risk for VTE. The review team thus recommends traditional approval of olaparib in combination with abiraterone only in patients with deleterious or suspected deleterious *BRCA*m mCRPC.

Two postmarketing commitments (PMCs) to update companion diagnostic devices for identifying *BRCA*m, one for ctDNA and one for tumor tissue, were agreed upon by the FDA and the Applicant.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Metastatic CRPC is a serious and life-threatening condition that is incurable with currently approved therapies. Standard FDA-approved treatment options for patients with mCRPC include the novel hormonal agents abiraterone (plus prednisone) or enzalutamide.

PROpel was a double-blind, placebo-controlled clinical trial in 796 patients with mCRPC that randomized patients 1:1 to receive olaparib 300 mg orally twice daily (n=399) or placebo (n=397). All patients received abiraterone 1000 mg orally once daily plus prednisone or prednisolone 5 mg orally twice daily in addition to ADT. Randomization was stratified by metastases (bone only, visceral, or other) and docetaxel treatment at mHSPC stage (yes or no).

A statistically significant improvement in rPFS for olaparib plus abiraterone compared to placebo plus abiraterone was observed in the ITT population, HR 0.66 (0.54, 0.81). In an exploratory analysis in the subgroup of 85 patients (11%) with an identified *BRCA*m, the rPFS HR was 0.24 (95% CI: 0.12, 0.46) and the OS HR was 0.3 (95% CI: 0.15, 0.6). In the subgroup of 711 patients (89%) without an identified *BRCA*m, the rPFS HR was 0.77 (95% CI: 0.63, 0.96) and the OS HR was 0.92 (95% CI: 0.74, 1.14), indicating that the improvement in the ITT population was primarily attributed to the results seen in the subgroup of patients with *BRCA*m. Additionally, in a subgroup of patients negative for *BRCA*m by both tumor tissue and ctDNA *BRCA* testing, there was concern for lack of efficacy and potential OS detriment (HR for OS = 1.06).

The safety profile of the combination of olaparib plus abiraterone was generally consistent with the known safety profiles of each drug individually. The most common treatment-emergent adverse events in PROpel occurring in the olaparib plus abiraterone arm included anemia (including need for transfusions), fatigue, nausea, diarrhea, decreased appetite, lymphopenia, abdominal pain, and dizziness. Clinically relevant adverse events occurring in <10% of patients in this arm included headache, VTE, rash, dysgeusia, acute kidney injury, and stomatitis.

Efficacy in the ITT population in PROpel appeared primarily attributable to the treatment effect in the *BRCA*m subgroup, consistent with results across trials of PARPi in mCRPC and in other solid tumors. FDA thus identified substantial evidence of efficacy for adding olaparib to abiraterone in patients with *BRCA*m. Due to modest rPFS improvement and concern for harm in patients with no identified *BRCA*m, the FDA review team concluded that that the risk/benefit was unfavorable for patients without an identified *BRCA*m. Additional considerations included the add-on trial design and the combination with an effective partner, which may lead to prolonged exposure to olaparib without evidence for lack of activity. Based on the above considerations and in line with the 11-1 ODAC vote on April 28th, 2023, the FDA review team recommended traditional approval of olaparib in combination with abiraterone for the treatment of patients with deleterious or suspected deleterious *BRCA*m mCRPC.

Two PMCs to update companion diagnostic devices for identifying *BRCA*m, one for ctDNA and one for tumor tissue, were agreed upon by the FDA and the Applicant.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Prostate cancer is the most commonly diagnosed cancer among men in the US and the second most common cause of cancer death. In 2021, ~248,530 new cases of prostate cancer cases were diagnosed in the US and ~34,130 men died from their disease. • Prostate cancer is amenable to curative therapy if detected early; however, advanced stages are life-threatening and generally incurable. Disease severity is worsened once patients	Metastatic CRPC is a serious and life-threatening disease and is currently incurable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	develop mCRPC.	
Current Treatment Options	• Novel hormonal therapies, consisting of abiraterone and enzalutamide are approved for the treatment of mCRPC in combination with ADT and are considered standard of care in this setting. • Docetaxel is also approved in this setting, although it is associated with chemotherapy-related toxicities. •Other therapies available to specific patients in this setting include sipuleucel-T, radium-223, and pembrolizumab (in the rare case of patients with MSI-high disease). These therapies are not considered curative.	Current treatment options for mCRPC may prolong survival but are not curative. Additional effective treatments are needed to improve clinical outcomes for patients with mCRPC.
Benefit	•PROpel randomized 796 patients with mCRPC 1:1 to olaparib or placebo plus prednisone/prednisolone and ADT; randomization was not stratified by *BRCA*m status. •A statistically significant improvement in rPFS for olaparib/ abiraterone vs. placebo/abiraterone was observed in the ITT population; OS was not significantly improved.	The rPFS improvement in the PROpel ITT is attributed to efficacy in the *BRCA*m subgroup. This subgroup demonstrated a clear clinical benefit for the addition of olaparib to abiraterone. A favorable risk/benefit ratio was not demonstrated in patients without an identified *BRCA*m. These conclusions are in line with an ODAC vote which favored restricting the indication to *BRCA*m and also took into account emerging data from other

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	•In an exploratory analysis in the 11% of patients with an identified *BRCA*m, the rPFS HR was 0.24 (95% CI: 0.12, 0.46) and the OS HR was 0.3 (95% CI: 0.15, 0.6). •In an exploratory analysis in 89% of patients without an identified *BRCA*m, the rPFS hazard ratio was 0.77 (95% CI: 0.63, 0.96) and the OS hazard ratio was 0.92 (95% CI: 0.74, 1.14), indicating that the improvement in the ITT population was primarily attributed to the results seen in the patients with *BRCA*m. •In a subgroup of patients with negative results on both tumor tissue and ctDNA *BRCA* tests, there was concern for lack of efficacy and potential OS detriment (HR for OS = 1.06). •Study 8 was similar in design to PROpel albeit smaller and in a later line of therapy, and similarly showed lack of OS benefit for the combination of olaparib plus abiraterone in the ITT population and concern for OS detriment in patients with negative results on both tumor tissue and ctDNA *BRCA* tests.	PARPi trials demonstrating efficacy primarily in patients with *BRCA*m.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The combination of olaparib and abiraterone was more toxic than abiraterone and placebo, with a higher incidence of ≥ Grade 3 adverse reactions, myelosuppression, nausea/vomiting, requirement for blood transfusion, and VTE. • Exploratory analyses of PRO showed higher side effect bother in patients receiving olaparib vs. placebo. • Added toxicity is especially concerning in patients without *BRCA*m, particularly in an add-on treatment setting where identifying lack of efficacy of olaparib is potentially challenging.	The safety profile of olaparib plus apalutamide is acceptable in patients with mCRPC and an identified *BRCA*m but the added toxicity was part of the reason for an unfavorable risk/benefit ratio in patients without *BRCA*m. No new Warnings and Precautions or boxed warnings were identified. No safety PMRs or REMs are required.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as			
			x	Patient reported outcome (PRO)	Section 8.1.2 subsection- Efficacy Results – Secondary or exploratory COA (PRO) endpoints
			☐	Observer reported outcome (ObsRO)	
			☐	Clinician reported outcome (ClinRO)	
			☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	☐	Patient-focused drug development or other stakeholder meeting summary reports			

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.		

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:
In the US, prostate cancer is the leading male cancer diagnosis, ranking as the second most common cause of cancer death. In 2021, it is estimated that there will be 248,530 newly diagnosed prostate cancer cases in the US and approximately 34,130 men will die from their disease (American Cancer Society 2021, Siegel et al 2021).

Prostate cancer is amenable to curative therapy if detected early; however, advanced stages are life-threatening. Almost all patients in advanced stages will ultimately develop into mCRPC, which progresses rapidly (Scher et al 2015). A systematic literature review identified that among patients with non-metastatic CRPC, nearly 60% developed metastatic disease during the first 5 years, with most of the metastases occurring within the first 3 years and one-third of patients developed bone metastases within 2 years (Kirby et al 2011).

Prostate cancer is a heterogeneous disease and ADT with luteinizing hormone releasing hormone analogues or orchiectomy is usually initially effective at controlling metastatic disease. However, patients inevitably progress from an androgen sensitive to a castration resistant phenotype, which is not curable, and is associated with 90% of overall mortality being attributable to the underlying malignant disease (Scher et al 2015). For patients diagnosed with metastatic disease, the 5-year survival rate is 30% (American Cancer Society 2021, Siegel et al 2021).

mCRPC is associated with a range of symptoms but is predominantly characterized by bone pain, fatigue, and urinary dysfunction (Gater et al 2011, Lindqvist et al 2008). Around 90% of patients with mCRPC have bone metastases (de Bono et al 2010, de Bono et al 2011, Scher et al 2012), which leads to significant morbidity, including pain and skeletal-related events such as spinal cord compression and pathological fractures, which require interventions such as bone surgery or radiation therapy (El-Amm et al 2013). Existing bone-targeted therapies (zoledronic acid, denosumab) reduce the number of bone complications incompletely without a documented positive impact on OS (Fizazi et al 2011, Saad et al 2004).

Symptoms of mCRPC can have an impact on daily lives and contribute to diminished levels of HRQoL observed in this population (Eton and Lepore 2002). As curative therapy is not possible in the metastatic setting, reducing disease burden and symptoms are critical objectives of any therapeutic intervention.

The FDA's Assessment:
FDA agrees with the Applicant's analysis of the condition.

2.2. Analysis of Current Treatment Options

For patients who have not received prior treatment with docetaxel or an NHA, the preferred NCCN regimens (NCCN Prostate Cancer Guidelines 2021) for systemic treatment for M1 CRPC include abiraterone, docetaxel, and enzalutamide. Sipuleucel-T (Category 1; US only) is only recommended for specific patients. Abiraterone and enzalutamide remain preferred Category-1 NHAs after systemic treatment with docetaxel in the M1 CRPC disease state.

Docetaxel was first approved in 2004 in combination with prednisone for mCRPC based on improvements in OS. Docetaxel has safety and tolerability challenges, particularly hematological toxicity, hypersensitivity reactions, gastrointestinal toxicities, and alopecia (Taxotere USPI). However, when patients present with signs of rapid progression and symptomatic or visceral metastatic disease, docetaxel-containing chemotherapy remains a valuable treatment option (NCCN Prostate Cancer Guidelines 2021).

Following its approval, from 2005 to 2013, docetaxel was used as a combination regimen in several Phase 3 trials including CALGB 90401 with bevacizumab (Kelly et al 2012). However, the regimens failed to demonstrate an improvement in treatment effect over docetaxel alone with median rPFS ranging between 9-11 months and median OS between 18-22 months in first-line mCRPC.

NHAs are potent, orally available treatment options with a favorable tolerability profile. Both abiraterone and enzalutamide have demonstrated robust improvements in PFS and OS (Beer et al 2014, Beer et al 2017, Ryan et al 2013, Ryan et al 2015). Although NHAs were studied in asymptomatic or mildly symptomatic patients with mCRPC in the first-line setting (COU-AA-302 and PREVAIL), the NCCN guidelines do not limit their use to this specific patient population and - since their approval in the first-line setting - NHAs have increasingly replaced docetaxel globally as the preferred choice of first-line therapy for mCRPC (Flaig et al 2016, Parker et al 2020).

Radium-223 is also used in certain circumstances in both first-line and later settings for bone metastases.

Treatment of patients who have developed mCRPC disease will vary depending on the regimens initially used in the early stage of disease. The NCCN guidelines recommend that patients with disease progression on a given therapy should not repeat that therapy, apart from docetaxel, which can be given as a rechallenge therapy in later stages of the disease, ie, if initially given in

the hormone-sensitive setting (NCCN Prostate Cancer Guidelines 2021). All approved therapy options for the first-line treatment of mCRPC are also available for later treatments. In addition, cabazitaxel and the PARP inhibitors olaparib (HRRm patients in the US, *BRCAm* patients in the EU) and rucaparib (*BRCAm* patients in the US) are approved as subsequent therapies for mCRPC.

The Applicant's Position:
Although there are several treatment options for mCRPC, the disease is incurable. A median PFS of approximately 16-18 months is obtained with early treatment initiation with NHAs (Ryan et al 2013, Beer et al 2017), and they are the preferred treatment choice in the first-line setting (Flaig et al 2016, Parker et al 2020).

However, following progression after first-line NHA therapy, the current treatment paradigm is either to re-treat with another NHA or to use a taxane-based chemotherapy agent (docetaxel or cabazitaxel). There is also evidence of significantly diminishing efficacy with subsequent lines of NHA therapy with no additional efficacy benefit of taxane-based therapies (Castro et al 2019, Romero-Laorden et al 2020, Swami et al 2020). As such, a new treatment option that would allow for early intervention in the course of mCRPC as well as prolong the treatment duration of available therapies, delay disease progression, and improve long-term outcomes in this setting is warranted.

The FDA's Assessment:
Pembrolizumab is a treatment option in for patients with unresectable or metastatic microsatellite-instability–high, mismatch-repair–deficient, or high tumor mutation burden solid tumors, including prostate cancer, who had disease progression following prior treatment and no satisfactory alternative treatment options.

With approvals of androgen receptor pathway inhibitors (NHAs) in nmCRPC and metastatic hormone-sensitive prostate cancer (mHSPC), the population of patients similar to the population enrolled in PROpel will likely decrease in the U.S. in the near future, as more patients receive NHAs in earlier lines of therapy. It mainly includes those who had stereotactic body ration therapy (SBRT) for mHSPC or those who want to receive abiraterone instead of taxanes following progression at least 12 months after an NHA in nonmetastatic setting. However, the proposed indication is just for patients with mCRPC without specifying the line of therapy.

There are additional therapies available to patients with mCRPC, however, these are approved in later lines of therapy than the one under review. These therapies include olaparib monotherapy for patients with HRR mutations and rucaparib for patients with *BRCA* mutations (under the accelerated approval pathway). Lutetium Lu 177 vipivotide tetraxetan has been

approved for patients with prostate-specific membrane antigen-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Table 1. Applicant – US Regulatory Actions – Marketing History

Date/Application	Action
December 19, 2014/ NDA 206162	Olaparib (capsule formulation) received accelerated approval as monotherapy in patients with deleterious or suspected deleterious *gBRCA*m (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. As of September 01, 2018, the capsule formulation is no longer commercially available in the US market.
August 17, 2017/ NDA 208558	Olaparib (tablet formulation) received approval for the following indications: Lynparza is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy; and for the treatment of adult patients with deleterious or suspected deleterious *gBRCA*m ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA approved companion diagnostic for Lynparza.
January 12, 2018/ Efficacy supplement sNDA 208558	Olaparib (tablet formulation) received approval for the following indication: Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious *gBRCAm*, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
December 19, 2018/ Efficacy supplement sNDA 208558	Olaparib (tablet formulation) received approval for the following indication: Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
December 27, 2019/ Efficacy supplement sNDA 208558	Olaparib (tablet formulation) received approval for the following indication: Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious *gBRCAm* metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Date/Application	Action
May 08, 2020/ Efficacy supplement sNDA 208558	Olaparib (tablet formulation) received approval for the following indication: Lynparza is indicated in combination with bevacizumab 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 HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* mutation, and/or • genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
May 19, 2020/ Efficacy supplement sNDA 208558	Olaparib (tablet formulation) received approval for the following indication: Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
March 11, 2022/ Efficacy supplement sNDA 208558	Olaparib (tablet formulation) received approval for the following indication: Lynparza is indicated for the adjuvant treatment of adult patients with deleterious or suspected deleterious *gBRCAm* human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

The FDA's Assessment:

FDA agrees with the summary of the U.S. regulatory actions and marketing history provided by the Applicant.

Regarding the May 19, 2020 regular approval, the FDA approved olaparib for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone. Efficacy was investigated in PROfound (NCT02987543), an open-label, multicenter trial randomizing (2:1) 256 patients to olaparib 300 mg twice daily and 131 patients to investigator's choice of enzalutamide or abiraterone acetate. All patients received a GnRH analog or had prior bilateral orchiectomy. Patients were divided into two cohorts based on their HRR gene mutation status. Patients with mutations in either *BRCA*1, *BRCA*2, or *ATM* were randomized in Cohort A (N=245); patients with mutations among 12 other genes involved in the HRR pathway were randomized in Cohort B (N=142); those with co-mutations (Cohort A gene and a Cohort B gene) were assigned to Cohort A. The major efficacy outcome of the trial was radiological progression-free survival (rPFS) (Cohort A). Additional efficacy outcomes included confirmed objective response rate (ORR) (Cohort A) in patients with measurable disease, rPFS (combined Cohorts A+B), and overall survival (OS) (Cohort A). A statistically significant improvement was demonstrated for olaparib compared to investigator's choice in Cohort A for rPFS with a median of 7.4 months vs 3.6 months (HR 0.34; 95% CI: 0.25, 0.47; p<0.0001), for OS with a median of 19.1 months vs. 14.7 months (HR 0.69; 95% CI: 0.50, 0.97, p=0.0175) and for ORR 33% vs 2% (p<0.0001). A statistically significant improvement for olaparib compared to investigator's choice was also

demonstrated for rPFS in Cohort A+B, with a median of 5.8 months vs. 3.5 months (HR 0.49; 95% CI: 0.38, 0.63; p<0.0001).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 2. Applicant – Summary of Key Regulatory History for PROpel

Date	Communication
May 24, 2018	FDA Type B meeting to obtain feedback on the results of Study 8 as a basis for an accelerated approval and on the study design for a proposed Phase III study (PROpel) as confirmatory evidence of the benefit of the combination of olaparib and abiraterone in mCRPC.
May 31, 2018	Type B meeting minutes received.
July 24, 2018	PROpel CSP submitted in the US.
September 29, 2020	FDA Type C meeting to obtain feedback on revisions to the PROpel study design and SAP, and registrational plans for olaparib and abiraterone in first-line mCRPC.
November 30, 2020	Type C meeting minutes received.
January 26, 2021	PROpel CSP version 2 (Table 5) and SAP submitted.
February 19, 2021	Proposed initial PSP for first-line prostate cancer submitted.
March 24, 2021	FDA email feedback to incorporate formal testing for OS at DCO1.
May 28, 2021	PROpel CSP version 3 (Table 5) and SAP (incorporating formal testing at DCO1) submitted.
June 04, 2021	Agreed PSP for first-line prostate cancer submitted.
November 09, 2021	Type B pre-submission meeting to obtain feedback on suitability of the proposed submission package.
February 04, 2022	Type B WRO to obtain feedback on the format and content of the planned sNDA.
May 18, 2022	Type B pre-submission meeting to obtain feedback on suitability of the proposed submission package.

The FDA's Assessment:

Overall, FDA agrees with the Summary of Key Regulatory History for PROpel provided by the Applicant.

On May 24, 2018, the Applicant met with the FDA in a Type B Meeting and proposed submission of an sNDA for accelerated approval for the combination of olaparib and abiraterone in patients with treatment-naïve mCRPC based on the results of Study 8 with PROpel as the confirmatory study. Study 8 randomized patients with mCRPC to abiraterone + either olaparib or placebo, and treated all patients, regardless of the presence of HRRm or *BRCA*m; study design is described in detail in 8.1.3 of this Assessment Aid. During the meeting, the FDA noted several concerns with the results of Study 8 and with the Applicant's plans to use the rPFS results to support an accelerated approval:

- FDA noted that Study 8 was a small study (n= 142 patients), and was exploratory in nature, which decreased the confidence in the results. This was detailed in the initial

IND review in June 2014, when the FDA noted "We consider your trial to be exploratory in nature. We encourage you to meet with the FDA should you reach the point in your drug development program where you wish to design a clinical trial to demonstrate efficacy." The type 1 error rate for testing the primary endpoint of rPFS was controlled at a level of two-sided 0.2. In general, when efficacy is evaluated for marketing approval, the type 1 error rate should be controlled at the level of 0.05 (two-sided).

- Although there have been two applications that used OS and rPFS as coprimary endpoints to support regular approval of abiraterone and enzalutamide in chemotherapy-naïve mCRPC, the approvals were not based on the improvement in rPFS alone, but rather on the totality of the data, including the data from trials of abiraterone and enzalutamide in the post docetaxel setting.

- FDA stated that the Sponsor should provide the BICR analysis, as well as the analysis of subsequent therapies, particularly in the absence of a large effect on overall survival.

- FDA expressed concern that the ~70% of patients without evaluable HRR deficiency might lead to imbalances between the two arms. The Sponsor acknowledged the need to evaluate the potential impact of HRR mutation status on efficacy of the combination, and the limitations of tissue testing in this disease setting and proposed to add plasma-based NGS testing as an alternative to tissue-based HRRm test.

The Applicant agreed to not pursue an accelerated approval based on Study 8 alone.
During the meeting, the Sponsor also discussed the basic outline of a proposed PROpel study design, a confirmatory study in the chemotherapy-naïve setting with investigator-assessed rPFS (with BICR sensitivity analysis) as a primary endpoint. The proposed trial planned to enroll non-biomarker selected patients with no prior abiraterone, enzalutamide, or apalutamide and would be stratified by site of metastases and prior taxane-treatment for hormone-sensitive disease. There would be one interim analyses at 324 events (89% power to show a difference in rPFS with a true HR of 0.68 – an 8-month increase), the final rPFS analysis would be conducted at 397 events (97% power for the above).

The Sponsor also met with the FDA in September 2020, to discuss a proposed PROpel study design amendment to add a co-primary endpoint of rPFS in the HRRm subgroup. The FDA disagreed with this amendment because HRR mutation status was not a stratification factor at randomization. The potential for imbalanced treatment assignment in this subgroup could result in an imbalance in known and unknown prognostic factors in this subpopulation and uninterpretable trial results. The FDA also stated that even if statistical significance were shown in the ITT population, it would be a review issue in terms of whether the results are driven by the HRRm, or potentially *BRCA*m-only, subpopulation. The FDA recommended the addition of

formal testing for OS at DCO1.

In November 2021, the Applicant presented the topline results of PROpel in a pre-NDA meeting with FDA and proposed to submit an sNDA based on DCO1 data from PROpel and supportive evidence from Study 8. FDA expressed concern that the totality of data did not clearly demonstrate a favorable risk-benefit at the interim analysis in the proposed population for first-line treatment patients with mCRPC, with add-on therapy. FDA strongly recommended that the Applicant should not submit an sNDA based on results of DCO1 analysis of PROpel.

In the pre-NDA meeting in May 2022 the FDA asked the Applicant to submit the topline results of the final OS analysis for PROpel (data cut-off date in October 2022). The Applicant agreed to submit these results within 5 months of the NDA submission (in November 2022) for FDA review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Four clinical investigators, Drs. Gary Buchschacher [Site 7822], Urban Emmenegger [Site 1004], Niven Mehra [Site 5001], and Cagatay Arslan [Site 7604], were inspected. The inspections found no significant regulatory deficiencies at the four investigator sites and the Applicant's submitted clinical data were verifiable with source records reviewed, with no inconsistencies identified. Overall, the inspection results reveal that PROpel appears to have been adequately conducted and the clinical data generated from these investigator sites are acceptable for this sNDA.

4.2. Product Quality

Refer to separate Product Quality review.

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

After determination that the approved population would be restricted to patients with *BRCA*m, two post-marketing commitments (PMCs) were agreed upon with the Applicant in order to

identify relevant patients with one of two companion diagnostic devices:

PMC#1:

Rationale: The indication for use for olaparib in combination with abiraterone is restricted to adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Current device labeling for the existing in vitro diagnostic device using tissue samples only includes data for the evaluation of homologous recombination repair gene alterations for treating patients with mCRPC with olaparib monotherapy and does not include an indication for the combination of olaparib plus abiraterone for patients with mCRPC, whose tumors harbor only *BRCA*1 or *BRCA*2 mutations

Language: Conduct an analytical and clinical validation study using clinical trial data, adequate to support the availability of an in vitro diagnostic device using tissue samples that is essential to the safe and effective use of olaparib plus abiraterone for patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC), whose tumors harbor *BRCA*1 or *BRCA*2 mutations.

PMC#2:

Rationale: The indication for use for olaparib in combination with abiraterone is restricted to adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Current device labeling for the existing in vitro diagnostic device using circulating tumor DNA (ctDNA) derived from plasma only includes data for the identification of *BRCA*1, *BRCA*2, and *ATM* alterations for treating patients with mCRPC with olaparib monotherapy and does not include an indication for the combination of olaparib plus abiraterone for patients with mCRPC whose tumors harbor only *BRCA*1 or *BRCA*2 mutations.

Language: Conduct an analytical and clinical validation study using clinical trial data, adequate to support the availability of an in vitro diagnostic device using ctDNA samples from plasma that is essential to the safe and effective use of olaparib plus abiraterone for patients diagnosed with mCRPC, whose ctDNA samples harbor *BRCA*1 or *BRCA*2 mutations.

Full details regarding the testing strategy for HRRm and *BRCA*m for patients on PROpel and trial results by mutational status are discussed fully in Section 8 of this Assessment Aid.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

The FDA's Assessment:

The Applicant submitted literature publications and nonclinical study reports to support changes in section 12.1 of the PI to support the mechanism of action for the proposed indication. Applicant-funded publications were used to support labeling.

- Treatment of LNCAP prostate cancer cells with olaparib and an androgen receptor inhibitor resulted in statistically significant increase in γH2AX nuclear accumulation, a marker of DNA damage, when compared to olaparib alone.
- Treatment of C4-2 prostate tumor cell line with hydrogen peroxide to induce DNA damage, resulted in increased DNA binding of the AR and PARP1. Treatment of cells with olaparib or PARP1 siRNA resulted in decreased AR DNA binding.
- The combination of olaparib and AR inhibition resulted in increased cytotoxicity of C4-2 prostate tumor cell line, in vitro (5).
- The anti-tumor effect of olaparib in combination with an androgen receptor inhibitor was evaluated in the LNCAP subcutaneous metastatic prostate cancer xenograft model. Treatment with the combination resulted in 98% tumor growth inhibition, and the effect was statistically significant when compared to vehicle control.

Overall, the submitted nonclinical data support the proposed mechanism of action for the combination and the approval of Lynparza for the proposed indication.

X X

Primary Reviewer
Haw-Jyh Chiu

Team Leader
Tiffany Ricks

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant is seeking a new indication for olaparib in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC. Results from PROpel were included in this submission to support the proposed indication. Refer to Section 1.3.
Patients received either Olaparib 300 mg orally twice daily, the recommended dosage for the approved olaparib monotherapy indications, or placebo in combination with abiraterone 1000 mg orally once daily and prednisone or prednisolone 5 mg orally twice daily in addition to either a GnRH analog or previous bilateral orchiectomy. The use of olaparib 300 mg bd in combination with abiraterone 1000 mg qd was also supported by safety and PK data from Study D081DC00008.

PK sampling was performed in a subset of patients (about 50 patients/treatment arm) after multiple dosing in PROpel study. Steady state PK exposure parameters of olaparib in mCRPC patients when dosed in combination with abiraterone in PROpel were similar to olaparib steady state exposures in other monotherapy studies. Steady state exposures for abiraterone were similar between the two treatment arms.

These results demonstrated that there that co-administration of olaparib did not affect the PK exposure parameters of abiraterone. There appeared to be no drug interaction between olaparib and abiraterone, as there was no sign of increased abiraterone exposure with olaparib or vice versa.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data/The Applicant's Position:

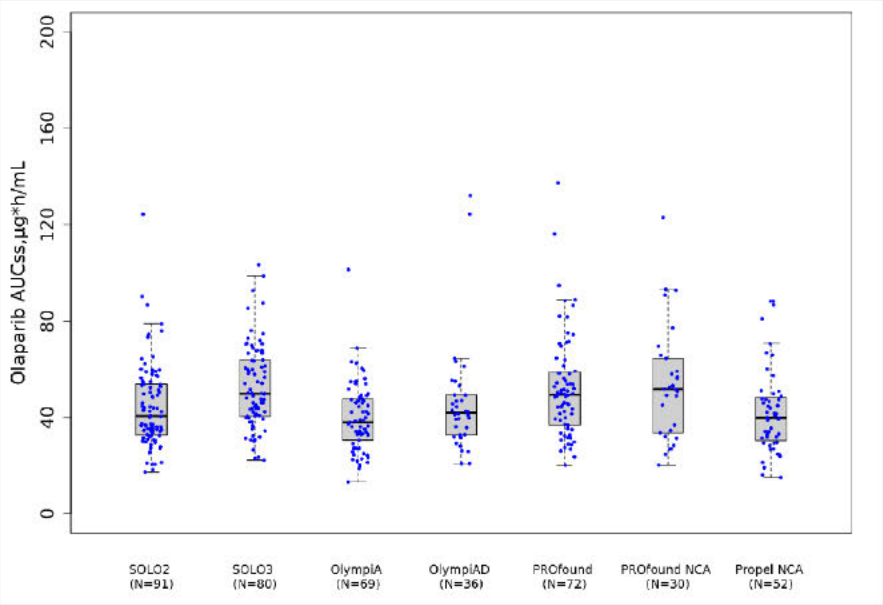
In both Study 8 and PROpel, there was no evidence of a DDI between olaparib and abiraterone. PK comparison across Phase III studies indicated that co-administration of abiraterone did not affect the PK of olaparib. Comparison of PK results within the study (PROpel) indicated that co-administration of olaparib did not affect the PK exposure parameters of abiraterone.

The FDA's Assessment:
We agree with the Applicant. Co-administration of olaparib did not affect the PK exposure parameters of abiraterone in PROpel.

The steady state exposures based on $C_{max,ss}$, AUC_{ss} or $C_{min,ss}$ for olaparib in PROpel were similar

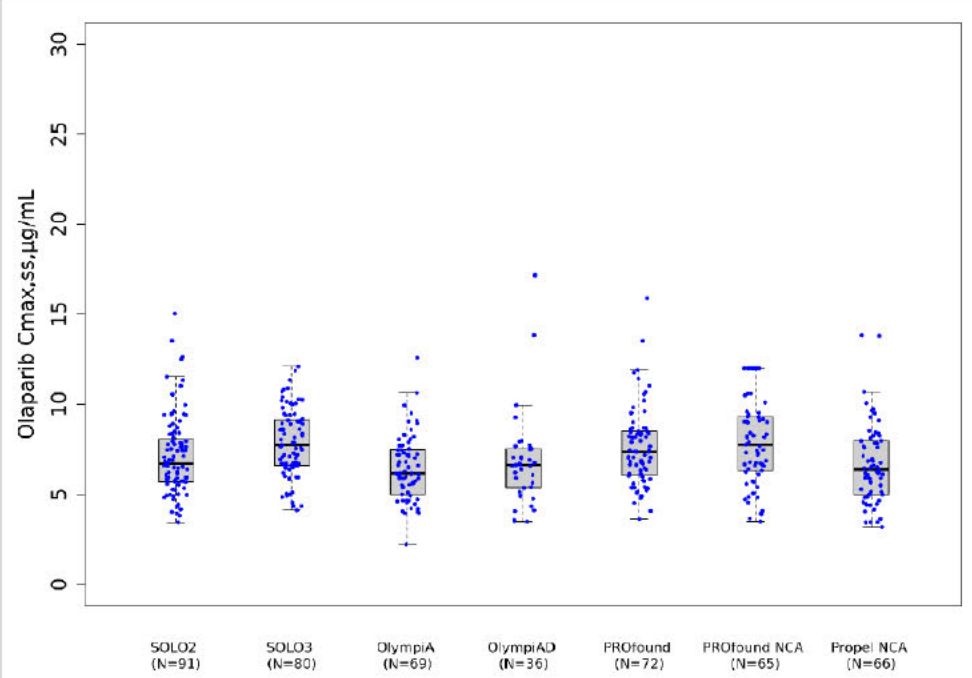
to olaparib steady state exposures in SOLO2, OlympiA and OlympiAD and are slightly lower to those in SOLO3 and PROfound. Box plots of olaparib AUC_{ss} and $C_{max,ss}$as stratified by phase III studies are shown in Figure 1, and Figure 2, respectively.

Figure 1. Comparison of olaparib AUCs in phase 3 studies by Box plot



Source: Applicant's Figure 2.7.2.5.1, Module 5.3.5.3; Symbols represent individual AUCss values

Figure 2. Comparison of olaparib Cmax,ss in phase 3 studies by Box plot



Source: Applicant's Figure 2.7.2.5.2, Clinical Pharmacology Outputs, Module 5.3.5.3 Where: Symbols represent individual Cmax,ss values

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data/The Applicant's Position:
Please refer to Section 6.3.2.2.

The FDA's Assessment:
FDA agrees with the Applicant regarding the proposed dosing regimen of olaparib 300 mg bid in combination with abiraterone 1000 mg qd and prednisone or prednisolone 5 mg bid. The PROpel data, supported by Study 8, demonstrated that the proposed dosing regimen provides a clinically meaningful benefit in the mCRPC patients with BRCA mutations.

6.2.2.2. Therapeutic Individualization

No new information is provided in the current submission.

6.2.2.3. Outstanding Issues

Data/The Applicant's Position:
None.

The FDA's Assessment:
There are no outstanding issues from clinical pharmacology viewpoint.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
Reference is made to the original NDA and supplemental NDAs previously submitted to the FDA (Table 1). New/updated information provided in this submission is summarized here.

In PROpel, PK sampling was performed in a subset of patients (approximately 50 patients per treatment group), at specific time points after multiple dosing. The PK results from PROpel confirmed that there were no relevant PK based DDIs between olaparib and abiraterone. The dose recommendation and description of the PK of abiraterone when used as a monotherapy would be applicable when abiraterone is used in combination with olaparib. Similarly, the dose recommendation and description of the PK of olaparib when used as a monotherapy would be applicable when olaparib is used in combination with abiraterone.

The Applicant's Position:
PK comparison across Phase III studies, indicated that co-administration of abiraterone did not affect the PK of olaparib in PROpel.

Comparison of PK results within the study (PROpel) indicated that co-administration of olaparib did not affect the PK exposure parameters of abiraterone. Based on the clearance pathways of abiraterone and olaparib and their known in vitro and in vivo DDI profiles, no clinically relevant DDI between olaparib and abiraterone is expected. Based on limited data, there appeared to be no DDI between olaparib and abiraterone; there was no sign of increased abiraterone exposure with olaparib and vice versa.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data/The Applicant's Position:
Yes. Evidence of effectiveness of the individual drugs, olaparib and abiraterone, has been submitted previously. No new information concerning exposure-response is provided in this submission.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:
Efficacy results are summarized for PROpel in Section 8.1.2, and for Study 8 in Section 8.1.4. Safety results are summarized in Section 8.2.4.

The Applicant's Position:
Yes.

The proposed dosing regimen is olaparib 300 mg bid in combination with abiraterone 1000 mg qd and prednisone or prednisolone 5 mg bid. It is recommended that treatment be continued until progression of the underlying disease. Treatment may be interrupted to manage AEs and dose reduction can be considered. The recommended dose reduction of olaparib is to 250 mg bid. If a further dose reduction is required, then reduction to 200 mg bid is recommended.

The proposed dosing regimen of abiraterone is as recommended for the treatment of patients with mCRPC (Zytiga USPI). Olaparib 300 mg bid was selected as the dose for use in combination with abiraterone in the safety run-in, Part A, of Study 8 (Section 8.1.3). It is also the dose recommended for indications for which olaparib is approved as a monotherapy.

The PROpel data, supported by Study 8, demonstrate that the proposed dosing regimen provides a clinically meaningful benefit, irrespective of biomarker status, for both treatment-naïve and pre-treated patients in the mCRPC setting.

The safety profile of the proposed dosing regimen was well characterized in PROpel and appears to be consistent with the known safety profiles of olaparib and abiraterone monotherapies, in the context of this patient population. The safety profile is further supported

by data from the olaparib and abiraterone pool, which is consistent with PROpel and overall the safety data demonstrate that the combination is tolerable and acceptable for the treatment of mCRPC.

Overall, the data from PROpel and Study 8 support the proposed dosing regimen in patients with mCRPC.

The FDA's Assessment:
FDA agrees with the Applicant for the proposed dosing regimen of olaparib 300 mg bid in combination with abiraterone 1000 mg qd and prednisone or prednisolone 5 mg bid.
The PROpel data, supported by Study 8, demonstrated that the proposed dosing regimen provides a clinically meaningful benefit in the mCRPC patients with BRCA mutations.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data/The Applicant's Position:
Yes. The current labelling for olaparib and abiraterone remains applicable in this respect. No new information concerning exposure in subpopulations based on intrinsic patient factors is provided in this submission.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.3.2.4 Are there clinically relevant food-drug or DDIs, and what is the appropriate management strategy?

Data:
See Section 6.3.1.

