

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number	208558
Priority or Standard	Priority
Submit Date(s)	February 22, 2017
Received Date(s)	February 22, 2017
PDUFA Goal Date	August 22, 2017
Division/Office	Division of Oncology Products 1/Office of Hematology and Oncology Products
Review Completion Date	August 14, 2017
Established Name	Olaparib tablets
Trade Name	Lynparza®
Pharmacologic Class	Poly (ADP-ribose) polymerase (PARP) inhibitor
Code name	N/A
Applicant	AstraZeneca Pharmaceuticals LP
Formulation	Tablet
Dosing Regimen	300 mg taken orally twice daily with or without food
Applicant Proposed Indication(s)/Population(s)	- Lynparza is indicated as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response (complete response or partial response) to platinum-based chemotherapy. - Lynparza is indicated as monotherapy in patients with deleterious or suspected deleterious germline <i>BRCA</i>-mutated (<i>gBRCAm</i>) [as detected by an FDA-approved test] advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	- Lynparza is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy. - Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline <i>BRCA</i>-mutated (<i>gBRCAm</i>) 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.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

NDA/BLA Multi-disciplinary Review and Evaluation NDA 208558
Lynparza™ (Olaparib)

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Olaparib (Lynparza™) is an inhibitor of poly (ADP-ribose) polymerase (PARP) 1, 2, and 3. The PARP family of proteins is involved in repair of single-strand DNA breaks. PARP inhibition may lead to the accumulation PARP-DNA complexes and single-strand breaks that give rise to double-strand DNA breaks during DNA replication. These double-strand breaks may lead to DNA damage, which is potentiated by loss of function of homologous recombination repair enzymes such as BRCA. The induced DNA damage may lead to the initiation of apoptotic pathways and cell death.

On December 19, 2014, olaparib received accelerated approval in a capsule formulation with a dose of 400 mg orally twice daily for the treatment of women with germline BRCA-mutated (gBRCAm) ovarian cancer following three prior lines of therapy. The current application is for the tablet formulation of olaparib with increased bioavailability and a lower pill burden with a standard dose of 300 mg administered orally twice daily with or without food, with the following indication, proposed at the time of NDA submission (February 22, 2017):

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

- for the maintenance treatment of patients with platinum-sensitive relapsed epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response (complete response or partial response) to platinum-based chemotherapy.
- in patients with deleterious or suspected deleterious germline BRCA-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

The recommended indication is:

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

- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a 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.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This recommendation for the regular approval of olaparib, according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), is based on efficacy and safety data from two double-blind, placebo-controlled, randomized, multi-center clinical trials of olaparib in the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who were in a complete or partial response to platinum-based chemotherapy. The first trial, Study 19, which enrolled patients without regard to their *BRCA* status, demonstrated a statistically significant improvement in progression-free survival (PFS) for patients randomized to olaparib (median PFS 8.4 months, 95% CI: 7.4m, 11.5m) versus placebo (median PFS 4.8 months, 95% CI 4.0m, 5.5m), with a hazard ratio of 0.35 (95% CI: 0.25, 0.49). Adverse reactions (incidence $\geq$ 20%) include nausea, fatigue (including asthenia), vomiting, diarrhea, anemia, constipation, respiratory tract infection, decreased appetite, and headache, and two patients in the olaparib arm were diagnosed with MDS/AML. The second trial, SOLO2, randomized gBRCAm patients 2:1 to olaparib tablets, 300 mg orally twice daily (n=196), versus placebo (n=99). Women treated with olaparib had a statistically and clinically significant improvement in their median PFS (19.1 months, 95% CI: 16.3m, 27.2m) versus placebo (5.5 months, 95% CI: 5.3m, 6.9m), with a hazard ratio of 0.30 (95% CI: 0.22, 0.41). Adverse reactions (incidence $\geq$ 20%) include nausea, fatigue including asthenia, anemia, vomiting, nasopharyngitis/upper respiratory tract infection/influenza, diarrhea, arthralgia/myalgia, dysgeusia, headache, decreased appetite, and stomatitis; four patients were diagnosed with MDS/AML. The safety profile of olaparib is acceptable for the intended population and additional long term follow up demonstrated no increased MDS/AML risk from what was previously appreciated at the time of initial approval. Additional safety measures in labeling and prescription fulfillment address concerns regarding the introduction of the new tablet formulation. Additional data submitted and PK analyses support the fourth-line indication in the tablet formulation. Data and analyses submitted for SOLO2 will fulfill the prior accelerated approval PMR for the olaparib capsule formulation, under NDA 206162. NDA 208558 is approved with three PMC agreements, including ORR from SOLO3 (an ongoing clinical trial of olaparib versus physician's choice single-agent chemotherapy for the third-line treatment of women with platinum-sensitive relapsed gBRCAm ovarian cancer), the overall survival (OS) final report for SOLO2, and the planned OPINION trial of maintenance olaparib treatment in women with gBRCA wildtype (gBRCAwt) relapsed ovarian cancer. All disciplines were in agreement with approval of olaparib, and did not identify any outstanding issues that precluded approval. In summary, olaparib for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy demonstrates a favorable benefit-risk profile with enough evidence to recommend approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Lynparza is an orally-available poly (ADP-ribose) polymerase (PARP) inhibitor currently under accelerated approval in capsule formulation since December 19, 2014, for the treatment of women with germline BRCA mutation-positive recurrent ovarian cancer following three prior lines of therapy. This submission is recommended for approval of olaparib tablets for the recommended indications:

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

Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers are serious and life-threatening diseases. In women, ovarian cancer is the fifth cause of cancer death and represents 5% of all cancer deaths. In 2017, it is estimated that in the United States, there will be 22,440 new cases of ovarian cancer and an estimated 14,080 women will die from these diseases. The majority of patients undergo initial treatment with debulking surgery, followed by adjuvant chemotherapy with platinum plus taxanes with or without bevacizumab. Response rates in this first-line setting are high, with outcomes correlated with the extent of post-surgical residual disease, but most patients recur within 2 years and die within 3-4 years after diagnosis. Currently, only bevacizumab and niraparib are FDA-approved as a maintenance therapy for the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Bevacizumab is typically administered in conjunction with the chemotherapy regimen (carboplatin and paclitaxel or carboplatin and gemcitabine) used in the relapse setting, and then is continued as a single agent in maintenance for patients who are in response at the end of the 6-8 cycles of combination chemotherapy. In 2017, niraparib received regular approval for the maintenance treatment of women regardless of their BRCA status with relapsed platinum-sensitive ovarian cancer who are in complete or partial response to their most recent platinum-containing regimen, and treatment is initiated immediately following completion of chemotherapy.

The safety and efficacy of olaparib was demonstrated in two separate clinical trials.

Study 19 was originally reviewed under NDA 206162 at the time of accelerated approval of olaparib for women with *gBRCAm*

ovarian cancer following their third line of treatment. During the prior review, the indication then sought by the applicant included maintenance treatment of the gBRCAm subset of patients, which was discussed at an Oncologic Drugs Advisory Committee (ODAC) meeting on June 25, 2014. The ODAC recommended against accelerated approval of olaparib in the gBRCAm selected patient population based solely on the results of Study 19. They instead favored delaying a possible approval for the proposed indication as a maintenance therapy until the primary endpoint of SOLO2 was analyzed. The current application involves analysis of all patients from Study 19, which includes women with gBRCAm as well as germline BRCA wildtype (gBRCAwt) ovarian cancer (N=265). On this trial, patients, without regard to their BRCA status, were randomized 1:1 to receive olaparib capsules, 400 mg twice daily (n=136), versus placebo (n=129) for the maintenance treatment of relapsed ovarian cancer following response (complete or partial) to their most recent platinum-containing regimen. All patients had received at least two prior platinum-containing regimens. The primary endpoint was investigator-assessed progression-free survival (PFS) as assessed by modified Response Evaluation Criteria in Solid Tumors (RECIST). The trial demonstrated a statistically significant improvement in PFS for patients randomized to olaparib (median PFS 8.4 months, 95% CI: 7.4m, 11.5m) versus placebo (median PFS 4.8 months, 95% CI: 4.0m, 5.5m), with a hazard ratio of 0.35 (95% CI: 0.25, 0.49). Overall survival (OS) analysis demonstrated median OS of 29.8 months in the olaparib-treated arm, vs 27.8 months in the placebo-treated arm, with a hazard ratio of 0.73 (95% CI: 0.55, 0.95); upon correction for multiplicity of statistical testing, this OS difference did not cross the boundary for statistical significance. The trial accrued a disproportionate number of women with gBRCAm as compared with the general population of women with ovarian cancer, which leads to questions of generalizability of the efficacy results from this trial in the gBRCA wild-type population. Adverse reactions (incidence $\geq 20\%$) include nausea, fatigue (including asthenia), vomiting, diarrhea, anemia, constipation, respiratory tract infection, decreased appetite, and headache; laboratory abnormalities occurring in $\geq 25\%$ of patients receiving olaparib include decrease in hemoglobin, increase in mean corpuscular volume (MCV), decrease in leukocytes, lymphocytes, absolute neutrophil count, increase in serum creatinine, and decrease in platelets. As a consequence of adverse reactions, dose interruptions occurred in 35% of patients, dose reductions occurred in 26%, and permanent discontinuation in 6%.

The second trial included in this submission, SOLO2, is a phase 3 trial that assessed the efficacy of olaparib as maintenance treatment in women with gBRCAm, relapsed, platinum-sensitive ovarian cancer who were in complete or partial response to their most recent platinum-containing regimen. All patients had received at least two prior platinum-containing regimens. Patients were randomized 2:1 to olaparib tablets, 300 mg orally twice daily (n=196), versus placebo (n=99). The primary endpoint was investigator-assessed PFS by modified RECIST, and a blinded independent centralized review (BICR) served as a sensitivity analysis. Women treated with olaparib had a statistically and clinically significant improvement in their median PFS (19.1 months, 95% CI: 16.3m, 27.2m) versus placebo (5.5 months, 95% CI: 5.3m, 6.9m), with a hazard ratio of 0.30 (95% CI:

0.22, 0.41).

(b) (4)

. At the time of this PFS analysis, limited OS data were available, with 27% of events recorded. Adverse reactions (incidence $\geq 20\%$) include nausea, fatigue including asthenia, anemia, vomiting, nasopharyngitis/upper respiratory tract infection/influenza, diarrhea, arthralgia/myalgia, dysgeusia, headache, decreased appetite, and stomatitis; laboratory abnormalities occurring in $\geq 25\%$ of patients receiving olaparib include increase in MCV, decrease in hemoglobin, leukocytes, lymphocytes, absolute neutrophil count, increase in serum creatinine, and decrease in platelets. Adverse reactions led to dose interruptions in 45% of patients, dose reductions in 27%, and permanent discontinuation in 11%. The rates of dose adjustments were higher in the SOLO2 trial as compared with Study 19, likely as an indication of the increased bioavailability of the tablet formulation used in SOLO2.

A known complication of treatment with PARP inhibition, and thought to be exacerbated by genetic limitation of DNA repair mechanisms and prior exposure to cytotoxic chemotherapy, is the development of Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML). Olaparib has been commercially available since its accelerated approval on December 19, 2014. In the current application, two cases of AML are taken from Study 19, and 4 cases from SOLO2. The applicant reports 21 cases of MDS/AML out of the 1,680 patients on clinical trials treated with olaparib monotherapy, resulting in an incidence of approximately 1.5% in these trials. Labeling adequately describes and conveys the MDS/AML concerns in the Warnings and Precautions section, and no further mitigation strategy such as a REMS is recommended.

A further safety concern stemming from the current application is the introduction of the tablet formulation of olaparib with an increased bioavailability as compared to the currently-available capsule formulation. The tablet formulation permits a significantly decreased pill burden to patients (two tablets twice daily as opposed to eight capsules twice daily for the recommended starting doses), but due to the difference in bioavailability, the two formulations are not interchangeable, and therefore the introduction of the new formulation poses a risk of medication error to patients currently receiving the capsule formulation. The strategy put into place in order to minimize the risk of patients receiving the wrong formulation or taking the incorrect number of pills was investigated through several information requests with the sponsor, as well as telephone conferences. The resulting risk mitigation strategy will include several steps: a plan to remove all capsule formulation from commercial availability within (b) (4) of introduction of the tablet formulation; all capsule prescriptions will be filled only from two specialty pharmacies with oversight from the applicant until that time; tablet labeling and updated capsule labeling will contain prominent warnings describing the lack of interchangeability of the two formulations. Ultimately, these strategies were deemed adequate to minimize risk to patients receiving the olaparib capsule formulation. Furthermore, approval of the tablet formulation in the fourth-line treatment indication of women with gBRCAm ovarian cancer is supported

by PK data and clinical data as discussed in the review.

In conclusion, olaparib maintenance demonstrated a statistically significant improvement in progression-free survival in two large, randomized, double-blind clinical trials, with a larger magnitude of effect demonstrated for those patients with gBRCAm ovarian cancer in SOLO2. OS data are still immature for this trial. The data and analyses from SOLO2 fulfills the prior olaparib capsule accelerated approval for the treatment of women with gBRCAm recurrent ovarian cancer following three prior treatment regimens, and, with fulfillment of the requirement for accelerated approval, the second PMR for data and analyses of SOLO3 will be released. The overall survival (OS) final report from SOLO2 and ORR from SOLO3 were agreed to as two PMCs under NDA 208558. An additional PMC, the planned single-arm OPINION trial, will further elucidate the benefit of maintenance olaparib for women with platinum-sensitive relapsed ovarian cancer who do not harbor germline BRCA mutation.