The Applicant's Position:
Yes. The current labelling for olaparib and abiraterone remains applicable in this respect. There is no evidence of a clinically relevant DDI between olaparib and abiraterone.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

X	X
Primary Reviewer	Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 3. Applicant – Listing of Clinical Trials Relevant to this sNDA

Trial identity/ NCT number	Trial design	Regimen/ schedule/ route	Study endpoints	Treatment duration/ follow up	Number of patients randomized	Study population	Number of centers and countries
Controlled Studies to Support Efficacy and Safety							
D081SC0001 (PROpel)/ NCT03732820	Phase III double-blind, randomized, placebo-controlled, multicenter study	Olaparib 300 mg or placebo orally bid + abiraterone acetate 1000 mg orally qd + prednisone/prednisolone 5 mg orally bid	Primary: rPFS (investigator) Key Secondary: OS Other Secondary: TFST, TTPP, time to SSRE, PFS2, time to opiate use for cancer pain, HRQoL, and subgroup analyses by HRR gene mutation status	Until objective radiological progressive disease as assessed by the investigator (using RECIST 1.1 for soft tissue lesions and PCWG-3 criteria for bone lesions), unacceptable toxicity, or any other treatment discontinuation criterion met or patient withdrew consent	796 overall: 399 olaparib +abiraterone 397 placebo +abiraterone	Patients with mCRPC. Patients may have previously received docetaxel at the mHSPC stage. No prior abiraterone. Any other NHAs must have been stopped ≥ 12 months prior to randomization	126 centers in 17 countries (excluding China)

Trial identity/ NCT number	Trial design	Regimen/ schedule/ route	Study endpoints	Treatment duration/ follow up	Number of patients randomized	Study population	Number of centers and countries
D081DC00008 (Study 8)/ NCT01972217	Phase II multicenter study Part A: open-label dose finding safety run-in Part B: double-blind, randomized, placebo-controlled	Part B: olaparib 300 mg or placebo orally bid + abiraterone acetate 1000 mg orally qd + prednisone/prednisolone 5 mg orally bid	Part B: Primary: rPFS (investigator) Secondary: PFS2, TFST, TSST, OS, ORR, DoR, PSA response, CTC conversion rate, and subgroup analyses by HRR mutation status	Until disease progression, a time when the investigator considered that clinical benefit was no longer derived, or any other treatment discontinuation criterion met	Part B: 142 overall: 71 olaparib +abiraterone 71 placebo +abiraterone	Patients with mCRPC who received up to two lines of prior chemotherapy including docetaxel	Part B: 36 centers in 11 countries

The Applicant's Position:
The proposed application is based on positive data from the pivotal study, PROpel (D081SC00001), and supportive evidence from Study 8 (D081DC00008) (Table 3).

An overview of studies included in the safety dataset is presented in Section 8.2.1.

The FDA's Assessment:
The Applicant submitted the efficacy and safety results of PROpel study as the basis for this sNDA and submitted the results from Study 8 as supportive evidence. FDA agrees with the summary of information provided by the Applicant for these two clinical trials.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. PROpel Design

Trial Design

The Applicant's Description:
PROpel was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, global Phase III study of olaparib in combination with abiraterone in patients with mCRPC (Section 1.3, PROpel CSP [Appendix 16.1.1, PROpel CSR, Module 5.3.5.1]).

Following the completion of global enrolment, patients were randomized at sites in China. Data from the China cohort will be analyzed separately from the global cohort.

As abiraterone is indicated in combination with prednisone or prednisolone for the treatment of patients with mCRPC, prednisone or prednisolone 5 mg bid was administered with abiraterone in both arms of PROpel. Prednisone or prednisolone with abiraterone is hereafter referred to as abiraterone in this document.

Olaparib monotherapy is approved for the treatment of patients with HRR gene-mutated mCRPC. In PROpel, olaparib in combination with abiraterone was investigated in a biomarker unselected population (ie, regardless of HRR status). This is largely based on the observation that PARP inhibition plus androgen deprivation could significantly reduce the growth of prostate cancer cells independent of HRR gene mutation status, in both in vitro and in vivo model systems (Schiewer et al 2012). Further details are provided in Section 2, PROpel CSP (Appendix 16.1.1, PROpel CSR, Module 5.3.5.1).

Placebo plus abiraterone was considered an appropriate control arm because abiraterone was an established standard of care in the US at the time of study planning. This choice of control is also supported by evidence from Study 8 (Section 8.1.4).

The diagnosis and management of patients in PROpel was in line with the NCCN, ASCO, and ESMO treatment guidelines and representative of clinical practice, which includes treatment with abiraterone. The intended patient population treated in PROpel included patients with confirmed prostate adenocarcinoma and metastatic status at the mCRPC stage (first-line setting). Both symptomatic and asymptomatic/mildly symptomatic patients were eligible as well as patients with visceral metastases (except brain metastases) as long as they were considered candidates for abiraterone by the investigator. All patients randomized in the study were selected based on the following key criteria:

- Treatment naïve in the mCRPC setting, ie, should not have received any cytotoxic chemotherapy, NHA, or other systemic treatment (approved drugs or experimental compounds). ADT was an exception.
    - Treatment with first-generation antiandrogen agents (eg, bicalutamide, nilutamide, and flutamide) before randomization was allowed, but there must have been a washout period of 4 weeks.
    - Docetaxel treatment was allowed during neoadjuvant/adjuvant treatment for localized prostate cancer and at mHSPC stage, as long as no signs of failure or disease progression occurred during or immediately after such treatment.
    - Prior to the mCRPC stage, treatment with second-generation antiandrogen agents (except abiraterone) without PSA progression/clinical progression/radiological progression during treatment was allowed, provided the treatment was stopped at least 12 months before randomization.
- Had ongoing androgen deprivation with gonadotropin-releasing hormone analogue or bilateral orchiectomy.
- Candidate for abiraterone therapy with documented evidence of progressive disease.
- Had normal organ and bone marrow function and an ECOG 0-1 performance status.

The study treatments administered were olaparib 300 mg or placebo orally bid, each in combination with abiraterone 1000 mg orally qd and prednisone or prednisolone 5 mg bid. The dosing regimen of abiraterone was as recommended for the treatment of patients with mCRPC (Zytiga USPI). The use of olaparib 300 mg bid in combination with abiraterone 1000 mg qd was supported by safety and PK data from Study 8. Olaparib 300 mg bid was the dose selected for Study 8, Part B, based on the results of Part A, the safety run-in. No DLT had been reported at this dose of olaparib in combination with abiraterone 1000 mg qd in Part A, and there was no evidence of changes in exposure to olaparib or abiraterone when co-administered. At the time of Study 8, olaparib 300 mg bid was being used in the monotherapy maintenance setting in the ovarian cancer Phase III program.

All patients were centrally assigned to randomized study treatment using a randomization and trial supply management system (interactive response technology). It was planned to randomize approximately 720 patients in a 1:1 ratio to receive either olaparib or placebo, each combined with abiraterone and prednisone or prednisolone. Randomization was stratified by:
• Site of distant metastases: bone only vs visceral vs other.
• Docetaxel treatment at mHSPC stage: yes vs no.

The study was conducted in a double-blind manner. The study medications were identical and presented in the same packaging. Treatment codes and results were kept strictly within AstraZeneca. Unblinding to treatment allocation was only permitted where necessary, eg, for packaging of study drug, or patient safety. Details are provided in Section 6.3.1, PROpel CSP (Appendix 16.1.1, PROpel CSR, Module 5.3.5.1).

Permitted dose reductions of olaparib to manage AEs, if the patient developed moderate renal impairment, or if the patient had to start taking a strong or moderate CYP3A inhibitor, are detailed in Section 6.6.1, PROpel CSP (Appendix 16.1.1, PROpel CSR, Module 5.3.5.1).

An external IDMC for the study included therapeutic area experts, a cardiologist, and a statistician. The committee reviewed accumulating study safety data, and efficacy data from the interim DCO. After review, the committee recommended whether the study should continue unchanged, be terminated, or be modified in any way.

The schedule of assessments is presented in Section 1.1, PROpel CSP (Appendix 16.1.1, PROpel CSR, Module 5.3.5.1).

Consumption of grapefruit juice was prohibited while on olaparib or placebo therapy. Patients were required to fast from at least 2 hours before until 1 hour after each dose of abiraterone, due to an effect of food on absorption. Water was allowed as desired.

Concomitant use of CYP3A4 inducers and CYP2D6 substrates with abiraterone had to be avoided (Zytiga USPI). Other prohibited concomitant medications during study treatment were anticancer therapy, live virus vaccines, and live bacterial vaccines. Restricted concomitant medications are listed in Section 6.5, PROpel CSP (Appendix 16.1.1, PROpel CSR, Module 5.3.5.1).

Treatment compliance in the study was measured by study site staff making tablet counts at regular intervals during treatment.

Study treatment continued until radiological progressive disease, or any other criterion defined in Section 7.1, PROpel CSP (Appendix 16.1.1, PROpel CSR, Module 5.3.5.1) was met. Once the patient discontinued all study treatments, assessments for study treatment discontinuation,

30-day follow-up, and survival follow-up were conducted as per Section 1.1, PROpel CSP (Appendix 16.1.1, PROpel CSR, Module 5.3.5.1).

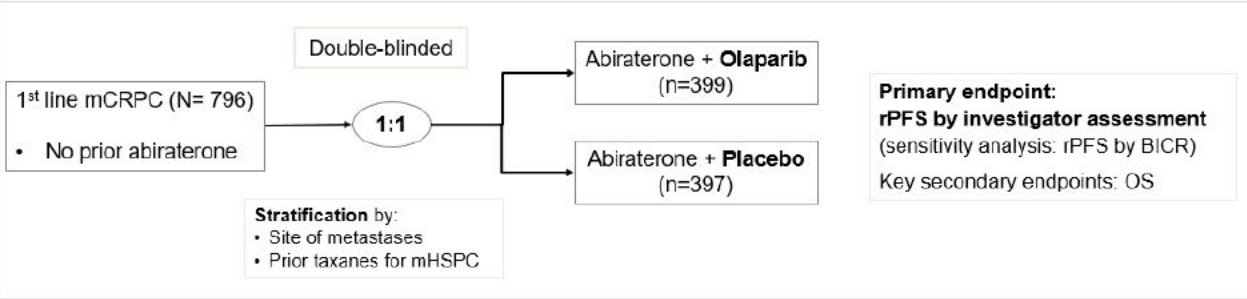
The FDA's Assessment:
FDA agrees with Applicant's description of the PROpel study design.

PROpel was a double-blinded, randomized, placebo-controlled clinical trial, which randomized 796 patients with mCRPC in a 1:1 ratio to receive abiraterone in combination with olaparib or placebo.

The primary endpoint of PROpel was rPFS by investigator assessment with a plan to assess rPFS by BICR as a sensitivity analysis. The key secondary endpoint was overall survival. The study was not stratified by tumor mutation status for *BRCA* or other HRR genes; and there was no pre-specified alpha-controlled analysis by tumor mutation status. HRR (including *BRCA*) mutation status was determined retrospectively, after randomization (and prior to treatment), using tumor tissue and ctDNA tests.

All patients were required to have treatment with medical or surgical androgen deprivation (i.e. GnRH analog or prior orchiectomy).

Figure 3. PROpel Study schema



Crossover was not allowed on-study in PROpel.

Study Endpoints

The Applicant's Description:

The primary endpoint was rPFS as assessed by the investigator using RECIST 1.1 (soft tissue) and PCWG-3 (bone). rPFS was defined as the time from randomization until the earlier date of radiological progression or death (by any cause in the absence of progression), regardless of

whether the patient withdrew from randomized therapy or received another anticancer therapy prior to progression.

In accordance with current regulatory guidelines, and precedent, prolonged PFS can constitute clinical benefit, and therefore support regulatory approval if the effect is of sufficient magnitude and duration (FDA Guidance 2018). PFS provides a relative assessment of treatment benefit of an experimental agent and is not influenced by the impact of post-progression therapy. The FDA agreed with rPFS as the primary endpoint at the Type B meeting on May 24, 2018 (Table 2).

The key secondary endpoint was OS, defined as the time from randomization to death from any cause. Assessments for survival were conducted every 12 weeks following objective disease progression or treatment discontinuation.

Subsequent therapies can have confounding effects on OS analyses, resulting in challenges in data interpretation. Crossover was not permitted within the PROpel study design. However, upon disease progression, patients were able to receive a PARP inhibitor outside of the study through other clinical trials or commercially available products.

TFST and TTPP were removed as key secondary endpoints in Version 2.0 of the PROpel CSP, in order to allow greater focus on OS as an important regulatory endpoint in this setting.

The FDA's Assessment:
FDA agrees with Applicant's description of the primary endpoint of rPFS by investigator and the key secondary endpoint of OS.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Three DCOs were planned for PROpel. This document reports data for DCO1 (interim rPFS analysis) and updated OS data for DCO2 (final rPFS analysis). DCO1 (interim rPFS analysis) was planned to be conducted when approximately 379 progression or death (by any cause in the absence of progression) events had accrued in 796 patients (47.6% maturity). The actual DCO1 was set as July 30, 2021, approximately 33 months after the first patient was randomized, with 394 rPFS events (49.5% maturity) available at the time of the analysis. A comprehensive SAP (Edition 4.0) was developed and finalized before DCO1. The DCO2 (final rPFS analysis) was 14 March 2022, with 457 rPFS events (57.4% maturity) and 319 OS events (40.1% maturity) available at the time of analysis.

Statistical Hypotheses and Multiplicity Strategy

The two hypotheses to be tested at the three DCOs were:

Primary endpoint, rPFS	H_{a0}: HR = 1	vs	H_{a1}: HR < 1
Key secondary endpoint, OS	H_{b0}: HR = 1	vs	H_{b1}: HR < 1

The 1-sided alpha of 0.025 was fully allocated to H_{a0} (rPFS). If the result for rPFS was statistically significant, H_{b0} (OS) was to be tested in a hierarchical fashion. A multiplicity testing procedure based on the graphical approach in group sequential trials of Maurer and Bretz (Maurer and Bretz 2013), analogous to a simple sequential gatekeeping method, strongly controlled the overall familywise 1-sided error rate of 2.5%.

It was planned to test rPFS at DCO1 and DCO2, and OS at all three DCOs. For each endpoint with an interim analysis, the O'Brien and Fleming spending function (Lan and DeMets 1983, O'Brien and Fleming 1979) calculated based upon actual observed events, was to be used to strongly control the overall type 1 error, with the restriction that alpha spend for the OS interim analysis at DCO1 would not exceed 0.0005 (1-sided).

OS testing was added at DCO1 in Version 3.0 of the PROpel CSP, at the FDA's request (Table 2).

Censoring
Patients who had not progressed and not died at the time of analysis were censored at the earliest date of their last evaluable RECIST assessment or bone scan assessment that showed non-progressive disease. If the patient progressed or died immediately after two or more consecutive missed visits, the patient was censored at the time of the earliest of either the previous RECIST 1.1 assessment or previous bone scan assessment prior to the two consecutive missed visits.

Analysis of the Primary Endpoint
The primary endpoint of rPFS was analyzed using a log-rank test stratified by the following factors:
- Site of distant metastases: bone only vs visceral vs other.
- Docetaxel treatment at mHSPC stage: yes vs no.

The HR and corresponding 95% CI were estimated using a Cox Proportional Hazards Model (with ties = Efron and the stratification variables as covariates) and the 2-sided CI calculated using a profile likelihood approach.

In addition to the stratification factors, subgroups of interest analyzed for rPFS included:

• HRRm status subgroup (HRRm, non-HRRm, unknown) based on a ctDNA-based test (FoundationOne Liquid CDx).
• HRRm status subgroup (HRRm, non-HRRm, unknown) based on a tissue test (FoundationOne CDx).
• ECOG performance status at baseline (0 or 1).
• Age at randomization (< 65, ≥ 65 years).
• Region (Asia, Europe, North and South America).
• Race (White, Black/African-American, Asian, Other).
• Baseline PSA (above/below median baseline PSA across both treatment groups).
If there were < 5 events in either treatment arm per subgroup, analyses were not presented.

A sensitivity analysis was conducted using rPFS as assessed for all patients by BICR, per RECIST 1.1 and PCWG-3 criteria. Supportive analyses included assessment of evaluation-time bias, attrition bias, censoring bias, sensitivity analysis using unequivocal clinical progression in addition to radiological progression, sensitivity analysis for confirmation of bone progression, and sensitivity analysis censoring patients with subsequent therapy or discontinuation of study drug prior to progression.

Analysis of the Key Secondary Endpoint
OS was analyzed using the same methods as for the rPFS analysis, stratified in accordance with the primary pooling strategy.

Analysis Populations
The FAS was used as the primary population for reporting efficacy data. This comprised all patients randomized into the study, analyzed according to randomized treatment (ITT principle).

Changes to the Planned Analyses
Important changes to the planned analyses are summarized in Table 4. Other changes are described in the PROpel CSR, Section 9.9.2.

Table 4. Applicant – Changes to Planned Analyses in PROpel

Timing of change	Details of change
Before unblinding of study data	• Key secondary objective amended to be solely overall survival (OS; all comers); thus, the multiplicity strategy was amended to remove TFST and TTPP. • Subgroup analyses and sensitivity analyses added/clarified for the primary endpoint (rPFS); subgroup analysis added for the key secondary objective (OS). • Sample size determination, populations for analyses and statistical analyses (including multiplicity strategy) updated in line with changes to endpoints. • Added formal testing of OS at DCO1; alpha spending for the 3 analyses of OS was adjusted. • Update to rPFS censoring rules to censor at the time of the earliest date of the patient's last evaluable RECIST 1.1 assessment or bone scan assessment that showed non-progressive disease.

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan. Per study design, PROpel was only powered adequately for the rPFS analysis in ITT (power =98.2% with target effect size of 8 months improvement of rPFS). OS is the only key secondary endpoint in the testing plan. All the other secondary endpoints are considered exploratory, and no statistical inference could be made. Additionally, final OS analysis (DCO3) was planned to be conducted when approximately 360 deaths had accrued in 796 patients (45% maturity). The statistical power for final OS analysis was only 55.1% with a target effect size of 9 months improvement of OS. On November 16, 2022, the FDA received the final OS analysis result (DCO3, data cut-off 10/12/2022) with a total of 381 deaths (47.9% maturity).

Per the SAP, the O'Brien and Fleming spending calculated based upon actual observed events were to be used for interim analysis of rPFS and OS.

Although not a stratification factor, exploratory subgroup analyses for rPFS were pre-planned by HRRm status. No subgroup analyses were pre-planned based on *BRCA* mutation status.

Protocol Amendments

The Applicant's Description:

Important amendments to the CSP are summarized in Table 5. Other amendments are described in Section 9.9.1, PROpel CSR, Module 5.3.5.1.

Table 5. Applicant – Important Protocol Amendments in PROpel

Protocol version / date of internal approval	Details of change
Version 2.0 / January 05, 2018 (after start of participant recruitment)	• Key secondary objective amended to be solely OS (all comers). • A China cohort was added to the study. • Inclusion of risk mitigation measures to provide sites with guidance related to the COVID-19 pandemic that could be implemented if a patient was unable to visit a study site. • Update to concomitant therapy. • Removed restrictions for palliative radiotherapy.
Version 3.0 / May 14, 2021 (after start of participant recruitment)	•Added formal testing of OS at DCO1. • Supply of Olaparib after the final DCO was clarified.

The FDA's Assessment:
FDA agrees with the Applicant's description of important protocol amendments in PROpel.

8.1.2. PROpel Results

Compliance with Good Clinical Practices

The Applicant's Position:
The CSP and patient informed consent documents were approved by an IRB/IEC and regulatory authorities where applicable before study initiation. Substantial changes to the CSP required IRB approval. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

The FDA's Assessment:
FDA has no additional comments.

Financial Disclosure

The Applicant's Position:

See Section 19.2.

The FDA's Assessment:
FDA has no additional comments.

Patient Disposition

Data:

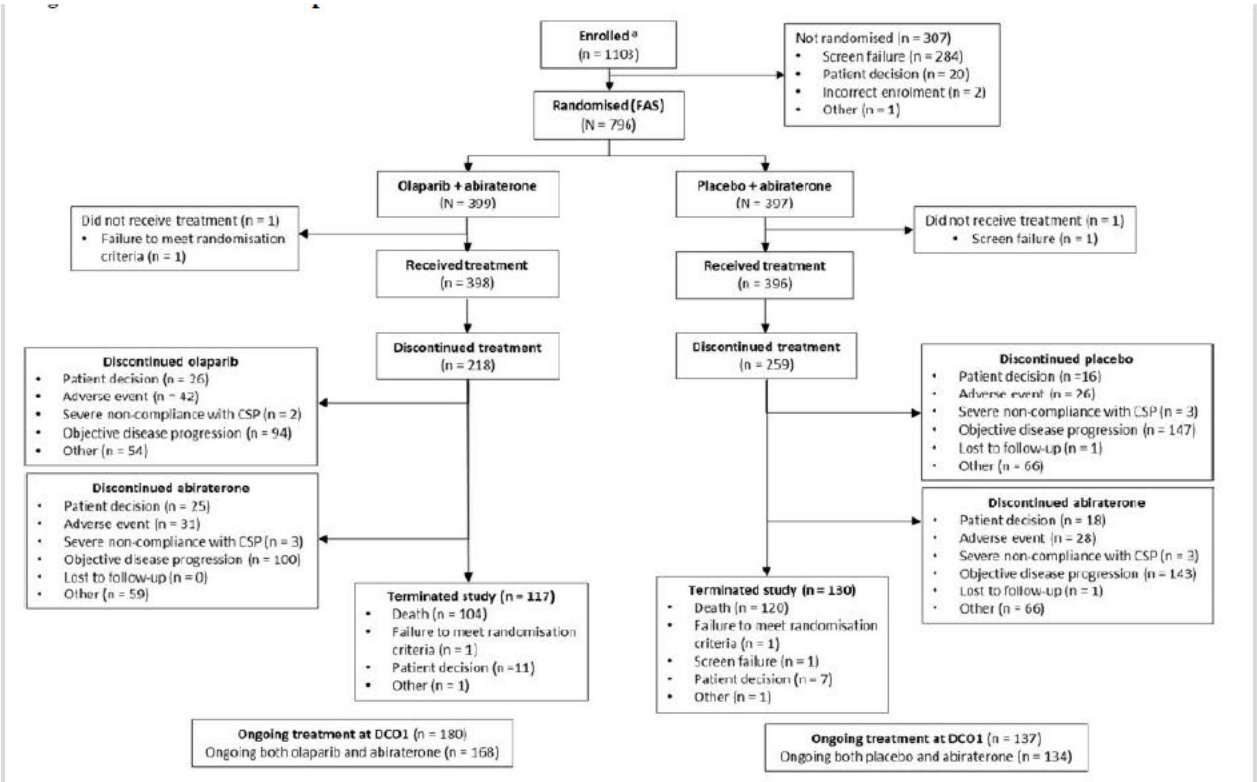
In total, 796 patients were randomized at 126 sites in 17 countries (excluding China): 251 (31.5%) in North and South America, 350 (44.0%) in Europe, and 195 (24.5%) patients in Asia.

Of 796 patients randomized into the study, 794 (99.7%) patients received their allocated treatment; 1 patient in the olaparib+abiraterone arm and 1 patient in the placebo+abiraterone arm did not receive treatment. At DCO1 (30 Jul 2021), a lower proportion of patients had discontinued study treatment in the olaparib+abiraterone arm (54.8%) than in the placebo+abiraterone arm (65.4%). The most common primary reason for discontinuation of olaparib/placebo was objective disease progression, reported less frequently in the olaparib+abiraterone arm (23.6%) than in the placebo+abiraterone arm (37.1%). Adverse event was the primary reason for discontinuation of olaparib/placebo in a higher proportion of patients in the olaparib+abiraterone arm (10.6%) than in the placebo+abiraterone arm (6.6%).

The Applicant's Position:
There were no notable differences in patient disposition between the 2 treatment arms.

The FDA's Assessment:
FDA agrees with the Applicant's description of patient disposition in the PROpel study. Below is the figure for patient disposition.

Figure 4. Patient Disposition



Source: Figure 2 from CSR

Protocol Violations/Deviations

Data:

A total of 7.5% of patients (7.3% in the olaparib+abiraterone arm vs 7.8% in the placebo+abiraterone arm) were defined as having at least one important deviation in the study. The most frequent important deviation was "failed inclusion criteria: metastatic status defined as at least one documented metastatic lesion on either a bone scan or a CT/MRI scan" (reported for 10 patients [1.3%] overall).

The Applicant's Position:

The low number of important deviations reported in PROpel was unlikely to have influenced the overall study conclusions, which are considered robust and representative of the overall study data. If more than 10% of patients in either treatment arm had important protocol deviations that could affect the efficacy, this would trigger a sensitivity analysis to assess deviation bias. The proportion of patients who had at least 1 important deviation that could trigger this sensitivity analysis was 3.5% on the olaparib+abiraterone arm and 3.3% in the placebo+abiraterone arm. As both of these were below 10% and so did not meet the criteria to initiate the analysis, this analysis was not performed.

The last patient randomized in PROpel occurred on March 11, 2020 at the start of the global

COVID-19 pandemic. The impact of COVID-19 on the study conduct, data collection, and patient safety is limited in magnitude and so the ascertainment of the majority of the efficacy and safety endpoints continued without interruptions. Overall, the COVID-19 pandemic is not considered to have had any meaningful impact on the quality of the study or the interpretation of the results.

The FDA's Assessment:

FDA agrees with the Applicant's position that the number/proportion of protocol deviations in PROpel was low and symmetric between the treatment arms. Important protocol deviations are summarized in the table below:

Table 6. Important Protocol Deviations (ITT)

Important protocol deviations*	Number (%) of patients		
	Olaparib 300 mg BID + abiraterone 1000 mg QD (N = 399)	**Placebo BID + abiraterone 1000 mg QD (N = 397)**	**Total (N = 796)**
Number of patients with at least 1 important deviation	29 (7.3)	31 (7.8)	60 (7.5)
Failed inclusion criteria: histologically or cytologically confirmed prostate adenocarcinoma	1 (0.3)	0	1 (0.1)
Failed inclusion criteria: metastatic status defined as at least one documented metastatic lesion on either a bone scan or a CT/MRI scan	3 (0.8)	7 (1.8)	10 (1.3)
Failed inclusion criteria: first line mCRPC	5 (1.3)	3 (0.8)	8 (1.0)
Met exclusion criteria: clinically significant cardiovascular disease	3 (0.8)	5 (1.3)	8 (1.0)
Met exclusion criteria: prior revascularization procedure (significant coronary, carotid, or peripheral artery stenosis)	2 (0.5)	5 (1.3)	7 (0.9)
Randomized but did not receive study treatment (olaparib or placebo)	1 (0.3)	1 (0.3)	2 (0.3)
Randomized but received randomized study treatment (olaparib or placebo) at an incorrect dose	1 (0.3)	1 (0.3)	2 (0.3)
Randomized but received an alternative study treatment (olaparib or placebo) to that which they were randomized; includes patients who received study treatment without IxRS	2 (0.5)	0	2 (0.3)
Randomized but received other steroid (eg, dexamethasone) than prednisone/prednisolone to support abiraterone treatment prior to study treatment discontinuation	4 (1.0)	5 (1.3)	9 (1.1)
Received prohibited anti-cancer medication/therapy (chemotherapy) during study treatment period	2 (0.5)	1 (0.3)	3 (0.4)
Received prohibited anti-cancer medication/therapy (radiotherapy (except palliative) during study treatment period	1 (0.3)	2 (0.5)	3 (0.4)
Received prohibited anti-cancer medication/therapy (other novel agents) during study treatment period	0	1 (0.3)	1 (0.1)
Met study treatment interruption or discontinuation criteria but continued study treatment and potentially had major impact to patient safety according to clinical judgement	3 (0.8)	0	3 (0.4)
Baseline tumor assessment more than 42 days before start	0	1 (0.3)	1 (0.1)

date of randomized treatment			
No baseline tumor assessment	1 (0.3)	0	1 (0.1)
Number of patients with at least 1 important deviation triggering a sensitivity analysis (deviation bias)	14 (3.5)	13 (3.3)	27 (3.4)
Number of patients with at least 1 important deviation related to the COVID-19 pandemic	0	0	0

* Important deviations before the start of treatment and during treatment, as defined in the PROpel Non-compliance Handling Plan.

Demographic and Other Baseline Characteristics

Data:

The median age overall was 69.0 years and the majority (71.5%) of patients were in the ≥ 65 years age group. 70.1% of patients had ECOG PS 0; median (range) baseline PSA was similar in the olaparib+abiraterone arm compared with the placebo+abiraterone arm (17.895 µg/mL [0.07 to 1869.48 µg/mL] vs 16.805 µg/mL [0.01 to 1888.00 µg/mL], respectively). Overall, 65.7% of the patients had a Gleason score of 8 to 10; 62.7% had de novo metastatic disease; 86.4% had bone metastases at baseline; 4.1% had liver metastases at baseline; median time from initial diagnosis was 36.9 months; 22.5% had received prior docetaxel treatment at mHSPC stage; and 18.7% had a BPI-SF Item 3 worst pain score ≥ 4 at baseline, indicating moderate or severe pain.

The Applicant's Position:
Demographics, baseline disease characteristics, stratification factors, HRRm status, and were generally well balanced between the two treatment arms. The patient demographics, including current and past medical history, were in line with expectations.

The FDA's Assessment:
FDA agrees that demographics and baseline disease characteristics were well balanced between the treatment arms. Table below summarizes the baseline characteristics for all patients randomized in PROpel.

Table 7. Baseline Characteristics in ITT Population

		Olaparib + abiraterone N=399	Placebo + abiraterone N=397
Age (y), median		69	70
Race (%)	White	71	69
	Black	4	3
	Asian	17	18
	Other	8	10
Gleason score (%)	≤7	30	34
	8-10	66	65
	Missing	3	1
Distant metastasis at initial diagnosis (%)	M0	29	33
	M1	64	61

	Mx	7	6
	Missing	<1	<1
ECOG PS (%)	0	72	69
	1	28	31
	Missing	<1	<1
Prior docetaxel for mHSPC (%)	Yes	23	22
Prior NHA for CRPC	Yes	<1	0
Baseline pain score (%)	no pain	33	35
	Mild	38	44
	Moderate	13	9
	Severe	8	7
	Missing	8	6
Opioid use at baseline (%)	Yes	14	11
Site of metastasis (%)	Bone only	55	55
	Visceral	13	13
	Other	32	32
LDH at baseline (median)		3.6	3.5

Of note, Black patients were underrepresented in PROpel, with only 3-4% accrual in each arm in the setting of an approximately 14% Black U.S. population. This is particularly notable given U.S. Black men are more likely to be diagnosed with prostate cancer (18%) and have higher prostate cancer mortality (4.4%) compared to non-Hispanic White men (13% and 2.4%, retrospectively) (DeSantis et al. CA Cancer J Clin. 2016 https://doi.org/10.3322/caac.21340).

One patient on the olaparib arm received enzalutamide prior to the mCRPC stage.

Subgroup Definition based on HRR or *BRCA* Mutation Status

Homologous Recombination repair (HRR) gene mutation status was assessed retrospectively by ctDNA and tumor tissue tests. The following 14 HRR genes were tested: *ATM*, *BRCA*1, *BRCA*2, *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D*, and *RAD54L*. Mutation classification criteria in line with the FDA approved assays were used to determine the deleterious and suspected deleterious somatic or germline mutation status. Concordance between tumor tissue and ctDNA test results are summarized in the table below.

Table 8. Concordance Between Tumor Tissue and ctDNA Assays (PROpel)

***BRCA* test results in PROpel**		**Tumor tissue test, n (%)**			
		Yes	**No**	**Unknown**	**Total**
ctDNA assay, n (%)	**Yes**	34 (4)	18 (2)	17 (2)	69 (9)
	No	12 (2)	427 (54)	226 (**28**)	665 (84)
	Unknown	4 (1)	40 (5)	18 (2)	62 (8)
	Total	50 (6)	485 (61)	**261 (33)**	796 (100)

Given both the large proportion of patients with unknown test results for at least one test and the concern for false negative results in the Applicant's aggregate definition of non-*BRCA*, FDA

defined the following 3 exploratory post-hoc subgroups based on results of tumor tissue and ctDNA tests:

a. ***BRCA*m** (11% of the ITT): Patients with *BRCA* mutation identified via either ctDNA or tumor tissue testing. The relatively high specificity of both tests leads to high certainty that these patients have *BRCA* mutated disease.

b. ***Non-BRCA*m** (54% of the ITT): Patients with negative *BRCA* mutation status confirmed by *both* ctDNA and tumor tissue testing, leading to high certainty that patients *do not* have *BRCA* mutated disease.

c. **Undetermined** *BRCA* status (35% of the ITT): Patients who had one negative *BRCA* mutation test result that was not confirmed by the other test, or for whom results of both tests were indeterminate. Based on the demonstrated prevalence of *BRCA* mutations in PROpel and in other studies of metastatic prostate cancer and the rate of non-concordance between the ctDNA and tissue results, the FDA estimates the incidence of underlying *BRCA* mutations in this undetermined *BRCA* group to likely be small (approximately 2% and 7%).

Table below shows the baseline prognostic factors of these subgroups.

Table 9. Baseline Prognostic Factors of Subgroups by *BRCA*m status

	***BRCA*m (N=85)**		**Undetermined (N=284)**		**non-*BRCA*m (N=427)**	
Prognostic factor	Olaparib + Abiraterone (N=47)	Placebo + Abiraterone (N=38)	Olaparib + Abiraterone (N=138)	Placebo + Abiraterone (N=146)	Olaparib + Abiraterone (N=214)	Placebo + Abiraterone (N=213)
Age median	67	70	69	69	70	71
ECOG 1	11 (23%)	18 (47%)	37 (27%)	42 (29%)	64 (30%)	64 (30%)
Have visceral metastasis	5 (11%)	8 (21%)	20 (14%)	21 (14%)	28 (13%)	23 (11%)
Taking opioids at baseline	6 (13%)	11 (29%)	16 (12%)	18 (12%)	33 (15%)	16 (8%)
LDH >1 ULN	13 (28%)	14 (37%)	41 (30%)	26 (18%)	66 (32%)	50 (24%)

Albumin (g/dL) mean	4.2	4.1	4.2	4.2	4.2	4.2
Hemoglobin (g/dL) mean	12.9	12.7	13.3	13.2	13.0	13.2
ALP (u/L) mean	148	171	180	157	195	178
PSA (ug/L) mean	64	50	73	73	99	64

Baseline characteristics in the subgroup with "undetermined" *BRCA* status and the non-*BRCA* subgroup were well-balanced between the treatment arms. In the *BRCA*m subgroup, there were slight imbalances in baseline characteristics favoring the olaparib arm.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment compliance was not assessed in this study.

The most common allowed concomitant medications administered are summarized in Section 10.6.1, PROpel CSR, Module 5.3.5.1. Disallowed concomitant medications received during the study are summarized in Table 14.1.16.4, PROpel CSR, Module 5.3.5.1.

The Applicant's Position:
The use of disallowed concomitant treatments did not raise any concerns regarding study conduct.

The FDA's Assessment:
Almost all patients (98.5%) received allowed concomitant medication(s). Based on allowed concomitant medications classification, the most frequently used allowed concomitant medications (≥ 25% of patients overall) were (excluding GnRH analogs): anilides, proton pump inhibitors, and HMG-CoA reductase inhibitors. The use of bisphosphonates was similar between the treatment arms: 11.3% versus 12.6% for the olaparib+abiraterone and placebo+abiraterone arms, respectively. Denosumab use was 15.0% in the olaparib+abiraterone arm compared with the 11.6% in the placebo+abiraterone arm. The study treatment period overlapped with the COVID-19 pandemic. COVID-19 vaccines were received by 26.1% of patients on the olaparib+abiraterone arm and 18.9% on the placebo+abiraterone arm.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

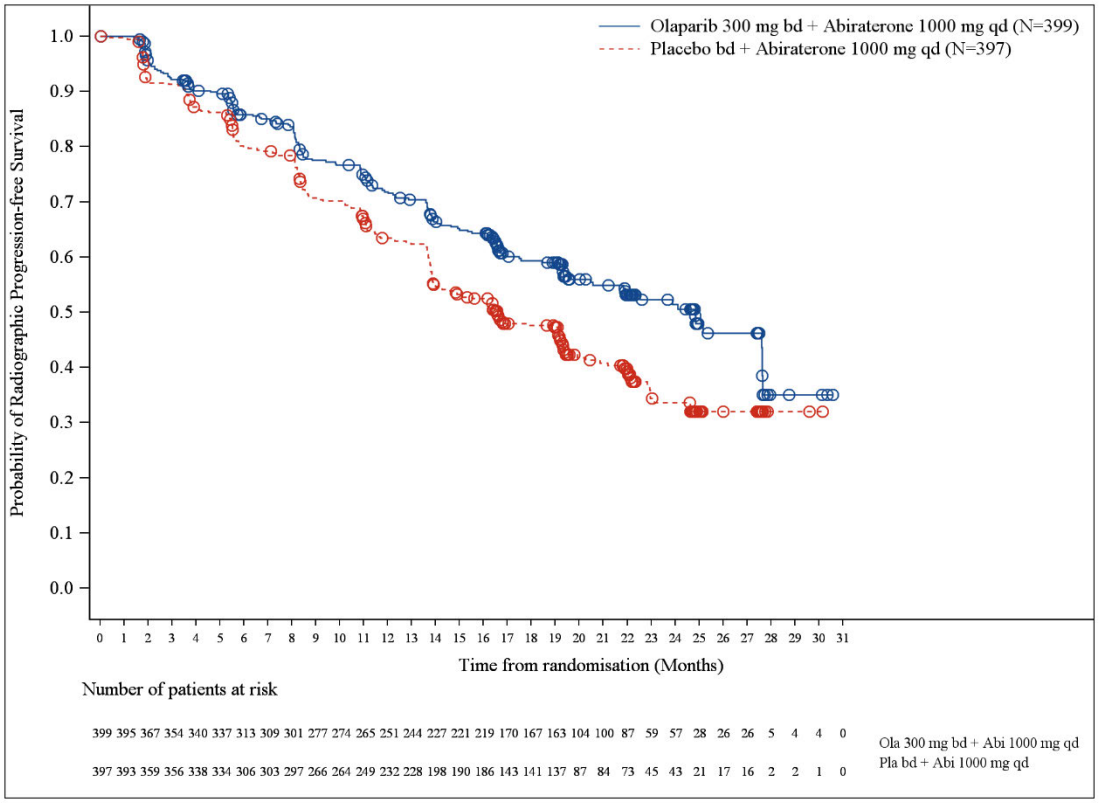
Data:

Table 10 . Applicant – Interim Analysis of rPFS by Investigator Assessment, PROpel (FAS) (DCO1: 30 Jul 2021)

	Number (%) of patients	
	Olaparib+abiraterone (N=399)	**Placebo+abiraterone (N=397)**
Number of events (%)	168 (42.1)	226 (56.9)
Median rPFS (95% CI) (months)	24.84 (20.47, 27.63)	16.59 (13.93, 19.22)
HR (95% CI)	0.66 (0.54, 0.81)	
p-value	p<0.0001	
Patients progression-free at 12 months (%)	71.84	63.44
Patients progression-free at 24 months (%)	51.41	33.59

Source: Data derived from Table 14.2.1.1.1, PROpel CSR, Module 5.3.5.1.
Dataset: ADTTE

Figure 5. Applicant - Kaplan-Meier Plot of rPFS by Investigator Assessment, PROpel (FAS) (DCO1: 30 Jul 2021)



Source: Data derived from Figure 14.2.1.2.1, PROpel CSR, Module 5.3.5.1.
Dataset: ADTTE

Exploratory Subgroup Analyses

Exploratory subgroup analyses of the primary endpoint of rPFS based on investigator assessment were performed for pre-defined subgroups based on the stratification factors, HRR

gene mutation status, and baseline characteristics (ECOG performance status, age at randomization, region, race, and baseline PSA). The results of the subgroup analyses of rPFS are presented in Section 11.1.1.4 of the PROpel CSR, Module 5.3.5.1. The results of these analyses across subgroups were generally consistent with the clinically meaningful treatment effect observed in the FAS.

Sensitivity Analyses

Table 11. Applicant - Sensitivity Analyses of rPFS, PROpel (FAS) (DCO1: 30 Jul 2021)

Analysis	Arm	N	Number (%) of patients with events	Median rPFS time (months)	HR	95% CI	2-sided p-value
rPFS by BICR assessment	Olaparib+abiraterone	399	157 (39.3)	27.60	0.61	0.49, 0.74	< 0.0001
	Placebo+abiraterone	397	218 (54.9)	16.39			
Evaluation time bias	Olaparib+abiraterone	399	168 (42.1)	24.11	0.66	0.54, 0.81	< 0.0001
	Placebo+abiraterone	397	226 (56.9)	15.24			
Attrition bias	Olaparib+abiraterone	399	168 (42.1)	24.11	0.71	0.57, 0.86	0.0007
	Placebo+abiraterone	397	210 (52.9)	18.96			
Unequivocal clinical progression in addition to rPFS	Olaparib+abiraterone	399	228 (57.1)	17.28	0.80	0.67, 0.96	0.0142
	Placebo+abiraterone	397	261 (65.7)	14.00			
Revised confirmation criteria for bone scan	Olaparib+abiraterone	399	181 (45.4)	22.08	0.69	0.57, 0.84	0.0002
	Placebo+abiraterone	397	233 (58.7)	16.39			
Censoring patients with subsequent therapy or discontinuation of study drug	Olaparib+abiraterone	399	135 (33.8)	27.60	0.66	0.53, 0.83	0.0003
	Placebo+abiraterone	397	178 (44.8)	19.35			

Source: Data derived from Tables 14.2.1.1.2, 14.2.1.3.1, 14.2.1.3.2, 14.2.1.3.4, 14.2.1.3.5, 14.2.1.3.6, and 14.2.1.3.7, PROpel CSR, Module 5.3.5.1.
Dataset: ADTTE, ADPRODEV

The Applicant's Position:

At the interim rPFS analysis (DCO1: 30 Jul 2021), PROpel met its primary objective, with an HR of 0.66 (95% CI 0.54, 0.81) and a p-value of < 0.0001 from the log-rank test (the primary analysis methodology), which is below the controlled alpha spending allocation at this interim analysis (0.0324 [2-sided]). This equates to a 34% reduction in the risk of radiological disease progression or death, which is statistically significant and clinically meaningful for patients treated with olaparib in combination with abiraterone (Section 2.2).

Exploratory analyses of rPFS were performed for pre-defined subgroups based on stratification factors, baseline characteristics, and HRR mutation status to assess the consistency of treatment effect. Acknowledging that the study was not powered to assess efficacy within individual subgroups and without control for multiplicity in this regard, the rPFS subgroup

analyses should be considered as exploratory and interpreted with caution.

The benefit of olaparib over placebo in combination with abiraterone was maintained across all pre-defined subgroups, with clinically meaningful reductions in the risk of radiological disease progression or death in olaparib+abiraterone-treated patients. The global interaction test was not significant at the 10% level (p=0.4129) indicating that overall the treatment effect was consistent across the subgroups.

HRRm subgroup analyses of rPFS by Investigator Assessment are presented in Table .

Table 12 . Applicant – rPFS Subgroup Analyses by Investigator Assessment – PROpel (DCO1: 30 Jul 2021)

	Olaparib+abiraterone	Placebo+abiraterone
Radiological Progression-Free Survival (rPFS) by investigator assessment		
Aggregate HRRm Subgroup Analyses*		
HRRm	**N=111**	**N=115**
Number of events (%)	43/111 (38.7)	73/115 (63.5)
Median (months)	NC	13.86
Hazard ratio (95% CI)	0.50 (0.34, 0.73)	
Non-HRRm	**N=279**	**N=273**
Number of events (%)	119/279 (42.7)	149/273 (54.6)
Median (months)	24.11	18.96
Hazard ratio (95% CI)	0.76 (0.60, 0.97)	

* Aggregate HRRm subgroups were derived from ctDNA and tissue based HRRm groupings.
Source: Data derived from Table 2928.1, Module 5.3.5.3.
Dataset: ADTTE

Of note, the benefit of the olaparib+abiraterone arm was maintained across HRRm subgroups with at least a 5-month prolongation of rPFS observed in all biomarker subgroups.

*BRCA*m subgroup analyses of rPFS by Investigator Assessment are presented in Table 13.

Table 13 . **Applicant – rPFS** Subgroup Analyses by Investigator Assessment – PROpel (DCO1: 30 Jul 2021)

	Olaparib+abiraterone	Placebo+abiraterone
Radiological Progression-Free Survival (rPFS) by investigator assessment		
Aggregate *BRCA*m Subgroup Analyses*		
***BRCA*m**	**N=47**	**N=38**

	Olaparib+abiraterone	Placebo+abiraterone
Number of events (%)	14/47 (29.8)	28/38 (73.7)
Median (months)	NC	8.38
Hazard ratio (95% CI)	0.23 (0.12, 0.43)	
Non-*BRCA*m	**N=343**	**N=350**
Number of events (%)	148/343 (43.1)	194/350 (55.4)
Median (months)	24.11	18.96
Hazard ratio (95% CI)	0.76 (0.61, 0.94)	

* Aggregate subgroups were derived from ctDNA and tissue-based groupings.
Source: Data derived from Table 3134, Module 5.3.5.3.
Dataset: ADTTE

Of note, the benefit of the olaparib+abiraterone arm was maintained across *BRCA*m subgroups with at least a 5 month prolongation of rPFS observed in all biomarker subgroups.

The sensitivity analysis of the primary analysis of rPFS using BICR data confirmed the robustness of the analysis by investigator assessment. The clinically meaningful treatment effect for rPFS was consistent across investigator and BICR assessments, indicating no systematic bias introduced by investigator assessment of treatment effect. Additionally, all other pre-planned sensitivity analyses were highly consistent with the investigator assessed rPFS analysis, confirming the robustness of the analysis of rPFS by investigator assessment.

The magnitude of improvement that olaparib adds to abiraterone is further quantified by the rPFS Kaplan-Meier estimates which showed a greater percentage of patients in the olaparib+abiraterone arm compared to the placebo+abiraterone arm progression-free at 12 months and 24 months, respectively.

The performance of the control arm in the PROpel trial was consistent with the assumed effect of abiraterone when the trial was designed. This estimation was based on the available evidence from the COU-302-AA trial, in which the median rPFS in the abiraterone arm was 16.5 months (Ryan et al 2013). There were some differences in the patient populations enrolled in the different trials, eg, COU-302-AA enrolled patients with a higher median PSA concentration at baseline which is an unfavorable prognostic factor, although variability was high. On the other hand, PROpel enrolled patients with visceral metastases and patients with symptomatic disease both of which were excluded in COU-302-AA. Altogether, while recognizing the challenges with cross-study comparisons, the performance of the placebo+abiraterone control arm in PROpel was as expected and is indicative of an efficacious comparator arm.

Data Quality and Integrity

The Applicant's Position:
Quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures, as detailed in Section 9 and Section 10 of the PROpel CSP (Appendix 16.1.1, PROpel CSR, Module 5.3.5.1).

AstraZeneca's quality assurance and quality control procedures provide reassurance that the clinical study program was carried out in accordance with GCP guidelines. AstraZeneca undertakes a GCP audit program to ensure compliance with its procedures and to assess the adequacy of its quality control measures. Audits, by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures, are directed towards all aspects of the clinical study process and its associated documentation.

Efficacy Results – Key Secondary Endpoint

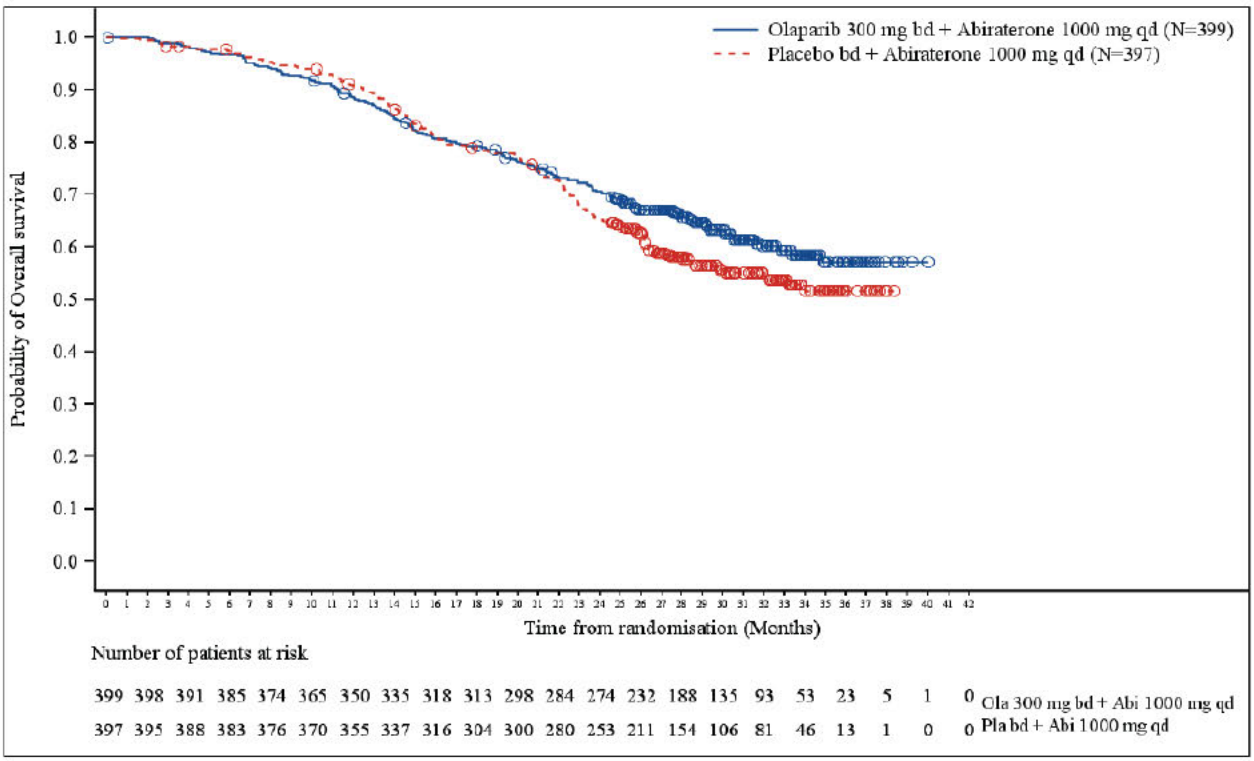
Data:

Table 14. Applicant - Analysis of OS at the Time of the Final rPFS Analysis (DCO2: 14 Mar 2022), PROpel (FAS)

	Number (%) of patients	
	Olaparib+abiraterone (N=399)	**Placebo+abiraterone (N=397)**
Death, n (%)	148 (37.1)	171 (43.1)
Median OS (95% CI) [months]	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.83 (0.66, 1.03)	
2-sided p-value	0.1126	
Alive at 6 months (%)	96.73	97.22
Alive at 12 months (%)	88.43	90.61
Alive at 18 months (%)	79.32	78.32
Alive at 24 months (%)	70.60	65.40
Alive at 30 months (%)	63.35	55.51
Alive at 36 months (%)	57.05	51.61

Source: Data derived from Table 14.2.4.1, PROpel CSR Addendum 1, Module 5.3.5.1.
Dataset: ADTTE

Figure 6. Applicant - Kaplan-Meier Plot of OS, at the Time of the Final rPFS Analysis (DCO2: 14 Mar 2022), PROpel (FAS)



Source: Data derived from Figure 14.2.4.2.1, PROpel CSR Addendum 1, Module 5.3.5.1.
Dataset: ADTTE

The Applicant's Position:

The interim OS data presented at the time of the final rPFS analysis (DCO2: 14 Mar 2022) were 40.1% mature (319 events/796 patients) with approximately 27 months follow up in FAS with a smaller proportion of events occurring in the olaparib+abiraterone arm. The OS HR point estimate numerically favored the olaparib+abiraterone vs placebo+abiraterone arm suggesting a continued trend towards improved OS for olaparib+abiraterone-treated patients. Importantly compared to the Kaplan-Meier curve at DCO1, the Kaplan-Meier curve at DCO2 showed clear separation between the arms after approximately 22 months before extensive censoring was observed. The median OS was not reached in either treatment arm and survival rates at 24 and 36 months were higher in the olaparib+abiraterone arm.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of quality and integrity of data.

At the time of sNDA submission, the Applicant submitted the OS results with data cutoff date as of DCO2 (14 Mar 2022) and the Applicant's OS analysis in this assessment aid was based on DCO2. During the review, the Applicant submitted the final OS dataset (DCO3: 12 Oct 2022) for

FDA review. Therefore, FDA's assessment of rPFS is mainly based on the interim analysis of rPFS (DCO1) and FDA's assessment of OS is based on final OS analysis (DCO3).

The major efficacy outcome measure was investigator-assessed rPFS evaluated according to RECIST, version 1.1 and Prostate Cancer Working Group (PCWG3) (bone) criteria. Overall survival (OS) was a secondary efficacy outcome measure.

The FDA notes that the interim analysis of rPFS was planned/expected at 379 events (=83% information fraction with planned 453 rPFS events at final rPFS analysis) but observed at 394 events (=87% information fraction). Per the SAP, the Applicant calculated the one-sided p-value cut-off at the first interim analysis of 0.016 with 87% observed information fraction (IF).

FDA agrees with the Applicant that at the first interim analysis (87% IF), the study demonstrated a statistically significant and clinically meaningful benefit on rPFS by INV in the olaparib+abiraterone arm compared to the placebo+abiraterone arm in the ITT population. However, the FDA does not agree with presenting p-values for sensitivity analyses (Table 11) as all sensitivity analyses are exploratory and p-values for those analyses should be considered nominal only.

In addition, for a study with stratified randomization, in general, the FDA uses a stratified Cox model for hazard ratio estimation to match the randomization method. In this submission, the applicant used a covariate-adjusted Cox model for hazard ratio estimation with stratification factors included as the covariates. To assess the impact of a stratified analysis versus a covariate adjusted analysis on the effect size estimation, the FDA did the calculation and confirmed that results from the stratified analyses are consistent to the primary results reported by the Applicant based on the covariate-adjusted cox proportional hazards model.

Sensitivity Analysis of rPFS based on BICR Assessment

The FDA agrees that the sensitivity analysis of rPFS using BICR data confirmed the robustness of the primary endpoint analysis of rPFS by investigator. Briefly, the HR for rPFS by BICR was 0.61 (95% CI: 0.49, 0.74; nominal p<0.0001) with an improvement of 11.2 months improvement of median rPFS. The median rPFS was 27.6 months in the olaparib+abiraterone arm versus 16.4 months in the placebo+abiraterone arm.

Table 15. Exploratory Subgroup Analyses of rPFS by INV based on Baseline Characteristics

Subgroup	Olaparib+abiraterone N (# of events)	Placebo+abiraterone N (# of events)	HR (95% CI)[1]
Stratification factor 1 at randomization			
BONE ONLY	217 (75)	217 (102)	0.73 (0.54, 0.98)
OTHER	129 (62)	128 (84)	0.62 (0.45, 0.86)
VISCERAL	53 (31)	52 (40)	0.62 (0.39, 0.99)
Stratification factor 2 at randomization			

Docetaxel treatment at (mHSPC) stage	95 (39)	94 (56)	0.61 (0.41, 0.92)
No Docetaxel treatment at (mHSPC) stage	304 (129)	303 (170)	0.71 (0.56, 0.89)
ECOG performance status at baseline			
ECOG 0	286 (113)	272 (151)	0.66 (0.52, 0.85)
ECOG 1	112 (55)	124 (75)	0.77 (0.54, 1.09)
Age			
<65	130 (47)	97 (59)	0.52 (0.35, 0.76)
>=65	269 (121)	300 (167)	0.78 (0.61, 0.98)
Region			
Asia	91 (34)	104 (53)	0.57 (0.37, 0.88)
Europe	178 (79)	172 (111)	0.65 (0.48, 0.86)
North and South America	130 (55)	121 (62)	0.85 (0.59, 1.23)
Baseline PSA			
Above or equal to median baseline	201 (94)	196 (132)	0.64 (0.49, 0.83)
Below median baseline	196 (73)	200 (93)	0.75 (0.55, 1.02)
Race			
Asian	66 (24)	72 (35)	0.61 (0.36, 1.04)
Black/African-American	14 (5)	11 (5)	0.85 (0.25, 2.93)
Other	15 (6)	9 (2)	NC
White	282 (124)	275 (166)	0.67 (0.53, 0.85)

[1]In each subgroup, the HR was estimated using unstratified Cox proportional hazards model with treatment as the only explanatory variable. Assuming proportional hazards, HR < 1 indicated a reduction in hazard rate in favor of the treatment arm.

Exploratory Subgroup analysis of rPFS by *BRCA* mutation status

The Applicant states above that "the benefit of the olaparib+abiraterone arm was maintained across *BRCA*m subgroups." The FDA disagrees with this general assertion, which will be discussed further below.

Of the 796 patients tested, 85 (11%) had *BRCA* mutation (*BRCAm*) determined by either a positive ctDNA test (9%) or a tumor tissue test (6%). The applicant provided the *BRCA*m subgroup analyses of rPFS in **Table 13**. In that table, the Applicant used an interaction model (i.e., Cox model with covariates of treatment group, the subgroup factor, and the interaction term) for hazard ratio estimation for each subgroup. However, FDA usually uses a subset model with data from each subgroup only for hazard ratio estimation. To assess the effect of interaction model vs. subset model, FDA calculated the HR based on the subset model and the result is shown in the Table below. In general, HRs from the subset model are consistent to the results reported by the Applicant based on the interaction model. However, to keep consistent with the labeling approach for interpretation of exploratory subgroup results, the FDA recommends the sponsor report the results from the subset model in the label.

As aforementioned, the FDA does not agree with the Applicant's aggregate method to define the non-BRCAm subgroup in **Table 13** due to concern for presence of false negative results in this subgroup. The following table shows the results of FDA's defined 3 subgroups (*BRCA*m, undetermined *BRCA*m status and non-*BRCA*m) based on tumor tissue and ctDNA tests.

Based on the exploratory subgroup analysis of primary and secondary endpoints by *BRCA* subgroup in PROpel (shown in the table and figure below), the efficacy results in the ITT population were largely attributable to a strong treatment effect in patients with tumor *BRCA* mutations. For the non-*BRCA*m subgroup, the upper bound of the 95% confidence interval for rPFS HR crosses 1, and the point estimate for the OS HR is above 1, indicating at best a modest improvement in rPFS and a potential for OS detriment. This non-*BRCA*m subgroup represented the majority of patients in PROpel (54%).

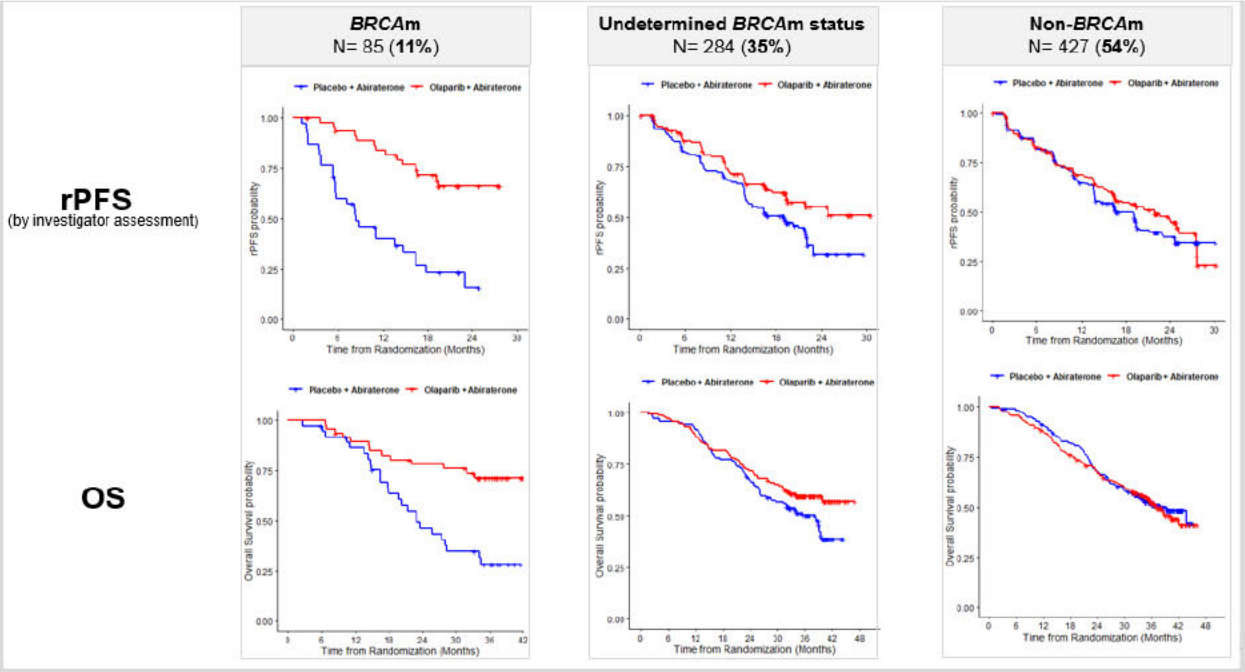
A sensitivity analysis of rPFS by BICR assessment was consistent with the investigator-assessed rPFS. The median rPFS difference in the non-*BRCA* subgroup by BICR assessment is only 3 months, which is approximately equal to the imaging interval, suggesting that the true rPFS difference may be smaller in this subgroup.

The difference in confirmed ORR by BICR between arms at the time of the final rPFS analysis was 32% for the *BRCA*m subgroup and only 4% for those in the non-*BRCA*m subgroup. Although assessment of ORR is limited by the small number of patients with prostate cancer who have measurable disease, this finding also suggests efficacy with the addition of olaparib largely isolated to those with *BRCA* mutated disease and a concern for lack of efficacy in the non-*BRCA*m subgroup.

Table 16. Primary and Selected Secondary Endpoints Analysis by *BRCA*m Status - PROpel

	BRCAm N= 85 (11%) Olaparib vs Placebo	**Undetermined *BRCAm* status** N= 284 (35%) Olaparib vs Placebo	**Non-*BRCAm*** N= 427 (54%) Olaparib vs Placebo
rPFS by INV			
Median, months	NR vs 8	NR vs 19	22 vs 17
HR (95% CI)	0.24 (0.12, 0.46)	0.66 (0.46, 0.94)	0.85 (0.66, 1.11)
rPFS by BICR			
Median, months	NR vs 8	NR vs 19	20 vs 17
HR (95% CI)	0.19 (0.1, 0.37)	0.59 (0.41, 0.85)	0.82 (0.62, 1.08)
OS			
Median, months	NR vs 23	NR vs 38	37 vs 38
HR (95% CI)	0.3 (0.15, 0.6)	0.73 (0.52, 1.03)	1.06 (0.81, 1.39)
Confirmed ORR by BICR			
Patients with evaluable disease at baseline	N= 20 vs 18	N= 50 vs 51	N= 92 vs 81
ORR % (95% CI)	60% (36, 81) vs 28% (10, 53) (Δ = 32%)	60% (45, 74) vs 43% (29, 58) (Δ = 17%)	52% (42, 63) vs 48% (37, 60) (Δ = 4%)

Figure 7. rPFS by INV (DCO1) and OS (DCO3), Kaplan-Meier plot



To account for potential imbalance in baseline covariates in these subgroups, the FDA examined the prognostic factor balance between two arms for the 3 subgroups described above.

Despite lack of stratification, baseline prognostic factors were well-balanced between treatment arms in the undetermined and non-*BRCA* subgroups, likely due to the large sample sizes. The individual prognostic factor examination did not identify any notable imbalance. Furthermore, a validated prognostic risk model for mCRPC (6) which combines 8 prognostic factors was employed to assess overall balance and the results showed balanced risk score.

There is an apparent imbalance of prognostic factors in the *BRCA*m subgroup in favor of the olaparib arm; this imbalance is not unexpected due to the small sample size of this subgroup. Nevertheless, adjustment methods for imbalance had little impact on the observed strong treatment effect in *BRCA*m.

Overall, after adjustment for baseline prognostic factors in the three *BRCA*-based subgroups in PROpel, there was no overall changes in the conclusion that the efficacy results in the ITT population appeared to be primarily attributed to efficacy in the *BRCA*m subgroup.
This is true despite the suboptimal design of PROpel to assess the efficacy by mutation status due to lack of stratification.

For patients who are negative for tumor *BRCA* mutations by two assays, the FDA is concerned that PROpel demonstrated a lack of efficacy and a potential overall survival detriment. This population comprises over half of the ITT population.

There was minimal impact of lack of stratification and results were consistent for the three *BRCA* subgroups after adjusting for baseline characteristics based on a prognostic model for mCRPC.

There is internal consistency between primary and secondary endpoints as shown above, demonstrating what appears to be modest efficacy from adding olaparib in the non-*BRCA*m subgroup.

Subgroup analysis of *BRCA*m and All Others
The FDA review team conducted an additional analysis combining the subgroups with undetermined *BRCA*m status and non-*BRCA*m status into one large subgroup called "All Others", comprising 89% of the ITT population. This is a very similar population to the non-*BRCA* subgroup defined by the Applicant in **Table 13**, but also includes 18 patients who had unknown results for both tests.

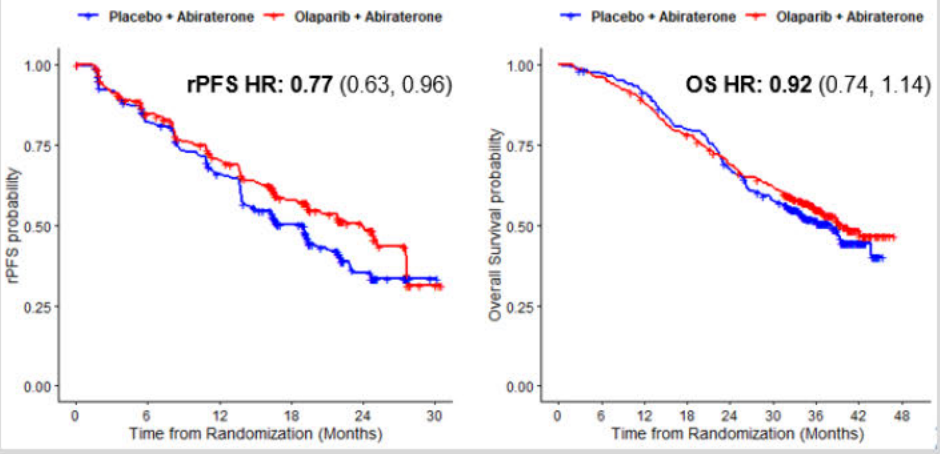
Results of the analysis of the breakdown of the ITT into *BRCA*m vs. "All Others" are shown in the following table and figure.

Table 17. PROpel: Analysis of Two *BRCA*-Based Subgroups (*BRCA*m vs. All others)

N = 796		***BRCA*m** N= 85 (11%)	**All Others** (Potentially includes patients with *BRCA*m) N= 711 (89%)
rPFS	HR (95% CI)	**0.24** (0.12, 0.46)	**0.77** (0.63, 0.96)

(Investigator assessment)	Median (months)	Olaparib: NR, placebo: 8	Olaparib: 24 vs Placebo: 19 (**Δ: 5 mo**)
rPFS (BICR)	HR (95% CI)	**0.19** (0.10, 0.37)	**0.73** (0.59, 0.9)
	Median (months)	Olaparib: NR, placebo:	Olaparib: 28 vs Placebo: 17 (**Δ: 11 mo**)
OS	HR (95% CI)	**0.3** (0.15, 0.6)	**0.92** (0.74, 1.14)
	Median (months)	Olaparib: NR, Placebo: 23	Olaparib: 40 vs Placebo: 38

Figure 8. KM curves for rPFS by investigator (DCO1) and OS (DCO3), for the Two-Subgroup analysis

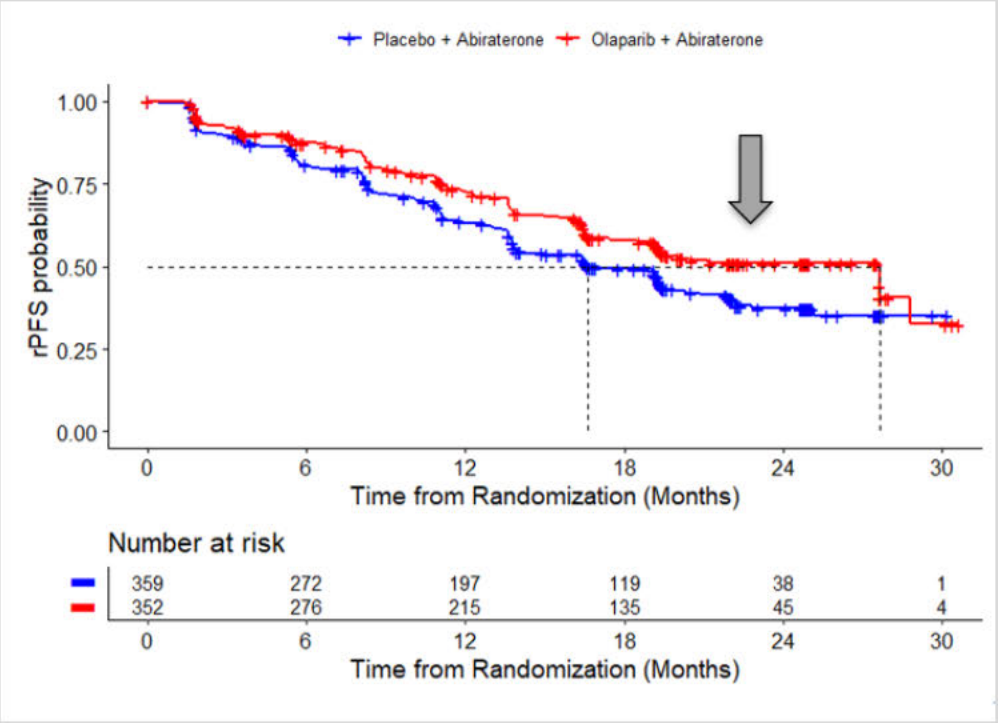


While these results demonstrate activity of olaparib in this subgroup, an important consideration of this study is whether the 5-month improvement in investigator-assessed rPFS is clinically meaningful given the add-on design, long duration of exposure to the toxicities of olaparib for over a year and a half, and lack of OS improvement. In addition, this subgroup potentially includes a small proportion of patients who had an unidentified *BRCA* mutation, and it is not clear to what extent the 5-month improvement in rPFS may be attributed to efficacy in these patients.

The median rPFS improvement by BICR in this subgroup was 11 months, however the FDA review team considered this 11-month improvement to be overestimated and unstable for the following reasons:

- As shown in the KM curve of rPFS by BICR in this subgroup in the figure below, the median was estimated towards the tail of the KM curve for the olaparib arm (which is the red curve), where there were very few events, which caused an over-estimation in the median rPFS difference between treatment arms.

Figure 9. rPFS by BICR in All Others subgroup (DCO1)



- In the subsequent analysis of rPFS at DCO-2, there was an 8-month difference between the arms by BICR assessment which shows that the BICR measurement of rPFS at data cut-off 1 was overestimated.
- rPFS by investigator was the primary endpoint and the secondary BICR results should be considered only as supportive.

As will be discussed in the integrated assessment of efficacy, after reviewing the above efficacy data divided by exploratory subgroups of *BRCA*m vs "All Others", and cognizant of the potential for OS detriment in the exploratory subgroup of patients with non-*BRCA*m confirmed by ctDNA and tumor tissue, the FDA review team determined that the indication for olaparib in combination with abiraterone should be limited to patients with *BRCA*m confirmed by either tissue or ctDNA testing. Section 14 thus presented data related to demographics and rPFS and OS in this subgroup of patients.

The review team did not consider clear efficacy for the addition of olaparib to abiraterone to have been demonstrated in PROpel in patients with identified HRR mutations other than *BRCA*m. In these patients, the HR for rPFS per investigator was 0.8 (95% CI 0.5, 1.27) and the HR for OS was 1.02 (95% CI 0.65, 1.59) in this subgroup of patients with non-*BRCA* HRRm. Thus, the FDA disagrees with the statement by the Applicant that "the benefit of the olaparib+abiraterone arm was maintained across HRRm subgroups."

Post-Discontinuation therapies

In PROpel, 7 patients (2 patients in the olaparib arm and 5 patients in the Placebo arm) received post-trial PARPi as of the final analysis of rPFS (DCO2). Post-discontinuation therapies with PARPi or platinum-based chemotherapies are shown in the table below.

The low number of patients with HRRm tumor who received post-discontinuation PARPi is likely mostly attributable to the fact that most patients in PROpel were enrolled prior to approval of olaparib for HRRm and rucaparib for *BRCA*m in May 2020. However, as a consequence of the timing of enrollment, the vast majority of patients with *BRCA*m on the placebo arm never received a PARPi at any point during their treatment. This may have negatively impacted OS in these patients. Few patients on either arm received platinum-based chemotherapy, which may also be effective for *BRCA*m tumors. Ultimately, the review team determined that the OS benefit demonstrated by patients with *BRCA*m tumors was of sufficient magnitude to overcome this concern.

Table 18. Post-discontinuation Anticancer Therapy- PROpel (DCO2)

post-discontinuation therapy			
		Olaparib+abiraterone	Placebo+abiraterone
PARPi	*BRCA*m	1	1
	Undetermined	0	3
	non-*BRCA*m	1	1
Platinum compounds	*BRCA*m	1	4
	Undetermined	2	5
	non-*BRCA*m	8	6

Dose/Dose Response

No new information is provided in the current submission.

Durability of Response

Data/The Applicant's Position:

At the interim rPFS analysis of PROpel (DCO1: 30 Jul 2021), the median DoR was 5.3 months longer in the olaparib+abiraterone arm (18.2 months) vs the placebo+abiraterone arm (12.9 months), with a similar median time to onset of response (2.2 months vs 2.0 months, respectively).

The FDA's Assessment:

The FDA agrees with the Applicant's above description of median DoR based on unconfirmed ORR by investigator. However, as previously noted, the increase in efficacy in the olaparib arm in all-comers appears primarily attributable to the treatment effect in patients with *BRCA*m tumor; this is also true for assessment of ORR.

The associated table is shown below.

Table 19. Unconfirmed ORR by investigator assessment in Evaluable for Response (EFR) population (DCO1)

	Olaparib + abiraterone N=161	Placebo+ abiraterone N=160
Number of responders (%)	94 (58)	77 (48)
Complete response (%)	7 (4)	10 (6)
Partial response (%)	87 (54)	67 (42)
PD (%)	22 (14)	31 (19)
Median Duration of Response months (95% CI)	18 (13, NC)	13 (10, 19)

Per FDA's request, the Applicant provided the following additional analysis for unconfirmed ORR per BICR at DCO1.

Table 20. Unconfirmed ORR per BICR in EFR population (DCO1)

	Olaparib + abiraterone N=162	Placebo + abiraterone N=149
Number of responders (%)	96 (54)	71 (48)
Complete response (%)	6 (4)	5 (3)
Partial response (%)	90 (56)	66 (44)
Median Duration of Response months (95% CI)	18 (12,NC)	15 (12,18)

As this is a randomized trial, unconfirmed ORR is used in these analyses per RECIST v1.1 which does not require confirmation of response for this endpoint in a randomized trial. ORR was evaluated under the evaluable for response (EFR) analysis set. The EFR analysis set is a subset of all patients in the ITT, who have measurable disease at baseline as per the RECIST 1.1 criteria. In PROpel, only 40% of patients overall were in EFR analysis set as bone is the most common site of metastasis in patients with prostate cancer and bone lesions are not evaluable for response by RECIST v1.1. Therefore, the ORR analysis is limited by the small number of patients.
Per FDA's request, the sponsor further provided the following additional analysis for confirmed ORR per BICR with more mature data at DCO2. A breakdown of ORR by the 3-subgroup population analysis is presented below.