Since advanced epithelial ovarian, fallopian tube, and peritoneal cancers are life-threatening and currently incurable diseases, the PFS improvements demonstrated represent clinically meaningful benefit by the delay of both disease progression and the requirement for subsequent cytotoxic treatment with its attendant toxicities. The safety profile is acceptable for the intended population and reflected by no boxed warnings. Appropriate labeling will include dose modification language and will include MDS/AML and pneumonitis in the warnings and precautions section. The label will also include alerts about the two different and non-interchangeable formulations, and will instruct prescribers to assist with appropriate management of this issue.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Ovarian cancer is the fifth-leading cause of cancer death and represents 5% of all cancer deaths in women in the United States. • In 2017, an estimated 22,440 new cases and 14,080 deaths from ovarian cancer in the U.S.	• Recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancers are serious, life-threatening, and incurable. There is an unmet medical need to develop therapies for these cancers.
Current Treatment Options	• Most patients undergo primary debulking surgery followed by platinum + taxane adjuvant chemotherapy with or without bevacizumab, with disease-free survival correlated with the	• Currently, bevacizumab and niraparib are FDA-approved maintenance therapies for the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	extent of surgical cytoreduction. For advanced ovarian cancer, recurrence is the norm, and survival is 3-4 years from diagnosis.	treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.
Benefit	• The current approval is based on two randomized, double-blind, placebo-controlled, multicenter clinical trials of olaparib versus placebo in women with recurrent platinum-sensitive ovarian cancer in response to their most recent platinum-based therapy and who had had at least two prior platinum-based therapies. • In Study 19, 265 women were randomized 1:1 to olaparib versus placebo, and the trial demonstrated a statistically significant improvement in PFS for patients treated with olaparib (HR 0.35 [95% CI: 0.25, 0.49]; p<0.00001). • In SOLO2, 196 women with gBRCAm were randomized to treatment with olaparib vs 99 to treatment with placebo, and the trial demonstrated a statistically and clinically meaningful improvement in PFS (HR 0.30 [95% CI: 0.22, 0.41], p<0.0001). • HRs were consistent between the two trials.	• Evidence of effectiveness was supported by a statistically-significant and clinically-meaningful PFS improvement, with the greatest improvement seen for women with gBRCAm-associated ovarian cancer. Because the trials were large, randomized, and blinded, trial evidence is strong and uncertainty is decreased. Consistency across trials is further evidence of the benefit of treatment with olaparib. Despite immature OS, improvement in PFS in this population represents a clinically meaningful benefit due to delay of progression and exposure to further cytotoxic treatments. • The magnitude of benefit in the gBRCAm subset is larger than in the overall population.
Risk	• The most common adverse reactions experienced in at least 20% of patients on Study 19 were nausea, fatigue (including asthenia), vomiting, diarrhea, anemia, constipation, respiratory tract infection, decreased appetite, and	• The safety profile of olaparib is acceptable for the intended population. • MDS/AML and pneumonitis are

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	headache; laboratory abnormalities occurring in $\geq 25\%$ of patients receiving olaparib include decrease in hemoglobin, increase in MCV, decrease in leukocytes, lymphocytes, absolute neutrophil count, increase in serum creatinine, and decrease in platelets. • The most common adverse reactions experienced in at least 20% of patients on SOLO2 were nausea, fatigue including asthenia, anemia, vomiting, nasopharyngitis/upper respiratory tract infection/influenza, diarrhea, arthralgia/myalgia, dysgeusia, headache, decreased appetite, and stomatitis; laboratory abnormalities occurring in $\geq 25\%$ of patients receiving olaparib include increase in MCV, decrease in hemoglobin, leukocytes, lymphocytes, absolute neutrophil count, increase in serum creatinine, and decrease in platelets.	the ARs described in the Warnings and Precautions section of the label. • Additional warnings about the non-interchangeability of the tablet and capsule formulations are in section 2 of the label.
Risk Management	• Olaparib is intended to be prescribed by oncologists. • Oncologists are well-versed in the identification and management of the toxicities associated with olaparib. • Labeling details dose interruption, reduction, or discontinuation. • MDS/AML, pneumonitis, and the two different formulations are being described in the label. • Laboratory and vital sign monitoring is recommended before and during treatment.	• The safe use of olaparib can be managed through accurate labeling and routine oncology care. • No REMS is indicated.

Sanjeeve Balsubramaniam
Cross-Disciplinary Team Leader

Appears this way on original

2 Therapeutic Context

Analysis of Condition

Ovarian cancer is the fifth cause of cancer death in women and represents 5% of all cancer deaths. In 2017 it is estimated that there will be 22,440 new cases of ovarian cancer and an estimated 14,080 women will die of the disease in the U.S. The 5-year overall survival rate of ovarian cancer patients is 46% across all stages and 29% in patients with metastatic disease. Ovarian cancer is predominantly a disease of postmenopausal women, and most patients have advanced disease (Stage III-IV) at the time of diagnosis, when the prognosis is particularly poor. Most patients undergo primary debulking surgery after diagnosis, followed by adjuvant chemotherapy with platinum plus taxanes with or without bevacizumab. Response rates are high in the first-line setting, but most patients experience disease recurrence within 2 years and die within 3-4 years of diagnosis. The choice of subsequent therapies upon recurrence is based upon the interval since the last platinum regimen, with patients who have recurrence more than 6 months from the last platinum regimen typically receiving additional platinum-based therapy. Despite relatively high response rates to retreatment with platinum, recurrence is inevitable. Patients with ovarian cancer typically experience multiple relapses and receive multiple lines of chemotherapy over the course of their disease.

2.2. Analysis of Current Treatment Options

The indication for approval for olaparib will be for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Other FDA approved treatments for this similar indication include bevacizumab, which was approved in 2016, and niraparib, which was approved in March 2017. The administration of bevacizumab differs from that of olaparib in that bevacizumab is typically first administered in conjunction with the chemotherapy regimen used in the relapse setting, and is then continued as a single agent in patients who are in response (typically complete or partial) at the end of 6-8 cycles of the combination chemotherapy, as maintenance. Niraparib is a PARP inhibitor, which was recently approved by the FDA in March 2017 for the maintenance treatment of patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer that are in response to platinum-based therapy. The niraparib approval was based upon a randomized, double-blind, placebo-controlled trial in patients with platinum-sensitive recurrent ovarian (including fallopian tube and peritoneal) cancer. Patients with and without an underlying germline BRCA mutation were included, and were randomized to separate cohorts based upon mutation status (gBRCA and non-gBRCA). The results demonstrated a statistically significant improvement in PFS for patients treated with niraparib, compared to placebo, in both cohorts, although the difference in PFS medians between arms was 15.5 months for the gBRCA cohort and 5.4 months for the non-gBRCA cohort.

Table 1 Summary of treatment armamentarium relevant to proposed indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Niraparib	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	2017	300 mg oral capsules once daily	One study (NOVA) was a double-blind, placebo-controlled trial which supported approval. Two cohorts: -gBRCAm cohort- 16 month PFS improvement over placebo (HR= 0.26, 95% CI= [0.17, 0.41]). -non-gBRCAm cohort - 5.4 month PFS improvement over placebo (HR= 0.45, 95% CI [0.34, 0.61]).	Niraparib's safety profile includes cytopenias, nausea, fatigue, MDS/AML, hypertension and cardiovascular events.
Bevacizumab (Avastin)	Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with either carboplatin/paclitaxel or carboplatin/gemcitabine followed by single agent	2016	15 mg/kg IV every 3 weeks in combination with carboplatin/paclitaxel or carboplatin/gemcitabine for 6-10 cycles followed by 15 mg/kg IV every 3 weeks as a single agent.	Two studies supported approval: -Study 11 (OCEANS)- statistically significant 4 month improvement in PFS (HR= 0.45, 95% CI= [0.35, 0.83]) of bevacizumab + chemotherapy over chemotherapy + placebo. ORR was also higher for bevacizumab (78% vs. 57%). -Study 12 (GOG-213)- Main efficacy outcome was OS. No statistically	Bevacizumab is associated with the following safety considerations: GI perforation/fistula, arterial thromboembolic events, VTE, hypertension, proteinuria, posterior reversible encephalopathy syndrome

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	maintenance			significant difference between arms was noted (42.6 m Bev vs. 37.6 m without Bev).	
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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Olaparib received accelerated approval under NDA 206162 on 12/19/14 for the following indication: Lynparza is indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer that have been treated with three or more prior lines of chemotherapy.

The current application, received on 2/22/17 under NDA 208558, was submitted by the Sponsor to fulfill a post-marketing requirement set forth at the time of accelerated approval of NDA 206162. Upon approval of the current application, the PMR for accelerated approval will be considered fulfilled. .

3.2. Summary of Presubmission/Submission Regulatory Activity

The major regulatory milestones for olaparib development in ovarian cancer are summarized in Table 2.

Table 2 Major olaparib regulatory milestones

Milestone	Time	Details
IND 75,918 activated	September 2006	
Guidance Meeting	October 2012	Discussed olaparib development program for patients with gBRCAm-associated ovarian cancer. FDA considered the gBRCAm subgroup results of Study 19 to be provocative but insufficient to support an approval.
Pre-submission Meeting	March 18, 2013	Joint meeting with FDA/CDER/CDRH and AstraZeneca and Myriad Genetics Inc. to discuss regulatory pathway for the companion diagnostic assay.
Breakthrough Therapy Designation Request	March 19, 2013	Request submitted on the basis of Study 19.
Breakthrough Designation Denial	May 16, 2013	
Pre-NDA Meeting	October 2, 2013	FDA stated its expectation for a potential concurrent NDA and PMA approval and the likelihood that the application would be discussed at an advisory committee
NDA 206162 Submission	February 3, 2014	Study 19 as the primary study to support the indication as maintenance therapy in patients with gBRCAm ovarian cancer.
Oncology Drug Advisory Committee	June 25, 2014	An Oncology Drug Advisory Committee meeting was held to discuss the benefit-risk profile of olaparib as maintenance therapy for gBRCAm-associated platinum sensitive ovarian cancer. The panel voted 11 versus 2 that the safety and efficacy results from Study 19

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		in the gBRCAm population DO NOT support an accelerated approval.
Post-ODAC Meeting	July 21, 2014	FDA agreed that the sponsor could submit data regarding olaparib monotherapy in patients with gBRCAm-associated ovarian cancer who have been treated with 3 or more lines of chemotherapy to the NDA as a major amendment to potentially support a non-maintenance indication.
Accelerated Approval under NDA 206162	December 19, 2014	Accelerated approval was granted for the following indication: Olaparib is indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advance ovarian cancer who have been treated with three or more prior lines of chemotherapy. Post-marketing requirements associated with this approval was that the Sponsor should submit results of the SOLO2 (and/or SOLO3) study for review. Conversion to regular approval would be contingent upon these study results, confirming the benefit of olaparib maintenance in patients with relapsed gBRCAm ovarian cancer who are in response to platinum-based chemotherapy.
NDA 208558 submission	February 22, 2017	Progression-free survival results from SOLO2 as the primary study to support the indication of olaparib as maintenance therapy in patients with gBRCAm ovarian cancer. Study 19 results from the ITT population were referenced in support of approval in an unselected patient population

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to perform site inspections as part of review of the olaparib NDA. Reference is made to the Clinical Inspection Summary by Lauren Iacono-Connors, PhD. Five sites were inspected including four clinical sites and the Sponsor, Astra Zeneca. The classifications given to each site by clinical reviewer are shown in Table 3.

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Table 3 OSI Inspection Sites and Results

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
Harter, Philipp Site # 2601 Henricistr. 92 Essen, NA 45136 DEU Western Europe	D0816C00002 (SOLO2) 10 subjects	6/19-6/22/17	Preliminary Classification NAI
Pautier, Patricia Site # 2307 114 rue Edouard Vaillant Villejuif Cedex, NA 94805 FRA Western Europe	D0816C00002 (SOLO2) 11 subjects	6/12-6/16/17	Preliminary Classification NAI
Penson, Richard Site # 7804 450 Brookline Ave Boston, MA 2215 USA United States	D0816C00002 (SOLO2) 6 subjects	4/18/17- 5/1/17	NAI
Penson, Richard Site 7803 55 Fruit Street, Yawkey 9E, Gillette Center for Gynecologic Oncology Boston, MA 2114 USA United States	D0816C00002 (SOLO2) 4 subjects	4/18/17- 5/1/17	NAI
Astra Zeneca Study Management and Operations Postepu 14, 02-676 Warsaw, Poland	Trial master files located at this site for SOLO2 study	8/7-8/11/17	Preliminary communication NAI via email 8/11/2017

Key to Compliance Classifications: NAI= No deviation from regulations; VAI= Deviation(s) from regulations; OAI= significant deviation from regulations, data unreliable; Pending = Preliminary classification based on information in 483 or preliminary communication with field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

4.2. Product Quality

Novel excipients: No

Any impurity of concern: No

The proposed specification limit of no more than (NMT) (b) (4)% for impurity (b) (4) is above the limit outlined in ICH Q3A and Q3B guidances. Because (b) (4) the tablet formulation leads to (b) (4) olaparib drug substance with greater solubility and bioavailability than the capsule formulation, it is likely that (b) (4) will also have greater bioavailability. The steady state exposure (AUC) following administration of 300 mg olaparib tablets twice daily (BID) was 77% higher compared to the exposure following administration of 400 mg capsules BID. The CMC review team requested an impurity assessment to determine if the applicant conducted toxicology studies with sufficient excess of (b) (4) to justify the higher specification limit considering the higher bioavailability of the tablet formulation.

The applicant has conducted repeat-dose toxicology studies with olaparib formulated with the previous manufacturing process. Rats have received doses up to 1000 mg/kg/day olaparib administered orally for up to 6 months. (b) (4) was detected in toxicology lots at (b) (4)%. The amount of this impurity administered to patients at the recommended clinical dose of 300 mg olaparib tablets BID would be approximately 6-fold lower than the levels of this impurity (b) (4)%) given at a non-severely toxic dose of 1000 mg/kg/day in a 3-month repeat-dose toxicology study in rats (Study # 526803). Therefore, (b) (4) is qualified at the proposed specification limit of NMT (b) (4)% even with higher bioavailability of the new tablet formulation.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

(b) (4)

The BRACAnalysis CDx was originally approved in 2014 as a companion diagnostic test for the selection of ovarian cancer patients with underlying deleterious or suspected deleterious germline BRCA1 or BRCA2 mutation in the fourth line setting who may be eligible for therapy with olaparib.

(b) (4)

FDA recommended a complementary diagnostic to inform the risk/benefit for patients taking olaparib, but

did not feel the device was essential for the safe and effective use of olaparib, since the indication in this maintenance setting is for unselected patients. (b) (4)

Current ovarian cancer practice guidelines do recommend genetic testing for germline BRCA mutation in all patients diagnosed with ovarian cancer; thus, while not associated with olaparib specifically, in the course of the standard practice of medicine, patients and prescribers should still be able to make an informed decision regarding the magnitude of benefit to expect from olaparib assuming they have knowledge of their BRCA status.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant submitted nonclinical pharmacology and toxicology data, which were reviewed previously under NDA 206162. The applicant updated the animal to human exposure ratios in sections 8.1 and 13.1 of the prescribing information to reflect the differences in exposures with the new tablet formulation. The applicant also updated information on the mechanism of action in section 12.1, which described olaparib activity in cell lines and mouse tumor models deficient in non-BRCA proteins involved in homologous recombination repair of DNA damage. This data also correlated with tumor response to platinum treatment. From the nonclinical perspective, Lynparza tablets are recommended for approval for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

NDA 206162

5.3. Pharmacology

Previously reviewed under NDA 206162

5.4. ADME/PK

Previously reviewed under NDA 206162

5.5. Toxicology

Previously reviewed under NDA 206162

Tiffany Ricks
Primary Reviewer

Todd Palmby
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The olaparib tablet dosing regimen of 300 mg (2 x 150 mg tablets) twice daily (BID) is proposed for both the maintenance treatment of ovarian cancer and for $\geq 4^{\text{th}}$ line treatment of gBRCAm ovarian cancer. The efficacy and safety of olaparib 300 mg tablet BID for the maintenance treatment were supported by a phase 3 trial, SOLO2, and a phase 2 trial, Study 19. In addition, SOLO2 was used to fulfill the accelerated approval PMR of olaparib capsule formulation 400 mg (8 x 50 mg capsules) and result in regular approval in the $\geq 4^{\text{th}}$ line treatment setting.

The key review issues focus on the oral bioavailability of olaparib tablet compared to capsule formulation, appropriateness of olaparib tablet 300 mg BID in $\geq 4^{\text{th}}$ line treatment setting, dose adjustment of olaparib tablet in patients with renal or hepatic impairment, and dose adjustment of olaparib tablet due to drug-drug interaction (DDI).

Recommendations

The Office of Clinical Pharmacology Division of Clinical Pharmacology V and Pharmacometrics, have reviewed the information contained in NDA 208558. This NDA is approvable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language. The key issues and recommendations are shown in Table 4.

Table 4 Key Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	<u>Maintenance Treatment</u> Study SOLO2 showed an average prolongation of 13.6 months in PFS with olaparib treatment (19.1 months) compared with placebo (5.5 months) in patients with gBRCAm ovarian cancer. A median PFS of 3.6 months longer with olaparib treatment was observed compared to placebo in Study 19. The greatest benefit was observed in the gBRCAm subgroup, where the median PFS was 11.2 months for olaparib versus 4.1 months for placebo. <u>$\geq 4^{\text{th}}$ Line Treatment</u> The effectiveness of 300 mg tablet should not be inferior to that of the 400 mg capsule as the steady state AUC following 300 mg tablet BID was 77% higher compared to that following 400 mg capsule BID. In addition, 300 mg tablet showed a similar magnitude of tumor shrinkage to the 400 mg capsule in a phase 1 study 24.
General dosing instructions	The proposed olaparib dosing regimen of 300 mg tablet BID is effective and appears to have a manageable safety profile for both proposed indications.

	The median PFS in olaparib treatment arm was 19.1 months compared to 5.5 months in placebo arm with a HR of 0.30 (95% CI 0.22 to 0.41; p<0.0001) in SOLO2. The safety profiles of olaparib 300 mg BID in SOLO2 was generally comparable to 400 mg capsule BID in Study 19. Anemia was reported at an increased frequency with the tablet formulation; however, this toxicity remained clinically manageable. The dosing regimen of olaparib 300 mg tablet BID appears to have comparable safety profile to 400 mg capsule BID in ≥4th line treatment setting based on the safety analysis in such population and exposure-safety analysis, although the steady state AUC following 300 mg tablet BID was 77% higher compared to that following 400 mg capsule BID.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• A dose reduction to 200 mg tablet BID is recommended for patients with moderate renal impairment. • A dose reduction to 100 mg tablet BID is recommended when concomitantly taking a strong CYP3A inhibitor. • A dose reduction to 150 mg tablet BID is recommended when concomitantly taking a moderate CYP3A inhibitor.
Bioavailability between the tablet and capsule formulations	The capsule and tablet formulations of olaparib are not interchangeable due to differences in the dosing and bioavailability of each formulation based on both PK study and population PK analyses. The review team added the language to describe the higher oral bioavailability of the tablet formulation compared to the capsule formulation.

Post-Marketing Requirements and Commitments

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Olaparib is an oral inhibitor of PARP enzymes, including PARP1, PARP2, and PARP3. Olaparib tablet formulations are available at 100 mg or 150 mg for oral administration.

The oral bioavailability of the tablet formulation is higher than the capsule formulation. Population PK analyses have shown that the steady state AUC following 300 mg tablet BID was 77% higher compared to that following 400 mg capsule BID.

Absorption: The median T_{max} was 1.5 hours with a range of 0.5 to 6 hours after a single 300 mg tablet. Olaparib AUC increases approximately proportionally with doses over the range of 25 mg to 450 mg. An

AUC mean accumulation ratio of 1.8 is observed at steady state. A high fat meal did not significantly alter the exposure to olaparib.

Distribution: The mean apparent volume of distribution is 158 ± 136 L after a single 300 mg dose of olaparib. The in vitro protein binding of olaparib is approximately 82%.

Metabolism: Olaparib is primarily metabolized by CYP3A.

Excretion: The mean terminal plasma half-life was 14.9 and mean apparent clearance was 7.4 L/h after a single 300 mg dose of olaparib. Olaparib showed time-dependent PK that the steady state clearance decreased by 15% after multiple dosing.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed tablet dose is 300 mg BID, orally, without regard to food, for patients with ovarian cancer in both maintenance treatment and gBRCAm treated with three or more prior lines of chemotherapy. Study SOLO2 demonstrated that olaparib 300 mg tablet BID is effective and safe for maintenance treatment with the support of efficacy and safety data from Study 19. The switch of two formulations for ovarian cancer patients in $\geq 4^{\text{th}}$ treatment setting is acceptable given the similar efficacy and comparable safety profiles between 400 mg capsule BID and 300 mg tablet BID.

Therapeutic Individualization

Hepatic Impairment: Based on the results of a dedicated hepatic impairment (HI) study, no dose adjustment is required for patients with mild HI (Child-Pugh A) (b) (4)

Renal Impairment: Based on the results of a dedicated renal impairment (RI) study, olaparib tablet dose will be reduced to 200 mg BID for patients with moderate RI (CLcr 31-50 ml/min). No dose adjustment is required for patients with mild RI (CLcr 51-80 ml/min).

CYP3A Inhibitors: Based on the clinical data and PBPK simulation, it is recommended to reduce the olaparib dose to 100 mg BID if a strong CYP3A inhibitor must be co-administered. If a moderate CYP3A inhibitor must be co-administered, reduce the olaparib dose to 150 mg BID.

CYP3A Inducers: Based on the clinical data and PBPK simulation, it is recommended to avoid concomitant use of strong or moderate CYP3A inducers as decreased efficacy can occur.

6.2.3. Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology and pharmacokinetic characteristics of olaparib tablet formulation are summarized in Table 5.

Table 5 Olaparib Tablet Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Olaparib is an inhibitor of PARP enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and DNA repair. 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.
QT Prolongation	No clinically relevant effect of olaparib on QT interval was observed in 119 patients following a single dose of 300 mg and in 109 patients following multiple dosing of 300 mg BID.
General Information	
Tablet vs. capsule formulation	The oral bioavailability of the tablet formulation is higher than the capsule formulation. Population PK analyses have shown that the steady state AUC following 300 mg tablet BID was 77% higher compared to that following 400 mg capsule BID.
Drug exposure following a single dose and at steady state from population PK model	Geometric mean AUC _{0-inf} and C _{max} following a single 300 mg tablet dose were 42.0 µg*h/mL and 5.8 µg/mL, respectively, and the steady state geometric mean AUC _{0-tau} and C _{max} following 300 mg tablet BID were 49.0 µg*h/mL and 7.7 µg/mL, respectively.
Absorption	
T _{max} (oral)	A median value of 1.5 hours with a range of 0.5 to 6 hours after a single 300 mg dose
Accumulation	A mean (± standard deviation (SD)) accumulation ratio of 1.8 ± 0.6 at steady state following 300 mg tablets BID
Dose proportionality	Single dose AUC to olaparib increases approximately proportionally with doses over the dose range of 25 mg to 450 mg, while C _{max} increased slightly less than proportionally for the same dose range.
Food effect	Mean AUC was increased by approximately 8% and C _{max} was decreased by 21% after a high fat meal, while t _{max} was delayed by 2.5 hours.
Distribution	
Volume of Distribution	A mean (±SD) value of 158 ± 136 L after a single 300 mg dose
Plasma Protein Binding	~ 82%
Substrate transporter systems (<i>in vitro</i>)	A substrate of P-gp
Elimination	
Mean terminal elimination	A mean (± SD) value of 14.9 ± 8.2 hours after a single 300 mg dose

half-life	
Clearance	A mean ($\pm$ SD) apparent plasma clearance of 7.4 ± 3.9 L/h after a single 300 mg dose of olaparib. Steady state clearance decreased by 15% after multiple dosing due to time-dependent PK
<i>Metabolism</i>	
Primary metabolic pathway (<i>in vitro</i>)	CYP3A4/5
Inhibitor/Inducer (<i>in vitro</i>)	- Both an inhibitor and inducer of CYP3A (net effect as a weak CYP3A inhibitor) - An inducer of CYP2B6 - An inhibitor of UGT1A1, P-gp, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K
<i>Excretion</i>	
Primary excretion pathways	Following a single dose of 14 C-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.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The primary evidence of effectiveness was obtained from the Phase 3 trial SOLO2, with supportive data obtained from Study 19.

Study SOLO2 was a double-blind, placebo-controlled, randomized (2:1), multicenter clinical study to evaluate olaparib 300 mg tablet BID as maintenance monotherapy vs. placebo in patients with platinum sensitive relapsed (PSR) BRCAm ovarian cancer who were in complete or partial response following platinum-based chemotherapy. Study SOLO2 demonstrated a large, statistically significant and clinically meaningful benefit of olaparib treatment in patients with gBRCAm ovarian cancer.

The relationship between exposure to olaparib (C_{ave} , C_{max} , or C_{min}) and efficacy endpoints (PFS, OS and PFS2) was examined in SOLO2. The applicant did not find any clear pattern that would suggest any of the efficacy responses differs at the different exposure to olaparib. However, the review team considers that the E-R relationship for efficacy in SOLO2 is not conclusive due to a potential confounding effect, which could be caused by dose modifications during treatment: patients who had longer treatment courses due to tumor responses may have had dose modifications, and, thus, have a lower average exposure compared to patients with short treatment intervals at the recommended dose. In addition, PK samples were collected in only half of the patients treated with olaparib. (For details, refer to pharmacometrics review in the OCP appendices 13.4). Based on the data from Study D0810C00012, the 400 mg capsule showed numerically better progression free survival experience as compared with 200 mg capsule, suggesting a trend of greater efficacy with increasing exposure.

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

Yes, the proposed dosing of olaparib 300 mg tablet BID appears to be effective and safe for both maintenance and $\geq 4^{\text{th}}$ line treatment setting in the patients with advanced gBRCAm ovarian cancer.

Maintenance Therapy

The olaparib dose of 300 mg tablet BID was selected for the pivotal phase 3 study SOLO2 on the basis of having similar efficacy in terms of tumor shrinkage with a similar tolerability profile in advanced gBRCAm ovarian cancer patients to the 400 mg capsule BID dose in Group 6 in Study 24, although the geometric mean steady state C_{max} , AUC_{ss} and C_{min} values for 300 mg tablet BID were 1.3 – 1.7 higher than those delivered by the 400 mg capsule dose BID. The greatest mean decrease in the tumor size at week 8 was observed in the 400 mg tablet BID dose (-28%), followed by the 400 mg capsule BID dose (-18%) and the 300 mg tablet BID dose (-16%) in the ovarian subset of Group 6. The difference in mean change in tumor size for either the 400 mg tablet BID dose or the 300 mg tablet BID dose compared to the 400 mg capsule BID dose was -10.5% (95%CI: -35.5, 14.6) and 1.8% (95%CI: -22.8, 26.4), respectively. Similar results of tumor shrinkage were observed at Week 16. The frequency and severity of common adverse events was reported higher in the 400 mg tablet BID dose level. Nausea, vomiting and fatigue were generally low grade (CTCAE Grades 1 and 2), while anemia was reported as CTCAE Grade 3 or higher in 22% of patients taking 300 mg tablet BID and 400 mg capsule BID and 29% of patients taking 400 mg tablet BID. In addition, a higher number of dose reductions and interruptions were reported in the 400 mg tablet BID cohort (65% and 59% respectively) compared with the 300 mg tablet BID (22% and 44%) and the 400 mg capsule BID cohort (17% and 33%). Therefore, it was concluded that the patients taking 300 mg tablet BID experienced a similar magnitude of tumor shrinkage to 400 mg capsule BID and a better safety profile than 400 mg tablet BID.