Table 21. Confirmed ORR per BICR in EFR population and the 3 *BRCA*m based subgroups (DCO2)

	Olaparib + abiraterone ORR (%)	Placebo + abiraterone ORR (%)
EFR	90/162 (56)	66/150 (44)
*BRCA*m	12/20 (60)	5/18 (28)
Undetermined	30/50 (60)	22/51 (43)
non-*BRCA*m	48/92 (52)	39/81 (48)

Persistence of Effect

Data:

Results of rPFS, the primary endpoint, are summarized in and . Duration of exposure data in PROpel are summarized in .

The Applicant's Position:
The primary endpoints of rPFS was a time-to-event endpoint, to which persistence of efficacy over time is integral. At the interim rPFS analysis (DCO1: 30 Jul 2021), the statistically significant and clinically meaningful improvement in rPFS (8.2 months) for olaparib+abiraterone compared to placebo+abiraterone provides direct evidence of the persistence of efficacy.

As patients continued study treatment until objective radiological progression, unacceptable toxicity, or any other treatment discontinuation criterion was met, the persistence of olaparib+abiraterone efficacy was also evaluated based on comparative assessment of exposure data. Consistent with the prolongation of rPFS, the median total duration of exposure to olaparib (17.5 months) was 1.1 times longer than the duration of exposure to placebo (15.7 months) (DCO1: 30 Jul 2021).

Whilst long-term efficacy and exposure data collected for this submission are limited by the DCO, the data obtained to date provide evidence that olaparib+abiraterone offers durable clinical benefit in the patient population treated.

The FDA's Assessment:
At the time of sNDA submission, the Applicant submitted the OS results with data cutoff date as of DCO2 (14 Mar 2022). There were 37% and 47% death events in the olaparib+abiraterone and placebo+abiraterone arms at DCO2, respectively. Since OS is both an efficacy and a safety endpoint and more mature OS data was needed for the benefit:risk assessment of adding olaparib to abiraterone, at the time of a preNDA meeting in May 2022, the FDA team asked the Applicant to submit the topline results of final OS analysis and OS dataset at DCO3 (12 Oct 2022) for FDA review. The final OS results showed that there was no OS decrement in ITT. However, as noted in the exploratory subgroup analysis by *BRCA*m status conducted by the FDA, the OS HR of the non-*BRCA*m subgroup is 1.06, indicating potential OS detriment for non-*BRCA*m. This, along with minimal OS benefit observed in the subgroup of "All Other" patients with a HR for OS of 0.92, contributed to the decision by the review team to limit the approved indication to patients with *BRCA*m.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Data:
FACT-P and BPI-SF scores are summarized in Section 11.1.5, PROpel CSR, Module 5.3.5.1.

The Applicant's Position:
The compliance rates for the BPI-SF and FACT-P were high in both treatment arms.

There was no overall differences in mean change from baseline of the BPI-SF pain severity and pain interference scores for olaparib+abiraterone-treated patients compared with

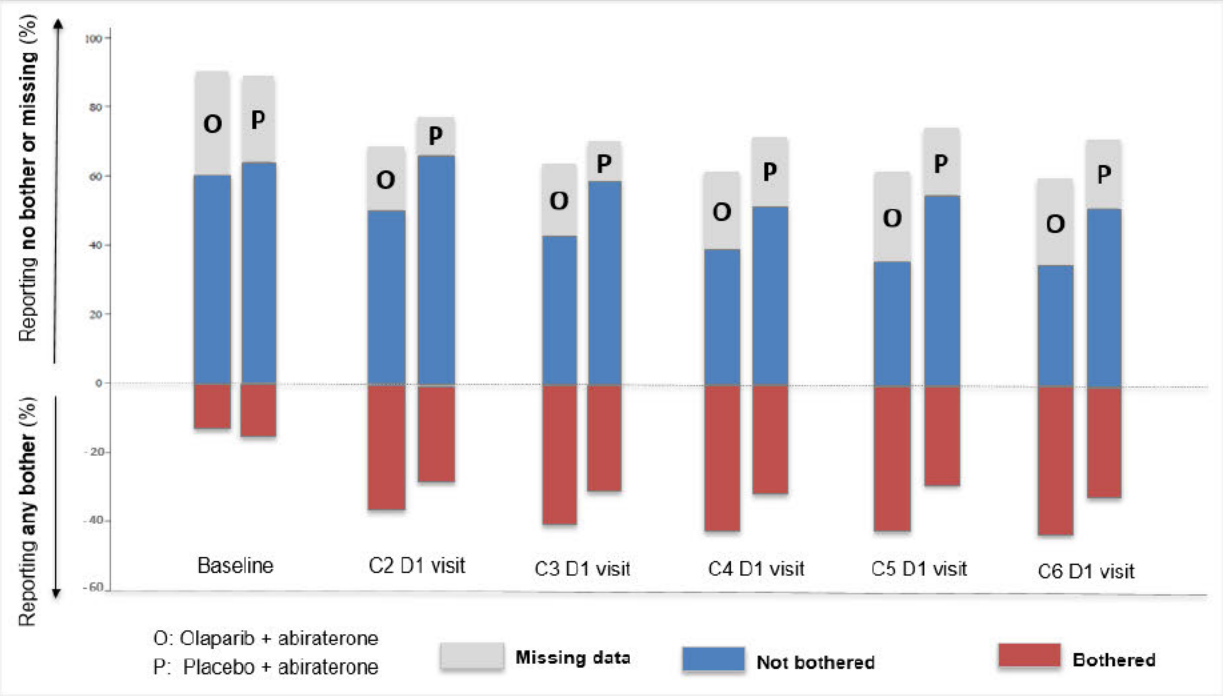
placebo+abiraterone-treated patients. Similar findings were observed for the FACT-P Total score and generally, with the subscale scores.

Taken together, the PRO data (HRQoL and disease-related symptoms) indicate that the combination of olaparib+abiraterone did not negatively impact patients' HRQoL.

The FDA's Assessment:

Patient-reported outcomes were collected in PROpel using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) instrument (7). FDA specifically focused on the descriptive results of the FACT GP5 overall side effect impact item to assess tolerability of the treatment regimen. This GP5 item asks patients if they are "bothered by side effects of treatment" and rates the level of bother from 0 to 4 (0: Not at all; 1: A little bit; 2: Somewhat; 3: Quite a bit; 4: Very much). Previous experience in the literature (8) suggested minimal NHA side effect impact compared to placebo using a patient-reported side effect bother item in patients with non-metastatic CRPC. In PROpel, PROs were included as exploratory and descriptive information and the adequate completion rate (greater than 70% at most timepoints in the first six cycles) allowed for analysis and interpretation of these results.
Patient-generated responses to GP5 question in FACT-P tool are shown in Figure 10. Although a formal comparative tolerability endpoint was not included in the PROpel study, FDA noted higher proportions of patients in the olaparib arm who reported side effect bother compared to placebo. Although the number of patients reporting bother was consistently higher in the olaparib arm, there were few patients who reported severe bother (score 3 or 4) in both arms at all time points.

Figure 10. CT-P GP5 Reports at Baseline and First 6 Months on Treatment (PROpel)



These descriptive and exploratory GP5 results support the observed increased clinician-reported adverse reactions observed when olaparib is added to abiraterone.

Additional Analyses Conducted on the Individual Trial

Data/The Applicant's Position:
No additional analyses were conducted.

The FDA's Assessment:

1. Summary of rPFS and OS in Subpopulations Defined by ctDNA vs. by Tumor Tissue

Table below summarized the rPFS and OS analysis for *BRCA*m or HRRm subgroups determined by individual mutation test. There is rPFS benefit (with a favorable HR estimate) for almost all the following exploratory subgroups defined by *BRCA* or HRR mutation status and by either test. However, it is noted for subgroup of HRRm/non-*BRCA* by ctDNA test, there is no rPFS benefit with HR of 0.93 and similar median rPFS values between two arms.

The OS analysis shows, for HRRm/non-*BRCAm*, both tumor tissue test and ctDNA test reported OS HR over 1. For the subgroups defined by tumor tissue test, the OS HRs for the non-*BRCA*m, HRRm/non-*BRCA*m and non-HRRm are 1.06,1.15 and 1.05 respectively, indicating potential OS detriment in non-*BRCA*m. However, FDA notes that the small sample size in each subgroup and

the exploratory nature of these subgroup analyses limited the interpretation of these results.

Table 22. rPFS (DCO1) and OS (DCO3) in Subpopulations Defined by Individual Test

	Olaparib + abiraterone N (# of events)	Placebo + abiraterone N (# of events)	Olaparib + abiraterone Median Survival (95% CI)	Placebo + abiraterone Median Survival (95% CI)	HR (95% CI)
Subgroup analysis for rPFS by INV					
ctDNA					
*BRCA*m	39 (12)	30 (25)	NR (17,NR)	8 (5,11)	0.18 (0.09, 0.36)
Non-*BRCA*m	328 (147)	337 (188)	24 (19,28)	17 (14,19)	0.78 (0.63, 0.97)
*HRR*m/Non-*BRCA*m	59 (30)	70 (41)	16 (9,NR)	17 (11,20)	0.93 (0.58, 1.48)
*HRR*m	98 (42)	100 (66)	NR (15,NR)	14 (9,17)	0.56 (0.38, 0.82)
Non-*HRR*m	269 (117)	267 (147)	24 (19,28)	19 (14,21)	0.76 (0.59, 0.96)
unknown	32 (9)	30 (13)	NR (19,NR)	NR (14,NR)	0.61 (0.26, 1.44)
Tumor tissue					
*BRCA*m	26 (9)	24 (18)	NR (15,NR)	10 (5,18)	0.31 (0.14, 0.69)
Non-*BRCA*m	243 (107)	242 (132)	24 (19,28)	17 (14,19)	0.78 (0.6, 1)
*HRR*m/Non-*BRCA*m	36 (13)	32 (19)	NR (15,NR)	19 (11,25)	0.62 (0.31, 1.25)
*HRR*m	62 (22)	56 (37)	NR (18,NR)	17 (11,19)	0.46 (0.27, 0.77)
Non-*HRR*m	207 (94)	210 (113)	23 (18,28)	17 (14,21)	0.82 (0.62, 1.07)
unknown	130 (52)	131 (76)	25 (17,NR)	16 (14,22)	0.64 (0.45, 0.92)
Subgroup analysis for OS					
ctDNA					
*BRCA*m	39 (12)	30 (21)	NR (NR,NR)	23 (16,28)	0.31 (0.15, 0.63)
Non-*BRCA*m	328 (154)	337 (175)	39 (36,NR)	36 (31,39)	0.89 (0.72, 1.11)
*HRR*m/Non-*BRCA*m	59 (36)	70 (39)	31 (24,39)	32 (26,NR)	1.18 (0.75, 1.87)
*HRR*m	98 (48)	100 (60)	36 (30,NR)	27 (24,34)	0.75 (0.51, 1.09)
Non-*HRR*m	269 (118)	267 (136)	42 (37,NR)	36 (32,40)	0.83 (0.65, 1.07)
unknown	32 (10)	30 (9)	NR (34,NR)	NR (31,NR)	1.01 (0.41, 2.48)
Tumor tissue					
*BRCA*m	26 (8)	24 (17)	NR (33,NR)	20 (16,34)	0.3 (0.13, 0.69)
Non-*BRCA*m	243 (115)	242 (110)	39 (35,NR)	44 (34,NR)	1.06 (0.81, 1.37)
*HRR*m/Non-*BRCA*m	36 (17)	32 (14)	36 (29,NR)	40 (33,NR)	1.15 (0.56, 2.33)
*HRR*m	62 (25)	56 (31)	NR (33,NR)	34 (26,NR)	0.63 (0.37, 1.06)

Non-*HRR*m	207 (98)	210 (96)	39 (35,NR)	44 (31,NR)	1.05 (0.79, 1.39)
unknown	130 (53)	131 (78)	NR (40,NR)	32 (26,39)	0.64 0.45, 0.91)

The table below shows the subgroup analysis results of *BRCA*m, *HRR*m and *HRR*m/non-*BRCA*m, aggregating the two test results. The aggregate analysis further confirmed that for patients who had *HRR* mutation but not *BRCA* mutation, i.e., *HRR*m/non-*BRCA*m, there was no clear efficacy benefit with a HR for rPFS per investigator of 0.8 (95% CI 0.5, 1.27) and a HR for OS of 1.02 (95% CI 0.65, 1.59).

Table 23. Efficacy results in *HRR*m and *HRR*m/non-*BRCAm* Subgroups with Aggregated Test Results

	Endpoint	*BRCA*m (n=85)	*HRR*m (n=226)	*HRR*m/non-*BRCA*m (n=141)
PROpel	rPFS (Investigator assessment)	0.24 (0.12, 0.46)	0.52 (0.36,0.76)	0.8 (0.5,1.27)
	OS	0.3 (0.15,0.6)	0.65 (0.45,0.94)	1.02 (0.65,1.59)

2. Comparison of ORR and OS among Patients with HRRm Genes

ORR and OS by each HRRm gene are shown in tables below. No consistent pattern suggesting clear evidence of harm was seen in efficacy analysis of any single HRR gene mutation in PROpel. In some of the HRRm/non*BRCA* subgroups (e.g., ATM and CDK12), the ORR was lower in the olaparib arm compared to the placebo arm. Caution regarding interpretation of these ORR results for individual HRRm genes is warranted given the small number of patients with each gene mutation.

Table 24. Confirmed ORR by BICR Subgroup Analyses by HRR gene mutations (DCO2)

	Confirmed ORR by BICR, n (%)	
HRR gene mutation	**Olaparib + Abiraterone**	**Placebo + Abiraterone**
Single gene mutation		
BRCA1	0	0/2 (0)
BRCA2	8/13 (62)	2/10 (20)
ATM	5/12 (42)	9/13 (69)
BARD1	0	1/ 2 (50)
BRIP1	0	0
CDK12	7/10 (70)	2/4 (50)
CHEK1		0
CHEK2	1/ 4 (25)	4/5 (80)
FANCL	1/3 (33)	0
PALB2	1/1 (100)	1/3 (33)
RAD51B	0	0
RAD51C	0	0
RAD51D	0	0

RAD54L	0	1/1 (100)

Table 25. OS Subgroup Analyses by HRR Gene Mutations (DCO3)

Single HRR gene mutation	Events, n (%)	
	Olaparib + Abiraterone	Placebo + Abiraterone
BRCA1	1/6 (17)	3/3 (100)
BRCA2	6/30 (20)	18/28 (64)
ATM	9/21 (43)	15/28 (54)
BRIP1	0	0/1
PALB2	2/3 (67)	¾ (75)
RAD51C	0	0
BARD1	0	½ (50)
CDK12	9/19 (47)	15/21 (71)
CHEK1	0	0
CHEK2	4/7 (57)	6/12 (50)
FANCL	2/3 (67)	0
RAD51B	0	0/1
RAD51D	0	1/1 (100)
RAD54L	2/3 (67)	0/2

3. Analyses Results of Other Efficacy Endpoints for ITT population

The Applicant provided the following results for other efficacy endpoints. These demonstrate that the olaparib arm has a numerically favorable improvement in the endpoints of time to first subsequent therapy or death, time to first symptomatic skeletal related event (SSRE) and PFS2. However, the HRs are >1 for the pain related endpoints including time to pain progression (TTPP) and time to opiate use for cancer-related pain. Since the study is not adequately powered for these exploratory endpoints, these efficacy analyses are considered exploratory only.

Table 26. Summary of Other Efficacy Endpoints (FAS, DCO1)

	Olaparib+abiraterone N = 399	Placebo+abiraterone N = 397
Time to first subsequent therapy or death		
Number of events (%)	183 (45.9)	221(55.7)
Median TFST (95% CI) (months)	25.0 (22.2, NC)	19.9 (17.1, 22.0)
HR (95% CI) [1]	0.74 (0.61, 0.90)	
TTPP (BPI-SF worst pain)		
Number of events (%)	56 (14.0)	54 (13.6)
Median TTPP (95% CI) (months)	NC	NC
HR (95% CI) [1]	1.01 (0.69, 1.47)	
Time to opiate use for cancer-related pain		

Number of events (%)	48 (14.0)	42 (11.9)
Median time to opiate use for cancer pain (95% CI) (months)	NC	NC
HR (95% CI) [1]	1.08 (0.71, 1.64)	
Time to first SSRE		
Number of events (%)	37 (9.3)	47 (11.8)
Median time to first SSRE (95% CI) (months)	NC	NC
HR (95% CI) [1]	0.72 (0.47, 1.11)	
PFS2		
Number of events (%)	70 (17.5)	94 (23.7)
Median PFS2 (95% CI) (months)	NC	NC
HR (95% CI) [1]	0.69 (0.51, 0.94)	

[1] HR and CI were calculated using a Cox proportional hazards model adjusted for Metastases and Docetaxel treatment at mHSPC stage as covariates, with the Efron approach used for handling ties. HR < 1 favors the olaparib arm.
Source: Table 34 of the CSR

8.1.3. Study 8, Part B Design

Trial Design

The Applicant's Description:

Study 8 was a 2-part study in patients with mCRPC. Part A was an open-label safety run-in study of olaparib when given in addition to abiraterone. Part B was a randomized, double-blind, placebo-controlled, parallel group study of the dose of olaparib selected from Part A in combination with abiraterone. Part B was conducted in North America and Europe.

Part B was similar in design to PROpel (Table 3). This section notes major design aspects of Part B that differed from PROpel (Section 8.1.1).

Patients randomized in Part B must have received chemotherapy in the form of docetaxel treatment for mCRPC, and had to have an ECOG performance status of 0 to 2.

Approximately 140 patients were to be randomized in a 1:1 ratio to receive either olaparib or placebo, each combined with abiraterone and prednisone or prednisolone. Randomization was not stratified.

Full details of the design of Part B are provided in the Study 8 CSP (Appendix 16.1.1, Study 8 CSR, Module 5.3.5.1).

The FDA's Assessment:

The efficacy of the combination of olaparib and abiraterone in an HRRm unselected population was also evaluated in Study 8 (NCT01972217), which was a randomized, double blind, placebo controlled, multicenter phase 2 study of olaparib vs placebo given in combination with abiraterone, in patients with mCRPC who had received prior chemotherapy containing docetaxel. Study 8 met its primary endpoint, demonstrating a statistically significant improvement in investigator-assessed rPFS in the olaparib plus abiraterone combination arm (14 months) vs placebo (8 months), in patients with mCRPC who had disease progression on prior taxane treatment.

As discussed in Section 7.1, the Applicant initially submitted Study 8 results to the FDA as part of the background package of a meeting request in 2018 in support of an accelerated approval. In May 2018, in a meeting with the Applicant, FDA discouraged submission of an application for accelerated approval, since Study 8 was a small exploratory study with low confidence in the results, and that the majority of patients had unknown HRR mutation status which might lead to imbalances between the two arms. The Applicant, agreed to not pursue an accelerated approval based on Study 8 alone.

At the time of submission of the PROpel results in June 2022, the Applicant also submitted updated Study 8 results including rPFS by BICR assessment and overall survival by HRR mutation status of the tumor. However, the analysis of rPFS by BICR assessment showed that there was no statistically significant difference between the arms in the ITT population with HR of 0.95. In addition, when considering the same three groups of *BRCA* status that FDA assessed in PROpel, 16% of patients in Study 8 had non-*BRCA*m status. In this subgroup, the observed HRs for rPFS by BICR assessment and OS were above 1, which is concerning for potential harm from olaparib in patients without a *BRCA* mutation in their tumor (See the FDA's table in Section 8.1.4).

Although interpretation of Study 8 results is limited by the small number of patients, the efficacy results in the subgroups with non-*BRCA*m and "Undetermined" status are consistent with the efficacy results for these subgroups in PROpel. When findings from two separate trials are consistent, they are less likely to be merely due to chance and further raises the concern for lack of efficacy and potential harm from olaparib in patients without a *BRCA* mutated tumor.

Results of Study 8 are consistent with the results of PROpel in ITT population. As the indicated population is *BRCA*m mCRPC and number of patients with *BRCA*m tumor in Study 8 was very small, FDA did not include information about Study 8 in product labeling although inclusion of the efficacy results in ITT was originally proposed by the Applicant.

Study Endpoints

The Applicant's Description:

The primary endpoint was rPFS, according to RECIST 1.1 (for soft tissue disease) and/or PCWG-2 criteria (for bone disease) as assessed by the investigator. rPFS was defined as the time from

randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomized therapy or received another anti-cancer therapy prior to progression.

No key secondary endpoints were defined.

The FDA's Assessment:
FDA has no additional comment.

Statistical Analysis Plan and Amendments

The Applicant's Description:
It was planned to perform an analysis of the primary endpoint, rPFS, of Part B, followed by a final analysis of PFS2 and OS. Owing to the anticipated number of deaths at the DCO for rPFS, it was decided to perform a single analysis to include all endpoints. A comprehensive SAP was prepared before database lock and unblinding of the data.

Censoring
Patients who were not known to have progressed or died at the time of the analysis were censored at the time of the latest date of assessment from either their last evaluable RECIST 1.1 assessment or their last evaluable PCWG-2 assessment. If the patient progressed or died after 2 or more missed visits they were censored at the time of the latest evaluable RECIST 1.1 or PCWG-2 assessment.

Analysis of the Primary Endpoint
rPFS was analyzed using the log rank test, with the HR and its corresponding 80% and 95% CIs estimated from the test. A 1-sided p-value was calculated to test the hypothesis of HR < 1 (olaparib improves survival) vs the null hypothesis of HR = 1 (no treatment effect).

Separate log rank tests compared rPFS between treatments in subsets of patients based on key baseline demographics and disease characteristics (eg, age, race, ECOG) as well as *ATM*, *BRCA*, composite *BRCA*/*ATM* and composite HRR mutation categories. Analyses were not presented if there were < 5 events in either treatment arm per subgroup.

Supportive analyses assessed time evaluation bias, attrition bias, and censoring bias. The primary rPFS analysis was also repeated using only PCWG-2 progression events.

Analysis Populations
The FAS (ITT) was used for the primary efficacy analysis. This included all randomized patients in Part B, regardless of the treatment actually received, including patients who did not receive study treatment.

Changes to the Planned Analyses
Important changes to the planned analyses are summarized in . Other changes are described in

Section 5.8.2, Study 8 CSR, Module 5.3.5.1.

Table 27. Applicant – Changes to Planned Analyses in Study 8, Part B

Timing of change	Details of change
Before unblinding of study data	• Log rank test replaced Cox proportional hazard model as primary analysis for time-to-event endpoints. • Changed the description of the log rank test such that it did not suggest using a stratified log rank test. Added 95% CI for HR to be reported. The 30-month survival rates were not to be provided in the associated statistics. • Updated primary efficacy subgroup analysis plans by inclusion of an additional subgroup consisting of patients with 12 other (beside *ATM*, *BRCA1/2*) gene mutations from the HRR group. Removed erythroblast transformation-specific related gene expression/fusion status subgroup. The minimum 20 endpoint events per subgroup/arm condition was replaced with minimum 5 events. • New category ("Not applicable [NA]") was added to the target lesions and nontarget lesions response outcomes. • The previously defined HRR mutation composite classification (including 12 additional genes but with *BRCA1*, *BRCA2*, *ATM* excluded) was replaced by a new composite mutation subgroup based on all 15 HRR genes.

The FDA's Assessment:
FDA has no additional comment.

Protocol Amendments

The Applicant's Description:
Important amendments to the CSP are summarized in . Other amendments are described in Section 5.8.1, Study 8 CSR, Module 5.3.5.1.

Table 28. Applicant – Important Protocol Amendments in Study 8, Part B

Protocol version / date of internal approval	Details of change
Version 2.0 / August 15, 2014 (after start of participant recruitment)	• Frequency of clinic visits increased to every 4 weeks for first 52 weeks. • Log rank test replaced Cox proportional hazard model as primary analysis for time-to-event endpoints. • Text referring to a separate study to be run in chemotherapy-naïve CRPC patients was removed. • Inclusion of additional ECOG assessments to randomized part of study, follow-up discontinuation of study treatment. • Changes to the text relating to definition of Hy's law cases. • Text added regarding paternal exposure.
Version 3.0 / October 13, 2015 (after start of participant recruitment)	• Changes to text relating to contraception during the study. • Text regarding olaparib DDIs updated. • Text added to state that once olaparib/placebo dose has been reduced, escalation is not permitted. • Text regarding olaparib anemia management updated.

The FDA's Assessment:

FDA has no additional comment.

8.1.4. Study 8, Part B Results

Compliance with Good Clinical Practices

The Applicant's Position:
Study 8 was performed in compliance with, similar to PROpel (Section 8.1.2).

The FDA's Assessment:
FDA has no additional comment.

Financial Disclosure

The Applicant's Position:
See Section 19.2.

The FDA's Assessment:
FDA has no additional comment.

Patient Disposition

Data/The Applicant's Position:
In Part B, a total of 142 patients were randomized at 36 sites in 11 countries: Europe (31 sites) and North America (5 sites). All randomized patients received treatment with olaparib or placebo, each co-administered with abiraterone and prednisone/prednisolone. In the olaparib+abiraterone arm, 64 (90.1%) patients discontinued treatment with olaparib and in the placebo+abiraterone arm, 63 (88.7%) patients discontinued treatment with placebo. The proportion of patients who discontinued olaparib/placebo due to an AE was lower in the placebo+abiraterone arm compared with the olaparib+abiraterone arm (7 [11.1%] patients vs 19 [29.7%] patients).

The FDA's Assessment:
FDA has no additional comment.

Protocol Violations/Deviations

Data/The Applicant's Position:
Important protocol deviations were reported for a total of 4 patients in the olaparib+abiraterone arm and 2 patients in the placebo+abiraterone arm. Eligibility criteria were violated in 3 patients in the olaparib+abiraterone arm and 1 patient in the placebo+abiraterone arm; the remaining deviations were related to investigational product compliance. These protocol deviations were not considered to have impacted either the data results, or their interpretation.

The FDA's Assessment:
FDA has no additional comment.

Demographic and Other Baseline Characteristics

Data/The Applicant's Position:
The 2 treatment groups differed in respect of some demographic and baseline characteristics that could have affected disease prognosis, being worse in the olaparib+abiraterone arm compared with the placebo+abiraterone arm:

- Patients in the olaparib+abiraterone arm were generally older than those in the placebo+abiraterone arm (median age: 70 years vs 67 years).
- The mean time from initial diagnosis of prostate cancer to first dose was longer in the olaparib+abiraterone arm compared with the placebo+abiraterone arm (68.1 months vs 59.5 months).
- A higher percentage of patients in the olaparib+abiraterone arm had AJCC Stage IV disease at diagnosis compared with the placebo+abiraterone arm (50.7% vs 38.0%).
- Median (range) baseline PSA was higher in the olaparib+abiraterone arm compared with the placebo+abiraterone arm (86.20 µg/mL [0.2 to 3475.4 µg/mL] vs 46.82 µg/mL [1.4 to 3140.0 µg/mL], respectively).

Overall, the demographic and baseline disease characteristics were representative of the intended patient population.

The FDA's Assessment:
FDA has no additional comment.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data/The Applicant's Position:
Mean (SD) compliance with olaparib/placebo was similar in the olaparib+abiraterone arm (95.23% [7.730%]) and the placebo+abiraterone arm (97.65% [7.117%]). The proportion of patients administered abiraterone to protocol was 85.9% in the olaparib+abiraterone arm and 88.7% in the placebo+abiraterone arm. Four patients in the olaparib+abiraterone arm were considered as noncompliant (ie, <80%). One of these patients had an important protocol deviation relating to compliance.

Allowed concomitant medications administered are summarized in the Study 8 CSR, Table 11.1.17. No disallowed concomitant medications were received.

The FDA's Assessment:
FDA has no additional comment.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

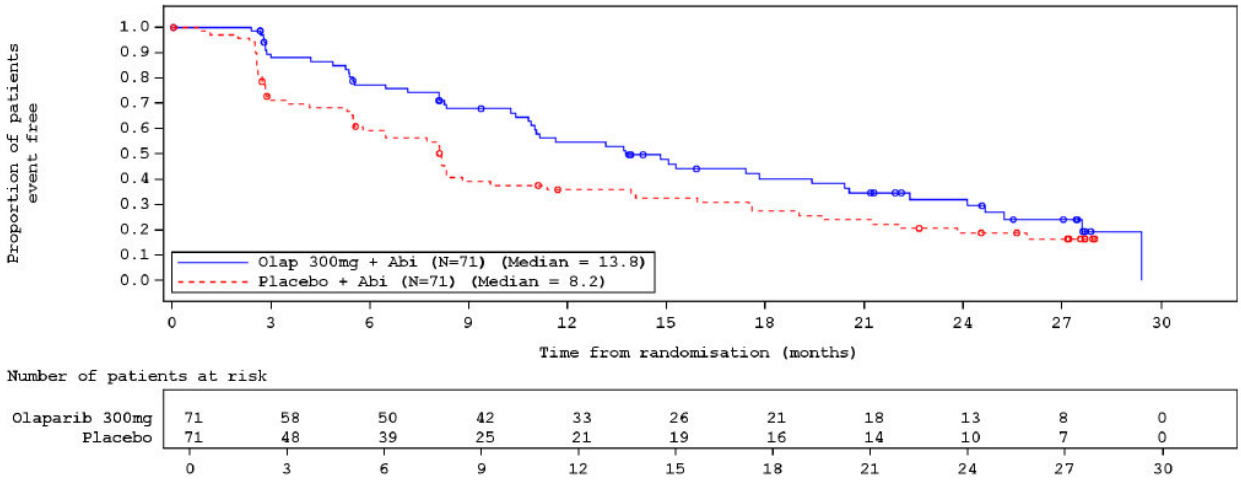
Data:

Table 29. Applicant - rPFS Using the Log Rank Test, Primary Analysis, Study 8, Part B (FAS)

Group	N	Number (%) of patients with events	Median rPFS time (months)	Comparison between groups				
				HR	80% CI	95% CI	2-sided p-value	1-sided p-value
Olaparib+ abiraterone	71	46 (64.8)	13.8	0.651	0.502, 0.844	0.438, 0.969	0.034	0.017
Placebo+ abiraterone	71	54 (76.1)	8.2					

Source: Data derived from Tables 11.2.2.2.1, 11.2.2.2.9 and 11.2.10.1, Study 8 CSR, Module 5.3.5.1 (DCO: 22 September 2017).
Dataset: ADEFFON, RSQS

Figure 11. Applicant – rPFS, Kaplan-Meier Plot, Study 8, Part B (FAS)



Source: Data derived from Figure 11.2.2.2.11.1, Study 8 CSR, Module 5.3.5.1 (DCO: 22 September 2017).
Dataset: ADEFFON

Subgroup Analyses

Results of all subgroup analyses are presented in the Study 8 CSR, Table 11.2.2.6.2.

Table 30 . Applicant – rPFS Using the Log Rank Test in HRR(15) Mutation Subgroups, Study 8, Part B (FAS)

Subgroup	Group	N	Number (%) of patients with events	Median rPFS time (months)	Comparison between groups				
					HR	80% CI	95% CI	2-sided p-value	1-sided p-value
HRRm positive	Olaparib+abiraterone	11	8 (72.7)	17.8	0.744	0.375, 1.477	0.261, 2.123	0.581	0.290
	Placebo+abiraterone	10	7 (70.0)	6.5					
HRRm negative	Olaparib+abiraterone	15	8 (53.3)	15.0	0.521	0.311, 0.873	0.237, 1.148	0.106	0.053
	Placebo+abiraterone	20	17 (85.0)	9.7					
HRRm	Olaparib+abiraterone	45	30 (66.7)	13.1	0.669	0.476,	0.398,	0.130	0.065

Subgroup	Group	N	Number (%) of patients with events	Median rPFS time (months)	Comparison between groups				
					HR	80% CI	95% CI	2-sided p-value	1-sided p-value
partly charact-erized	Placebo+abiraterone	41	30 (73.2)	6.4		0.940	1.126		

Source: Data derived from Tables 11.2.10.1 and 11.2.10.2, Study 8 CSR, Module 5.3.5.1 (DCO: 22 September 2017).
Dataset: ADEFFON, RSQS, RSPF

Sensitivity Analyses

Table 31. Applicant – Sensitivity Analyses for rPFS Using the Log Rank Test, Study 8, Part B (FAS)

Assessment for	Group	N	Number (%) of patients with events	Comparison between groups			
				HR	80% CI	95% CI	1-sided p-value
Attrition bias	Olaparib+abiraterone	71	47 (66.2)	0.672	0.514, 0.878	0.446, 1.011	0.028
	Placebo+abiraterone	71	49 (69.0)				
Evaluation time bias	Olaparib+abiraterone	71	46 (64.8)	0.648	0.500, 0.839	0.436, 0.963	0.016
	Placebo+abiraterone	71	54 (76.1)				
Excluding patients with deviations	Olaparib+abiraterone	71	46 (64.8)	0.651	0.502, 0.844	0.438, 0.969	0.017
	Placebo+abiraterone	71	54 (76.1)				
Only bone scan PCWG-2 progression events	Olaparib+abiraterone	71	30 (42.3)	0.733	0.519, 1.036	0.432, 1.244	0.125
	Placebo+abiraterone	71	28 (39.4)				

Source: Data derived from Tables 11.2.2.2.4, 11.2.2.2.6, 11.2.2.2.7 and 11.2.2.2.8, Study 8 CSR, Module 5.3.5.1 (DCO: 22 September 2017).
Dataset: ADEFFON

The Applicant's Position:

Study 8, Part B met its primary objective, demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed rPFS for olaparib vs placebo in combination with abiraterone with a median rPFS improvement of 5.6 months in the olaparib+abiraterone arm. The primary endpoint was tested at a 1-sided significance level of 2.5%.

Benefit of olaparib+abiraterone over placebo+abiraterone was seen across all predefined subgroups; median rPFS in these subgroups was generally consistent with the primary rPFS analysis. Subgroup analysis by HRRm status showed a consistent treatment effect across the HRRm, non-HRRm, and HRRm partly characterized subgroups.

All prespecified sensitivity analyses were consistent with the assessment of rPFS, confirming the robustness of the primary analysis.

The FDA's Assessment:

Study 8 met its primary efficacy endpoint by demonstrating an improvement in rPFS by investigator assessment with olaparib + abiraterone (N=71) compared to placebo + abiraterone (N=71) (HR 0.65 [95% CI 0.44, 0.97]); median rPFS was 13.8 months with olaparib + abiraterone vs 8.2 months with placebo + abiraterone. However, a subsequent sensitivity analysis of rPFS by BICR assessment submitted to the FDA during review of PROpel demonstrated a median rPFS of only 11.1 months in the olaparib + abiraterone arm vs 8.2 months with placebo + abiraterone; this difference was not statistically significant (HR 0.95 [95% CI: 0.62, 1.44]). There was also no statistically significant difference in OS between the two treatment arms in the ITT population (HR 0.91 [95% CI: 0.60,1.38]).

Study 8 subgroup analysis by *BRCAm* status

In an exploratory analysis by the three *BRCAm* status subgroups defined by the FDA for analysis of PROpel and described previously, 23 (16%) of 142 patients in Study 8 were found to have non-*BRCAm* status. In this subgroup, there was no statistically significant difference in rPFS by investigator assessment between arms. The HRs for rPFS by BICR assessment and for OS for olaparib + abiraterone vs. placebo + abiraterone in the non-*BRCAm* subgroup were both above 1, which raises concern for potential harm from the addition of olaparib in patients with non-*BRCAm* status. The detailed results are shown in the table below. Although not shown in the table, the HR of OS was consistently over 1 for non-*BRCAm* subgroups when two other classification methods proposed by Applicant were used to combine the tumor tissue, ctDNA and germline test results.

Table 32. Final Efficacy Results of Study 8

	ITT (N=142) Olaparib vs Placebo	*BRCAm* (5%) Olaparib vs Placebo	Undetermined *BRCAm* status (79%) Olaparib vs Placebo	Non-*BRCAm* (16%) Olaparib vs Placebo
N (Olaparib vs Placebo)	71 vs 71	2 vs 5	56 vs 56	13 vs 10
rPFS by INV				
Median, in months	14 vs 8	20 vs 3	15 vs 8	12 vs 11
HR (95% CI)	0.65 (0.44, 0.97)	NE[a]	0.62 (0.39, 0.98)	0.88 (0.33, 2.37)
rPFS by BICR				
Median, in months	11 vs 8	20 vs 3	11 vs 8	12 vs 11
HR (95% CI)	0.95 (0.62, 1.44)	NE	0.89 (0.56, 1.41)	1.72 (0.56, 5.76)
OS				
Median, in months	23 vs 21	23 vs 17	26 vs 21	**12 vs 25**
HR (95% CI)	0.91 (0.60 ,1.38)	NE	0.71 (0.43, 1.16)	**2.77 (1.06, 8.06)**

[a] Not estimable

Although interpretation of Study 8 results is limited by its small sample size, the efficacy results by exploratory subgroups based on *BRCA* mutation status are consistent with those of PROpel.