Study SOLO2 showed a median PFS of 19.1 months for olaparib 300 mg tablet BID versus 5.5 months for placebo with a hazard ratio (HR) of 0.30 (95% CI 0.22 to 0.41; $p < 0.0001$), suggesting an average prolongation of 13.6 months in PFS with olaparib treatment and a 70% reduction in risk of disease progression or death in patients with PSR gBRCAm ovarian cancer. This study met its primary objective and demonstrated a large, clinically meaningful and statistically significant improvement in PFS with olaparib 300 mg tablet BID maintenance therapy compared with placebo. Moreover, the efficacy results from SOLO2 were consistent with those shown in the Study 19, which was conducted with olaparib 400 mg capsule BID in a broad patient population with PSR ovarian cancer with and without gBRCAm. Study 19 showed a median PFS of 3.6 months longer for olaparib-treated patients (8.4 months) compared with placebo-treated patients (4.8 months) with a HR of 0.35 (95% CI 0.25 to 0.49; $p < 0.00001$) indicating a 65% reduction in the risk of progression or death in patients with PSR ovarian cancer. The greatest benefit was observed in the gBRCAm subgroup where the median PFS was 11.2 months for olaparib versus 4.1 months for placebo with a HR of 0.17 (95% CI 0.09 to 0.31; $p < 0.00001$). The safety profiles from SOLO2 of the tablet formulation and from Study 19 of capsule formulation were generally comparable. Hematological toxicity (primarily anemia) was reported at an increased frequency with the

tablet formulation (43%) compared with the capsule formulation (21%); however, anemia remained manageable by interrupting or reducing olaparib dose or providing blood transfusion, when indicated, and treatment discontinuation was rarely required. Nausea and vomiting as well as grouped events of fatigue and asthenia were reported with a similar frequency and severity with the tablet and capsule formulations.

Exposure Response for Efficacy

Exposure-response relationship for PFS in SOLO-2 was not conclusive due to the potential confounding effects, which may be caused by dose modifications during the treatment. However, based on the data from Study D0810C00012, the 400 mg capsule showed numerically better progression free survival experience as compared with 200 mg capsule, suggesting a trend of greater efficacy with increasing exposure.

Exposure Response for Safety

There was an exposure-safety relationship for anemia either using the data in SOLO2 or the pooled tablet data. An observed hemoglobin (Hb) mean baseline of 11.6 g/dL was predicted to decrease to 10.3 g/dL (95% CI: 10.0-10.6 g/dL) at median steady-state 300 mg BID olaparib exposure in SOLO2. If exposure to olaparib doubled, Hb was predicted to decrease to 8.9 g/dL (95% CI: 8.3-9.5 g/dL). This is comparable with the prediction using pooled tablet data, which predicted Hb concentrations to decrease on average to 8.7 and 9.3 g/dL for baseline Hb concentrations of 11 and 12 g/dL, respectively, when AUC is doubled. Overall, approximately half of the events of anemia reported on both the tablet and capsule formulations were mild or moderate in severity and the rest were CTCAE grade ≥ 3 . Anemia remains clinically acceptable and manageable at the 300 mg tablet dose.

Refer to pharmacometrics review in the OCP appendices 13.4 for the detailed discussion of exposure response analysis for efficacy and safety.

$\geq 4^{\text{th}}$ line Treatment

The applicant proposed that the $\geq 4^{\text{th}}$ line treatment indication should also be conferred to the tablets at the time of approval as the tablet offers significant convenience due to reduced pill burden over the capsule formulation and submitted data from patients treated with the tablet formulation in a $\geq 4^{\text{th}}$ line setting.

In study 24, efficacy was assessed in late line ovarian cancer patients based on tumor shrinkage and response rate between the cohort of 300 mg tablet BID and the cohort of 400 mg capsule BID. The mean percent change in tumor size from baseline was numerically similar between two cohorts. The response rate was comparable among gBRCAm ovarian cancer patients in two formulation cohorts (39% for tablet and 30% for capsule) and was consistent with that observed in Study 42 (34%) which formed the basis for approval of the capsule formulation in the $\geq 4^{\text{th}}$ line treatment setting. In addition, the comparable efficacy was shown between SOLO2 and Study 19 in the $\geq 2^{\text{nd}}$ line PSR maintenance treatment.

Therefore, 300 mg tablet BID is considered to show a similar efficacy to the 400 mg capsule BID in late line treatment setting.

The capsule and tablet are concluded to be not bioequivalent in Study 24 as the olaparib AUC after a single dose of the 250 mg tablet of olaparib was 1.7 times higher than that following a single dose of 400 mg capsule. The population PK analysis also showed that the steady state AUC following 300 mg tablet BID was 77% higher compared to that following 400 mg capsule BID. The review team raised the safety concern on the ovarian cancer patients switched to the proposed 300 mg tablet BID from 400 mg capsule BID in $\geq 4^{\text{th}}$ line treatment setting as such patient population are assumed more vulnerable to high exposure to olaparib compared to patients in maintenance treatment setting. Given the relationship between increased steady state exposure (AUC and C_{max}) for both tablet and capsule formulations and decreased Hb identified in population PKPD modelling, it is expected that the incidence or severity of anemia could be higher in patients administered 300 mg tablet BID than those given 400 mg capsule BID in $\geq 4^{\text{th}}$ line treatment setting.

Subsequently, to clarify the safety concern mentioned above, the clinical reviewer compared the frequency and severity of AEs in a subgroup dataset of 90 patients isolated from the integrated tablet safety dataset to those from capsule safety data pool. These 90 patients had ovarian, fallopian tube, primary peritoneal cancers and were treated with 3 or more prior lines of anticancer therapy. The AEs of interest, with a higher incidence in the 90 patients compared to patients in capsule safety data pool, are listed in the Table 6 (refer to clinical review for detailed comparison of all AEs). Overall, the magnitude of the difference in AE frequency or severity is considered to be small either for anemia or gastrointestinal disorders. Thus, the two dosing regimen of 300 mg tablet and 400 mg capsule appear to have comparable safety profile in patients in $\geq 4^{\text{th}}$ line treatment setting.

Table 6: Comparison of AEs for 300 mg Tablet BID vs. 400 mg Capsule BID in $\geq 4^{\text{th}}$ line Ovarian Cancer Treatment Setting

Adverse Event	Subset of 300 mg BID Tablet pool n=90		400 mg BID Capsule pool N=223	
	Grade 1-4 (%)	Grade 3-4 (%)	G1-4 (%)	G3-4 (%)
Blood and Lymphatic disorders				
Anemia	41 (46)	18 (20)	77 (35)	41 (18)
Gastrointestinal disorders				
Abdominal pain/discomfort	47 (52)	4 (4)	100 (45)	19 (9)
Constipation	25 (28)	0	38 (17)	3 (1)
Decreased appetite	37 (41)	1 (1)	51 (23)	2 (1)
Nausea	63 (70)	2 (2)	145 (65)	5 (2)
Diarrhea	33 (37)	2 (2)	69 (31)	2 (1)

Moreover, the applicant was requested to provide prediction of safety profile, especially myelosuppressive adverse events, at exposure level 50%, 70% and 100% higher than 400 mg BID capsule in $\geq 4^{\text{th}}$ line treatment setting in ovarian cancer patients using exposure response model for safety (refer to clinical pharmacology IR 3(b) sent on May 2, 2017). The prediction suggested that the predicted mean decrease in hemoglobin concentration is small and the absolute values were >10 g/dL, even at 100% higher geometric mean AUC for 4th line ovarian cancer patients following ≥ 6 months olaparib 400 mg BID capsule treatment. The pharmacometrics team deems the model and prediction are acceptable to evaluate the impact of formulation switch on hemoglobin for patients in the $\geq 4^{\text{th}}$ line treatment setting. Given the AUC at steady state would increase by 77% when the formulation/dose is switched from 400 mg capsule to 300 mg tablet reported from the population PK analysis, the incidence of myelosuppressive adverse events would have a small increase for $\geq 4^{\text{th}}$ line ovarian cancer patients. (Refer to pharmacometrics review in OCP Appendices 13.4 for detailed analysis and reports).

Altogether, it is reasonable to anticipate that the switch of 300 mg tablet BID in ovarian cancer patients treated with $\geq 4^{\text{th}}$ line therapy will provide a similar effective and comparable safety profile in a more convenient manner compared to the treatment of 400 mg capsule BID.

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

Studies D0816C00005 (Study 05) and D0816C00006 (Study 06) evaluated the impact on olaparib exposure in patients with hepatic and renal impairment, which were reviewed under NDA 206162. For study details, refer to the clinical pharmacology review for labeling supplement 2 (dated October 5, 2016) and supplement 3 (dated January 4, 2017) in DARRTs under NDA 206162, respectively.

The dedicated RI study 06 showed that there was an increase of 44% in AUC (mean ratio 1.44; 90% CI: 1.10, 1.89) and increase of 26% (mean ratio 1.26; 90% CI: 1.06, 1.48) in C_{max} in patients with moderate RI ($\text{CLcr}=31$ to 50 mL/min) compared to normal renal function ($\text{CLcr} \geq 81$ mL/min) after a single oral dose of olaparib 300 mg tablet formulation. The increase in AUC was 24% (mean ratio 1.24; 90% CI: 1.06, 1.47) and was 15% (mean ratio 1.15; 90% CI: 1.04, 1.27) in C_{max} in patients with mild RI ($\text{CLcr}=51$ to 80 mL/min) compared to normal renal function. Consequently, the applicant proposed to reduce olaparib tablet dose to 200 mg BID for patients with moderate RI. Patients with mild RI do not require a dose adjustment. The review team agrees with the proposed dose adjustment for patients with mild or moderate RI.

The dedicated HI study 05 showed that there was an increase of 15% in AUC (mean ratio 1.15; 90% CI: 0.77, 1.73) and 13% in C_{max} (mean ratio 1.13; 90% CI: 0.82, 1.55) in patients with mild HI (Child-Pugh A) compared to normal hepatic function after a single oral dose of olaparib 300 mg tablet. In addition, olaparib 300 mg tablet BID demonstrated an acceptable and manageable tolerability profile in patients with mild HI in the second part of the same study. Altogether, no dose adjustment of olaparib in patients with mild HI is needed. For a single patient with moderate HI (Child-Pugh B), C_{max} was 8.52 $\mu\text{g/mL}$ and AUC was 40.3 $\mu\text{g}\cdot\text{h/mL}$ which was within the exposure range of patients with normal hepatic

function. (b) (4) will be reported in an addendum to the CSR. Consequently, the applicant proposed that patients with mild HI do not require a dose adjustment of olaparib. The review team agrees with the proposed dose adjustment for patients with mild HI.

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

Food-Drug Interactions

Study D0816C00004 (Study 04) is a randomized, open-label, three-part (A, B and C), phase 1 study to formally evaluate the effect of a high fat meal on the PK of olaparib and to provide data on the effect of olaparib on QT Interval following oral dosing of a tablet formulation in patients with advanced solid tumors. One of the objects in part A was to determine the effect of food on the PK of olaparib. Of the 60 patients randomized to the study, 32 were randomized to the fed/fasted sequence and 28 to the fasted/fed sequence. Each patient received a single 300 mg oral dose of olaparib after an overnight fast or following a high fat breakfast with at least 5 days washout between doses in Part A. A total of 55 and 54 patient profiles were evaluable for the fasted and high fat fed arms, respectively. There was an increase of 8% in both AUC_{0-inf} and AUC_{0-last} (mean ratio 1.08; 90% CI: 1.01, 1.16) in patients given high fat breakfast compared to those fasted and the C_{max} was decreased by 21% (mean ratio 0.79; 90% CI: 0.71, 0.86) in the fed state. Median t_{max} was delayed to 4 hours (range 1 to 11.97 hours) with food compared to median t_{max} 1.5 hours (range 0.5 to 5.85 hours) in fasted status. Because both the mean ratio and 90% CI for AUCs lay within the bounds of 0.80 to 1.25, the food effect on olaparib exposure was minimal and the applicant concluded that olaparib tablet formulation can be given with or without food in the label. The pivotal tablet safety and efficacy phase 3 study SOLO2 has permitted a light snack to be given with olaparib. The reviewer agrees with the proposed labeling language for the administration of olaparib tablets with regard to food.

Drug-Drug Interactions

Drug-drug interaction information for olaparib is shown in Table 7.

Table 7 Olaparib Drug-Drug Interactions

Olaparib as a victim of DDI	
Olaparib as a substrate of CYP3A	<u>Clinical DDI studies</u> Studies D0816C00007 and D0816C00008 evaluated the magnitude of effect on olaparib exposure of co-administered itraconazole (strong CYP3A inhibitor) and rifampicin (strong CYP3A inducer), which were reviewed under NDA 206162. For study details, refer to the clinical pharmacology review dated November 26, 2014 in DARRTs under NDA 206162. Briefly, co-administration of olaparib 100 mg tablet with itraconazole (oral dose of 200 mg od) increased olaparib C_{max} by 42% and increased AUC by 170%. Co-

	administration of olaparib 300 mg tablet with rifampicin (600 mg od) decreased olaparib C_{max} by 71% and AUC by 87%. The review team agrees with the proposed dose adjustment and labeling language for the co-administration of olaparib tablets with regard to strong CYP3A inhibitors or inducers. <u>PBPK Predictions</u> Physiologically based pharmacokinetic (PBPK) models were used to predict the effect of moderate and weak CYP3A inhibitors as well as moderate and weak CYP3A inducers. For detailed evaluation of the applicant's PBPK simulations, please refer to the PBPK review in appendix in the clinical pharmacology review for labeling supplement 2 in DARRTs dated October 5, 2016. An updated version of Simcyp software (V15R1) was used in the olaparib tablet PBPK report (dated January 12, 2017) in the current NDA submission. The predicted olaparib C_{max} increased by 14% and the AUC_{0-t} increased by 121% when co-administered with fluconazole (a moderate CYP3A inhibitor). There was no change in exposure of olaparib when given with weak CYP3A inhibitor such as fluvoxamine. The predicted olaparib C_{max} decreased by 31% and the AUC_{0-t} decreased by 60% when co-administered with efavirenz (a moderate CYP3A inducer). There was no change in exposure of olaparib when given with weak CYP3A inducer such as dexamethasone. The review team agrees with the proposed dose adjustment and labeling language for the co-administration of olaparib tablets with regard to moderate CYP3A inhibitors or inducers. No dose adjustment is needed for co-administration with weak CYP3A inhibitors or inducers. Of note, the predicted decrease in AUC of olaparib by efavirenz is changed from approximately 50% to 60% using the updated PBPK model, which seems reasonable from the PBPK review team.
Olaparib as a substrate of Transporter Proteins	In vitro study showed that olaparib is a substrate of the efflux transporter P-gp (IC₅₀ = 76μM). In vitro studies indicated that olaparib is not a substrate for BCRP, MRP2, OATP1B1, OATP1B3 or OCT1. Thus, drug interactions with inhibitors of these transporter systems would not be anticipated.
Olaparib as a perpetrator of DDI	
Olaparib as an inhibitor and inducer of CYP3A and its Net effect as a perpetrator of CYP3A	In vitro studies showed that olaparib acted as a CYP3A4 inhibitor in time dependent and reversible manner, as well as a potential CYP3A4 inducer. The PBPK simulation indicated olaparib can be considered to be a weak CYP3A inhibitor in vivo by including both CYP3A inhibition and induction parameters. For simulation details, refer to PBPK review in OCP appendices 13.4. In addition, clinical study D081CC00001 in the current submission is submitted to support the above DDI predictions using PBPK modelling. The drug interaction between olaparib and the anti-hormonal agents, such as, anastrozole, letrozole and tamoxifen (CYP3A substrates) were investigated. Tamoxifen steady state exposure was increased by 13% and 16% for C_{max} and AUC, respectively. There

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	was little effect on exposure to anastrozole or letrozole. Based on those PBPK predictions and supportive data in the study D081CC00001, the review team agrees the applicant's proposed statement that olaparib is predicted to be a weak CYP3A inhibitor in humans.
Olaparib as an inhibitor or inducer of other CYP enzymes	No new updates are reported in the current submission. For details, refer to the clinical pharmacology reviews for NDA 206162 original and supplement submissions. Briefly, in-vitro data suggested little or no direct inhibitory effect of olaparib on CYPs 1A2, 2A6, 2B6, 2C8, 2D6, CYP2C9, CYP2C19 or 2E1 at concentrations up to 43.5 µg/mL (100 µM). Olaparib was not considered to be an inducer of CYP1A2, 2C9, or 2C19, but a weak inducer of CYP2B6 at the highest olaparib concentration studied.
UGT inhibition	The simulations using raltegravir as a UGT1A1 substrate to predict effect of olaparib on the PK of sensitive UGT1A1 substrates were newly added to the current PBPK modeling as olaparib exhibited concentration dependent inhibition of UGT1A1 between 9 µM and 100 µM in vitro. Briefly, the mean geometric ratio of raltegravir with or without olaparib were 1.07-fold for AUC and 1.04-fold for C_{max}, (b) (4) For the internal sensitivity analysis conducted by the PBPK reviewer using the worst case scenario, the simulation results indicated a two-fold increase in raltegravir AUC by olaparib. (b) (4) For simulation details, refer to PBPK review in OCP appendices 13.4.
Transporter proteins inhibition	The simulations using digoxin as a probe P-gp substrate to predict effect of olaparib on the PK of sensitive P-gp substrates was updated in the current PBPK modeling. Briefly, the mean geometric ratio of digoxin with or without olaparib were 1.02-fold for AUC and 1.05-fold for C_{max}, (b) (4) the capability of the PBPK model to predict olaparib as a P-gp perpetrator has not yet been evaluated as the predictive performance of PBPK for P-gp inhibition has not been established. For details, refer to PBPK review in OCP appendices 13.4. No new updates are reported in the current submission regarding olaparib acting as an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K in vitro. For details, refer to the clinical pharmacology reviews for NDA 206162 original and supplement submissions.

Is the tablet formulation bioequivalent to the capsule formulation?

The capsule and tablet formulations of olaparib are not interchangeable due to differences in the dosing and bioavailability (BA) of each formulation. The tablet formulation has an enhanced solubility due to the different technologies used to improve the BA relative to the capsule formulation.

To improve patient convenience, a tablet formulation (150 mg and 100 mg in dose strength) was developed for the phase 3 program to deliver the therapeutic dose in fewer dose units. Most new studies, including phase 3 registration studies, have been performed with the tablet formulation since 2013. Study 24 was conducted to compare the relative BA of the capsule and tablet formulations of olaparib in cancer patients with advanced solid tumors. The relative BAs at three dose levels of tablet vs. capsule are presented in the Table 8. The mean AUC ratio is close to 1 in the comparison of 25 mg tablet vs 50 mg capsule and 50 mg tablet vs. 100 mg capsule, although the mean C_{max} was 29% to 53% higher following tablet dosing compared to that following capsule dosing respectively. At the highest dose level of 250 mg tablet vs. 400 mg capsule, the mean ratio was 2.49 for C_{max} (90% CI: 1.87, 3.31) and 1.74 for AUC (90% CI: 1.36, 2.23) because exposure following capsule dosing increases less than proportionally with dose at dose levels greater than 100 mg. In addition, the exposure at steady state following the 300 mg tablet BID and 400 mg capsule BID were evaluated in patients at the efficacy expansion phases as shown in Table 9. The mean steady state C_{max} , C_{min} , and AUC were 1.3 to 1.7 times higher following 300 mg tablet BID than those following 400 mg capsule BID.

Table 8: Relative Bioavailability of Tablet vs. Capsule formulation

Parameter	25 mg Tablet vs. 50 mg Capsule	50 mg Tablet vs. 100 mg Capsule	250 mg Tablet vs. 400 mg Capsule
GLS mean C_{max} ratio	1.29	1.53	2.49
90% CI	1.10 – 1.52	1.11 – 2.11	1.87 – 3.31
GLS mean AUC ratio	1.03	0.99	1.74
90% CI	0.85 – 1.24	0.69 – 1.42	1.36 – 2.23

(Source: Table 70 on page 180 in study report of Study 24)

Table 9: Steady State (Day 29) PK Parameters Following Multiple Dosing of the Tablet and the Capsule

PK Parameter Mean (CV%)	300 mg Tablet BID in Group 6	400 mg Capsule BID in Groups 1 and 6
$C_{max,ss}$ (µg/mL)	9.37 (47%)	6.11 (41%)
AUC _{ss}	58.4 (44%)	42.1 (61%)
$C_{min,ss}$	1.84 (67%)	1.29 (133%)

(Source: Table 72 on page 184 in study report of Study 24)

The high relative BA of tablet formulation was also supported by using an integrated population PK analysis combining all available PK data from different patient populations and healthy subjects (refer to clinical pharmacology IR on April 13, 2017). The pooled PK dataset included data from capsule pool (MS-01), tablet pool excluding study SOLO-2 (MS-02) and study SOLO-2 (MS-03). Based on pharmacometrics reviewer's analysis by employing a more accurate function to describe the absorption of capsule olaparib, the mean BA of the 300 mg tablet formulation relative to the 400 mg capsule formulation was estimated to be 236%. The steady state AUC following 300 mg tablet twice daily was 77% higher compared to that following 400 mg capsule twice daily. (Refer to pharmacometrics review in the OCP appendices 13.4 for detailed modeling and analysis).

Of note, the exposure to olaparib at 300 mg tablet observed in study SOLO2 (MS-03) was approximately 30-70% lower than that was observed in the pooled population PK analysis for the tablet formulation at the same dose (MS-02); however, the exposure was within the range observed in the pooled population PK analysis for the approved capsule formulation at 400 mg BID (MS-01) as shown in Table 10. To address this discrepancy, the review team requested the applicant to conduct the population PK analysis using integrated PK data to explore the potential reasons by including treatment lines, disease severity and tumor types as additional covariates. According to the applicant's PPK model, the greater disease severity (ECOG>0) was associated with lower drug clearance. This could partially explain the lower exposure at Study SOLO-2, where 78% of the subject had ECOG=0, as compared with 51.3% at pool tablet phase I studies as the applicant mentioned. The potential mechanism for the association between disease severity and drug clearance could due to the possible reduced enzyme activity of CYP3A in oncology patients. (Refer to pharmacometrics review in the OCP appendices 13.4 for detailed modeling and analysis).

Table 10: Comparison of Steady State Olaparib Exposure for the Capsule and Tablet Formulations Determined Using Population PK Analysis

PK Parameter Gmean (range) [GCV]	Capsule 400 mg BID Pooled Capsule PK (MS-01)	Tablet 300 mg BID Study SOLO2 (MS-03)	Tablet 300 mg BID Pooled Tablet PK (MS-02)
C _{max,ss} (µg/mL)	5.73 (1.57–14.2)	7.12 (3.9-15) [26.9]	9.10 (4.26-25.5) [38.7]
AUC _{ss} (µg*h/mL)	48.1 (8.57–154)	40.7 (17-120) [39.5]	59.7 (25.5-183) [49.7]
C _{min, ss} (µg/mL)	1.26 (0.08–8.08)	1.15 (0.28-6.2) [72.3]	1.95 (0.35-11.5) [86.5]

(Source: Table 7 on page 54 in the summary of biopharma)

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7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

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Trial Identity	Trial Design	Regimen/ schedule/ route	Study Primary Endpoint(s)	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
SOLO2	Phase 3, randomized, double-blind, placebo controlled multicenter trial to compare olaparib with placebo in BRCAm patients relapsed ovarian cancer	Olaparib tablet 300 mg BID vs. matching placebo	PFS by inv. assessment (Blinded Independent Central Review [BICR] assessment as sensitivity analysis)	Until disease progression/death or unacceptable toxicity	295	Patients with BRCA mutated platinum-sensitive high-grade serous ovarian or endometrioid cancer following treatment with ≥ 2 platinum-containing regimens	119 sites in 16 countries
Study 19	Phase 2 randomized double-blind placebo controlled multicenter trial	Olaparib capsule 400 mg BID vs. matching placebo	PFS by inv. assessment	Until disease progression/death or unacceptable toxicity	265	Patients with platinum sensitive serous ovarian cancer following treatment with ≥ 2 platinum-containing regimens	82 sites in 16 countries

7.1.2. Review Strategy

Data Sources

The data for NDA 208558 were submitted by the Applicant electronically on 2/22/2017. Data were submitted in ADaM and SDTM format. The path to the submission's datasets is <\\CDSESUB1\evsprod\NDA208558\0002\m5\datasets>. The data source for SOLO2 is located in the path <\\CDSESUB1\evsprod\NDA208558\0002\m5\datasets\d0816c00002>. The derived efficacy dataset is ADTTE.

The clinical and statistical review was primarily based on the clinical study reports and data sets for the SOLO2 and Study 19 trials. Within each section under 7.2, results for both SOLO2 and Study 19 will be described.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

SOLO2 and Study 19

Trial Design and Endpoints

SOLO2

SOLO2 was a phase 3, randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy of olaparib as maintenance treatment in relapsed high grade serous ovarian, fallopian tube, and primary peritoneal cancer or high grade endometrioid cancer with BRCA mutation (documented deleterious or suspected deleterious mutation in BRCA1 or BRCA2) who were in response (PR or CR) to platinum based chemotherapy. Patients were to be platinum sensitive after completion of their penultimate platinum-based chemotherapy prior to enrollment. Platinum sensitivity was determined as > 6 months after completion of their final platinum chemotherapy until disease progression (as determined by investigator). Patients must have received at least 2 previous lines of platinum therapy before study entry, with no non-platinum regimens allowed to treat progression between the penultimate and last chemotherapy course, and bevacizumab during the most recent chemotherapy course was not allowed (maintenance treatment was allowed at the end of the penultimate platinum regimen, including bevacizumab). Patients need to demonstrate an objective PR or CR at baseline (per RECIST and/or CA-125) after completion of their last platinum regimen to be enrolled; randomization was to be within 8 weeks after last dose of chemotherapy.