Notably, the results of both trials point to a possible OS detriment in patients with non-*BRCA*m tumors. When findings from two separate trials are consistent, they are less likely to be merely due to chance. This further raises the concern for lack of benefit and potential harm of treatment with olaparib for patients without *BRCAm* tumors.

Data Quality and Integrity

The Applicant's Position:
Quality assurance and quality control procedures were similar to PROpel (Section 8.1.2).

The FDA's Assessment:
FDA has no additional comment.

Dose/Dose Response

No new information is provided in the current submission.

Durability of Response

Data/The Applicant's Position:
For patients with an objective response and measurable disease at baseline, median DoR was similar in the olaparib+abiraterone arm (13.7 months) and the placebo+abiraterone arm (12.1 months).

The FDA's Assessment:
FDA has no additional comment.

Persistence of Effect

Data:
Results of rPFS, the primary endpoint, are summarized in Table 28 and Figure 11.

The Applicant's Position:
The primary endpoint was a time-to-event endpoint, to which persistence of efficacy over time is integral. The statistically significant and clinically meaningful improvement in rPFS for olaparib+abiraterone compared to placebo+abiraterone provides direct evidence of the persistence of efficacy.

The FDA's Assessment:
FDA has no additional comment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:
Results for FACT-P total score improvement rate, BPI-SF worst pain deterioration, and worst bone pain deterioration are presented in the Study 8 CSR, Section 7.1.3.

The Applicant's Position:
The results from the analyses of PRO measures showed no detriment for the olaparib+abiraterone arm compared with the placebo+abiraterone arm.

The FDA's Assessment:
FDA did not assess the PROs in study 8. As mentioned in Section 8.1.2, in PROpel, the number of patients reporting bother was consistently higher in the olaparib arm.

Additional Analyses Conducted on the Individual Trial

Data/The Applicant's Position:
No additional analyses were conducted.

The FDA's Assessment:
FDA has no additional comment.

8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:
See Section 8.1.7, "Integrated Assessment of Effectiveness" for assessment of effectiveness in the pivotal PROpel trial.

8.1.6. Assessment of Efficacy Across Trials

The data submitted and reviewed from PROpel was viewed in the context of emerging data from other clinical trials of PARPi, both in mCRPC and in other disease settings. These data contributed to the body of evidence showing that PARPi are most effective in patients with *BRCA*m, with less efficacy demonstrated, and possible OS detriment, in patients without *BRCA*m.

Large randomized, controlled trials of PARPi as monotherapy or in combination with NHAs in patients with prostate cancer have consistently shown a strong correlation between the presence of *BRCA* mutation and efficacy. The following table summarizes publicly available results from these clinical trials. Both 2nd line trials administered olaparib as monotherapy versus investigator's choice (PROfound: abiraterone or enzalutamide, TRITON-3: abiraterone, enzalutamide, or docetaxel) whereas MAGNITUDE randomized patients to abiraterone with or without niraparib and TALAPRO-2 randomized patients to enzalutamide with or without talazoparib. The rPFS improvement for subgroups with *BRCA*m is consistently greater than that in other subgroups, which suggests that efficacy is strongly attributable to the effect in these patients. For MAGNITUDE, enrollment into the cohort of patients with non-HRR tumor was stopped early due to futility in demonstrating efficacy for the addition of niraparib to abiraterone. In addition, all trials in the table below included *BRCA*m or HRRm as a stratification factor and/or selected patients based on their prospectively assessed tumor mutation status.

Table 33. rPFS Analysis in Other Trials of PARPi in mCRPC

Clinical Trial	PARPi	Line	Stratified by HRRm or *BRCA*m	HR for rPFS (PARPi arm vs. control)		
				*BRCA*m	HRRm	Non-HRRm
PROfound[a]	Olaparib	2nd	All patients selected for tumor HRRm	0.22	0.49	None Enrolled
TRITON-3[b]	Rucaparib	2nd	Yes	0.50	0.61 (*BRCA* + ATM)	None Enrolled
MAGNITUDE[b]	Niraparib	1st	Yes	0.55	0.76	Stopped early for futility
TALAPRO-2[b]	Talazoparib	1st	HRRm only	Not Presented	0.46	0.69

[a] sNDA submission for olaparib; [b] ASCO GU 2023

The strength of *BRCA* mutation as a predictive biomarker for PARPi, including lack of benefit in patients without tumor *BRCA* mutations, has also been demonstrated across other solid tumors such as ovarian cancer (Table 33). In two trials (NOVA and ARIEL3) for patients with metastatic ovarian cancer in which PARPi were used for maintenance treatment in the frontline setting, the rPFS benefit was substantially greater in the *BRCA*m subgroup. The hazard ratio (HR) estimates for OS in the non-*BRCA*m subgroups at the final analysis in both trials were above 1. Due to concern for potential OS detriment from treatment with PARP inhibitors in non-*BRCA*m subgroups, the FDA subsequently restricted both indications to patients with *BRCA*-mutated tumors.

Table 34. Selected Clinical Trials of PARPi in Ovarian Cancer

Clinical Trial	PARPi	Setting	Endpoint	HR (PARPi vs. control arm)		Change to Labeling Non-*BRCA*m
				*BRCA*m	*Non-BRCA*m	
NOVA[a-c]	Niraparib	2nd-line maintenance	PFS	0.26	0.45	Restricted indication to g*BRCA*m[g] (Dec 8, 2022)
			Final OS	0.85	1.06	
ARIEL3[d, e]	Rucaparib	2nd-line maintenance	PFS	0.23	0.44 and 0.58 (high and low LOH[f])	Restricted indication to t*BRCA*m (Dec 21st, 2022)
			Final OS	0.83	1.08	

[a] Mirza et al. NEJM 2016; [b] USPI for niraparib; [c] www.gsk.com; [d] Coleman et al. Lancet 2017; [e] https://clovisoncology.com; [f] LOH = loss of heterozygosity; [g] g*BRCA*: germline *BRCA* mutation; [h] t*BRCA*: tumor *BRCA* mutation.

In summary, there is accumulating clinical evidence across trials of solid tumors showing lack of benefit and potential OS detriment from treatment with PARPi in patients without *BRCA*m tumors.

8.1.7. Integrated Assessment of Effectiveness

Data/The Applicant's Position:

In the PROpel FAS at the interim rPFS analysis (DCO1: 30 Jul 2021), there was a statistically significant and clinically meaningful 34% reduction in the risk of radiological disease progression or death (HR 0.66; 95% CI 0.54, 0.81; p < 0.0001) with a median rPFS improvement of 8.2 months in the olaparib+abiraterone arm (24.8 months vs 16.6 months) over the current standard of care. The magnitude of improvement that olaparib adds to abiraterone can be further quantified by the rPFS Kaplan-Meier estimates which show that over half (51.4%) of olaparib+abiraterone-treated patients were alive and progression free after two years compared to approximately a third (33.6%) of placebo+abiraterone-treated patients. The sensitivity analysis of rPFS by BICR (HR 0.61; 95% CI 0.49, 0.74; nominal p < 0.0001) with a median rPFS improvement of 11.2 months in the olaparib+abiraterone arm (27.6 months vs 16.4 months) was consistent with the investigator-based analysis. Furthermore, all pre-planned sensitivity analyses of rPFS were consistent with the primary rPFS analysis, indicating robustness of the results.

The median rPFS with olaparib+abiraterone (24.8 months by the investigator and 27.6 months by BICR) was the longest reported to date in a population consisting of both symptomatic and asymptomatic/mildly symptomatic patients were eligible as well as patients with visceral metastases as long as they were considered candidates for abiraterone by the investigator. The median rPFS achieved with olaparib+abiraterone in the PROpel trial now exceeds the median OS achieved with docetaxel in this setting (TAX327: 18.9 months and CALGB 90401: 21.5 months) demonstrating the step change the combination of olaparib+abiraterone brings to patients with mCRPC.

In PROpel, the control arm performed as anticipated. Median rPFS was 16.6 months in the placebo+abiraterone arm which is similar to the median rPFS of 16.5 months reported on the abiraterone arm of the COU-AA-302 trial (Ryan et al 2013). Recognizing the limitations with cross-study comparisons, including differences in patient populations, this shows that abiraterone in the control arm in PROpel performed consistently in comparison to prior trials. PROpel was not fully powered to demonstrate a statistically significant difference in OS. OS data takes longer to mature than rPFS data and are confounded by crossover and multiple subsequent lines of therapy.

The interim OS data at the time of the final rPFS analysis (DCO2: 14 Mar 2022) were 40.1% mature (319 events/796 patients) with a smaller proportion of deaths reported in the olaparib+abiraterone arm (37.1% vs 43.1% in the placebo+abiraterone arm). There was a continued trend towards improved OS for olaparib+abiraterone-treated patients. Importantly compared to the Kaplan-Meier curve at DCO1, the Kaplan-Meier curves at DCO2 showed clear separation between the arms after approximately 22 months before extensive censoring was observed. No survival detriment was observed in any pre-defined subgroup. A final OS analysis is scheduled to take place approximately 48 months after the first patient was randomized (4Q2022), when a minimum follow-up of 32 months is expected.

At DCO1 (30 Jul 2021), clinical benefit was also seen in the pre-defined rPFS exploratory subgroup analyses based on stratification factors, baseline characteristics, and HRRm status. In

line with the scientific rationale and the clinical evidence provided in Study 8, a clinically meaningful rPFS improvement was observed with olaparib+abiraterone compared with placebo+abiraterone across the HRRm, non-HRRm, and HRRm unknown subgroups. Despite some numerical differences, all observed HR point estimates were associated with a clinically meaningful improvement of at least 5 months in favour of the olaparib+abiraterone arm, irrespective of HRR gene mutation status.

In PROpel, there was no overall detriment to HRQoL (ie, FACT-P and BPI-SF scores) observed across time points in either treatment arm indicating that the combination of olaparib+abiraterone did not negatively impact patients' HRQoL.

Supportive evidence for olaparib in combination with abiraterone in patients with mCRPC is derived from Study 8. Study 8 also met its primary endpoint, which demonstrated a statistically significant and clinically meaningful improvement in investigator-assessed rPFS for olaparib vs placebo in combination with abiraterone (HR 0.651; 95% CI 0.438, 0.969; p=0.034) with a median rPFS improvement of 5.6 months in the olaparib+abiraterone arm (13.8 months vs 8.2 months). Compared with PROpel, patients in Study 8 had received up to two prior lines of chemotherapy in the mCRPC setting including docetaxel.

In Study 8, the secondary endpoints of PFS2, TFST, TSST, and OS numerically favored the olaparib+abiraterone arm. Subgroup analysis showed a clinically meaningful effect in both HRRm and non-HRRm subgroups. Results from the PRO analyses in Study 8 also showed that the combination of olaparib+abiraterone did not negatively impact patients' HRQoL and symptoms compared with placebo+abiraterone.

Overall, the PROpel study, supported by the data from Study 8, demonstrates that olaparib in combination with abiraterone provides significant benefit to patients in the intended indication. When taken together, olaparib in combination with abiraterone provides meaningful clinical efficacy for both treatment-naïve and pre-treated patients in the mCRPC setting delaying the progression or relapse of mCRPC without a detrimental effect on HRQoL.

The FDA's Assessment:

In PROpel, the primary efficacy endpoint of rPFS by investigator was statistically met for the ITT population at DCO1 with 394 rPFS events (87% IF and 49.5% maturity) and this was thus considered to be the final rPFS analysis. The median rPFS was 25 months (95% CI: 20, 28) in the olaparib+abiraterone arm and 17 months (95% CI: 14, 19) in the placebo+abiraterone arm, respectively. The stratified hazard ratio (HR) for rPFS was 0.66 (95% CI: 0.54, 0.81; p<0.0001). At the final OS analysis (DCO3) with 381 OS events (47.9% maturity), the key secondary endpoint of OS was not met for the ITT population. The stratified HR for OS was 0.81 (95% CI: 0.67, 1.00; p=0.0544) and the median OS was 42 months (95% CI: 38, not reached) in the olaparib+abiraterone arm and 35 months (95% CI: 31, 39) in the placebo+abiraterone arm, respectively.

Subgroup analysis by *BRCA*m status was conducted post-hoc. *BRCA* gene mutation status was

assessed retrospectively by both NGS-based tissue and ctDNA tests. Mutation classification criteria in line with the FDA-approved assays were used to determine the deleterious and suspected deleterious somatic or germline mutation status. Of the 796 patients tested, 85 (11%) had *BRCA* mutation (*BRCA*m) determined by either a positive ctDNA test (9%) or a tumor tissue test (6%).

A statistically significant improvement in rPFS for olaparib+abiraterone compared to placebo+abiraterone was observed in the subgroup of patients with *BRCA*m. The HRs for rPFS and OS for *BRCA*m were 0.24 (95% CI: 0.12,0.46) and 0.3 (95% CI: 0.15,0.6). In the subgroup of 711 patients (89%) without a positive *BRCA* test result, the rPFS hazard ratio was 0.77 (95% CI: 0.63, 0.96) and the OS hazard ratio was 0.92 (95% CI: 0.74, 1.14), indicating that the improvement in the ITT population was primarily attributed to the results seen in the *BRCA*m population. Thus, given modest rPFS benefit in the 89% of patients without a positive *BRCA* test result, coupled with the add-on design, the FDA review team concluded that substantial evidence of efficacy was demonstrated only in patients with *BRCA*m.

FDA does not agree with the Applicant's statement about no detrimental effect of olaparib on HRQOL. Although a formal comparative tolerability endpoint was not included in the PROpel study, FDA noted higher proportions of patients in the olaparib arm who reported side effect bother compared to placebo. This is of greater concern for a population like that enrolled to PROpel, in which patients were mostly (70%) asymptomatic or minimally symptomatic at baseline compared to a later-line population with few available treatment options.

In the subgroup of 427 patients with non-*BRCA*m status defined by FDA where negative results were detected by both ctDNA and tissue-based tests, the HR estimate for rPFS was 0.85 (95% CI: 0.66, 1.11) and the HR estimate for OS was 1.06 (95% CI: 0.81, 1.39). The observation of OS HR over 1, together with the unfavorable Kaplan-Meier curves, indicated potential OS detriment for patients without *BRCA* mutation. Study 8, a similar but smaller trial to PROpel, similarly demonstrated lack of OS benefit from the combination of olaparib+abiraterone and possible harm in patients with *BRCA*m negative status by two tests. These results, combined with the accumulating clinical evidence across trials of solid tumors showing lack of benefit and potential OS detriment from treatment with PARPi in patients without *BRCA*m tumors (described in Section 8.1.6), as well as a nearly unanimous ODAC vote in favor of restricting the indication to *BRCA*m mCRPC (See Section 9) contributed to the decision to restrict the indication for the combination of olaparib+abiraterone.

The review team did not consider efficacy demonstrated in patients enrolled on PROpel with identified *HRR* mutations other than *BRCA*m. In this population, the HR for rPFS per investigator was 0.8 (95% CI 0.5, 1.27) and the HR for OS was 1.02 (95% CI 0.65, 1.59).

8.2. **Review of Safety**

Data/The Applicant's Position:

See individual sections below.

The FDA's Assessment:
See individual sections below for FDA's review.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety assessment is based primarily on DCO1 data (30 Jul 2021) from PROpel, the pivotal Phase III study in patients with mCRPC. The PROpel SAF comprises 398 patients exposed to olaparib+abiraterone and 396 patients exposed to placebo+abiraterone.

Data from PROpel is supported by the following:
• "Olaparib 300 mg bid pool": a large pooled safety database of olaparib 300 mg bid tablet data from 19 AstraZeneca-sponsored monotherapy studies (n=3155).
• "Olaparib and abiraterone pool": a pool of olaparib 300 mg bid tablet in combination with abiraterone 1000 mg qd data from Study 8, Part B and PROpel (n=469).
• "Olaparib monotherapy combined therapeutic dose pool": a large pool of olaparib capsule and tablet studies (n=4098).

The pooled data are presented to provide a robust analysis of the safety of olaparib. Since the olaparib safety profile is not considered dependent on a specific tumor type, the safety pools include patients with recurrent prostate cancer as well as patients with other solid tumors.

The FDA's Assessment:

In a written response only (WRO) meeting in February 2022, the FDA stated that the submitted data from DCO1 was not sufficient to provide a definitive response on whether the efficacy data would be sufficiently mature to support review of an sNDA. The FDA recommended that the Sponsor request another meeting to discuss the topline results from DCO2. At a Pre-NDA teleconference on 18 May 2022, the Applicant confirmed plan to submit an sNDA submission with PROpel as the pivotal study based on efficacy and safety data from DCO2. On 16 June 2022, the Applicant submitted the full application for this supplemental NDA, including complete safety datasets for both DCO1 and DCO2.

Therefore, after submission and review of data from DCO2, FDA based the safety evaluation on DCO2 because this more mature data cutoff provides a more complete picture of the safety profile from longer exposures that result from introducing therapy in the first-line treatment setting.

The following safety section was written by the Applicant primarily using safety data from DCO1. FDA's analyses use data from DCO2, which is also used as the basis of safety labeling.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Across the entire clinical program, as of June 15, 2021 (PBRER alignment), an estimated 17923 patients with prostate, ovarian, breast, pancreatic, gastric, or other solid tumors have received treatment with olaparib, both as a monotherapy and in combination with other agents. The number of patients exposed to study treatment in PROpel and the safety pools is presented in Section 8.2.1.

Table 35. Applicant – Duration of Treatment Exposure, PROpel (SAF) (DCO1: 30 Jul 2021)

Treatment	Treatment duration (days)	Olaparib+abiraterone N=398	Placebo+abiraterone N=396
Olaparib/ placebo	Median (range) total treatment duration	531.5 (13, 991)	476.5 (12, 927)
	Median (range) actual treatment duration	519.0 (11, 978)	464.5 (10, 927)
Abiraterone	Median (range) total treatment duration	555.0 (29, 991)	477.0 (12, 927)
	Median (range) actual treatment duration	534.0 (28, 988)	464.5 (10, 927)

Source: Data derived from Table 14.3.1.1, PROpel CSR, Module 5.3.5.1.
Dataset: RDEXON

Table 36. Applicant – Overall Extent of Olaparib or Placebo Exposure, PROpel (SAF) and Pooled Data (DCO1: 30 Jul 2021)

Month (days)	Number of patients (%)			
	PROpel SAF		Olaparib and abiraterone pool N=469	Olaparib 300 mg bid pool N=3155
	Olaparib+abiraterone N=398	Placebo+abiraterone N=396		
≥ Day 1	398 (100)	396 (100)	469 (100)	3155 (100)
≥ 1 month (30.4 days)	394 (99.0)	392 (99.0)	465 (99.1)	2981 (94.5)
≥ 3 months (91.3 days)	359 (90.2)	365 (92.2)	422 (90.0)	2577 (81.7)
≥ 6 months (182.6 days)	314 (78.9)	321 (81.1)	360 (76.8)	2107 (66.8)
≥ 12 months (365.3 days)	248 (62.3)	237 (59.8)	273 (58.2)	989 (31.3)
≥ 18 months (547.9 days)	191 (48.0)	159 (40.2)	206 (43.9)	548 (17.4)
≥ 24 months (730.5 days)	62 (15.6)	50 (12.6)	72 (15.4)	366 (11.6)
≥ 36 months (1095.8 days)	0	0	0	117 (3.7)
≥ 48 months (1461.0 days)	0	0	0	92 (2.9)
≥ 60 months (1826.3 days)	0	0	0	65 (2.1)
≥ 72 months (2191.5 days)	0	0	0	9 (0.3)

Source: Data derived from Table 2.7.4.1.9.2, Pooled Safety Outputs, Module 5.3.5.3.
Dataset: ADSL

The Applicant's Position:

The clinical program and associated safety data for olaparib are broader than the indication being sought in this application. The ICH E1 criterion for adequate exposure in support of

long-term use was met in both PROpel and the olaparib 300 mg bid pool (at least 100 patients treated for ≥ 1 year; ICH E1 Guideline 1995).

The FDA's Assessment:
At DCO2, the median total duration of exposure to olaparib and abiraterone in PROpel was 18.8 months and 20.1 months, respectively. This represents a relatively long duration of exposure in this relatively early line of therapy, which is a factor that the review team considered in the general assessment of the impact of toxicities in this clinical setting and in the context of the addition of olaparib to a highly effective therapy (abiraterone).

Relevant characteristics of the safety population:

Data:
Baseline demographic and disease characteristics are summarized in Section 8.1.2 for patients in PROpel, and in Section 8.1.4 for patients in Study 8, Part B.

The primary tumor location of most patients in the olaparib 300 mg bid pool was breast (40.9%) or ovary (36.2%). Patients with other primary tumor locations, including prostate (8.5%), pancreas (3.2%), fallopian tube (2.6%), and primary peritoneal (2.1%), were also treated in these studies.

The Applicant's Position:
In PROpel, the demographic and baseline characteristics were generally well balanced between the two treatment arms, in line with expectations and representative of the proposed indication. In addition to patients who were treatment naïve at the mCRPC stage in PROpel, the olaparib and abiraterone pool included patients in Study 8 who received up to two lines of prior chemotherapy in the mCRPC setting including docetaxel.

When comparing data from PROpel to the olaparib 300 mg bid pool, it is important to consider that the PROpel study investigated a combination of two active drugs while the olaparib 300 mg bid pool comprises data for olaparib monotherapy. In addition, pool consists of studies in heterogenous patient populations, with different demographic characteristics, the presence of concomitant medication, different tumor types, and different stages of disease. These differences might help to explain the observed differences in safety data between the olaparib 300 mg bid pool and PROpel:

• The majority of patients were female with ovarian/breast cancer (N = 2430, 77.1% of the olaparib 300 mg bid pool).
• Patients in the olaparib 300 mg bid pool were younger (mean age ranged between 43.3 and 68.6 years), compared to the older population in PROpel (mean age 68.5 years).
• Notably, patients in OlympiA (N = 911, 28.9% of the olaparib 300 mg bid pool) were treated with olaparib for one year in the adjuvant treatment setting.
• Stage of disease is variable. The olaparib 300 mg bid pool includes a wide range of patients with early breast cancer, to patients with advanced metastatic disease including mCRPC

(N = 256, 8.1% of the olaparib 300 mg bid pool).
• In general, patients with ovarian, breast and pancreatic cancer in the olaparib 300 mg bid pool did not have bone metastases, while in PROpel 87.5% of patients in the olaparib+abiraterone arm had bone metastases, which might increase the incidence and severity of hematological toxicity.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. The FDA safety assessment primarily focused on data from PROpel.

Adequacy of the safety database:

The Applicant's Position:
The safety data for the pivotal study PROpel, supplemented by pooled safety data for both olaparib in combination with abiraterone and olaparib monotherapy, are considered adequate to support the proposed indication in the US population.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Important protocol deviations were reported in 29 patients (7.3%) in the olaparib + abiraterone arm and 31 (7.8%) patients in the placebo + abiraterone arm. The most common important protocol deviation (10 patients [1.3%] overall) was 'failed inclusion criteria: metastatic status defined as at least one documented metastatic lesion on either a bone scan or a CT/MRI scan'.

Reviewer's comment: The incidence of protocol deviations was high but similar in terms of frequency and type between treatment arms, and they did not raise concerns regarding conduct.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
The submission contains all required components of the eCTD. The overall quality and integrity of the application is adequate for a substantive review to be completed. No meaningful concerns affecting a complete review of safety have been reported.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Categorization of Adverse Event

The Applicant's Position:

Adverse events and the AESI of pneumonitis are summarized descriptively as the number and percentage of patients reporting an AE with an onset from the time of first dose of study treatment to 30 days after last dose of study treatment. While study treatment is defined as olaparib, placebo, or abiraterone for PROpel, it is defined as olaparib for the olaparib and abiraterone pool. For the majority of studies with olaparib, reports for events of MDS/AML and NPMs continue to be collected beyond 30 days after the last dose of olaparib through the survival follow-up.

Standard terms for reported AEs were assigned using MedDRA Version 24.0 for the PROpel study, Version 24.0 for the olaparib 300 mg bid pool, and Version 24.0 for the olaparib and abiraterone pool. The severity of any AE was graded according to the NCI-CTCAE Version 4.03, where applicable.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Routine Clinical Tests

The Applicant's Position:
Safety measurements were conducted as per the schedule of assessments in the CSP for each study.

In line with the prescribing information for olaparib, baseline hematological testing was followed by monthly monitoring of complete blood counts for the first 12 months, and periodically after that time, to monitor for clinically significant changes during treatment.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

8.2.4. Safety Results

The incidence of AEs by category was similar between the olaparib+abiraterone arm of PROpel and the olaparib and abiraterone pool.

Deaths

Data/The Applicant's Position:
Narratives for all patients in PROpel who had an SAE leading to death on treatment or who died within 30 days of last dose are provided in Section 14.4, PROpel CSR, Module 5.3.5.1.

Most deaths in both arms were attributed by the investigator to progression of the disease under investigation only (71.0% of deaths [olaparib+abiraterone arm] and 76.0% of deaths [placebo+abiraterone arm]).

As of the interim rPFS analysis DCO of July 30, 2021, there were 33 AEs with a fatal outcome (16

patients [4.0%] in the olaparib+abiraterone arm and 17 patients [4.3%] in the placebo+abiraterone arm) during randomized treatment or 30 days following the last dose of randomized treatment.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment above, which reflects DCO1 data.

As of DCO2 (14 March 2022), there were 41 AEs with a fatal outcome (23 patients [5.8%] in the olaparib + abiraterone arm and 18 patients [4.5%] in the placebo + abiraterone arm) during randomized treatment or 30 days following the last dose of randomized treatment.

Table 37. PROpel: Grade 5 AEs (DCO2)

Preferred Term	Olaparaib + abiraterone (N=398)	Placebo + abiraterone (N = 396)
Any	23 (5.8%)	18 (4.5%)
COVID-19[a]	12 (3.0%)	3 (0.8%)
Pneumonia[b]	2 (0.5%)	1 (0.3)
Craniocerebral injury	1 (0.3%)	0
Duodenal ulcer	1 (0.3%)	0
Myocardial ischemia	1 (0.3%)	0
Respiratory failure	1 (0.3%)	0
Sudden death	1 (0.3%)	0
Death	0	3 (0.5%)
Sepsis[c]	0	3 (0.8%)
Acute kidney injury	0	1 (0.3%)
Acute pulmonary edema	0	1 (0.3%)
Coronary artery disease	0	1 (0.3%)
Diffuse large B-cell lymphoma	0	1 (0.3%)
Infection	0	1 (0.3%)
Intraventricular hemorrhage	0	1 (0.3%)
Ischemic stroke	0	1 (0.3%)

[a] Includes COVID-19, Covid 19 pneumonia, and suspected COVID-19
[b] Includes pneumonia, pneumonia bacterial, pneumonia aspiration
[c] Includes sepsis, pneumococcal sepsis, and staphylococcal sepsis

A higher incidence of death due to COVID-related AEs (COVID-19, COVID-19 pneumonia, or Suspected COVID-19) occurred in the olaparib + abiraterone arm of PROpel compared to the placebo + abiraterone arm (12 vs. 3). Investigators considered all 15 fatal COVID-related AEs to be unrelated to study treatment. Because PROpel was initiated before the availability of COVID-19 vaccines and effective anti-COVID drugs and biological products (the last patient was randomized on March 11, 2020), it is unclear what effect these would have had on the risk of severe COVID-19 in trial participants. Table 37 below summarizes the neutrophil counts of all patients on PROpel who experienced Grade 5 COVID-related AEs. With the exception of Subject (b) (6) in the olaparib + abiraterone arm, whose ANC was 0.7 on Study Day 906 when his AE of Confirmed COVID-19 pneumonia met SAE criteria, no subjects were neutropenic near the time of their events. This observation argues against olaparib-induced neutropenia as causal.

Table 38. PROpel Neutrophil Counts and COVID-19-Related Deaths (DCO2)

Subject ID	Preferred Term	Study day of onset	Study day met SAE criteria	Treatment arm	ANC near Study Day of onset	ANC near Study Day met SAE criteria	ANC at baseline
(b) (6)	COVID-19	724	724	Placebo + Abiraterone	2.81 (Day 707)	2.81 (Day 707)	3.42
	COVID-19	338	338	Placebo + Abiraterone	7.63 (Day 306)	7.63 (Day 306)	4.46
	Suspected COVID-19	564	567	Olaparib + Abiraterone	4.07 (Day 561)	4.07 (Day 561)	6.27
	COVID-19	348	348	Olaparib + Abiraterone	5.25 (Day 336)	5.25 (Day 336)	7.7
	COVID-19	196	206	Olaparib + Abiraterone	1.73 (Day 196)	1.73 (Day 196)	8.49
	COVID-19	436	437	Olaparib + Abiraterone	8.5 (Day 431)	8.5 (Day 431)	9.8
	COVID-19 pneumonia	990	995	Olaparib + Abiraterone	4.90 (Day 956)	4.90 (Day 956)	7.2
	COVID-19	601	601	Olaparib + Abiraterone	3.3 (Day 608)	3.3 (Day 608)	5.47
	COVID-19 pneumonia	361	361	Olaparib + Abiraterone	6.5 (Day 336)	6.5 (Day 336)	4.4
	COVID-19	666	666	Placebo + Abiraterone	7.7 (Day 648)	7.7 (Day 648)	6.27
	COVID-19 pneumonia	901	906	Olaparib + Abiraterone	2 (Day 901)	0.7 (Day 906)	7.5
	COVID-19 pneumonia	352	364	Olaparib + Abiraterone	5.75 (Day 337)	5.75 (Day 337)	3.4
	COVID-19	336	336	Olaparib + Abiraterone	7.38 (Day 312)	7.38 (Day 312)	12.95
	COVID-19	998	1000	Olaparib + Abiraterone	10.9 (Day 981)	10.9 (Day 981)	6.9
	COVID-19	189	192	Olaparib + Abiraterone	8.1 (Day 169)	8.1 (Day 169)	6.6

Serious Adverse Events

Data/The Applicant's Position:

In PROpel, SAEs were reported in a higher proportion of olaparib+abiraterone-treated patients (33.9%) compared with placebo+abiraterone treated patients (27.0%). The most common SAEs (≥ 2%) in the olaparib+abiraterone arm were anemia (5.8%), pulmonary embolism (3.3%), COVID-19 (3.0%), pneumonia (2.0%), and urinary tract infection (2.0%) and in the placebo+abiraterone arm, this was COVID-19 (9 patients [2.3%]). Serious adverse events were reported in a similar proportion of patients in the olaparib+abiraterone arm of PROpel (33.9%) and the olaparib and abiraterone pool (33.0%) and at a higher incidence than in the olaparib 300 mg bid pool (19.5%). These differences may be attributed to the reasons discussed in Section 8.2.2 – relevant characteristics of the safety population.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment above, which reflects DCO1 data.

In PROpel based on DCO2 data, SAEs were reported in a higher proportion of olaparib + abiraterone-treated patients (38.7%) compared with placebo + abiraterone treated patients (29.5%). The most common SAEs (≥ 2%) in the olaparib + abiraterone arm were COVID-19 and anemia (5.8% each), pneumonia (4.5%), pulmonary embolism (3.5%), and urinary tract infection (3.0%) and in the placebo + abiraterone arm, this was COVID-19 (3.0%).

Table 39. PROpel Serious Adverse Events Reported by ≥2% of Safety Population (DCO2)

Preferred Term	Olaparaib + abiraterone (N=398)	Placebo + abiraterone (N = 396)
Any	154 (38.7%)	117 (29.5%)
COVID-19[a]	23 (5.8%)	12 (3.0%)
Anemia	23 (5.8%)	3 (0.8%)
Pneumonia[b]	18 (4.5%)	7 (1.8%)
Pulmonary embolism	14 (3.5%)	3 (0.8%)
Urinary tract infection[c]	12 (3.0%)	5 (1.3%)

[a] Includes COVID-19, COVID-19 pneumonia, and suspected COVID-19
[b] Includes atypical pneumonia, Pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia viral
[c] Includes pyelonephritis, urinary tract infection, and urosepsis

Dropouts and/or Discontinuations Due to Adverse Effects

Data/The Applicant's Position:
In PROpel, the incidence of AEs leading to discontinuation of study treatment (either olparaib/placebo, and/or abiraterone, and/or prednisone/prednisolone) was 14.3% in the olaparib+abiraterone arm and 10.1% in the placebo+abiraterone arm. Adverse events leading to discontinuation of olaparib or placebo, regardless of action taken with abiraterone, were reported in a higher proportion of olaparib+abiraterone-treated patients (13.8%) than placebo+abiraterone-treated patients (7.8%). In line with the improved efficacy and tolerability of the combination arm in PROpel, the median total duration of exposure to olaparib was longer than that to placebo, and the median total duration of exposure to abiraterone was longer when combined with olaparib.

The most common Aes that led to discontinuation of olaparib in the olaparib+abiraterone arm were anemia (3.8%), COVID-19, and fatigue (0.8% each), which is consistent with the known safety profile of olaparib. The most common Aes that led to discontinuation of placebo in the placebo+abiraterone arm were ALT increased (1.0%), anemia, arthralgia, and AST increased (0.8% each). The incidence of adverse events leading to the discontinuation of olaparib was higher in the olaparib+abiraterone arm of PROpel (13.8%) than in the olaparib 300 mg bid monotherapy pool (9.5%).The most common Aes leading to discontinuation of olaparib in the olaparib 300 mg bid pool, were anemia, nausea, fatigue, and vomiting, consistent with the type of Aes leading to discontinuation of olaparib across the program.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment above, which reflects DCO1 data.

Per DCO2 data, AEs leading to discontinuation of olaparib or placebo, regardless of action taken with abiraterone, were reported in a higher proportion of olaparib + abiraterone-treated patients (15.8%) than placebo + abiraterone-treated patients (8.0%). The most common AEs leading to discontinuation of olaparib or placebo were anemia and pneumonia. The higher incidence of pneumonia leading to discontinuation of olaparib compared to placebo did not count known cases of COVID-19, as these were reported as a separate category.

Table 40. PROpel Dropouts/Discontinuations due to Adverse Events Reported by ≥1% of Safety Population (DCO2)

Preferred Term	Olaparaib + abiraterone (N=398)	Placebo + abiraterone (N = 396)
Any	63 (15.8%)	32 (8.1%)
Anemia	17 (4.3%)	3 (0.8%)
Pneumonia[a]	6 (1.5%)	0

[a] includes pneumocystis jirovecii pneumonia, pneumonia, and pneumonia bacterial

Dose Interruption/Reduction Due to Adverse Effects

Data/The Applicant's Position:
In PROpel, the incidence of AEs leading to dose reduction of study treatment (either olparaib/placebo, and/or abiraterone, and/or prednisone/prednisolone) was 25.1% in the olaparib+abiraterone arm, and 13.1% in the placebo+abiraterone arm. Adverse events leading to olaparib/placebo dose reductions were reported by a higher proportion of patients in the olaparib+abiraterone arm (20.1%) compared with the placebo+abiraterone arm (5.6%). The most common AE leading to olaparib dose reduction was anemia (10.3%), and the most common AE leading to placebo dose reduction was creatinine renal clearance decreased (1.0%). Adverse events leading to olaparib dose reductions were reported at a lower incidence in the olaparib+abiraterone arm of PROpel (20.1%) than in the olaparib 300 mg bid pool (22.3%).

In PROpel, the incidence of AEs leading to dose interruption of study treatment (either olparaib/placebo, and/or abiraterone, and/or prednisone/prednisolone) was 47.5% in the olaparib+abiraterone arm, and 29.8% in the placebo+abiraterone arm. Adverse events leading to olaparib/placebo dose interruptions were reported in a higher proportion of patients in the olaparib+abiraterone arm (44.7%) compared with placebo in the placebo+abiraterone arm (25.3%). The most common AE leading to olaparib dose interruptions was anemia (15.3%) and the most common AE leading to placebo dose interruptions was COVID-19 (2.0%). Adverse events leading to dose interruption of olaparib occurred at a higher incidence in the olaparib+abiraterone arm of PROpel (44.7%) compared with the olaparib 300 mg bid pool (37.8%).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment above, which reflects DCO1 data.

In PROpel based on DCO2 data, the incidence of AEs leading to olaparib/placebo dose reductions were reported by a higher proportion of patients in the olaparib + abiraterone arm (21.4%) compared with the placebo + abiraterone arm (5.6%). The most common AEs leading to olaparib dose reduction was anemia (10.3%) and fatigue (2.5%).

Table 41. PROpel Adverse Events Leading to Dose Reduction in ≥2% of Safety Population (DCO2)

Preferred Term	Olaparaib + abiraterone (N=398)	Placebo + abiraterone (N = 396)
Any	85 (21.4%)	22 (5.6%)
Anemia	41 (10.3%)	3 (0.8%)
Fatigue[a]	10 (2.5%)	3 (0.8%)

[a] Includes fatigue and anemia

In PROpel based on DCO2 data, the incidence of AEs leading to olaparib/placebo dose interruptions were reported in a higher proportion of patients in the olaparib + abiraterone arm (47.7%) compared with placebo in the placebo + abiraterone arm (27.3%). The most common AE leading to olaparib dose interruptions was anemia (16.3%), COVID-19 (6.0%), fatigue (3.5%), nausea (2.8%), pulmonary embolism (2.3%), and diarrhea (2.3%).