Patients were randomized (using Interactive Voice Response/ Interactive Web Response system) in a 2:1 ratio to either:

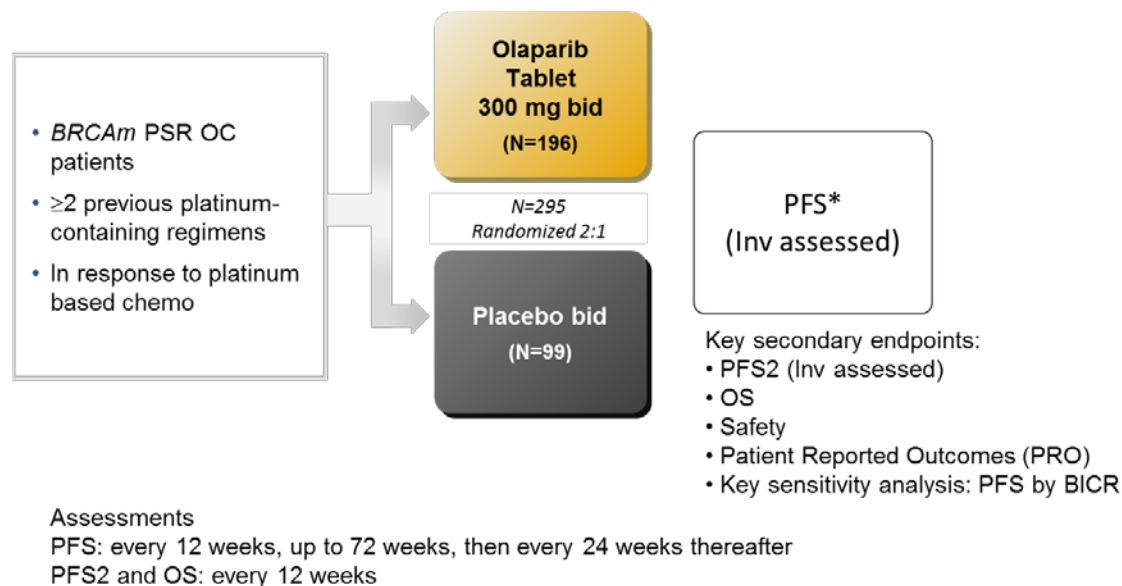
- Olaparib tablets 300 mg PO BID
- Placebo tablets PO BID

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Randomization was stratified by:

- Response to last platinum chemotherapy (CR or PR)
- Time to disease progression in the penultimate platinum based chemotherapy prior to enrollment (>6 to ≤12 months and > 12 months).

Figure 1 SOLO2 Study Design



Source: Applicant's orientation slides

Key eligibility:

Inclusion:

- Patients with histologically diagnosed relapsed high grade serous ovarian cancer (including primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer.
- Documented mutation in BRCA1 or BRCA2 that was predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/ lead to loss of function).
- Patients who had received at least 2 previous lines of platinum-containing therapy prior to randomization.
- For the penultimate chemotherapy course prior to enrollment:
 - Treatment must have contained a platinum agent (carboplatin or cisplatin)
 - Patient must be defined as platinum sensitive after the treatment; defined as disease

progression greater than 6 months after completion of last dose of platinum chemotherapy

- o Maintenance treatment allowed at the end of the penultimate platinum, including bevacizumab
- For the last chemotherapy course immediately prior to randomization:
 - o Must be, in investigator opinion, in PR or CR, or have NED (if surgery conducted prior to chemotherapy), and no evidence of rising CA-125, following completion of this last chemotherapy regimen
 - o Must have received a platinum-based chemotherapy regimen (carboplatin or cisplatin) and have received at least 4 cycles.
 - o Must not have received bevacizumab during this course of treatment
- Required pre-randomization Myriad gBRCA status sample to determine eligibility.
- Pre-treatment CA-125 measurements had to meet specified criteria
- Adequate organ and marrow function within 28 days:
 - o Hemoglobin ≥ 10 g/dL with no transfusions in 28 days
 - o ANC $\geq 1.5 \times 10^9$ /L
 - o Platelets $\geq 100 \times 10^9$ /L
 - o Total bilirubin $\leq 1.5 \times \text{uln}$.
 - o AST/ ALT $\leq 2.5 \times \text{ULN}$ unless liver metastases, then $\leq 5 \times \text{uln}$.
 - o Serum creatinine $\leq 1.5 \times \text{uln}$.
- ECOG 0-1
- Life expectancy ≥ 16 weeks.
- Post-menopausal or non-childbearing status.
- Willing and able to comply with the protocol.

Exclusion:

- BRCA1 and/or BRCA2 mutations that are considered to be non-detrimental (variants of unknown or uncertain significance or variant of favorable polymorphism).
- Patients who have had drainage of ascites during the final 2 cycles of last chemotherapy

regimen prior to enrollment on study.

- Previous randomization in present study.
- Participation in another clinical study with investigational product during the chemotherapy course immediately prior to randomization.
- Any previous treatment with a PARP inhibitor, including olaparib.
- Hypersensitivity to olaparib or any of the excipients.
- Other malignancy within past 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cervical cancer, DCIS, grade 1/stage 1 endometrial cancer, other solid tumors including lymphoma (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 years.
- QTc >470 msec on 2 or more time points within 24 hours or family history of long QT syndrome.
- Patients receiving any systemic chemotherapy or radiotherapy (except palliative) within 3 weeks prior to study treatment (or longer period, depending on defined characteristics of agents used).
- Concomitant use of known potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin, nelfinavir.
- Persistent $\geq$ G2 toxicity caused by previous chemotherapy except for alopecia.
- MDS or AML
- Symptomatic uncontrolled brain metastases. Scan to confirm absence not required. Patient can receive stable dose of steroids before and during study as long as these were started at least 4 weeks prior to treatment. Patients with cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
- Major surgery within 2 weeks of starting and recovery for any effects of surgery.
- Considered poor medical risk due to uncontrolled medical disorder, infection, disease. Examples include uncontrolled ventricular arrhythmia, recent (3 months) MI, uncontrolled major seizure disorder, SVC syndrome, interstitial lung disease on high resolution CT, or psychiatric disorder that may prohibit informed consent.
- Unable to swallow oral medications.
- Breast feeding.
- Immunocompromised patients, e.g., patients with HIV.
- Patients with known active hepatitis C or B.

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- Previous allogeneic stem cell transplant.
- Whole blood transfusion within 120 days (packed RBC or platelets acceptable within 28 days, as above).

The primary endpoint, PFS by investigator assessment (PFS-Inv) was determined by modified RECIST from radiographic scans (MRI/CT) performed every 12 weeks up to week 72 then every 24 weeks thereafter. Imaging was performed until disease progression.

The secondary endpoints to be tested statistically were time to the second progression event (PFS2) and overall survival (OS). PFS2 was the time from randomization to second progression defined as the time from date of randomization to the earliest of the progression event subsequent to that used for the primary variable PFS or death. The date of second progression was to be recorded by Investigator and was defined according to local standard clinical practice, which could involve any of; objective radiological, CA-125 or symptomatic progression or death.

Reviewer comment: It is noted that although PFS2 was one of the secondary endpoints of the trial, as defined by the Sponsor, this is not an endpoint that FDA considers as a valid regulatory endpoint and this endpoint was not considered in the FDA's risk-benefit analysis of this application.

Other secondary endpoints were time to earliest progression by CA-125 or death and HRQoL assessed by trial outcome index (TOI) using the FACT-O questionnaire. The FACT-O is composed of the following sub-scales: physical, social/ family, emotional and functional well-being, as well as additional concerns scales of specific ovarian cancer symptoms. The TOI score was derived from the sum of scores of the three derived subscale scores. The actual change from baseline TOI score was to be derived for each visit where data were available. A change of 10 points in TOI score was considered as a clinically relevant or minimally important difference.

The EQ-5D-5L is an additional health-related quality of life questionnaire which was also administered to patients during the study. This consists of two sets of questions. The first is a descriptive system, which includes one question on each of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, which are rated on an ordinal five-level scale. This is complemented by a visual analog scale. The EQ-5D was to be utilized as an exploratory analysis.

Diagnostic Assay

The Myriad Integrated BRCA^{Analysis}® assay was performed under Clinical Laboratory Improvement Amendments (CLIA). The Myriad BRCA^{Analysis} CDx® assay was performed under Quality Systems Regulations. Patients known to have BRCA mutation/s from germline (blood) or tumor specimens prior to randomization could be entered on the study based upon this result. The result had to be made available to AZ. Patients who had BRCA mutation identified via tumor assessment could enter the study provided that all testing be undertaken in appropriately accredited laboratories. Patients also had to give consent to give 2 blood samples (b) (4)

(b) (4)
Patients with unknown BRCA status had to provide 2 blood samples for gBRCA testing; one for BRCA mutation testing using the Myriad CLIA Integrated BRACAnalysis® test prior to study entry, the second to (b) (4)
When the result indicated a patient did have a deleterious or suspected deleterious BRCA mutation, the patient could be randomized to the study.

Safety analyses:

On-study safety assessments are depicted in the Sponsor's schedule shown in Figure 2.

Figure 2 SOLO2 On-study schedule of assessments

Visit Number	2	3	4	5	6	Subsequent on treatment visits every 4 or 12 weeks ^a Tumour assessment visits every 12 or 24 weeks ^{a,c} Visit No. 7 onwards	Study treatment discontinued	Follow-up 30 days after last dose of study medication
Day	1	8	15	22	29	Day 1 of next visit period (Visit 7 equals day 57 (week 9) then visit 8 equals day 85 (week 13) etc)		
Visit Window		±3d	±3d	±3d	±3d	±3d	±7d	±7d
Blood sample for confirmation of BRCA status (via Myriad) and (b) (4)	X							
Blood sample for PK analysis (Subset of patients) ^f	X		X		X			
Tumour Assessment (CT or MRI according to modified RECIST v1.1) ^g						X ^g [Every 12 weeks (±7d) ^g]		
Adverse Events ^a	X	X	X	X	X	X	X	X
Concomitant medications including blood transfusions	X	X	X	X	X	X	X	X
EQ-5D-5L ^h	X				X	X	X	X
FACT-O ^h	X				X	X	X	X
Resource use ^m	X				X	X	X	X

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Visit Number	2	3	4	5	6	Subsequent on treatment visits every 4 or 12 weeks ^a Tumour assessment visits every 12 or 24 weeks ^a Visit No. 7 onwards	Study treatment discontinued	Follow-up 30 days after last dose of study medication
Day	1	8	15	22	29	Day 1 of next visit period (Visit 7 equals day 57 (week 9) then visit 8 equals day 85 (week 13) etc)		
Visit Window		±3d	±3d	±3d	±3d	±3d	±7d	±7d
Olaparib / placebo dispensed/returned ^e	X				X ^c	X ^c	X	
Subsequent cancer therapy following discontinuation of study treatment ^j								X
Blood sample for pharmacogenetics (optional patient consent required)	X							
Tumour biopsy on progression (optional) ⁱ						X		
Blood samples for biomarker analysis (e.g. cfDNA) ^l (optional)	X					X		
Survival						X		

^a Visit to take place on Day 1 of a 4 week (28 day) visit period up to 72 weeks, then on Day 1 of a 12 week visit period relative to date of randomisation
^b If assessed within 7 days before randomisation and meets the stated eligibility criteria (if applicable), it need not be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly. Physical examination should be performed according to the schedule, after the baseline assessment it is not necessary to record the details on an eCRF, any clinically significant changes should be recorded as adverse events.

- ^c ECG is performed at baseline, at week 9 (day 57), at safety follow-up and if clinically indicated at any other time see Section 6.2. ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case.
- ^d Safety blood samples do not need to be repeated on Day 1 of study treatment if there have been separate assessments within 7 days before starting study treatment and which must have been 3 weeks after last dose of chemotherapy, unless the investigator believes that it is likely to have changed significantly. Coagulation analysis is only required at baseline unless clinically indicated.
- ^e BRCA1/2 mutation status: Blood sample taken for Myriad BRCA testing for patients with a local result.
- ^f PK sampling to be performed in a subset of patients. Sampling times: Day 1 pre-dose & 1 hour; Day 15 pre-dose & 1 hour; Day 29 pre-dose, 0.5-1 hour, 1-3 hours 3-6 hours and 6-12 hours (see section 6.6)
- ^g RECIST follow-up assessments will be performed every 12 weeks (±1 week), up to 72 weeks, then every 24 weeks (±1 week) relative to date of randomisation. Follow-up assessment will include CT or MRI assessments of abdomen and pelvis for all patients. Follow-up chest CT will be performed (in those patients with thoracic lesions or upper abdomen lymphadenopathy identified at baseline assessment). Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until RECIST disease progression. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Following disease progression further RECIST assessments will not be performed and assessment of disease will be as per local clinical practice.
- ^h At baseline, at Day 29, then in line with the RECIST assessments (every 12 or 24 weeks) until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.
- ⁱ Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice.
- ^j All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigators opinion of response to them plus the date of progression, post discontinuation of study treatment need to be recorded
- ^k Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting treatment and a confirmatory test before treatment on Day 1. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately
- ^l Optional blood samples for biomarker analysis (e.g., circulating free DNA (cfDNA)) to be taken at randomisation and at objective radiological disease progression (so not at every treatment visit). Optional tumour biopsy to be taken at objective radiological disease progression (so not at every treatment visit).
- ^m At baseline, at Day 29, then in line with the RECIST assessments (every 12 or 24 weeks) until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.
- ⁿ When an AE for nausea and vomiting occurs, an additional eCRF will require completion
- ^o Temperature and weight only required if clinically indicated. Blood pressure and pulse taken in line with RECIST assessments

Dose modifications

Dose reductions (tablet formulation) due to adverse event were as follows in Table 11.