Table 42. PROpel Adverse Events Leading to Dose Interruption in ≥2% of Safety Population (DCO2)

Preferred Term	Olaparaib + abiraterone (N=398)	Placebo + abiraterone (N = 396)
Any	190 (47.7%)	108 (27.3%)
Anemia	65 (16.3%)	10 (2.5%)
COVID-19[a]	24 (6.0%)	10 (2.5%)
Fatigue[b]	14 (3.5%)	7 (1.8%)
Nausea	11 (2.8%)	5 (1.3%)
Diarrhea	9 (2.3%)	5 (1.3%)
Pulmonary embolism	9 (2.3%)	1 (0.3%)

[a] Includes COVID-19, COVID-19 pneumonia, and suspected COVID-19
[b] Includes fatigue and anemia

Significant Adverse Events

Data/The Applicant's Position:

Adverse Events of Grade 3 or Higher

A higher proportion of patients in the olaparib+abiraterone arm reported AEs of CTCAE Grade ≥ 3 (47.2%) compared with the placebo+abiraterone arm (38.4%). The most common AEs of CTCAE Grade ≥ 3 reported in the olaparib+abiraterone arm (≥ 2%) were anemia, pulmonary embolism, hypertension, lymphocyte count decreased, COVID-19, neutrophil count decreased, and urinary tract infection. In the placebo+abiraterone arm, they were anemia, hypertension,

and ALT increased. Adverse events of CTCAE Grade ≥ 3 occurred in a similar proportion of patients in the olaparib+abiraterone arm of PROpel (47.2%) and the olaparib and abiraterone pool (47.5%), and at a higher incidence than in the olaparib 300 mg bid pool (36.5%). These differences may be attributed to the reasons discussed in Section 8.2.2 – relevant characteristics of the safety population.

Myelodysplastic Syndrome/Acute Myeloid Leukemia
MDS/AML is considered an AESI for olaparib. At the time of DCO1 for PROpel, there were no reports of MDS/AML in the study. In the olaparib monotherapy combined therapeutic dose pool the estimated cumulative incidence for MDS/AML is 0.8%. Across the entire olaparib clinical development program with 17923 patients (as of June 15, 2021), the estimated cumulative incidence for MDS/AML is 0.5%, which includes events of MDS/AML from placebo controlled, blinded, monotherapy studies in which the treatment arm is unknown.

Venous thromboembolism
Venous thromboembolism is a common comorbidity in metastatic prostate cancer patients, especially in those receiving ADT (O'Farrell et al 2016). In PROpel, analysis of the 'Embolic and thrombotic events, venous' MedDRA SMQ showed a higher rate of VTE events (7.3% [olaparib+abiraterone arm] vs 3.3% [placebo+abiraterone arm]). The most common VTE event was pulmonary embolism (6.5% [olaparib+abiraterone arm] vs 1.8% [placebo+abiraterone arm]).

A review of data from across the olaparib clinical program has resulted in VTE being added as an ADR to the Lynparza core company datasheet. A higher incidence of VTE events has been noted in the olaparib arms of PROfound (7.8% on olaparib monotherapy vs 3.1% physician's choice of NHA treatment in patients with mCRPC) and PAOLA-1 (4.7% olaparib plus bevacizumab vs 1.7% placebo plus bevacizumab in the first-line treatment of ovarian cancer). In Study 8, the frequency of VTE events was low: pulmonary embolism was reported in 2 patients (2.8%) in the olaparib+abiraterone arm, and pulmonary embolism and thrombosis were reported in 1 patient each (1.4%) in the placebo+abiraterone arm (see Table 11.3.2.3, Study 8 CSR, Module 5.3.5.1). Although the incidence and event rate of VTEs are lower in other monotherapy studies, a slightly higher incidence of VTEs can be noted in the olaparib arms of SOLO2 and SOLO1.

A direct comparison between PROpel and the published literature data is challenging due to differences in follow-up time, patient selection, patient monitoring, and medical care. However, the incidence of VTEs observed in PROpel and additionally in PROfound and PAOLA-1 are consistent with the incidence reported in prostate cancer patients from the literature (Wong et al 2018, Deka et al 2019, Nguyen-Nielsen et al 2014, Sun et al 2016) and in the bevacizumab SmPC (described as a 'very common' ADR; Avastin SmPC). Although the observed incidence of VTEs across these Phase III studies is similar to the background rate in the respective patient populations, the consistent imbalance of VTEs between study arms and the lack of apparent alternative explanation suggest that there is at least a reasonable possibility for a causal association between olaparib and VTEs.

New Primary Malignancies
NPMs are an AESI and important potential risk of olaparib treatment. The incidence of NPMs reported in the olaparib+ abiraterone arm (3.0%) and the placebo+abiraterone arm (2.5%) in PROpel was similar to that reported in the olaparib and abiraterone pool (2.5%). In the larger olaparib monotherapy combined therapeutic dose pool, the estimated cumulative incidence for new primary malignancies is 1.0%. Across the entire olaparib clinical trial program with 17,923 patients (as of June 15, 2021), the estimated cumulative incidence for NPMs is 0.6%, which includes events of NPMs from placebo-controlled, blinded, monotherapy studies in which the treatment arm is unknown.

Following the marketing authorisation in December 2014 for olaparib capsules, and as of June 15, 2021, there have also been reports of NPMs from post-marketing surveillance, consistent with the characterization of the events reported from monotherapy clinical studies. This safety topic will continue to be kept under close surveillance as part of routine pharmacovigilance practice.

The types of new primary cancers reported in the olaparib clinical trial program were generally in line with secondary cancers observed in ovarian and breast cancer populations reported in the literature (Bergfeldt et al 1995, Fowble et al 2001, Wesolowski et al 2007) or were cancers, such as skin cancer, known to be the most common cancer in the general population and associated with high cure rates. Patients with *BRCA* mutations are also at increased risk of developing other primary cancers.

The number of reported events of new malignant tumors is low. A causal relationship between olaparib treatment and the development of NPMs has not been established. The benefits that patients may expect to receive from olaparib for the treatment of mCRPC are considered to outweigh the risk of the potential development of an NPM.

Pneumonitis
Pneumonitis is an AESI and important potential risk of olaparib treatment. The incidence of pneumonitis in the olaparib+ abiraterone arm (0.8%) and the placebo+abiraterone arm (0.8%) in PROpel was low and similar to that reported in the olaparib and abiraterone pool (1.1%) and the olaparib monotherapy combined therapeutic dose pool (0.9%).

The OlympiA study (D081CC00006) provided the most robust data source to assess the possible contribution of olaparib to the risk of developing pneumonitis, as the patient population was the largest (more than 900 patients per arm) and the youngest of the entire olaparib monotherapy therapeutic dose pool (median age: 42 years old). The review of new information received from PROpel, as well as the OlympiA study read-out and the cumulative review of pneumonitis events reported in the clinical development program and post-marketing setting did not provide evidence to support a causal relationship between olaparib and pneumonitis.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment above, which reflects DCO1 data.

Adverse Events of Grade 3 or Higher

A higher proportion of patients in the olaparib + abiraterone arm reported AEs of CTCAE Grade ≥ 3 (52.8%) compared with the placebo + abiraterone arm (40.4%). The most common AEs of CTCAE Grade ≥ 3 reported in the olaparib + abiraterone arm (≥ 2%) were anemia, pulmonary embolism, COVID-19, lymphocyte count decreased, hypertension, pneumonia, neutrophil count decreased, urinary tract infection and fatigue.

Table 43 . PROpel Grade ≥ 3 Adverse Events in ≥2% of Safety Population (DCO2)

Preferred Term	Olaparaib + abiraterone (N=398)	Placebo + abiraterone (N = 396)
Any	210 (52.8%)	160 (40.4%)
Anemia	63 (15.8%)	13 (3.3%)
Pulmonary embolism	28 (7.0%)	7 (1.8%)
COVID-19[a]	22 (5.5%)	10 (2.5%)
Lymphocyte count decreased[b]	20 (5.0%)	7 (1.8%)
Hypertension	15 (3.8%)	14 (3.5%)
Pneumonia[c]	14 (3.5%)	5 (1.3%)
Neutrophil count decreased[d]	14 (3.5%)	4 (1.0%)
Urinary tract infection[e]	12 (3.0%)	7 (1.8%)
Fatigue[f]	9 (2.3%)	6 (1.5%)

[a] Includes COVID-19, COVID-19 pneumonia, and suspected COVID-19
[b] Includes lymphocyte count decreased and lymphopenia
[c] Includes Pneumoncystis carinii pneumonia, pneumonia, pneumonia aspiration, and pneumonia bacterial
[d] Includes neutropenia and neutrophil count decreased
[e] includes pyelonephritis, urinary tract infection, urinary tract infection pseudomonal, and urosepsis
[f] Includes fatigue and asthenia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)

MDS/AML is considered an AESI for olaparib. At the time of DCO2 for PROpel, one report of MDS had been received (Subject (b) (6)). The olaparib prescribing information contains a warning and precautions for MDS/AML and this was not updated during review of the current application.

Venous thromboembolism (VTE)

The approval of olaparib in May 2020 for patients with deleterious or suspected deleterious germline or somatic HRR gene mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone was supported by the PROfound trial, which randomized patients to olaparib vs investigator's choice of enzalutamide or abiraterone. VTE was observed in a higher percentage of patients receiving olaparib arm of PROfound than in the enzalutamide or abiraterone arm (7% vs 3.1%). This difference was driven by higher numbers of reports of pulmonary embolism (6% vs 0.8%). This difference persisted after adjustment for differences in exposure between the two arms.

The incidence of VTE in PROpel was higher than that in the trials that supported earlier approvals of olaparib in patients with breast and ovarian cancer, and this led to the addition of VTE subheading in Section 5 of the USPI which only included information on incidence of VTE in patients with mCPRC on PROfound. This review updated those numbers to also include patients on PROpel with VTE.

Table 44 below summarizes the incidences of VTE in PROfound and PROpel. The incidence of VTE was comparable in the olaparib arm of each trial and was higher to a comparable extent than in the respective control arm. This supports the current restriction of the VTE subheading in Section 5 of the Lynparza PI to patients with mCRPC. The FDA updated section 5.3 with numbers from the pooled PROfound-PROpel population.

Table 44. Reports of VTE in PROfound and PROpel (DCO2)

	PROfound				PROpel				Pooled PROfound + PROpel			
	Olaparib (N=256)		Abiraterone/ Enzalutamide (N=130)		Olaparib (N=398)		Placebo (N=396)		Olaparib (N=654)		Control (N=526)	
	All grade	Grade 3-5	All grade	Grade 3-5	All grade	Grade 3-5	All grade	Grade 3-5	All grade	Grade 3-5	All grade	Grade 3-5
Pulmonary embolism	11 (4.3%)	6 (2.3%)	1 (0.8%)	1 (0.8%)	28 (7.0%)	28 (7.0%)	7 (1.8%)	7 (1.8%)	39 (6.0%)	34 (5.2%)	8 (1.5%)	8 (1.5%)
Embolism	4 (1.6%)	2 (0.8%)	0	0	0	0	0	0	4 (0.6%)	2 (0.3%)	0	0
Embolic stroke	0	0	0	0	1 (0.2%)	1 (0.2%)	0	0	1 (0.2%)	1 (0.2%)	0	0
Deep vein thrombosis	4 (1.6%)	0	2 (1.5%)	1 (0.8%)	9 (2.3%)	1 (0.2%)	3 (0.8%)	0	13 (2.0%)	1 (0.2%)	5 (1.0%)	1 (0.2%)
Thrombosis	0	0	1 (0.8%)	0	2 (0.5%)	0	0	0	2 (0.3%)	0	1 (0.2%)	0
Vena cava thrombosis	1 (0.4%)	0	0	0	0	0	0	0	1 (0.2%)	0	0	0
Venous thrombosis	1 (0.4%)	0	1 (0.8%)	0	0	0	0	0	1 (0.2%)	0	1 (0.2%)	0
Mesenteric vein thrombosis	1 (0.4%)	0	0	0	0	0	0	0	1 (0.2%)	0	0	0
Total	**19 (7.4%)**	**8 (3.1%)**	**4 (3.1%)**	**2 (1.5%)**	**34 (8.5%)**	**30 (7.5%)**	**10 (2.5%)**	**7 (1.8%)**	**53 (8.1%)**	**38 (5.8%)**	**13 (2.5%)**	**9 (1.7%)**

New Primary Malignancies

The incidence of NPMs reported in the olaparib + abiraterone arm (4.3%) and in the placebo + abiraterone arm (3.8%) of PROpel were both slightly higher than that reported in the olaparib and abiraterone pool (2.5%), in the larger olaparib monotherapy combined therapeutic dose pool (1.0%), or across the 17,923-patient olaparib clinical trial program (0.6%). Differences in patient populations, follow-times, and other factors limit the ability to draw conclusions from such cross-trial cross-trial comparisons. The types of new primary cancers reported in PROpel

were generally in line with those expected in the general population.

Table 45. PROpel Second Primary Malignancies other than MDS/AML (Safety Population, DCO2)

Preferred Term	Olaparaib + abiraterone (N=398)	Placebo + abiraterone (N = 396)
Any	17 (4.3%)	15 (3.8%)
Squamous cell carcinoma of skin	5 (1.2%)	2 (0.5%)
Colorectal cancer[a]	3 (0.8%)	3 (0.8%)
Melanoma[b]	2 (0.5%)	0
Urothelial cancer	2 (0.5%)	(%)
Basal cell carcinoma	1 (0.3%)	3 (0.8%)
Non-small cell lung cancer[c]	1 (0.3%)	2 (0.5%)
Transitional cell carcinoma[d]	1 (0.3%)	1 (0.3%)
Bowen's disease	1 (0.3%)	0
Neoplasm skin	1 (0.3%)	0
Neuroendocrine carcinoma of the skin	1 (0.3%)	0
Squamous cell carcinoma	1 (0.3%)	0
Small intestinal carcinoma	1 (0.3%)	0
Diffuse large B-cell lymphoma	0	1 (0.3%)
External ear neoplasm malignant	0	1 (0.3%)
Esophageal neoplasm	0	1 (0.3%)
Penile squamous cell carcinoma	0	1 (0.3%)
Oropharyngeal cancer	0	1 (0.3%)

[a] Includes adenocarcinoma of colon, colon cancer, colorectal cancer, and rectal cancer
[b] Includes malignant melanoma and melanoma in situ
[c] includes lung adenocarcinoma and non-small cell lung cancer
[d] Includes bladder cancer and transitional cell carcinoma

Pneumonitis

Pneumonitis is an AESI and important potential risk of olaparib treatment, and currently appears as a Warning and Precaution in Section 5 of olaparib labeling. The incidence of pneumonitis in the olaparib + abiraterone arm of PROpel (1.3%) was numerically slightly higher than the that reported in the placebo + abiraterone arm of PROpel (0.8%), the olaparib and abiraterone pool (1.1%), the olaparib monotherapy combined therapeutic dose pool (0.9%), and Section 5 of the Lynparza Prescribing Information (<1%). Differences in patient populations, follow-times, and other factors limit the ability to draw conclusions from such cross-trial comparisons.

Table 46. PROpel Pneumonitis Events (Safety Population, DCO2)

Preferred Term	Olaparaib + abiraterone (N=398)	Placebo + abiraterone (N = 396)
Any	5 (1.3%)	3 (0.8%)
Pneumonitis	3 (0.8%)	2 (0.6%)
Interstitial lung disease	1 (0.3%)	1 (0.3%)
Radiation pneumonitis	1 (0.3%)	0

On the olaparib + abiraterone arm, 72 (18.1%) patients were transfused at least one blood product, compared to 14 (3.5%) on the placebo + abiraterone arm, and 16 (4.0%) patients received at least 6 units of blood product, compared to 2 (0.5%) on the placebo + abiraterone arm (Table 49).

Table 47. PROpel Summary of Transfusion Requirements (Safety Population, DCO2)

Preferred Term	Olaparaib + abiraterone (N=398)	Placebo + abiraterone (N = 396)
Patients with at least one transfusion	72 (18.1%)	16 (4.0%)
Blood product type		
PRBCs	52 (13.1%)	12 (3.0%)
Whole blood	20 (5.0%)	5 (1.3%)
Platelets	4 (1.0%)	0
Fresh frozen plasma	1 (0.3%)	1 (0.3%)
Number of units transfused		
1-5	56 (14.0%)	14 (3.5%)
6-10	10 (2.5%)	1 (0.3%)
>10	6 (1.5%)	1 (0.3%)

Source: Applicant's response to FDA information request

Reviewer's comment: Although the clinical interpretability of transfusion data may be limited by the lack of standardization across countries of what constitutes unit per volume in relation to PRBC and whole blood transfusion, the addition of olaparib to abiraterone clearly led to a substantial transfusion requirement.

Treatment Emergent Adverse Events and Adverse Reactions

Data/The Applicant's Position:

In the olaparib+abiraterone arm of PROpel the most common AEs, reported at an incidence ≥15%, were anemia, nausea, fatigue, diarrhea, constipation, and back pain with all but constipation and back pain reported at ≥5% frequency differences in the olaparib+abiraterone arm compared to the placebo+abiraterone arm. In the placebo+abiraterone arm, the most common AEs, reported at an incidence ≥15%, were fatigue, back pain, arthralgia, hypertension, and anemia. The most common AEs in the olaparib+abiraterone arm are consistent with the ADR profiles of olaparib and abiraterone, except for constipation and back pain. All AEs of constipation were classed as low grade (CTCAE Grade 1 or 2), and none were classed as serious.

In the olaparib and abiraterone pool the most common AEs, reported at an incidence ≥15%, were anemia, nausea, fatigue, constipation, back pain, and diarrhea, and in the olaparib 300 mg bid pool, the most common AEs, reported at an incidence ≥15%, were nausea, fatigue, anemia, vomiting, diarrhea, decreased appetite, headache, and constipation. These most common AEs are consistent with the ADR profiles of olaparib and abiraterone. Constipation and back pain were most likely reported due to underlying disease. In general, the most common events with olaparib were mild or moderate in severity, and resolved on continued treatment.

The common AEs of urinary tract infection, hypokalemia, atrial fibrillation, and electrocardiogram QT prolonged are known to be associated with abiraterone treatment and are listed in its product information (Zytiga USPI). Although numerical imbalances were observed for these terms, the observed rates are still consistent with the labelled frequency for abiraterone. These AEs were generally CTCAE Grade 1 or 2.

Overall, the most common AEs associated with olaparib and abiraterone appears to be consistent with the known safety profiles of olaparib and abiraterone monotherapies, in the context of this patient population.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment above, which reflects DCO1 data.

In the olaparib + abiraterone arm of PROpel the most common AEs, reported at an incidence ≥15%, were anemia, fatigue, nausea, diarrhea, constipation, and back pain with all but constipation and back pain reported at ≥5% frequency differences in the olaparib + abiraterone arm compared to the placebo + abiraterone arm. The most common AEs in the olaparib + abiraterone arm are consistent with the ADR profiles of olaparib and abiraterone, except for constipation and back pain (the incidences of constipation and back pain in PROfound were 7% and 14%, respectively).

Table 48. PROpel Adverse Reactions in ≥10% of the Safety Population (DCO2)

Adverse Reactions	Lynparza/abiraterone (N=398)		Placebo+abiraterone (N=396)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Blood and Lymphatic Disorders				
Anemia[a]	190 (47.7%)	63 (15.8%)	70 (17.7%)	13 (3.3%)
Lymphopenia[b]	54 (13.6%)	20 (5.0%)	22 (5.6%)	7 (1.8%)
General Disorders and Administration Site Conditions				
Fatigue[c]	152 (38.2%)	9 (2.3%)	117 (29.5%)	6 (1.5%)
Peripheral edema[d]	47 (11.8%)	0	46 (11.6%)	1 (0.3%)
Gastrointestinal Disorders				
Nausea	118 (29.6%)	1 (0.3%)	55 (13.9%)	1 (0.3%)
Diarrhea	75 (18.8%)	4 (1.0%)	39 (9.8%)	1 (0.3%)
Constipation	71 (17.8%)	0	58 (14.6%)	1 (0.3%)
Vomiting	55 (13.8%)	6 (1.5%)	36 (9.1%)	1 (0.3%)
Musculoskeletal and connective tissue disorders				
Back pain	80 (20.1%)	4 (1.0%)	76 (19.2%)	4 (1.0%)
Arthralgia	56 (14.1%)	0	75 (18.9%)	2 (0.5%)
Musculoskeletal pain[e]	41 (10.3%)	1 (0.3%)	33 (8.3%)	1 (0.3%)
Metabolism and nutrition disorders				
Decreased appetite	64 (16.1%)	4 (1.0%)	28 (7.1%)	0
Vascular disorders				
Hypertenion	58 (14.6%)	15 (3.8%)	67 (16.9%)	14 (3.5%)
Hot flush[f]	38 (9.5%)	0	52 (13.1%)	0
Infections and infestations				
Urinary tract infection[g]	48 (12.1%)	9 (2.3%)	40 (10.1%)	7 (1.8%)

Nervous System Disorders				
Dizziness[h]	54 (13.6%)	0	29 (7.3%)	0
Headache[i]	39 (9.8%)	1 (0.3%)	28 (7.1%)	0
Respiratory, thoracic, and mediastinal disorders				
Cough[j]	47 (11.8%)	0	30 (7.6%)	0
Dyspnea[k]	43 (10.8%)	(0.3%)	33 (8.3%)	0

[a] Includes anemia, anemia macrocytic, and red blood cell count decreased
[b] Includes lymphocyte count decreased and lymphopenia
[c] Includes fatigue and asthenia
[d] Includes edema and edema peripheral
[e] Includes musculoskeletal chest pain, musculoskeletal discomfort, and musculoskeletal pain
[f] Includes hot flush and flushing
[g] Includes cystitis, cystitis bacterial, Escherichia urinary tract infection, pyelonephritis, urinary tract infection, and urinary tract infection pseudomonal
[h] Includes dizziness and vertigo
[i] Includes headache, head discomfort, and migraine
[j] Incudes cough and productive cough
[k] Includes dyspnea and dyspnea exertional

Laboratory Findings

Data:
Clinical laboratory results for PROpel are summarized in Section 12.4, PROpel CSR, Module 5.3.5.1.

The Applicant's Position:
In general, the laboratory evaluations for PROpel, the olaparib and abiraterone pool, and the olaparib 300 mg bid pool were comparable. Changes in hemoglobin, neutrophils, leukocytes, lymphocytes, platelets, and mean corpuscular volume were the only significant hematological parameters with clinically relevant changes; these parameters are recognized ADRs for olaparib. The majority of the changes in laboratory hematological parameters on olaparib had a maximum grade of CTCAE Grade 1 or 2; there were few patients with Grade 3 or 4 changes in these hematological parameters.

The only significant changes in clinical chemistry parameters occurred for blood creatinine. Creatinine increases are a recognized ADR for olaparib. For PROpel, the olaparib and abiraterone pool, and the olaparib 300 mg bid pool, small increases were observed early in olaparib treatment, which then stabilized, with a trend back to baseline after 30 days off olaparib treatment; this pattern of effect is consistent with OCT2 and MATE1 inhibition.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment, which reflects DCO1 data, but which is also true of DCO2 data.

Vital Signs

Data:
Vital signs in PROpel are summarized in Section 12.5, PROpel CSR, Module 5.3.5.1.

The Applicant's Position:
There were no unexpected changes noted in vital signs in either treatment arm in PROpel, and no individual abnormalities raised any safety concerns.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment, which reflects DCO1 data, but which is also true of DCO2 data.

Electrocardiograms (ECGs)

Data:
ECG findings in PROpel are summarized in Section 12.5, PROpel CSR, Module 5.3.5.1.

The Applicant's Position:
No clinically significant differences in ECG findings were seen between the two treatment arms in PROpel, and similar proportions of patients had abnormal ECG findings in each treatment group.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment, which reflects DOC1 data, but which is also true of DCO2 data.

QT

No new information is provided in the current submission.

Immunogenicity

The Applicant's Position:
This is not applicable for olaparib.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

8.2.5. Analysis of Submission-Specific Safety Issues

Data/The Applicant's Position:
MDS/AML, NPMs, and pneumonitis are evaluated in Section 8.2.4. Following database lock and upon assessment of the PROpel data for the primary analysis, VTE was added as an ADR to the Lynparza core company datasheet; see Section 8.2.4.

The last patient was randomized in PROpel on March 11, 2020 at the start of the global COVID-19 pandemic; however, the COVID-19 pandemic is not considered to have had any

meaningful impact on the quality of the study or the interpretation of the results.

The FDA's Assessment:
See above under Treatment Emergent Adverse Events and Adverse Reactions.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data/The Applicant's Position:
FACT-P and BPI-SF scores in PROpel are evaluated in Section 8.1.2.

The FDA's Assessment:
Please see Section 8.1.2.

8.2.7. Safety Analyses by Demographic Subgroups

Data/The Applicant's Position:
In order to have sufficient numbers of patients, the olaparib and abiraterone pool and the olaparib 300 mg bid pool have been used, rather than PROpel. The safety profile of the olaparib+abiraterone arm in PROpel appeared to be consistent with the safety profiles of olaparib and abiraterone, suggesting that the intrinsic factor effects in PROpel were comparable with those for the olaparib and abiraterone pool and the olaparib 300 mg bid pool.

Within the context of a low number of male patients, no clinically meaningful gender-related differences in the safety profile of olaparib have been identified in the olaparib 300 mg bid pool. No unexpected age-related differences were observed in either pool. Taking the imbalance in size of subgroups into account, no clinically significant differences in the safety profile of olaparib in White versus Asian patients have been observed in either pool. In addition, no effect of race on the PK of olaparib has been identified.

The FDA's Assessment:
Examining the incidences of TEAEs reported in PROpel, the FDA notes no unexpected differences by age, race, or geographic region (Table 49).

Table 49. PROpel Adverse Reactions by Demographic Subgroups (Safety Population, DCO2)

Adverse Reactions	Lynparza/abiraterone (N=398)		Placebo+abiraterone (N=396)	
	All Grades	Grades 3-5	All Grades	Grades 3-5
Age				
< 65	125/130 (96.2%)	55/130 (42.3%)	92/97 (94.8%)	33/97 (34.0%)
≥ 65	264/268 (98.5%)	155/268 (57.8%)	286/299 (95.7%)	127/299 (42.5%)
Region				
Asia	91/91 (100%)	51/91 (56.0%)	97/104 (93.3%)	48/104 (46.2%)
Europe	170/177 (96.0%)	88/177 (49.7%)	163/171 (95.3%)	62/171 (46.2%)
North and South America	128/130 (98.5%)	71/130 (54.6%)	118/121 (97.5%)	50/121 (41.3%)
Race				
White	272/281 (96.8%)	144/281 (51.2%)	266/274 (97.1%)	111/274 (40.5%)
Non-White	117/117 (100%)	66/117 (56.4%)	112/122 (100%)	49/122 (40.2%)

Section 8.5 (Geriatric Use) of product labeling was updated to include the numbers of patients who received olaparib + abiraterone and were 65 years or older and 75 years or older. No overall differences in the safety or effectiveness of olaparaib were observed between these patients and younger patients.

8.2.8. Specific Safety Studies/Clinical Trials

No new information is provided in the current submission.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
No new information is provided in the current submission.

Human Reproduction and Pregnancy
No new information is provided in the current submission.

Pediatrics and Assessment of Effects on Growth
No new information is provided in the current submission.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
No new information is provided in the current submission.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:
Olaparib (both capsule and tablet formulations) has been approved for use in several countries worldwide for a range of indications across multiple tumor types. Angioedema and erythema nodosum were recently added as ADRs for olaparib based on data gathered in the post-marketing setting. The reports received do not change the benefit risk profile of olaparib.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting
The Applicant's Position:
Not applicable. There is already considerable postmarket experience with olaparib.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

8.2.11. Integrated Assessment of Safety

Data/The Applicant's Position:
The safety data from PROpel appears to be consistent with the safety profiles of olaparib and abiraterone monotherapies, in the context of this patient population. The overall safety data demonstrate that the combination is tolerable and acceptable for the treatment of mCRPC.

In line with the improved efficacy and tolerability of the combination arm in PROpel, the median total duration of exposure to olaparib was longer than to placebo, and the median total duration of exposure to abiraterone was longer when combined with olaparib.

While there were generally similar frequencies and severities of olaparib ADRs when combined with abiraterone, there were more AEs of CTCAE Grade ≥3, AEs with outcome of death, SAEs, and AEs leading to discontinuation or dose interruption of olaparib reported in the olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bid pool of monotherapy studies, about a third of which comprises patients with *gBRCA* early breast cancer who received olaparib in the adjuvant disease-free setting. These differences may be attributed to the older male patient population with comorbidities in PROpel, and the mainly younger female patients with ovarian or breast cancer and a lower rate of bone metastases in the olaparib 300 mg bid pool, longer median exposure time to olaparib in PROpel, as well as the varying time to disease progression for the range of tumor types investigated in studies comprising the 300 mg bid pooled dataset. In addition, the PROpel study investigated a combination of two active drugs while the olaparib 300 mg bid pool comprises data for olaparib monotherapy. In the context of prostate cancer treatment, the olaparib safety profile in PROpel was in line with the monotherapy safety profile in PROfound in patients with mCRPC who have failed a prior NHA (see Section 8.2.4).

Hematological toxicity associated with olaparib when given in combination with abiraterone in PROpel was consistent with previous knowledge: anemia (grouped terms: any AE 46.0%; any AE

of CTCAE ≥3 15.1%) neutropenia (grouped terms any AE 8.3%; any AE of CTCAE ≥3 3.8%) and thrombocytopenia (grouped terms any AE 5.5%; any AE of CTCAE ≥3 0.8%). Similarly, most common non-hematological olaparib ADRs reported in PROpel were consistent with previous knowledge on fatigue/asthenia, nausea, and diarrhea.

Following database lock and upon assessment of the PROpel data for the primary analysis, VTE was identified as an ADR for olaparib. In PROpel, there were numerical imbalances in events of pulmonary embolism with higher proportions of olaparib+abiraterone-treated patients experiencing an event of pulmonary embolism (6.5%) compared to the placebo+abiraterone arm (1.8%). The majority of pulmonary embolism AEs were detected incidentally on radiographic imaging in both treatment arms (69.2% and 71.4% in the olaparib+abiraterone and placebo+abiraterone arm, respectively). Some minor imbalances in baseline risk factors were noted between the arms, such as a history of pulmonary embolism or other VTE events, but there were no additional confounders relating to medical history or co-morbidity between arms other than mCRPC and ADT. The events occurred with no apparent chronological pattern and the majority of patients remained on treatment with no pattern in time to onset observed. While no clear biological mechanism has been established, an imbalance in events of pulmonary embolism was also observed in PROfound and PAOLA-1, suggesting that there is at least a reasonable possibility for a causal association between olaparib and VTE events.

The imbalance in the incidence of CTCAE Grade ≥3 AEs within the SOC of Cardiac Disorders in Study 8 led to the implementation of safety monitoring procedures in the PROpel study, consistent with cardiac safety monitoring used in previous abiraterone clinical studies. In the significantly larger dataset of PROpel, cardiac failure and arterial thrombotic events were balanced between the treatment arms (cardiac failure SMQ: 1.5% vs 1.3% of patients, respectively; Embolic and thrombotic events, arterial SMQ: 2.0% vs 2.5% of patients, respectively). This is also supported by the rest of the olaparib clinical development program, with no observed imbalance in cardiac events.

There were no events of MDS/AML in PROpel. For the AESIs of NPMs and pneumonitis, the data from PROpel do not change previous assessments that a causal relationship has not been established between olaparib treatment and these AESIs. These safety topics will continue to be kept under close surveillance.

Safety Profile of Olaparib Across the Clinical Program
With the availability of the PROpel data, the safety profile of olaparib remains generally consistent with the previously established safety profile when used in monotherapy. The common low grade ADRs of nausea, vomiting, and fatigue are routinely managed by oncologists treating cancer patients. The low grade, intermittent nature means that nausea and vomiting can be treated empirically, and antiemetic prophylaxis is not required. Hematological changes including anemia should be routinely monitored for, using standard assessments of hematological laboratory parameters as specified in the proposed product information, which are routine for patients receiving anticancer therapies. Where necessary, ADRs can be managed according to oncology medical practice and by interrupting or reducing the olaparib dose,

treating symptomatically with standard procedures (eg, antiemetics for nausea and vomiting, blood transfusions for anemia) or uncommonly by permanently discontinuing olaparib treatment.

Abiraterone
The adverse reactions of abiraterone were manageable and as per label.

The FDA's Assessment:

The FDA considers the Applicant's statement that "The overall safety data demonstrate that the combination is tolerable and acceptable for the treatment of mCRPC" only insofar as it applies to the patient population in which substantial evidence of efficacy has been demonstrated (i.e., patients with *BRCA*m). In the remainder of the PROpel population (i.e., the 89% of patients in whom no *BRCA*m was identified,), FDA remains concerned regarding the toxicity resulting from the addition of olaparib to abiraterone.

The addition of olaprarib to abiraterone added substantial toxicity compared to placebo, as reflected by higher reported incidences of Grade 3 and above AEs, SAEs, and AEs leading to discontinuation, dose reduction, and dose interruption in the olaparib + abiraterone arm compared to the placebo + abiraterone arm of PROpel.

In PROpel, hematological toxicity was reported more frequently in the olaparib + abiraterone arm than in the placebo + abiraterone arm: grouped-term AEs of Grade 1-4 anemia 47.7% vs. 17.7%, Grade 3-4 anemia 15.8% vs. 3.3%, Grade 1-4 neutropenia 9.3% vs 3.5%, Grade 3-4 neutropenia 4.3% vs 1.8%, Grade 1-4 thrombocytopenia 5.7% vs. 4.0%, and Grade 3-4 thrombocytopenia 0.7% vs 0.5%. This higher rate of anemia in the olaparib + abiraterone arm translated to an increased transfusion requirement, reflected in the fact that 18% of patients on the olaparib + abiraterone arm received transfusions on PROpel, compared to 4% of patients on the placebo + abiraterone arm.

In PROpel, there were numerical imbalances in events of VTE, with higher proportions of olaparib + abiraterone-treated patients experiencing a VTE event (8.5%) compared to the placebo + abiraterone arm (2.5%). This imbalance was largely driven by increased numbers of ≥ Grade 3 pulmonary embolism (7.0% vs. 1.8%). Information about VTE observed with the combination of olaparib + abiraterone was added to the existing Warnings and Precautions section of product labeling.

One patient in the olaparib + abiraterone arm of PROpel experienced new-onset MDS. The existing Warning and Precautions in the Lynparza Prescribing Information adequately informs prescribers of this risk.

Higher percentages of patients in the olaparib + abiraterone arm of PROpel compared to the control arm experienced new primary malignancies and pneumonitis. These data do not change

previous assessments that a causal relationship has not been established between olaparib treatment and these AESIs.

PRO data, although exploratory, demonstrated a higher level of side effect burden in patients treated with olaparib + abiraterone vs. patients treated with placebo + abiraterone.

In conclusion, patients without *BRCA*m may be exposed to the toxicities of olaparib for a prolonged duration in a combination arm with a known highly effective therapy (abiraterone). Patients may be exposed to treatment for a prolonged duration without demonstration of futility. This is different than a monotherapy setting, where lack of efficacy may be clear much earlier and therapy could be stopped for early disease progression. PROpel evaluated an early line of therapy and a minimally symptomatic population at baseline (with 70% of patients reporting that they were asymptomatic or minimally symptomatic at baseline), so toxicity may be particularly impactful given prolonged treatment duration in a setting where standard of care is NHA monotherapy, which is generally well-tolerated. Thus, the FDA does not consider the toxicity of the combination to be acceptable in patients without *BRCA*m. FDA does consider the toxicity of the combination acceptable in patients with *BRCA*m.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There are four major issues that limit and confound the interpretation of ITT results in PROpel:
1) The study enrolled a heterogenous patient population without stratification by *BRCA*m status, which is a known strong predictor of efficacy with PARPi treatment.
2) *BRCA*m status was determined retrospectively after randomization leading to a high incidence of missing tumor tissue test results.
3) There was no pre-specified strategy to determine *BRCA* subgroups aggregating the results of tumor tissue test and ctDNA test.
4) There was no alpha-controlled subgroup analysis based on *BRCA*m status.

After thorough review of the available data from Study 8, PROpel, the strong biologic rationale, and a discussion at an ODAC meeting, the review team concluded that the benefit demonstrated in the ITT population was mainly attributed to the *BRCA*m subgroup, leaving modest rPFS improvement and potential harm to patients without *BRCA* mutation. This finding is reinforced by multiple exploratory subgroup analyses based on *BRCA*m status (i.e., *BRCA*m, undetermined *BRCA*m status and non-*BRCA*m). Subgroup analysis results are consistent between primary and other efficacy endpoints.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The review team recommends traditional approval for olaparib 300 mg taken orally twice daily in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*m mCRPC.