Table 11 SOLO2 Dose levels for olaparib dose reductions (tablet formulation)

Initial dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg	250 mg	200 mg

Toxicities observed during study were managed with dose interruption, with a maximum of 14 days of interruption allowed on each occasion. When toxicity recurred following re-challenge, dose reduction or discontinuation was considered by the investigator. Interruption for any CTCAE Grade 3-4 toxicity was mandatory. The specific management of prolonged hematologic toxicities and of new/worsening pulmonary symptoms was as follows:

Prolonged hematologic toxicities

If a patient developed any of the following:

- ≥ 2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥ 2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia ($ANC < 1 \times 10^9/L$)
- ≥ 2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (platelets $< 50 \times 10^9/L$)

Weekly CBC including reticulocyte count and peripheral smear were to be performed. If any parameters remained abnormal after 4 weeks of dose interruption, referral to a hematologist for further evaluation was recommended. Bone marrow analysis and/or blood cytogenetics were recommended. Development of MDS or other clonal blood disorder was to be reported to AZ as an SAE. Study treatment was to be permanently discontinued if MDS was confirmed.

New or worsening pulmonary symptoms

If new or worsened pulmonary symptoms (eg, dyspnea) or radiological abnormality developed, interruption of study treatment was recommended and diagnostic work up including high resolution CT was to be performed to exclude pneumonitis. Following investigation, if no evidence of abnormality on CT was seen and symptoms resolved, study treatment could be restarted if deemed appropriate by investigator. Significant pulmonary abnormalities were to be discussed with AZ.

Discontinuation rules:

Patients were to be discontinued from study therapy for the following reasons:

- Patient decision

- Adverse event
- Severe protocol non-compliance
- Bone marrow findings consistent with MDS or AML.
- Objective radiological disease progression according to RECIST (unless in investigator's opinion they are benefitting from treatment and do not meet other discontinuation criteria above).

The statistical analysis plan for SOLO2 is reviewed in detail later in this section.

Study 19

Study 19 was a randomized, double-blind, multicenter study to assess the efficacy of olaparib in platinum sensitive serous ovarian cancer patients following treatment with two or more platinum containing regimens.

Patients were randomized 1:1 to receive olaparib (400 mg twice daily) in capsule formulation versus placebo. Randomization was stratified by:

- 1) Time to disease progression from the completion of the penultimate platinum-containing therapy (end of last dose) prior to enrolment on the study (6-12 months versus >12 months),
- 2) Objective response to the last platinum-containing regimen prior to enrolment on the study (CR versus PR),
- 3) Ethnic descent of the patient (Jewish versus non Jewish).

The primary endpoint was investigator-assessed progression free survival (PFS) via modified RECIST, to be conducted on the intent-to-treat (ITT) population. Patients underwent tumor assessments every 12 weeks until week 72 then every 24 weeks thereafter. The secondary endpoints included overall survival (OS), best overall response (BOR), response rate (RR) and disease control rate.

Protocol Amendments

SOLO2

The protocol underwent three major amendments; two notable amendments were those dated September 15, 2014 (Amendment 2), and April 12, 2016 (Amendment 3). Amendment 2 allowed for the addition of a cohort of patients from China and the collection of HRQoL data past a patient's progression date. Changes to the protocol following Amendment 3 resulted in a change in the primary endpoint from PFS BICR assessed to PFS investigator assessed. The PFS BICR analysis was to be used as a supportive analysis. Amendment 3 also increased the number of required progression events (investigator assessed) for the primary analysis from 152 to 192.

The SAP also underwent major revisions to coincide with the protocol amendments; the final SAP version is dated January 16, 2017.

Reviewer comment: Although the FDA agreed to the Sponsor's proposal (in February 2016) to change the primary endpoint from BICR assessment to Investigator assessment, FDA also advised the Sponsor on 3/3/16 that they should still conduct the independent central review of all patient scans to confirm the investigator assessment. FDA further stated that both PFS analyses (by investigator and central review) should be consistent with each other. The SOLO2 protocol was formally amended to change the primary endpoint on 4/12/16. At that time all 295 patients had been randomized to SOLO2. Sites submitted scans to the BICR central vendor on an ongoing basis, though reading of scans was not initiated until the investigator determined disease progression. In addition, scans for all subjects who had not yet progressed at the time of data cut off were read between data cut off (19th September 2016) and the database lock (19th October 2016). It was discovered through the course of the NDA review that despite the FDA's advice to the Sponsor regarding the BICR analysis, no further scans were sent for BICR review following investigator assessed progression after April 2016. We performed a sensitivity analysis for PFS, comparing BICR and investigator assessed PFS at the point of protocol change. This is discussed in the efficacy analysis of this review.

Study 19

Amendment 6 for Study 19 dated October 17, 2012, increased the number of deaths required for final OS analysis to approximately 222. Further details of Study 19's protocol amendments can be obtained from the primary statistical review for NDA206162 in DARRTs dated 11/21/14.

Statistical Analysis Plan

SOLO2

The ITT and efficacy population for SOLO2 included all randomized patients. PFS-Inv, PFS2 and OS were analyzed via a stratified log-rank test, stratified by time to disease progression in the penultimate platinum treatment (6-12 months, >12 months) and response to last platinum chemotherapy prior to study entry (CR or PR). The stratification variables were defined according to data from the interactive voice/web response system (IVRS/IWRS). The Kaplan-Meier method and Kaplan-Meier probabilities were used to compute medians. The 95% CIs for medians of the time-to-event endpoints were computed using the Brookmeyer and Crowley method. The analysis was performed in two stages. The first stage was set to coincide with 192 investigator-assessed PFS events. The second stage was set to coincide with 60% deaths. The primary analysis of PFS-Inv performed at the first stage and the analysis of OS performed at the second stage.

The primary analysis was set to coincide with the occurrence of 192 PFS-Inv events. The specified Type I error rate was set at 2.5% (one-sided). Analysis was via a stratified log-rank test, testing for the superiority of olaparib. Pre-specified sensitivity analysis to assess the robustness of PFS-Inv results were:

1. Assessment of ascertainment bias – This was performed using BICR assessment.

2. Assessment of evaluation-time bias – The progression date in this analysis was defined as the midpoint between the time of progression and the previous evaluable assessment.
3. Assessment of attrition bias – This analysis used actual progression dates for patients who progressed following two or more missed/non-evaluable tumor. Patients who take subsequent therapies prior to progression are censored at their last evaluable assessment prior to taking the therapy.
4. Assessment of deviation bias - This analysis excluded patients with deviations and was to be performed provided if more than 10% of patients did not have the intended disease or indication, or did not receive any randomized therapy

Secondary endpoints

The secondary endpoints to be tested statistically were time to the second progression event (PFS2) and overall survival (OS). PFS2 progression was defined according to local standard clinical practice, involving radiological, CA-125, symptomatic progression or death.

Interim analyses for PFS2 and OS were to be performed hierarchically with PFS2 tested first after the primary analysis, provided that the PFS-Inv results were significant. The alpha allocated for the interim analysis of PFS2 was 0.0125. Results from the interim analysis of OS would demonstrate an OS advantage provided that the resulting p-value from a log-rank test was less than 0.0001 and the number of deaths was equal to or greater than 20.

The second analysis was timed to occur with 60% deaths. If the interim results for PFS2 were not significant then PFS2 would only be tested again with alpha adjusted using a Bespoke spending function (Stone 2010). The final OS analysis would be performed with stopping boundaries determined by the Haybittle–Peto method (Haybittle 1971).

Reviewer comment: It is noted that although PFS2 was one of the secondary endpoints of the trial, as defined by the Sponsor, this is not an endpoint that FDA considers as a valid regulatory endpoint and this endpoint was not considered in the FDA's risk-benefit analysis of this application.

Other secondary endpoints included time to earliest progression by CA-125 or death and health-related quality of life (HRQoL) assessed by the Functional Assessment of Cancer Therapy – Ovarian (FACT-O). No multiplicity adjustments were made for the PRO endpoint.

Study 19

Trial 19 was designed to have 80% power to detect a hazard ratio (HR) of 0.75 with a one-sided alpha of 0.2. A total of 137 PFS events from approximately 250 patients were needed for the primary PFS analysis. One interim analysis for OS was planned with 100 deaths, with the final OS analysis timed to

coincide with approximately 222 deaths. The stopping boundaries for the interim OS analysis were determined by the Haybittle–Peto method.

7.2.2. Study Results

Compliance with Good Clinical Practices

SOLO2

The Sponsor provided a statement that the SOLO2 study was conducted in compliance with Good Clinical Practice. The SOLO2 study was also approved by an independent IRB/Ethics Committee in association with each study center. The study was performed in accordance with ethical principles from the Declaration of Helsinki. The conduct was also consistent with the ICH and GCP requirements. Informed consent was obtained from all patients prior to initiation of the study.

Financial Disclosure

Financial disclosures for the SOLO2 study are addressed in Section 13.2 of this review.

Patient Disposition

SOLO2

Patient disposition at the time of data cutoff for the SOLO2 study is shown in Table 12. More patients had discontinued placebo than olaparib at that time, mainly due to more events of disease progression on placebo. Conversely, more patients discontinued olaparib due to adverse event, as compared to placebo. The specific adverse events leading to treatment discontinuation are discussed further in the safety review.

Table 12 Patient disposition SOLO2 (ITT population)

Disposition	Olaparib N=196 (%)	Placebo N=99 (%)
Patients ongoing treatment at data cutoff	83 (42)	13 (13)
Patients who discontinued study treatment	112 (57)	86 (87)
Adverse event	22 (11)	2 (2)
Disease progression	75 (38)	76 (77)
Patient decision	5 (3)	4 (4)

Other*	10 (5)	4 (4)
--------	--------	-------

* All were due to clinical progression/deterioration or investigator decision.

Adverse events leading to discontinuation on the olaparib arm included: anemia (6), neutropenia (3), MDS/leukemia (3), gastric cancer (1), erythroblast count increased (1), pneumonitis (1), allergic dermatitis (1), abdominal pain (1), peripheral edema (1), muscular weakness (1), extremity pain (1), nausea (1), depression/ attention disturbance (1). On the placebo arm, the two adverse events leading to discontinuation included invasive ductal breast cancer and thrombocytopenia.

Study 19

The disposition of patients from the ITT population of Study 19 is shown in Table 13.

Table 13 Patient disposition Study 19 (ITT population)

	Olaparib N=136 (%)	Placebo N=129
Patients ongoing treatment at data cut off	23 (17)	4 (3)
Patients discontinued from study treatment	113 (83)	125 (97)
Adverse event	7 (5)	2 (2)
Disease progression	87 (64)	110 (85)
Patient decision	11 (8)	8 (6)
Severe protocol non- compliance	2 (2)	1 (1)
Lost to follow-up	1 (1)	0
Other	6 (4)	4 (3)

Protocol Violations/Deviations

SOLO2

The key protocol deviation categories on SOLO2 are shown in Table 14. The number of deviations was balanced between arms. Deviations related to eligibility were slightly higher on the olaparib arm. Within this category, there were 2 patients (one of each arm) who had BRCA mutations which were considered to be deleterious/suspected deleterious by local testing, but were found to be non-deleterious with the Myriad test. There were 6 patients on olaparib and 1 on placebo who did not meet the criterion of “receiving at least 2 prior lines of platinum therapy prior to randomization.”

Table 14 SOLO2 Protocol deviations

	Olaparib N=195 (%)	Placebo N=99 (%)
Any protocol deviation	71 (36)	39 (39)
GCP violation	28 (14)	13 (13)
Did not fulfill eligibility criteria	23 (12)	7 (7)
Did not fulfill RECIST and tumor sample criteria	8 (4)	4 (4)
Treatments and randomization	18 (9)	11 (11)
PK violation	13 (7)	8 (8)
Incorrect dosing	5 (3)	3 (3)

Reviewer comment: An Information Request was sent to the Sponsor regarding details of 7 patients with protocol deviations involving not fulfilling eligibility criteria. The specifics of the eligibility criteria were such that patients must have received at least 2 prior lines of platinum-based therapy, including that both the last regimen and the penultimate regimen should have contained platinum. The details of all 7 cases were reviewed and involved deviations in timing of previous regimens by a few days, receipt of less than the required number of cycles of platinum therapy due to AE, and lack of platinum being contained in the penultimate regimen. Based upon the Sponsor’s explanations, it is unlikely that these deviations affected the study results in a substantial way.

Study 19

The protocol deviations for the ITT population from Study 19 are shown Table 15.

Table 15 Study 19 Protocol deviations

	Olaparib N=136 (%)	Placebo N=129 (%)
Any protocol deviation	77 (57)	62 (48)
IVRS mis-stratification	48 (35)	31 (24)
Scans outside of window	23 (17)	19 (15)
Did not demonstrate CR/PR prior to study entry	1 (1)	1 (1)
Failed to demonstrate sensitivity to penultimate platinum	3 (2)	1 (1)
Disallowed concomitant med	4 (3)	3 (2)
PD outside of RECIST criteria	4 (3)	9 (7)
Noncompliance	7 (5)	3 (2)
Eligibility criteria (organ function or CA-125)	2 (1)	4 (3)
Informed consent violation (biomarker blood work)	5 (4)	8 (6)

Reviewer comment: The only notable protocol deviation on Study 19, where there was an imbalance between treatment arms, was regarding the IVRS stratification process. At the time of randomization, investigators determined the appropriate stratification variables for each patient among the following factors: time to disease progression from completion of penultimate platinum regimen prior to enrollment (6-12 mos vs. > 12 mos), response to last platinum regimen (CR vs. PR), and ethnicity (Jewish vs. non-Jewish). Randomization was stratified by these 3 factors. According to the study report, although patients were stratified using the IVRS stratification system, which was where the error occurred in Study 19, the primary efficacy analysis of the treatment effect was adjusted, instead, based upon source-data-verified CRF data. Despite that a larger proportion of patients on olaparib (35% vs. 24%) were mis-stratified in the IVRS, the correct (CRF) data was actually used in the statistical analysis of study results and was not thought to have impacted the study results.