FDA restricted the indication to the *BRCA*m subgroup for the following reasons:

1. Despite the suboptimal design of PROpel to assess the efficacy by mutation status, the rPFS improvement in all-comers is attributed to efficacy in the *BRCA*m subgroup.
2. For patients who are negative for tumor *BRCA* mutations by two assays, FDA is concerned that PROpel demonstrated a lack of efficacy and a potential overall survival detriment. This population comprises over half of the ITT population. Even if considering the 89% of the population without a demonstrated tumor *BRCA* mutation, the rPFS improvement in this setting is of dubious clinical meaningfulness given the add-on design and exposure to additional toxicity for the large proportion of patients with true underlying lack of tumor *BRCA* mutation who are unlikely to benefit from therapy.
3. There was minimal impact of lack of stratification and results were consistent for the three *BRCA* subgroups after adjusting for baseline characteristics based on a prognostic model for mCRPC.
4. There is internal consistency between primary and secondary endpoints, demonstrating modest efficacy from adding olaparib in the non-*BRCA*m subgroup.
5. There is external consistency across trials, showing modest efficacy and potential harm from PARP inhibitors in patients without *BRCA* mutation. These trials include Study 8, which was another study of olaparib + abiraterone, studies of other PARP inhibitors in prostate cancer, and studies in patients with other cancers, including advanced ovarian cancer. *BRCA* mutation status consistently appears to be a strong predictive biomarker for PARP inhibitor efficacy.
6. Due to the addition of olaparib to abiraterone, patients with non-*BRCA* tumors are at risk of exposure to toxicities of olaparib > 1 year without likelihood of benefit.

FDA concluded that there is substantial evidence of efficacy from adding olaparib to abiraterone in patients with *BRCA*m tumor.

The FDA review team considered the results in the ITT population to be primarily attributed to the treatment effect in *BRCA*m subgroup. The review team concluded that, in light of the modest rPFS improvement and concern for harm in patients with non-*BRCA* (including those with non-*BRCA*/HRRm tumor), the Applicant had not demonstrated a favorable risk/benefit profile in patients without a *BRCA*m tumor.

Based on the above considerations and in line with ODAC vote on April 28th, 2023, the FDA review team recommended traditional approval of olaparib in combination with abiraterone only in patients with deleterious or suspected deleterious *BRCA*m mCRPC.

Two postmarketing commitments (PMCs) to submit companion diagnostic devices for identifying BRCAm, one for ctDNA and one for tumor tissue, were agreed upon by the FDA and the Applicant.

X X

Primary Statistical Reviewer Statistical Team Leader

X X

Primary Clinical Reviewer Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This sNDA was discussed in an Oncologic drug advisory committee (ODAC) on April 28, 2023, asking the committee to answer the following question:

> *"As FDA reviews the proposed indication for olaparib in combination with abiraterone for initial treatment of mCRPC, should the indication be restricted to patients whose tumors have a BRCA mutation?*
>
> *If you feel the combination should not be approved at all, please abstain from voting and explain your thinking regarding approvability during the post-voting discussion period."*

In an 11-1 vote (with one abstention), FDA's ODAC voted in favor of restricting the indication to patients with *BRCA*m tumors.

> **Vote Result: Yes: 11 No: 1 Abstain: 1**

The majority of the Committee members voted "Yes", indicating that the proposed indication for olaparib in combination with abiraterone for initial treatment of mCRPC should be restricted to patients whose tumors have a *BRCA* mutation. These Committee members noted that the study did not show clinical benefit in the subgroup of the non-*BRCA* mutation. One Committee member voted against the restriction, noting that the trial met the primary endpoint. Another Committee member abstained the vote, explaining that it was difficult to make the choice based on a suboptimal study design. Please see the transcript for details of the Committee's discussion.

10 Pediatrics

The Applicant's Position:
On the February 19, 2021 a proposed initial PSP for first-line prostate cancer was submitted, and on June 04, 2021 an agreed PSP for first-line prostate cancer was submitted.

The FDA's Assessment:
Prostate cancer is common in older adults and does not occur in children. This makes pediatric studies impossible or highly impractical to conduct. Based on these considerations, on [date], the FDA issued an Agreed initial Pediatric Study Plan (iPSP) granting a full waiver from the requirements of PREA.

11 Labeling Recommendations

Table 50. Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1. INDICATIONS AND USAGE (section 1.8)	"in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC)."	"in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC)."
2.1 Patient Selection		A row was added to the table for Biomarker Testing for Patient Selection, in Section 2.1, for selection of patients with *BRCA*-mutated Metastatic castration-resistant prostate cancer in combination with abiraterone and prednisone or prednisolone.
5. WARNINGS AND PRECAUTIONS		Information from PROpel was added to Venous Thromboembolic Events section.

6. ADVERSE REACTIONS	The Applicant added a new subsection describing safety results from PROpel, including tables summarizing adverse reactions and selected laboratory abnormalities.	The FDA made minor modifications to this section based on grouping of similar adverse event terms.
14 CLINICAL STUDIES	The Applicant proposed to (b) (4)	FDA replaced the table and figure (b) (4) FDA added the results of OS analysis to the tables, since OS is an efficacy and safety endpoint and OS data is necessary for benefit:risk assessment and interpretation of rPFS data particularly in an add-on design. (b) (4) (b) (4) efficacy results in *BRCA*m subgroup.

The Applicant's Position:
AstraZeneca has provided the proposed labeling in the sNDA (Sequence 1080).

The FDA's Assessment:
FDA has no additional comments.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
No REMS was required for this application.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

Two postmarketing commitments (PMCs) to submit companion diagnostic devices for identifying *BRCA*m, one for ctDNA and one for NGS tumor tissue, were agreed upon by the FDA and the Applicant.

PMC#1:

Rationale: The indication for use for olaparib in combination with abiraterone is restricted to adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Current device labeling for the existing in vitro diagnostic device using tissue samples only includes data for the evaluation of homologous recombination repair gene alterations for treating patients with mCRPC with olaparib monotherapy and does not include an indication for the combination of olaparib plus abiraterone for patients with mCRPC, whose tumors harbor only *BRCA*1 or *BRCA*2 mutations

Language: Conduct an analytical and clinical validation study using clinical trial data, adequate to support the availability of an in vitro diagnostic device using tissue samples that is essential to the safe and effective use of olaparib plus abiraterone for patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC), whose tumors harbor *BRCA*1 or *BRCA*2 mutations.

PMC#2:

Rationale: The indication for use for olaparib in combination with abiraterone is restricted to adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Current device labeling for the existing in vitro diagnostic device using circulating tumor DNA (ctDNA) derived from plasma only includes data for the identification of *BRCA*1, *BRCA*2, and *ATM* alterations for treating patients with mCRPC with olaparib monotherapy and does not include an indication for the combination of olaparib plus abiraterone for patients with mCRPC whose tumors harbor only *BRCA*1 or *BRCA*2 mutations.

Language: Conduct an analytical and clinical validation study using clinical trial data, adequate to support the availability of an in vitro diagnostic device using ctDNA samples from plasma that

is essential to the safe and effective use of olaparib plus abiraterone for patients diagnosed with mCRPC, whose ctDNA samples harbor *BRCA*1 or *BRCA*2 mutations.

14 Division Director (DHOT) (NME ONLY)

X _____

15 Division Director (OCP)

X _____

16 Division Director (OB)

X _____

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

The Applicant's References:

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The FDA's References:

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19.2. Financial Disclosure

The Applicant's Position:

Information on investigators who conducted the pivotal PROpel study and supportive Study 8 described in the current application that do not have any disclosable financial interests or arrangements, including statements of due diligence in cases where the applicant was unable to obtain a signed form from the investigator, is provided along with FDA form 3454. The financial disclosure package for Study 8 has already been provided as part of the Supplement S-014 initial submission dated November 20, 2019 (SN0618).

A total of 5 investigators in the PROpel study reported positive financial disclosures which are provided in FDA form 3455. These investigators enrolled a total of 10 patients and randomized a total of 9 patients. In Study 8, there were no investigators that reported positive financial disclosures.

AstraZeneca has determined that the impact on PROpel and Study 8 is minimal, and has taken the following steps (as applicable for both studies) to minimize potential bias including:
- Use of multiple clinical investigators and study sites.
- Use of a double-blind, placebo-controlled study design.
- Review of study endpoint data by an independent and adjudicated central vendor.

The FDA's Assessment:
FDA has no additional comment.

Covered Clinical Study (Name and/or Number):* PROpel (D081SC00001)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1118		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: The study sponsor is AstraZeneca and the other study sponsor/co-		

development partner is Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., as well as the affiliates, joint ventures and subsidiaries.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

No new information is provided in the current submission.

The FDA's Assessment:
N/A

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
N/A

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Haw-Jyh Chiu	OOD/DHOT	Sections: 5	**Select one:** X Authored X Approved
	Signature: Haw-jyh Chiu -S Digitally signed by Haw-jyh Chiu -S Date: 2023.05.26 08:23:54 -04'00'			
Nonclinical Team Leader	Tiffany Ricks	OOD/DHOT	Sections: 5	**Select one:** X Authored X Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S Date: 2023.05.25 16:02:18 -04'00'			
Clinical Pharmacology Reviewer	Christy John	OTS/OCP/DCPII	Sections: 6	**Select one:** X Authored __Approved
	Signature: Christy S. John -S Digitally signed by Christy S. John -S Date: 2023.05.26 08:55:52 -04'00'			
Clinical Pharmacology Team Leader	Salaheldin Hamed	OTS/OCP/DCP II	Sections: 6	**Select one:** X Authored X Approved
	Signature: Salaheldin S. Hamed -S Digitally signed by Salaheldin S. Hamed -S Date: 2023.05.26 08:47:24 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Jaleh Fallah	OOD/DO1	Sections: 2, 3, 4, 7, 8, 9, 10, 11, 12, 13	**Select one:** X Authored _Approved
	Signature: Jaleh Fallah -S Digitally signed by Jaleh Fallah -S Date: 2023.05.26 11:04:13 -04'00'			
Clinical Reviewer	Michael Brave	OOD/DO1	Sections: 5 and 6	**Select one:** X Authored _Approved
	Signature: Michael H. Brave -S Digitally signed by Michael H. Brave -S Date: 2023.05.26 12:38:15 -04'00'			
Clinical Team Leader	Chana Weinstock	OOD/DO1	Sections: 1,2,3,7,8	**Select one:** X Authored X Approved
	Signature: ***See appended electronic signature page***			
Statistical Reviewer	Jianjin Xu	OTS/OB/DBV	Sections: 8	**Select one:** X Authored _Approved
	Signature: Jianjin Xu -S Digitally signed by Jianjin Xu -S Date: 2023.05.26 13:04:12 -04'00'			
Statistical Team Leader	Erik Bloomquist	OTS/OB/DBV	Sections: 8	**Select one:** X Authored X Approved
	Signature: Erik W. Bloomquist -S Digitally signed by Erik W. Bloomquist -S Date: 2023.05.26 12:48:46 -04'00'			
Division Director (OB)	Shenghui Tang	OTS/OB/DBV	Sections: 8	**Select one:** X Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2023.05.26 13:08:09 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling (ADL)	William Pierce	OND	Sections: 11, Prescribing Information	**Select one:** X Authored X Approved
	Signature: William F. Pierce -S Digitally signed by William F. Pierce -S Date: 2023.05.26 15:42:47 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Chana Weinstock	OOD/DO1	Sections: All	**Select one:** _ Authored X Approved
	Signature: ***See appended electronic signature page***			
Deputy Division Director (Clinical)	Daniel Suzman	OOD/DO1	Sections: All	**Select one:** X Approved
	Signature: ***See appended electronic signature page***			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHANA WEINSTOCK
05/31/2023 02:17:50 PM

DANIEL L SUZMAN
05/31/2023 02:26:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s025

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA-208558-SUPPL-025
   sNDA Recommendation: Approval
   sNDA Managed by: OND

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	06/16/2022	06/16/2022	06/30/2022	12/16/2022	07/26/2022
Clinical information		06/30/2022	06/30/2022			
Response to IR		07/15/2022	07/15/2022			
Response to IR		07/20/2022	07/20/2022			

3. **Provides For:**
   expansion of indication to include the following: Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC).

4. **Review #**: 01

5. **Clinical Review Division**: OOD/DO I

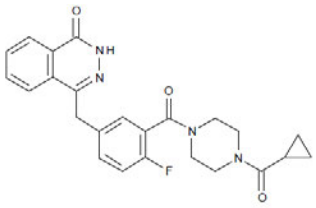
6. **Name and Address of Applicant**:
   AstraZeneca Pharmaceuticals LP
   1800 Concord Pike
   Wilmington, DE, USA 19803

   Contact: Yuchao Xie, PhD, Regulatory Affairs Director
   Phone: (240) 782-5341
   Email: yuchao.xie@astrazeneca.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
LYNPARZA® (olaparib)	Tablets	100 mg, 150 mg	Oral	Rx	no

8. Chemical Name and Structure of Drug Substance:

	USAN: olaparib IUPAC: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one Molecular Formula: $C_{24}H_{23}FN_4O_3$ Molecular Mass: 434.46

9. Indication:

Ovarian cancer:

- for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
- for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Breast cancer:

- for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Pancreatic cancer:

- for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

10. Supporting/Relating Documents: none

11. Consults: none

12. Executive Summary:

This efficacy supplement provides for expansion of indication to include following: Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC).

The applicant claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part25.31 (b). Under 21CFR 25.31(b), a categorical exclusion is allowable for: “Action on an NDA, abbreviated application, or a

supplement to such applications, or action on an OTC monograph, if the action increases the use of active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.". To the best of the sponsor's knowledge, no extraordinary circumstances, as referenced in 21 CFR 25.21, exist relative to this action. Therefore, the request for categorical exclusion may be granted.

The applicant had provided updated PI. There are no changes in CMC related sections 3, 11, and 16.

There are no other CMC related changes in this supplement.

From a CMC perspective the proposed changes in S025 are CMC adequate.

13. Conclusions & Recommendations: This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Qi Liu, Ph.D., CMC reviewer, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
Ramesh Raghavachari, Ph.D., Branch Chief, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

Qi Charles Liu

Digitally signed by Qi Charles Liu
Date: 7/26/2022 02:49:16PM
GUID: 53b4299e000120abe375af2240eda3f5

Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 7/26/2022 05:32:52PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s025

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 1, 2022

To: Christal Lee, Regulatory Project Manager, Division of Oncology I (DO1)

William Pierce, Associate Director for Labeling, DO1

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Ray Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for LYNPARZA® (olaparib) tablets, for oral use

NDA: 208558/S-025

Background: In response to DO1's consult request dated July 8, 2022, OPDP has reviewed the proposed Prescribing Information (PI) for supplement 25 for LYNPARZA® (olaparib) tablets, for oral use (Lynparza). This supplement provides for the use of Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 18, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Koung Lee at 240-402-8686 or Koung.lee@fda.hhs.gov.

Section	Statement from Draft	OPDP Comments
6.1 Clinical Trial Experience Treatment of Metastatic Castration-resistant Prostate Cancer in combination with Abiraterone and Prednisone or Prednisolone *PROpel* 2nd paragraph	Fatal adverse reactions occurred in 6% of patients, including COVID-19 (3%) and pneumonias (0.5%).	In the previous paragraphs describing the fatal adverse reactions in the other studies, they specify that the affected patients were taking Lynparza or a combination of Lynparza and something else. Should this sentence be revised to state that the fatal adverse events occurred in patients treated with Lynparza/abiraterone and prednisone or prednisolone? OPDP defers to DO1.
6.1 Clinical Trial Experience Treatment of Metastatic Castration-resistant Prostate Cancer in combination with Abiraterone and Prednisone or Prednisolone *PROpel* 3rd paragraph	Serious adverse reactions occurred in 39% of patients. Serious adverse reactions reported in > 2% of patients included anemia (6%), COVID-19 (6%), pneumonia (4.5%), pulmonary embolism (3.5%), and urinary tract infection (3%).	In the previous paragraphs describing the serious adverse reactions in the other studies, they specify that the affected patients were taking Lynparza or a combination of Lynparza and something else. Should this paragraph be revised to state that the serious adverse events occurred in patients treated with Lynparza/abiraterone and prednisone or prednisolone? OPDP defers to DO1.

65 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KOUNG U LEE
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	November 22, 2022
To:	Christal Lee Regulatory Project Manager **Division of Oncology I (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Medication Guide (MG)
Drug Name (established name):	LYNPARZA (olaparib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208558
Supplement Number:	S-025
Applicant:	AstraZeneca Pharmaceuticals, LP

1 INTRODUCTION

On June 16, 2022, AstraZeneca Pharmaceuticals, LP submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to New Drug Application (NDA) 208558/S-025 for LYNPARZA (olaparib) tablets. With this supplement, the Applicant proposes an indication in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC).

On July 11, 2022, the Division of Oncology I (DO1) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for LYNPARZA (olaparib) tablets.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed MG for LYNPARZA (olaparib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft LYNPARZA (olaparib) tablets MG received on June 16, 2022, and received by DMPP on November 18, 2022.
- Draft LYNPARZA (olaparib) tablets Prescribing Information (PI) received on June 16, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on November 18, 2022.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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11/22/2022 01:23:40 PM

Clinical Inspection Summary

Date	November 15, 2022
From	Yang-Min (Max) Ning, M.D., Ph.D. Min Lu, M.D., M.P.H. Jenn Seller, M.D., Ph.D. GCPAB/DCCE/OSI/CDER/FDA
To	Jaleh Fallah, M.D. Michael Brave, M.D. Chana Weinstock, M.D. Christal Lee, RPM DO1/OOD/CDER/FDA
NDA #	208558-S25
Applicant	AstraZeneca Pharmaceuticals LP
Drug	Olaparib
NME (Yes/No)	No
Therapeutic Classification	Inhibitor of mammalian poly-ADP ribose polymerases (PARP)
Proposed Indication	In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC)
Consultation Date	07/22/2022
Summary Goal Date	11/18/2022
Action Goal Date	12/02/2022
PDUFA Date	12/16/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from an ongoing Phase 3 study (Protocol D081SC00001) were submitted to the Agency in support of a supplemental New Drug Application (sNDA) for olaparib for the proposed indication as listed above. Four clinical investigators, Drs. Gary Buchschacher [Site 7822], Urban Emmenegger [Site 1004], Niven Mehra [Site 5001], and Cagatay Arslan [Site 7604], were inspected.

The inspections found no significant regulatory deficiencies at the four investigator sites and the Applicant's submitted clinical data were verifiable with source records reviewed, with no inconsistencies identified. Overall, the inspection results reveal that Study D081SC00001 appears to have been adequately conducted and the clinical data generated from these investigator sites are acceptable for this sNDA.

II. BACKGROUND

Olaparib is a PARP inhibitor that has been marketed since 2014 in the United States, with multiple indications approved for use in patients with different advanced malignancies who have deleterious or suspected deleterious breast cancer (*BRCA*) gene mutations, including one for use in patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. For this sNDA, the Applicant provided clinical data from a Phase 3 study (Protocol D081SC00001) and proposed a new indication for olaparib, in combination with abiraterone and prednisone or prednisolone, for use in patients with mCRPC regardless of their HRR gene mutation status.

Study D081SC00001 [NCT03732820] is an ongoing Phase 3 trial, titled "A Randomized, Double-blind, Placebo-controlled, Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men with Metastatic Castration-resistant Prostate Cancer". The primary efficacy endpoint of this study was investigator-assessed radiological progression-free survival (rPFS) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for soft tissue metastases and Prostate Cancer Working Group criteria (PCWG-3) for bone lesions. The key secondary efficacy endpoint was overall survival (OS).

To be eligible for the study, subjects were required to have: 1) no prior chemotherapy or new hormonal agent (NHA) at the mCRPC stage; 2) histologically or cytologically confirmed prostate adenocarcinoma; 3) evidence of metastatic disease defined as having at least one documented metastatic lesion on either a bone scan or a CT/MRI scan; 4) documented evidence of progressive disease per PCWG-3 guidelines; 5) castrate serum testosterone levels of <50 ng/dL (<2.0 nmol/L) and castration maintenance with androgen deprivation therapy (ADT) during study; 6) written confirmation of the availability of tumor tissue to enable HRR
mutation status testing and/or analysis. Eligible subjects consented for the study were to be randomized (1:1) to receive olaparib plus abiraterone or placebo plus abiraterone. Randomization was stratified by metastases (bone only, visceral, or other) and docetaxel treatment administered at mCRPC (yes or no).

Following randomization, subjects assigned to the olaparib arm were to receive olaparib 300 mg orally twice daily plus abiraterone 1000 mg orally once daily and subjects assigned to the placebo arm were to receive matching placebo plus abiraterone 1000 mg orally once daily. Subjects in both arms also were to receive either prednisone or prednisolone 5 mg orally twice daily. Study treatment was to be continued until objective radiological disease progression as determined by investigator, unacceptable toxicity, consent withdrawal, or other protocol-specified requirements for discontinuation in the protocol. Crossover from the olaparib arm to the placebo arm was not allowed in this study.

For the primary efficacy endpoint rPFS, tumor assessments were performed with CT/MRI and bone scans at baseline, every 8 weeks (± 7 days) for the first 24 weeks, and then every

12 weeks (±7 days) until investigator-confirmed radiological disease progression according to the RECIST 1.1 and PCWG-3 criteria. All scans were also to be collected and submitted to the sponsor's designated CRO (b) (4) for blinded independent central review (BICR) and results from BICR were not to be communicated to study sites but for sensitivity analysis. For safety assessments, adverse events (AE) and the protocol-required examinations and tests were to be collected or performed per the Schedule of Assessments of the protocol. Severity of AEs and abnormal laboratory results was to be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

From 10/31/2018 through 03/11/2020, the study enrolled 796 subjects from 126 sites in 17 countries, with 74 subjects (9%) from 24 sites in the United States. Of the total enrolled, 399 subjects were randomly assigned to the olaparib arm (olaparib plus abiraterone) and 397 to the placebo arm (placebo plus abiraterone). One subject in each arm did not receive study treatment following randomization and was not included in the population of safety analysis. The study was ongoing as of the data cutoff date of 07/30/2021 for analyses in the current submission.

The DO1 and OSI review teams selected the above four investigators for clinical inspection following discussion on the study design, number of subjects and reported rPFS events by investigator site, and geographical location of study sites. Relative to other investigator sites, these selected investigators enrolled large numbers of study subjects and reported fewer rPFS events in the olaparib arm, favoring treatment with the investigational product.

III. RESULTS

1. **Gary Buchschacher, M.D. [Site 7822]**
   4950 Sunset Blvd, 6th Floor
   Los Angeles, CA 90027

Dr. Buchschacher was inspected on September 26-30, 2022, as a surveillance and data audit for Study D081SC00001. For the investigator, this was the first FDA inspection. The site enrolled 16 subjects, with 9 subjects randomized to the olaparib arm and 7 to the placebo arm. All the subjects received study treatment as randomized. As of the data cutoff date, three subjects (b) (6) in the olaparib arm and one subject (b) (6) remained on study treatment and the rest of subjects were discontinued from study treatment due to disease progression, adverse events(s), or other reasons (e.g., consent withdrawal, non-compliance). At the time of this inspection, the study was ongoing at the site but was closed to enrollment.

Source records for all the 16 subjects were reviewed and compared with the Applicant's submitted data for the site. The reviewed records included but were not limited to the informed consents, case history and eligibility, screening and enrollment log, randomization, study treatment administered, scans performed and RECIST assessments, adverse events, concomitant medications, laboratory tests, and protocol deviations. Regulatory documentation and study conduct oversight at the site were also examined, including the institutional review board (IRB) approvals of the protocol/amendments and

the informed consents as well as its continuing reviews of the study conduct, Delegation of Duties, training activities, signed Form FDA 1572s, financial disclosures, study monitoring, and access to the study electronic case report form (eCRF) system and related data entry processes.

The inspection found no regulatory violations and the Applicant's submitted data were verified with source records reviewed at the site. There was no evidence of underpotting of adverse events. No Form FDA 483 was issued to Dr. Buchschacher at the conclusion of this inspection.

2. Urban Emmenegger, M.D. [Site 1004]
Sunnybrook Research Institute
2075 Bayview Ave
Toronto, M4N 3M5
Canada

Dr. Emmenegger was inspected on October 11-13, 2022, as a surveillance and data audit for Study D081SC00001. This was the initial FDA inspection of the investigator. The site enrolled 11 subjects into the study, with 8 subjects randomized to the olaparib arm and 3 to the placebo arm. As of the data cutoff date, 3 subjects in the olaparib arm (b) (6) - (b) (6)) and 1 subject (b) (6) in the placebo arm were on study treatment and the rest of subjects in each arm were discontinued from study treatment due to disease progression, adverse event, or consent withdrawal. At the time of this inspection, 2 subjects in the olaparib arm (b) (6)) and 1 subject ((b) (6)) in the placebo arm were receiving study treatment; one subject ((b) (6)) was found to have been discontinued due to disease progression during the interim and was on survival follow-up; and all the subjects who were discontinued from study treatment as of the data cutoff were reported to have deceased. As of the inspection, the study was open but closed to enrollment.

The inspection reviewed source records for all the 11 enrolled subjects and compared the submitted data with source data at the site. Subject records reviewed included the signed informed consents, eligibility documentation, Screening and Enrollment Log, randomization and study treatment administration, protocol assessments, adverse events, and protocol deviations. The inspection also reviewed regulatory documentation specific to the administration and oversight of this study at the site, including the Central Ethics Board (CEB) approvals and correspondences related to the continuing reviews, site's training on the study, Duty Delegation Log, financial disclosures, test article shipping and accountability logs, study monitoring activities and correspondences with the sponsor, data entry and audit trails in the electronic data collection system Medidata Rave used for the study.

The inspection identified no significant regulatory deficiencies in the investigator's conduct of this study. The Applicant's submitted data for the site are verifiable with source documentation at the site, with no differences observed in the reported rPFS data, survival

status, and adverse events. At the conclusion of this inspection, no Form FDA 483 was issued to Dr. Emmenegger.

3. Niven Mehra, M.D. [Site 5001]
Radboud Universitair Medisch Centrum
Geert Grooteplein Zuid 10
Nijmegen, NA 6525 GA
Netherlands

Dr. Mehra was inspected on October 17-21, 2022, as a data audit for Study D081SC00001. This was the first FDA inspection of the investigator. The Established Inspection Report is not currently available.

Based on the preliminary summary from the filed inspector, Dr. Mehra's site enrolled 18 subjects for the study, with 11 subjects randomized to the olaparib arm and 7 to the placebo arm. As of data cutoff, a total of 12 subjects were discontinued from study treatment due to disease progression or adverse event, including 5 subjects in the olaparib arm and all the 7 subjects in the placebo arm. The rest of subjects in the olaparib arm remained on study treatment. This study was closed to enrollment but was active at the time of the inspection.

The inspection reviewed source records and CRFs for all the enrolled subjects as well as regulatory documents for the study conduct and oversight. The investigator was found to be in general compliance with the regulations and the submitted clinical data, including protocol deviations, were verifiable with source data reviewed at the site. A Form FDA 483 was not issued at the closeout of the inspection.

Reviewer's Note: An addendum to this summary will be made if the final Establishment Inspection Report for Dr. Mehra's conduct contains substantial differences that can alter the current compliance assessment.

4. Cagatay Arslan, M.D. [Site 7604]
Izmir Medical Park Hospital
Yeni Girne Bulvari 1825 Sok. No. 12
Karsiyaka, NA 35575
Turkey

Dr. Arslan was inspected on October 24-28, 2022, as a data audit for Study D081SC00001. This was the first FDA inspection of the investigator. The established inspection report for this inspection is not currently available. Based on the inspector's preliminary summary, Dr. Arslan's site enrolled 19 subjects into the study, with 11 randomized to the olaparib arm and 8 to the placebo arm. One subject [(b) (6)] assigned to the olaparib arm did not receive study treatment following randomization due to elevated creatinine levels. As of data cutoff, 7 subjects in each arm were discontinued from study treatment due to disease progression or adverse event. At the time of the inspection, 2 subjects (b) (6) and (b) (6) in the olaparib arm continued receiving study treatment. Two subjects, one in

each arm [(b) (6) in the olaparib arm and (b) (6) in the placebo arm], were found to have discontinued study treatment during the interim.

The inspection reviewed the study conduct at the site, audited source records for all the subjects, and found no compliance issues. All the subjects were found eligible for the study and the Applicant's submitted data for the site were consistent with source data reviewed at the site. There were no unreported adverse events and protocol deviations. No Form FDA 483 was issued at the conclusion of this inspection.

Reviewer's Note: An addendum to this summary will be made if the final Establishment Inspection Report for Dr. Arslan's conduct of this study contains substantial differences that can alter the current compliance assessment and data integrity.

{See appended electronic signature page}

Yang-Min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Lead
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Jenn Seller, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Room
Review Division /Division Director
Review Division /Project Manager
Review Division/Clinical Team Lead
Review Division/Clinical Reviewer
OSI/Office Director
OSI/DCCE/ Division Director
OSI/DCCE/ Acting Branch Chief
OSI/DCCE/ Team Lead
OSI/DCCE/GCP Reviewer
OSI/ GCP Program Analysts
OSI/Database PM

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/s/

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JENN W SELLERS
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 14, 2022
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 208558/S-025
Product Name, Dosage Form, and Strength:	Lynparza (olaparib) tablets, 150 mg, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
FDA Received Date:	June 16, 2022
TTT ID #:	2022-306
DMEPA 1 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 1 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

AstraZeneca Pharmaceuticals LP submitted an Efficacy Supplement for Lynparza (olaparib) tablets to for the following indication:

> *Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer.*

Subsequently, the Division of Oncology 1 (DO1) requested that we review the proposed Lynparza Prescribing Information and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-– N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F- – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed changes to the Lynparza PI in Section 2 Dosage and Administration and the Lynparza Medication Guide, and we find them acceptable from a medication error perspective. We noted that there are no changes to Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, or Section 17 Patient Counseling Information. Further, there are no proposed changes to the container labels. Additionally, our routine postmarket safety surveillance did not identify any medication errors related to label and labeling that is relevant for this review. Therefore, we have no recommendations for the proposed Lynparza PI or Medication Guide from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Lynparza PI and Medication Guide are acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lynparza received on June 16, 2022 from AstraZeneca Pharmaceuticals LP.

Table 2. Relevant Product Information for Lynparza	
Initial Approval Date	8/17/2017
Active Ingredient	olaparib
Indication	Ovarian cancer Breast cancer Pancreatic cancer Prostate cancer *Proposed addition:* in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC). *See PI for more information:* \\CDSESUB1\EVSPROD\nda208558\1080\m1\us\nonannotated-draft-label-propel-26may22.pdf
Route of Administration	oral
Dosage Form	tablets
Strength	150 mg, 100 mg
Dose and Frequency	300 mg taken orally twice daily, with or without food
How Supplied	Bottle of 60 tablets and bottles of 120 tablets.
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in original bottle to protect from moisture.
Container Closure	The primary pack is a 110 and a 190 mL bottle made of white, high-density polyethylene (HDPE) with a (b) (4) Inside the bottle are desiccant containers, containing silica gel.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 12, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Lynparza. Our search identified 7 previous reviews[a,b,c,d,e,f,g], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Gao, T. Label and Labeling Review for Lynparza (NDA 208558). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUNE 21. RCM No.: 2017-225.

[b] Gao, T. Label and Labeling Review for Lynparza (NDA 208558). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JULY 10. RCM No.: 2017-225-1.

[c] Gao, T. Label and Labeling Review for Lynparza (NDA 208558/S-012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 5. RCM No.: 2019-1519.

[d] Gao, T. Label and Labeling Review for Lynparza (NDA 208558/S-014). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 11. RCM No.: 2019-2475.

[e] Mahmoud, S. Label and Labeling Review for Lynparza (NDA 208558/S-016). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jun 16. RCM No.: 2020-927.

[f] Mahmoud, S. Label and Labeling Review for Lynparza (NDA 208558/S-016). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Nov 18. RCM No.: 2020-927-1.

[g] Gao, T. Label and Labeling Review for Lynparza (NDA 208558/S-023). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Dec 14. RCM No.: 2021-2020.

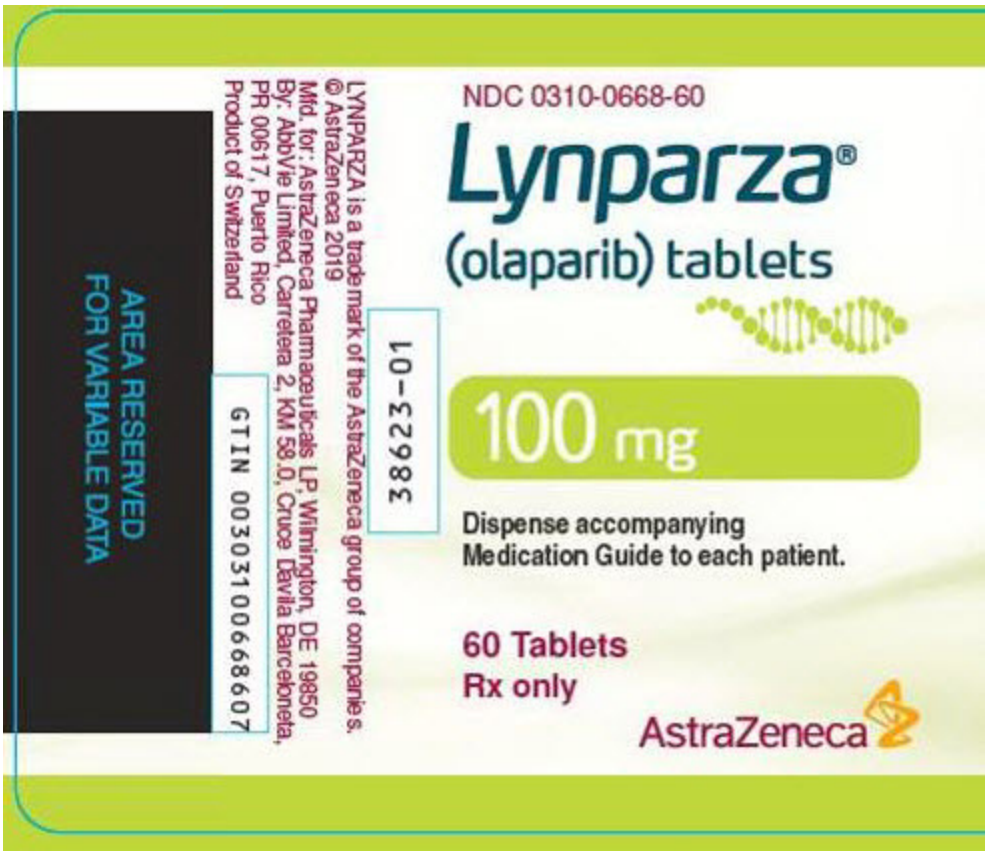
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Lynparza labels and labeling submitted by AstraZeneca Pharmaceuticals LP.

- Container labels received on June 16, 2022
- Prescribing Information with Medication Guide (Image not shown) received on June 16, 2022, available from \\CDSESUB1\EVSPROD\nda208558\1080\m1\us\nonannotated-draft-label-propel-26may22.docx

G.2 Label and Labeling Images



[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.


NDC 0310-0679-12
Lynparza®
(olaparib) tablets
150 mg
Dispense accompanying
Medication Guide to each patient.
120 Tablets
Rx only
AstraZeneca
LYNPARZA is a trademark of the AstraZeneca group of companies. ©AstraZeneca 2019
Manufactured for: AstraZeneca Pharmaceuticals LP,
Wilmington, DE 19850
By: AbbVie Limited, Carretera 2, KM 58.0, Cruce Davila
Barceloneta, PR 00617, Puerto Rico
Product of Switzerland
GTIN 00303100679122
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s025

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 121413

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Yuchao Xie, PhD
Regulatory Affairs Director
430 East, 29th Street, 16th Floor
New York, NY 10016

Dear Dr. Xie:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for olaparib.

We also refer to the teleconference between representatives of your firm and the FDA on May 18, 2022. The purpose of the meeting was to seek feedback and agreement on the planned clinical data package and analyses on key efficacy and safety endpoints to support the sNDA submission as well as format and content of the planned sNDA.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call Rajesh Venugopal, Chief, Regulatory Project Management Staff at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Chief, Regulatory Project Management Staff-Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Chana Weinstock, MD
Clinical Team Lead
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Guidance

Meeting Date and Time: May 18, 2022/ 9:00 AM – 10:00 AM EST
Meeting Location: Teleconference

Application Number: IND 121413
Product Name: Olapraib
Indication: Prostate Cancer

Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP
Regulatory Pathway: 505(b)(1)

Meeting Chair: Chana Weinstock, MD
Meeting Recorder: Rajesh Venugopal, MPH, MBA

FDA ATTENDEES

Laleh Amiri-Kordestani, MD, Director, DO1
Daniel Suzman, MD, Supervisory Associate Director, DO1
Chana Weinstock, MD, Clinical Team Leader, DO1
Sundeep Agrawal, MD, Clinical Team Leader, DO1
Jaleh Fallah, MD, Clinical Reviewer, DO1
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Hui Zhang, PhD, Biostatistics Reviewer, OB/DBV
Erik Bloomquist, PhD, Biostatistics Team Leader, OB/DBV
Mehrnoosh Hadadi, MD, Clinical Reviewer, DO1
Reena Philip, PhD, Associate Director of Biomarkers and Precision Oncology, OCE
Paul Kluetz, MD, Deputy Center Director, OCE
Soma Ghosh, PhD, Chief, CDRH/OIR/DMGP/MPCB
Oluseyi Adeniyi, PharmD, PhD, Genomics Reviewer, OCP/DTPM
Rosane Charlab Orbach, PhD, Genomics Team Leader, OCP/DTPM
Rajesh Venugopal, MPH, MB, Chief, Project Management staff, OOD-OOD/DO1

SPONSOR ATTENDEES

AstraZeneca
Cristian Massacesi, Chief Medical Officer
Jacques Mascaro, Senior Vice President, Regulatory Affairs
Gavin Fitzgerald, MRes, Director, Regulatory Affairs, Oncology
Yuchao Xie, PhD, Director, Regulatory Affairs, Oncology
Fabrice Marsicano, PharmD, Executive Director, Regulatory Affairs, Oncology
Debbie Mackenzie, MSc, Vice President, Regulatory Affairs, Oncology

Laurence Toms, MD, Global Clinical Head
Alice Kang, MD, Global Clinical Program Lead
Arnold Degboe, MD, PhD, Global Development Medical Director
Chintu Desai, PhD, Director, Statistics
Edit Lukacs, MD, PhD, Patient Safety Physician
Yu-Zhen Liu, MD, PhD, Senior Director, Diagnostics
Elizabeth Harrington, PhD, Executive Director, Translational Medicine
Simon Hollingsworth, PhD, Global Product Leader
Catherine Hollingdale, Director, Regulatory Affairs, Oncology

Merck
Nadine, Margaretten, PhD, Executive Director, Regulatory Affairs
Christian Poehlein, MD, Product Development Team Lead

1.0 BACKGROUND

Purpose of the meeting: The Sponsor (AstraZeneca) requested this Type B (pre-NDA) meeting to present the topline results of PROpel Study at DCO2 and discuss the sNDA submission for olaparib based on these results.

PROpel Study

The PROpel Study is a multicenter, randomized, double-blind, phase 3 study in patients with metastatic castration resistant prostate cancer (mCRPC), all comers, regardless of HRR gene mutation status, which compares the efficacy of abiraterone plus olaparib versus abiraterone plus placebo. The primary endpoint of the study is rPFS using RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), assessed by the investigator (supported by BICR sensitivity analysis) in the ITT population. Imaging frequency was every 8 weeks (±7 days) after randomization within the first 24 weeks, and then every 12 weeks. The key secondary endpoint is overall survival.

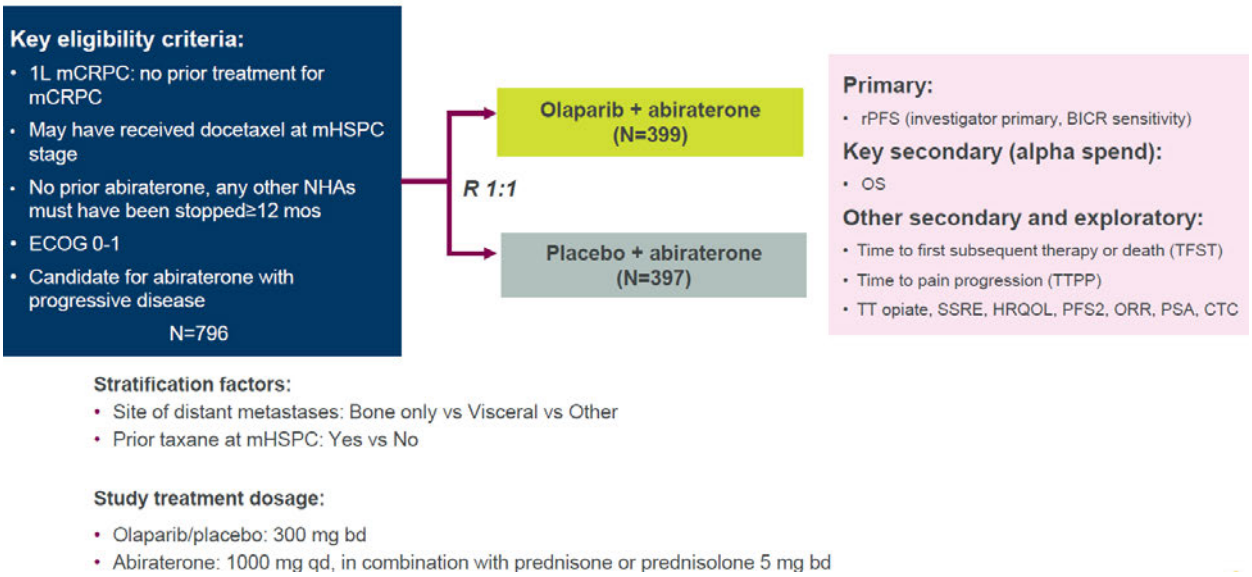
The rationale for a biomarker-independent all comer (ITT) design involving olaparib plus abiraterone combination in the PROpel study, per the Sponsor, is based on preclinical and clinical evidence linking PARP inhibition with suppression of transcription of several androgen receptor (AR) targets and the ability of the combination to induce an HRR-deficient phenotype through non-genetic mechanisms, via inhibition of AR signaling which sensitizes cells and xenograft models to olaparib. Per the Sponsor, the efficacy of the combination of olaparib and abiraterone in an HRRm unselected population was also corroborated through clinical evidence from Study 8, a randomized, double blind, placebo-controlled, multicenter phase 2 study of olaparib vs placebo given in combination with abiraterone, in patients with mCRPC who had received prior chemotherapy containing docetaxel. Per the Sponsor, Study 8 met its primary objective, demonstrating a statistically significant improvement in investigator-assessed rPFS in the olaparib plus abiraterone combination arm (13.8 months) vs placebo (8.2 months), in patients with mCRPC who had disease progression on prior taxane treatment (5.6 months improvement in rPFS, regardless of the HRR status).

A pre-sNDA teleconference was held in November 2021, to discuss the clinical data package in support of a planned sNDA based on PROpel results. The FDA recommended that the Sponsor not submit the sNDA at the time and instead first provide top-line results from the next prespecified interim analysis. The FDA stated that the Sponsor should justify clinical benefit from addition of olaparib in the BRCA 1&2, other HRR, and non-HRR sub-populations in PROpel.

In the written response only (WRO) meeting in February 2022, the FDA stated that the submitted data from DCO1 was not sufficient to provide a definitive response on whether the data would be appropriate/sufficient to support review of the sNDA. The FDA recommended that the Sponsor request another meeting to discuss the topline results from DCO2.

A final OS analysis for PROpel is scheduled to take place 48 months after the first patient was randomized (4Q2022), when a minimum follow-up of 32 months is expected. Subgroup analyses by homologous recombination repair gene mutation (HRRm) status were conducted post-hoc. HRRm status was retrospectively determined by testing ctDNA and tumor tissue for mutations in the following 14 genes: ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L.

PROpel: Study Design



Overall, the baseline disease characteristics appear well-balanced between the two arms, with approximately 62% of patients overall having M1 disease at first diagnosis.

OS maturity at DCO2: 40%
Efficacy and safety results at DCO2 (March 14th, 2022) are summarized in tables below; HRR and BRCA results are both aggregates of patients who were positive by either one or both of ctDNA and/or tumor tissue assays:

- **Efficacy results at DCO2**

ITT population	Abiraterone + **Olaparib** **(n=**399)	Abiraterone + placebo (n=397)	HR (95% CI)
rPFS per investigator (Median in months)	25	16	0.67 (0.56, 0.81)
rPFS (per BICR) (Median in months)	28	16	0.61 (0.49,0.74)
OS	Not reached	Not reached	**0.83** (0.66, 1.03)
ORR	59%	48%	
Median DoR (months)	24	13	
HRRm (-)	Abiraterone + **Olaparib** **(n=**279)	Abiraterone + placebo (n=273)	HR (95% CI)
rPFS (by investigator)	25	19	0.77 (0.62, 0.97)
rPFS (by BICR)	28	19	0.72 (0.56, 0.93)
OS	Not reached	Not reached	**0.90** (0.69, 1.18)
ORR	59%	45%	
Median DoR (months)	19	13	

HRRm (+)	Abiraterone + **Olaparib** (n=111)	Abiraterone + placebo (n=115)	HR (95% CI)
rPFS (by investigator)	25	14	0.55 (0.38, 0.79)
rPFS (by BICR)	29	14	0.45 (0.31, 0.65)
OS	Not reached	28	**0.69** (0.46, 1.03)
ORR	57%	55%	
Median DoR (months)	Not reached	11	

BRCA (-)	Abiraterone + **Olaparib**	Abiraterone + placebo	HR (95% CI)

	(n=343)	(n=350)	
rPFS (by BICR)	28	17	0.74 (0.60, 0.91)
OS	Not reached	Not reached	0.93 (0.73, 1.17)
ORR	Not provided		

BRCA (+)	Abiraterone + **Olaparib** (n=47)	Abiraterone + placebo (n=38)	HR (95% CI)
rPFS (by BICR)	Not reached	8	**0.20 (0.10, 0.36)**
OS	Not reached	23	**0.32 (0.15, 0.64)**
ORR	65%	33%	
Median DoR (months)	Not reached	9	

- **Safety outcomes**

AEs by category (in the safety analysis set) at DCO2

	Abiraterone + Olaparib	Abiraterone + placebo
Any AE	98%	96%
Any Grade 3-5 AE	53%	40%
Any SAE	39%	30%
Fatal AEs	5.8%	4.5%

AEs of special interest

N (%)	Olaparib + abiraterone	Placebo + abiraterone
MDS/AML	1 (0.3) new since DCO1	0
Pneumonitis	4 (1.0) + 1 since DCO1	3 (0.8)
New primary malignancies	14 (3.5) + 2 since DCO1	11 (2.8) + 1 since DCO1

The Sponsor plans to submit an sNDA submission with PROpel as the pivotal study based on data from DCO2 with additional supportive evidence from Study 8 (described earlier) in support of the proposed indication (to provide support on efficacy of Olaparib in HRR (-) subgroup).

2.0 DISCUSSION

Question 1: Does the Agency agree that the results from the analysis of the pivotal study PROpel (DCO1 data supplemented with DCO2 data and additional analyses requested by the Agency), in addition to the supportive evidence from Study 8 are sufficient to enable an evaluation of the safety and efficacy of olaparib in combination with abiraterone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC)?

FDA Response to Question 1: The provided topline results appear to be sufficient for evaluation of the safety and efficacy of olaparib in combination with abiraterone for the treatment of adult patients with BRCA(+) and/or HRR(+) mCRPC, although see response to Question 4. regarding submission of analyses of all data in the HRR(+) subgroups, including for all 14 included genes.

An assessment of a favorable benefit: risk assessment in patients with HRR(-) and/or BRCA(-) disease is still unclear at this time and may require discussion at an oncologic drug advisory committee.

Assessment of clinical benefit based on imaging endpoints such as rPFS relies on large absolute and relative magnitude of effect, and internal consistency among key secondary endpoints including OS in the context of an acceptable safety profile. The rPFS benefit in the ITT population appears to be driven by the large magnitude of effect in the BRCA(+) and/or HRR(+) subgroup. The magnitude of rPFS benefit in the HRR(-) subgroup which comprises 70% of patients in PROpel is relatively small and the OS data is immature. In the absence of clinically meaningful rPFS benefit, mature OS data from DCO3 is required for complete benefit: risk assessment in the HRR(-) subgroup.

While PROpel results appear sufficient for an sNDA submission at this time, results in the HRR(-) subgroup and possibly in each of the included genes will be a review issue. You should plan to submit topline results of DCO3 during the course of the review (per briefing deck, these will be available 4Q2022). These could result in a major amendment especially if there is evidence of an adverse effect in the HRR (-) subgroup.

(b) (4)

We may consider addition of a complementary or companion diagnostic device to approval of an sNDA in this setting.

AstraZeneca Response to Question 1 dated May 17, 2022: The sponsor thanks the Agency for the comments and would like to present the appended slide deck during the

meeting with more comprehensive subgroup efficacy and safety data at DCO2 in the non-HRRm subpopulation to further support the benefit-risk assessment.

The sponsor also would like to request further feedback from the Agency at the meeting for the following,

1) With respect to the non-HRRm subgroup, does the agency consider that the clinical context for 1L mCRPC patients and the totality of evidence from PROpel demonstrate meaningful clinical benefit?

Meeting Discussion: Possibly. The final benefit:risk assessment of adding olaparib to abiraterone in this setting in patients with non-BRCAm and/or non-HRRm disease (i.e., the ITT population) will be a review issue and will be determined after reviewing the totality of data in the sNDA submission in addition to the data from DCO3.

Note that internal consistency between primary and secondary endpoints is required but not sufficient for benefit:risk assessment. For an rPFS improvement to be considered clinically meaningful, there should be a sufficient magnitude of effect to outweigh the toxicities of the study drug (particularly in an "add-on design") in addition to consistency with efficacy endpoints.

The Sponsor should provide subgroup analyses (DCO1 and DCO2) for the primary and secondary endpoints by HRRm status (HRRm vs non-HRRm vs unknown) and BRCA status (BRCAm vs non-BRCAm vs unknown). In addition, you should provide subgroup analyses for HRRm/non-BRCAm subpopulation.

Question 2: AstraZeneca will submit updated safety data from DCO2 with the initial sNDA submission as requested and requests a waiver for an additional safety update to the proposed supplement. Does the Agency agree that this is an acceptable approach?

FDA Response to Question 2: While this generally appears reasonable, you should submit information on any additional cases of myelodysplastic syndrome and/or acute leukemias in study patients. Additionally, you should submit frequency of grouped terms for the following adverse reactions:

- **Thromboembolic events**
- **Infection/Sepsis with concurrent neutropenia/leukopenia**
- **Bleeding with concurrent thrombocytopenia**

AstraZeneca Response to Question 2 dated May 17, 2022: The sponsor acknowledges the feedback and no further discussion is requested in the meeting.

Meeting Discussion: No further discussion took place.

Question 3: AstraZeneca would like to offer application orientation and/or technical walkthrough teleconferences subsequent to the sNDA submission to facilitate the FDA's review of the application. Does the FDA agree with this proposal?

FDA Response to Question 3: Yes.

AstraZeneca Response to Question 3 dated May 17, 2022: The sponsor acknowledges the feedback and no further discussion is requested in the meeting.

Meeting Discussion: No further discussion took place.

Question 4: Per feedback from the Agency at the 04 February 2022 pre-sNDA meeting (Written Response Only), AstraZeneca proposes the sNDA submission plan with the clinical efficacy and safety data as follows. Does the Agency agree with the proposal?

AstraZeneca will submit on 16 June 2022 for the sNDA,
1) PROpel DCO1 and study 8 documents (primary submission package)
- sNDA Module 5 CSR for PROpel DCO1 and Study 8, and Module 2 documents (2.5 Clinical Overview, 2.7.3 Summary of Clinical Efficacy, and 2.7.4 Summary of Clinical Safety, and other clinical summaries) summarizing data from the PROpel interim analysis at DCO1 (July 30, 2021) and Study 8.
- Full eCRT package including all efficacy and safety SDTM and ADaM datasets based on PROpel DCO1 and study 8.

2) PROpel DOC2 documents (supportive submission package)
- Module 2.5 clinical overview appendix to summarize results at DCO2 including data requested by the Agency at the pre-sNDA meeting on 04 February 2022
- eCRT packages for efficacy and safety SDTM and ADaM datasets at DCO2
- Assessment Aid incorporating OS data from DCO2
- USPI incorporating OS data from DCO2

During the sNDA review, a CSR addendum for DCO2 including safety narratives up to DCO2 will be provided by the end of July 2022 as a supportive document.

FDA Response to Question 4: Although the proposed plan for data submission is acceptable, you should also plan to submit topline results from DCO3 during the course of the review.

At the time of initial submission of the sNDA, submit an analysis of all primary and secondary endpoints and safety outcomes from DCO2 in ITT population and in the following subgroups:

1. HRR mutation
2. No HRR mutation
3. BRCA mutation
4. Non-BRCA HRR mutations
5. Unknown HRR status

You should also plan detailed analyses of observed efficacy in each of the 14 genes included in the "HRR mutation" group. See the FDA Response to Question 1. regarding submission of DCO3 OS data to determine the final risk/benefit consideration in all enrolled patients in the ITT. If a substantial scientific issue essential to determining the safety or effectiveness of the drug in some molecular subset included in the trial is identified, the indicated patient population may be narrower than the clinical trial enrollment criteria.

We reiterate that you should describe ORR to include only confirmed responses. This applies to the BICR-assessed ORR analysis and the investigator-assessed ORR analysis.

AstraZeneca Response to Question 4 dated May 17, 2022: The sponsor acknowledges the comments. The proposed Table of Contents for the sNDA is presented in Appendix A.

AstraZeneca commits to providing the OS in the FAS and subgroups for DCO3 similar to the DCO2 outputs and would like to seek further feedback from the Agency at the meeting for the DCO3 data as follows.

1) *Does FDA agree that confirmation of no survival detriment in the non-HRRm subgroup at DCO3 would be sufficient to support a positive benefit: risk profile in this subgroup?*

   Meeting Discussion: This will be a review issue.

2) *Can FDA comment on the latest date for submission of the DCO3 data to support label finalization?*

   Meeting Discussion: The Sponsor should make every effort to submit the DOC3 high-level OS data including subgroups within 5 months of sNDA submission, if not earlier. Submission of these data may trigger a major amendment and may impact the review timeline.

Based on the HLR and detailed analyses of DCO1+ DCO2 submitted to date, does FDA agree that the totality of data meets the requirements for Priority Review for the sNDA?

Meeting Discussion: This will be determined during the review.

ADDITIONAL COMMENTS:

Meeting Discussion:

1. **For Study-8, submit the safety and efficacy results in subgroups with HRRm and non-HRRm in addition to the ITT population.**

2. **A diagnostic device is under consideration. For PROpel and Study-8, submit an analysis of efficacy in patients with discordant HRR results (both in those with test failure in one modality and those with evaluable results in both tests that were discordant) by ctDNA and tumor tissue. We note that there is no currently approved companion or complementary diagnostic that includes non-BrCA/ATM mutations by ctDNA.**

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that the FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with the FDA. (In the absence of an EOP2 meeting, refer to the

draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or Sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the Sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the FDA's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review Division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The FDA strongly advises the complete meeting package to be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate the FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review Division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[4]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[5]

3.0 ATTACHMENTS AND HANDOUTS

Slides presented during the meeting are attached.

13 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

[4] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[5] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RAJESH VENUGOPAL
05/20/2022 09:13:31 PM

CHANA WEINSTOCK
05/22/2022 05:24:01 PM

IND 121413

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Varadamurthy Srinivasan PhD
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Srinivasan:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lynparza (olaparib).

We also refer to the teleconference between representatives of your firm and the FDA on November 9, 2021. The purpose of the meeting was to discuss the planned clinical data package and analyses for key safety, efficacy endpoints, and the format and content of a planned sNDA.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, contact Amy Tilley, Regulatory Project Manager at amy.tilley@fda.hhs.gov or 301.796.3994.

Sincerely,

{See appended electronic signature page}

Amy Tilley
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations
for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation & Research

Elaine Chang, MD
Acting Team Leader
Division of Oncology 1
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Center for Drug Evaluation & Research

Enclosure:

- Meeting Minutes
- Slides

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	November 9, 2021 4:00 pm – 5:00 pm EST
Meeting Location:	Teleconference
Application Number:	IND 121413
Product Name:	Lynparza (olaparib)
Indication:	Lynparza in combination with abiraterone and prednisone or prednisolone is indicated for treatment of adult patients with metastatic castration resistant cancer (mCRPC).
Sponsor Name:	AstraZeneca Pharmaceuticals LP
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Elaine Chang, MD, Acting Clinical Team Leader
Meeting Recorder:	Amy Tilley, Regulatory Project Manager

FDA ATTENDEES

Paul Kluetz, MD, Deputy Center Director, OCE
Laleh, Amiri-Kordestani, MD, Director, DO1
Amna Ibrahim, MD, Deputy Director, DO1
Elaine Chang, MD, Acting Clinical Team Leader, DO1
Sundeep Agrawal, MD, Acting Clinical Team Leader, DO1
Mehrnoosh Hadadi, MD, Clinical Reviewer, DO1
Jallah Fallah, MD, Clinical Reviewer, DO1
Brian Heiss, MD, Clinical Reviewer, DO1
Erik Bloomquist, PhD, Biostatistics Team Leader, OTS/OB/DBV
Hui Zhang, PhD, Biostatistics Reviewer, OTS/OCP/DCPV
Salaheldin Hamed, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCPV
Runyan Jin, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Rosane Charlab Orbach, PhD, Genomics/DTPM
Oluseyi Adeniyi, PhD, Genomics/DTPM
Francisca Reyes Turcu, PhD, Scientific Reviewer, CDRH/OIR/DMGP/MPCB
Amy Tilley, Senior Regulatory Project Manager, ORO/DRO-OD

SPONSOR ATTENDEES

AstraZeneca Attendees:

Jacques Mascaro, PhD, MBA, Senior Vice President, Regulatory Affairs
Gavin Fitzgerald, MRes, Director, Regulatory Affairs, Oncology
Varadamurthy Srinivasan, PhD, DABT, Director, Regulatory Affairs, Oncology
Fabrice Marsicano, PharmD, Executive Director, Regulatory Affairs, Oncology
Debbie Mackenzie, MSc, Vice President, Regulatory Affairs, Oncology
Christian Massacesi, MD, Chief Medical Officer
Tsveta Milenkova, MD, Global Clinical Head
Alice Kang, MD, Global Clinical Program Lead
Arnold Degboe, MD, PhD, Global Development Medical Director
Chintu Desai, PhD, Director, Statistics
Edit Lukacs, MD, PhD, Patient Safety Physician
Yu-Zhen Liu, PhD, Senior Director, Diagnostics
Elizabeth Harrington, PhD Executive Director, Translational Medicine
Khanh Bui, PhD, Senior Director, Clinical Pharmacology
Simon Hollingsworth, PhD Global Product Leader

Merck Attendees:

Peggy McCann, DVM, PhD, Associate Vice President, Regulatory Affairs
Nadine, Margaretten, PhD Executive Director, Regulatory Affairs
Nageatte Ibrahim, MD, Vice President, Clinical Development
Christian Poehlein, MD, Product Development Team Lead

Carolina Urologic Research Center

Neal Shore, MD, FACS, Medical Director, CPI

1.0 BACKGROUND

The purpose of this meeting is to discuss the Sponsor's proposal to submit a supplemental New Drug Application (sNDA) for regular approval for olaparib for the treatment of mCRPC.

Regulatory history

Olaparib was approved for the treatment of adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone by the FDA on May 19, 2020. This finding was supported by the randomized trial PROfound, which showed a significant and meaningful improvement in rPFS in Cohorts A+B, improved ORR in Cohort A (*BRCA1*, *BRCA 2*, or *ATM* mutation-positive), and improved overall survival in Cohort A. A postmarketing commitment to better characterize responses to olaparib in patients with HRR gene mutations from Cohort B with 5 or fewer patients enrolled to PROfound was agreed upon with the Sponsor.

On May 24, 2018, the Sponsor met with the FDA in a Type B Meeting. The FDA indicated the importance of demonstrating a trend towards improved OS to ensure no treatment detriment especially given the toxicity concerns of the combination of olaparib + abiraterone from Study D081DC00008 ("Study 8").). Study 8 was a phase 1/2 trial (described below) that evaluated abiraterone in combination with either olaparib or placebo in patients with mCRPC, and excess toxicity was observed on the combination arm. The Sponsor agreed to not pursue an accelerated approval based on Study 8 alone. The Sponsor also met with the FDA on September 29, 2020, to discuss a proposed PROpel study design amendment to add a co-primary endpoint of rPFS in the HRRm subgroup. The FDA disagreed with this amendment because HRR mutation status was not a stratification factor at randomization. The potential for imbalanced treatment assignment in this subgroup could result in an imbalance in known and unknown prognostic factors in this subpopulation and uninterpretable trial results. The FDA also stated that even if statistical significance is shown in the ITT population, it would be a review issue whether the results are driven by the HRRm, or potentially BRCAm-only, subpopulation. The FDA recommended the addition of formal testing for OS at DCO1.

The Sponsor provided hypothetical mechanistic explanations for the activity of PARP inhibitor + abiraterone activity in non-HRR-mutated cancers, including PARP-mediated transcriptional changes of the androgen receptor pathway and induction of an HRR-deficient phenotype (or *BRCA*ness) via inhibition of AR signaling.

The proposed application is based on data from Study D081SC00001 (referred to as "PROpel") and supportive evidence from Study D081DC00008 (Study 8).

PROpel Design and Results

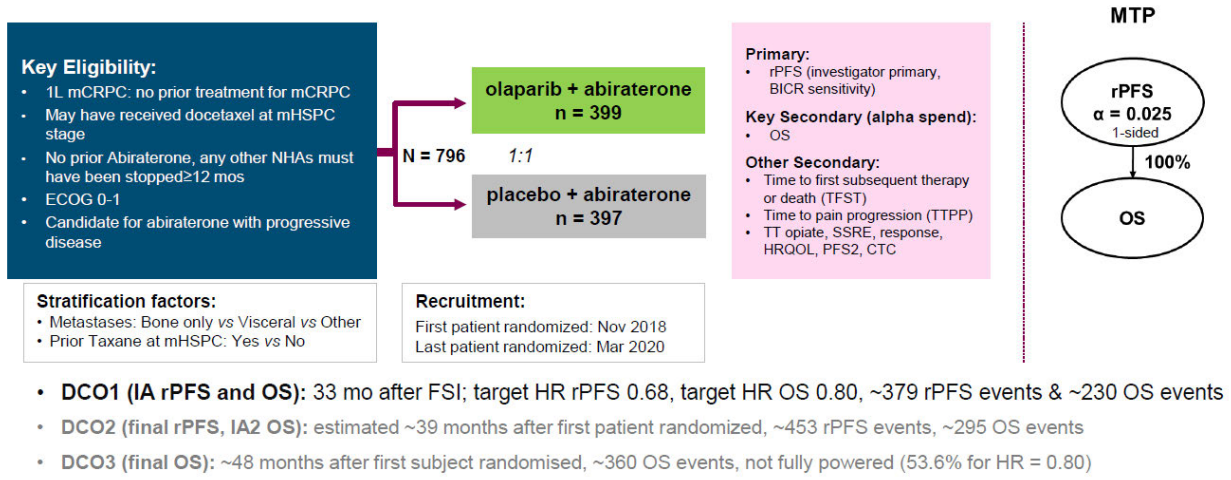
PROpel is a phase 3 randomized, double-blind, placebo-controlled study with "add-on" design evaluating olaparib vs placebo in combination with abiraterone as first-line treatment for men with mCRPC. In PROpel, patients with metastatic prostate adenocarcinoma, regardless of biomarker status, in the mCRPC setting were randomized to receive either olaparib or placebo in combination with abiraterone and prednisone or prednisolone (Figure 1 below). Patients were not selected based on any biomarker status. Stratification factors were metastases (bone only vs. visceral vs. other) and prior taxane in mHSPC (yes vs. no).

Endpoints:
Primary endpoint: rPFS, as assessed by the investigator, using RECIST 1.1 and PCWG-3 criteria for all randomized patients (ITT population).
Key secondary endpoint: OS.
A sensitivity analysis was conducted using rPFS by BICR for all patients.

The multiplicity testing procedure (MTP), as shown in Figure 1, includes analysis at three data cutoffs (DCOs). Radiological PFS analyses at DCO1 and DCO2 were planned. As statistical significance of rPFS was achieved at DCO1, formal rPFS

analysis at DCO2 will not be done and analysis of this endpoint at DCO2 will be considered supportive (with nominal p-values provided). Overall survival was formally analyzed at DCO1 (interim analysis), and will be at DCO2 (interim analysis), and DCO3 (final analysis).

Figure 1. PROpel Study Design and Multiplicity Testing Procedure



The Sponsor's proposed sNDA would be based on results of DCO1 (IA rPFS and OS), with 394 pFS events by investigator (49.5% maturity) and 228 OS events (28.6% maturity). The data cutoff was July 30, 2021.

PROpel met its primary endpoint, with investigator-assessed rPFS HR 0.66; 95% CI 0.54, 0.81; p<0.0001 and median rPFS 24.8 months vs 16.6 months, in the olaparib + abiraterone versus placebo + abiraterone arms, respectively.

A sensitivity analysis of rPFS by BICR showed consistent results: rPFS HR 0.61 (95% CI 0.66, 0.74). The concordance between investigator and central review for rPFS events was 80.5%.

The interim OS data are immature. The proportion of deaths were 26.8% versus 30.5% on the olaparib + abiraterone versus placebo + abiraterone arms, respectively. The OS HR was 0.86 (95% CI, 0.66, 1.12, p=0.2923, where the boundary for significance was 0.001). The Kaplan Meier curves show a separation of survival curves between the arms at approximately 20 months.

PROpel Subgroup Analyses

Though patient enrollment was not based on biomarker selection, both tumor tissue and blood samples were collected at baseline for biomarker tests: mutation status (HRRm) was determined using a ctDNA-based test (FoundationOne Liquid CDx), a tumor tissue test (FoundationOne CDx), or germline blood test (Myriad myRisk).

Pre-defined subgroup analyses for rPFS included:

- HRRm per ctDNA
  - Yes (n=198): HR 0.54 (95% CI 0.36, 0.79)
  - No (n=536): HR 0.76 (95% CI 0.59, 0.97)
  - Unknown (n=62): HR 0.62 (0.26, 1.44)
- HRRm per tumor tissue test
  - Yes (n=118): HR 0.44 (95% CI 0.26, 0.74)
  - No (n=417): HR 0.81 (95% CI 0.62, 1.07)
  - Unknown (n=261): HR 0.64 (95% CI 0.45, 0.90)

Additional exploratory subgroup analyses, as requested by the FDA, for rPFS included:

- BRCAm per ctDNA:
  - Yes (n=69): HR 0.17 (95% CI 0.08, 0.34)
  - No (n=105): HR 0.77 (95% CI 0.62, 0.95)
- BRCAm per tumor tissue test:
  - Yes (n=50): HR 0.30 (95% CI 0.13, 0.65)
  - No (n=746): HR 0.73 (95% CI 0.59, 0.89)

Exploratory subgroup analyses for OS, as requested by the FDA, showed:

- HRRm per ctDNA
  - Yes (n=198): HR 0.84 (95% CI 0.51,1.39)
  - No (n=536): HR 0.87 (95% CI 0.64,1.19)
  - Unknown (n=62): not calculated (5 vs. 4 events in olaparib+abiraterone vs. placebo+abiraterone arms, respectively)
- HRRm per tumor tissue test
  - Yes (n=118): HR 0.62 (95% CI 0.30,1.26)
  - No (n=417): HR 1.10 (95% CI 0.77,1.57)
  - Unknown (n=261): HR 0.69 (95% CI 0.43,1.09)
- BRCAm per ctDNA:
  - Yes (n=69): HR 0.42 (95% CI 0.18, 0.96)
  - No (n=105): HR 0.93 (95% CI 0.71, 1.23)
- BRCAm per tumor tissue test:
  - Yes (n=50): HR 0.31 (95% CI (0.10, 0.83)
  - No (n=746): HR 0.94 (95% CI 0.72, 1.23)

The Sponsor provided unconfirmed ORRs per investigator with breakdown by genetic subgroups according to ctDNA and tissue testing. The number of patients with measurable disease and ctDNA results were 59 vs. 51 (in olaparib + abiraterone vs. placebo + abiraterone arms, respectively), and in each genetic subgroup, besides BRCA, per arm were generally ≤10. The subgroups were smaller in tissue testing-based grouping.

Per Sponsor, of 782 patients with samples available for analysis, 247 patients did not have a valid test result. Laboratory failure at either DNA extraction stage or post-DNA extraction stage were the most common reasons, followed by “Quality Control metric failure.”

Grade 3 or higher adverse events (AEs), serious AEs, and AEs leading to discontinuation of olaparib/placebo were higher in the olaparib+abiraterone arm. Approximately 4% of patients in each arm experienced an AE with outcome of death, which was higher compared to olaparib studies in other indications.

Study 8

The Sponsor states that Study 8 provides supportive evidence for an sNDA. Study 8 is a randomized, double-blind, placebo-controlled, phase 2 trial of abiraterone in combination with either olaparib or placebo (1:1 randomization) in men with mCRPC who have progressed after docetaxel chemotherapy. Patients were not selected on the basis of HRRm status. Compared with PROpel, patients in Study 8 received up to two lines of prior therapy in the mCRPC setting including docetaxel.

The primary endpoint was rPFS by investigator assessment. Results favored olaparib+abiraterone compared to placebo+abiraterone: rPFS HR 0.651; 95% CI 0.438, 0.969; p=0.034. OS HR was 0.91 (95% CI 0.60, 1.38) in the ITT population and not reported for subgroups.

An imbalance in events of pulmonary embolism (6.5% [26 patients] in the Olaparib + abiraterone arm versus 1.8% [7 patients] in the placebo + abiraterone arm) was observed. One patient in the olaparib arm died due to olaparib-related pneumonitis.

FDA sent Preliminary Comments to AstraZeneca Pharmaceuticals LP on November 3, 2021.

2.0 Discussion

1. Does the Agency agree that the results from the analysis of the pivotal study PROpel, in addition to the supportive evidence from Study 8 are sufficient to enable an evaluation of the safety and efficacy of olaparib in combination with abiraterone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC)?

FDA Response: No. Although PROpel statistically met its primary endpoint in the ITT population, the totality of data does not demonstrate a favorable risk-benefit ratio at this interim analysis.

- **Abiraterone as a single agent demonstrated improvement in OS in patients with mCRPC. The contribution of olaparib to the combination is, however, unclear in patients with tumors that do not harbor HRR mutations. We find the potential for decrement in OS with an HR of 1.10 (95% CI 0.77,1.57) in this subgroup in the combination arm concerning. We also note that multiple trials have not confirmed benefit from PARP inhibitors in patients with tumors that do not harbor BRCA mutations. The interpretation of ORR**

in PROpel is limited due to lack of confirmation of responses, missing tissue and ctDNA genomic data, and small numbers of patients in subgroups.

- **The overall survival data remains immature at DCO1. The separation in the OS curves appears after substantial censoring and additional follow up may allow better resolution of the OS endpoint.**

- **Patients in the olaparib + abiraterone arm had higher rates of grade ≥3 adverse events, adverse events leading to discontinuation of olaparib/placebo, and serious adverse events.**

We strongly recommend that you do not submit an sNDA based on results of this interim analysis of PROpel.

Meeting Discussion: The FDA reiterated concerns that the totality of data does not clearly demonstrate a favorable risk-benefit at this interim analysis in the proposed population for first-line treatment patients with mCRPC, with add-on therapy.

The FDA stated that radiographic PFS is challenging to assess due to uncertainties surrounding measurement of bone metastases, and the FDA has relied upon the totality of evidence when interpreting rPFS in trials of drugs for prostate cancer. The FDA referred the Sponsor to the preliminary responses regarding immaturity of OS at DCO1 and the KM curve for OS. More mature data and supportive results from OS data should be provided prior to submission of an sNDA. Toxicity concerns from treatment in a first-line indication may need a longer follow up for PROpel.

The FDA noted that any imbalance in the two arms may prevent interpretation of efficacy results of subgroups. It has not been clinically demonstrated that addition of olaparib to abiraterone provides added benefit to patients with tumors that do not harbor HRR mutations. In addition, the FDA expressed concern over uncertainty regarding interpretation of the results of PROpel due to small numbers of patients with evaluable ORR.

Due to the multiple limitations and uncertainties with the data, the FDA continued to recommend that the Sponsor not submit the sNDA at this time and instead first provide top-line results from the next prespecified interim analysis. The FDA stated that the Sponsor should justify clinical benefit from addition of olaparib in the BRCA 1&2, other HRR, and non-HRR sub-populations in PROpel.

2. Does the Agency agree that the proposed Table of Contents is appropriate and sufficient to support review of the sNDA?

FDA Response: See the FDA Response to Question 1.

Meeting Discussion: None.

3. AstraZeneca requests a waiver for the safety update to the proposed supplement. Does the Agency agree that this is an acceptable approach?

FDA Response: See the FDA Response to Question 1.

Meeting Discussion: None.

4. AstraZeneca proposes to provide both electronic and written patient narratives within the sNDA for patients who experienced a fatal AE, a serious AE or discontinuation from study treatment due to an AE during treatment or within 30 days following completion of study treatment. Additionally, narratives for AESIs (MDS/AML, new primary malignancies, and pneumonitis) that occur at any time on study will be provided. Does the Agency agree?

FDA Response: See the FDA Response to Question 1.

Meeting Discussion: None.

5. In order to assess the impact of the Covid-19 pandemic, summaries of data relating to patients diagnosed with COVID-19 infection, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatments, and other protocol deviations) will be generated. Does the Agency agree with this approach?

FDA Response: See the FDA Response to Question 1.

Meeting Discussion: None.

6. Does the Agency agree with the proposal to provide electronic case report tabulation (eCRT) packages in support of the sNDA review?

FDA Response: See the FDA Response to Question 1.

Meeting Discussion: None.

ADDITIONAL COMMENTS

1. You should describe ORR to include only confirmed responses per RECIST 1.1 and PCWG3. This applies to the BICR-assessed ORR analysis and the investigator-assessed ORR analysis.

Meeting Discussion: None.

2. Submit the reports of population PK and exposure-response analyses for efficacy and safety in the targeted patient population to support your dose selection in a future sNDA submission.

Meeting Discussion: None.

3. In a future sNDA submission, please include the following patient-level data (xpt file format) for PROpel in different columns: patient unique subject ID, study ID, treatment arm, central test method, biospecimen type, HRR mutation(s), HRR group (HRRm/Non-HRRm/HRRm unknown), BRCA group (BRCA2/BRCA1/non BRCA). In addition, submit test reports if available.

Meeting Discussion: None.

3.0 OTHER IMPORTANT MEETING LANGUAGE

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric

Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020, or Sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the Sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the FDA's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review Division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The FDA strongly advises the complete meeting package to be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor Slides

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[6] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMY R TILLEY
11/18/2021 10:37:27 AM

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