Table of Demographic Characteristics

SOLO2

The baseline demographics for patients enrolled on the SOLO2 study are shown in Table 16. The two study arms were well balanced with most patients being white, with ECOG status of 0. Approximately 20% of patients came from the US, with the rest coming mostly from Europe and Asia. Information on whether patients were of Jewish descent was not collected on SOLO2.

Table 16 SOLO2 Baseline demographics

	Olaparib N=196 (%)	Placebo N=99 (%)
Age		
Mean (SD)	57 (9.2)	57 (8.9)
Median	56	56
Range	28, 83	39, 78
18-64y	156 (79.5)	77 (77)
≥65y	40 (20)	22 (22)
≥75y	6 (0.5)	3 (3)
Race		
White	173 (88)	91 (92)
Black	1 (1)	0
Asian	22 (11)	7 (7)
Other	0	1 (1)
Ethnic group		
Hispanic or Latino	10 (5)	1 (1)
Not Hispanic or Latino	186 (95)	98 (99)
ECOG		
0	162 (83)	77 (78)
1	32 (16)	22 (22)
Missing	2 (1)	0
Geographic region		
North America	36 (19)	13 (13)
Rest of world*	160 (81)	86 (87)

*Countries included: Austria, Belgium, Brazil, Germany, Spain, France, Great Britain, Israel, Italy, Netherlands, Poland, Russia, Japan, Korea

Study 19

The baseline demographics for patients in the ITT population on Study 19 are shown in Table 17. The breakdown between arms is similar to that of the SOLO2 study.

Table 17 Baseline demographics ITT population Study 19

	Olaparib N=136 (%)	Placebo N=129 (%)
Age		
Mean (SD)	58.9 (11.0)	58.5 (9.9)
Median	58	59
Range	21, 89	33, 84
18-64y	91 (67)	94 (73)
≥65y	45 (33)	35 (27)
≥75y	12 (9)	5 (4)
Race		
White	130 (96)	126 (97)
Black	2 (1.5)	1 (1)
Asian	2 (1.5)	2 (2)
Other	2 (1.5)	0
Ethnic group		
Jewish descent	21 (15)	17 (13)
Non-Jewish descent	115 (85)	112 (87)
ECOG		
0	110 (81)	95 (74)
1	23 (17)	30 (23)
2	1 (1)	2 (1.5)
Missing	2 (1)	2 (1.5)
Geographic region		
North America (US, Can)	26 (19)	24 (19)
Rest of world*	110 (81)	105 (81)

*Countries included: Australia, Belgium, Czech Republic, Germany, Spain, Estonia, France, Great Britain, Israel, Netherlands, Poland, Romania, Russia, Ukraine

Reviewer comment: A difference between data collected on SOLO2 compared with Study 19 is that ethnicity of patients on SOLO2 was categorized by Hispanic/Latino status (yes or no), whereas ethnicity on Study 19 focused on the presence or absence of Jewish descent. Patients harboring a gBRCA mutation may be more likely to be of Jewish descent, but certainly not exclusively. It would have been interesting to have information on the prevalence of Jewish heritage in patients on the SOLO2 trial, since all patients enrolled had an underlying gBRCA mutation, but the information was not collected in the SOLO2 study. Likewise, only about 23% of patients out the n=96 gBRCA subgroup from Study 19 were of Jewish descent, which is not depicted in the table above.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

SOLO2

The baseline disease characteristics for patients enrolled onto SOLO2 are shown in Table 18. The key stratification factors at randomization were response to last platinum (CR vs. PR) and time to disease progression after the penultimate platinum-based chemotherapy (6-12 months vs. >12 months). The majority of patients had serous ovarian tumors with poor differentiation at baseline, according to the underlying pathologic diagnosis. This is consistent with the general population of patients diagnosed with this group of gynecologic tumors.

Slightly more than half of patients on both arms were in PR at study baseline, according to IVRS categorization of disease status.

The SOLO2 study required all subjects to have documented underlying deleterious or suspected deleterious gBRCA mutation, which required that gBRCAm status be confirmed by Myriad testing (Myriad CDx). Most patients randomized onto SOLO2 (236/295 [80%]) entered based upon a previously known BRCA mutation status tested in a local laboratory. The remainder of patients (20%) was randomized based upon BRCA mutation which was identified via centralized testing with the Myriad CLIA Integrated BRCA^{Analysis}® test. In the final analysis, there were only 9 patients (3%), including 6 on olaparib and 3 on placebo, who were treated on SOLO2 who did not have a confirmed BRCA mutation using the Myriad CDx. Six of the 9 patients had a deleterious/suspected deleterious mutation by local testing, but were not confirmed by the Myriad CDx. Two further patients could not have the Myriad CDx test performed, and one final patient was randomized based upon the Myriad CLIA test but did not have confirmation by the Myriad CDx for technical reasons. The Sponsor conducted additional analyses of efficacy in which these 9 patients were excluded; however, it was determined that exclusion of these 9 patients did not appear to have a significant impact on the primary analysis of efficacy.

Table 18 SOLO2 Baseline disease characteristics

	Olaparib N=196 (%)	Placebo N=99 (%)
Primary tumor		
Ovary	162 (83)	86 (87)
Fallopian tube	13 (7)	4 (4)
Primary peritoneal	18 (9)	9 (9)
Other (mullerian origin, ovarian carcinoma)	2 (1.5)	0
Missing	1 (0.5)	0
Histology		
Serous	183 (93)	86 (87)
Endometrioid	9 (5)	8 (8)
Mixed, epithelial	3 (1.5)	4 (4)
Other (serous, papilliferum, endometrioid)	0	1 (1)
Missing	1 (0.5)	0

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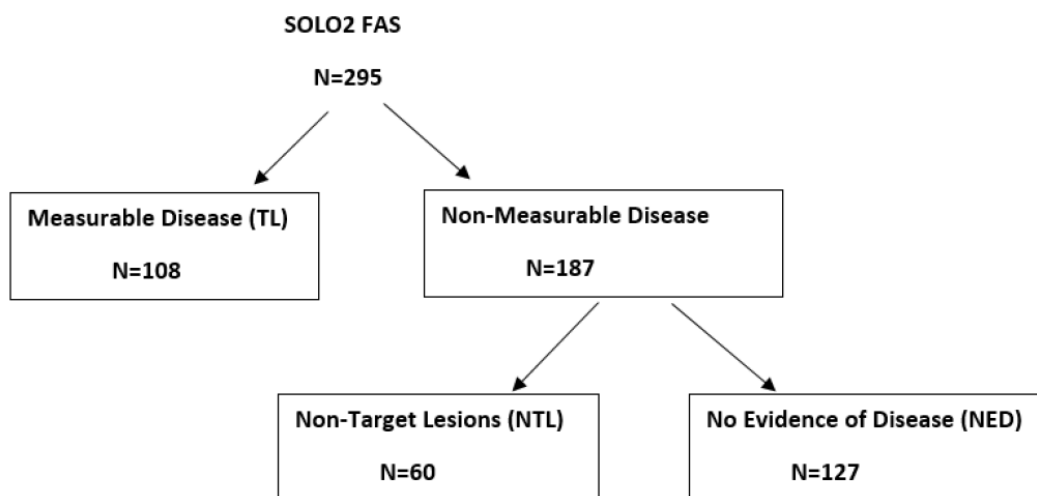
Tumor grade		
Well differentiated	0	0
Moderately differentiated	16 (8)	6 (6)
Poorly differentiated	167 (85)	85 (86)
Undifferentiated	5 (2)	3 (3)
Not assessable	7 (4)	5 (5)
Missing	1 (1)	0
Prior cytoreductive surgery*		
Yes	18 (9)	10 (10)
No	178 (91)	89 (90)
Time from last platinum to randomization		
≤8 weeks	187 (95)	97 (98)
> 8 weeks	8 (4)	2 (2)
Missing	1 (1)	0
Response to last platinum (status at study baseline per IVRS data)		
CR	91 (46)	47 (47)
PR	105 (54)	52 (53)
Interval from penultimate platinum to progression		
6-12 mos	79 (40)	40 (40)
> 12 mos	117 (60)	59 (60)
Prior Bevacizumab		
Yes	33 (17)	20 (20)
No	163 (83)	79 (80)
BRCA status confirmed by Myriad gBRCA test**		
BRCA1	132 (67)	61 (62)
BRCA2	58 (30)	35 (35)
Missing (not confirmed, or VUS/ WT)	6 (3)	3 (3)

*Prior cytoreductive surgery defined as surgery between date of most recent progression and randomization to the study.

**There were 6 patients who had deleterious/ suspected deleterious mutation by local testing who were not confirmed by Myriad testing. There were 2 further patients for whom Myriad CDx could not be performed and 1 patient randomized based upon Myriad CLIA test that was not confirmed with the Myriad CDx. Therefore, these 9 patients were excluded by the Sponsor from analyses using the “confirmed by Myriad gBRCA test” set. They are included in ITT analyses.

There were inconsistencies between IVRS and investigator reported stratification variables in the eCRF shown in Figure 3. In stratification of response to last platinum treatment prior to study entry, a total of 44 patients had IVRS misclassification. In the stratification of time to disease progression prior to study entry, 19 patients had an IVRS misclassification. Following an information request (IR), the sponsor performed a sensitivity analysis using eCRF stratification variables. We confirmed this analysis and discuss in the section on FDA sensitivity analyses.

Figure 3 SOLO2 Baseline tumor measurements by INV vs. IVRS response to last chemotherapy



	CR			PR			Total
IVRS response to prior chemotherapy	138			157			295
Tumor lesions by INV at baseline	TL	NT	NED	TL	NT	NED	
	13	11	114	95	49	13	295

TL = Target Lesions; NT = Non Target Lesions; NED = No Evidence of Disease

Non Target Lesions = 11 + 49 = 60

NED = 114 + 13 = 127

No baseline tumor measurements by Investigator = NT + NED
= 60 + 127
= 187

Source: Sponsor Teleconference presentation 5/25/17.

Study 19

The baseline disease characteristics for the ITT population of Study 19 are shown in Table 19.

Table 19 Study 19 Baseline disease characteristics ITT

	Olaparib N= 136 (%)	Placebo N= 129 (%)
Primary tumor		
Ovary	119 (88)	109 (84)
Fallopian tube	3 (2)	3 (3)
Primary peritoneal	14 (10)	16 (12)
Other	0	1 (1)
FIGO Stage at original diagnosis		
Stage I (IB or IC)	3 (2)	4 (3)
Stage II (II, IIA, IIB, IIC)	11 (8)	8 (6)
Stage III	10 (7)	7 (5)
Stage IIIA	4 (3)	3 (3)
Stage IIIB	8 (6)	12 (9)
Stage IIIC	81 (60)	76 (59)
Stage IV	17 (13)	17 (13)
Unknown	2 (1)	2 (2)
Tumor grade at diagnosis		
Grade 2 (moderately differentiated)	36 (26)	34 (26)
Grade 3 (poorly differentiated)	97 (71)	89 (69)
Grade 4 (undifferentiated)	2 (2)	4 (3)
Grade X (unassessable)	1 (1)	2 (2)
Prior Bevacizumab		
Yes	8 (6)	7 (5)
No	128 (94)	122 (95)
Objective Response to last platinum		
CR	57 (42)	63 (49)
PR	79 (58)	66 (51)
Interval from penultimate platinum to progression		
6-12 mos	53 (39)	54 (42)
> 12 mos	83 (61)	75 (58)
Mutation status		
gBRCA mutation (any)	53 (39)	43 (33)
BRCA1	40 (29)	30 (23)
BRCA2	13 (10)	13 (10)

A summary of the number of prior lines of chemotherapy and platinum-containing regimens received prior to patient enrollment on SOLO2 is shown in Table 20, and a summary for Study 19 is shown in Table 21. There was no notable difference between the specific numbers for prior chemotherapy, in general, compared with prior platinum regimens, so the two were summarized together. The most common specific agents received by patients enrolled on SOLO2 are shown in, and are consistent with agents typically used to treat patients with recurrent ovarian cancer.

Table 20 SOLO2 Number of prior chemotherapy regimens

	Olaparib N=196	Placebo N=99
Number of prior chemotherapy (including platinum) regimens		
Median	2	2
Range	2, 7	2, 12

Table 21 Study 19 Number of prior chemotherapy regimens

	Olaparib N=136	Placebo N=129
Number of prior chemotherapy regimens		
Median	3	3
Range	2, 11	2, 8
Number of prior platinum regimens		
Median	2	2
Range	2, 7	2, 8

On Study 19, only 8 patients on olaparib (0.6%) and 7 (0.5%) on placebo had received prior bevacizumab therapy. This is markedly lower than the number of patients on SOLO2 (Table 22) who received bevacizumab previously, and reflects the changing standard since the conduct of Study 19, where more patients with ovarian cancer are receiving bevacizumab therapy earlier than in the course of their disease than they were previously (at the time that Study 19 was initiated).

Table 22 Previous chemotherapy agents received SOLO2

	Olaparib N=196 (%)	Placebo N=99 (%)
Paclitaxel	191 (97)	96 (97)
Doxorubicin (including liposomal)*	93 (47)	53 (54)
Cisplatin	62 (32)	22 (22)
Gemcitabine (includes gemcitabine hydrochloride)	61 (31)	29 (29)
Bevacizumab	33 (17)	20 (20)

*Includes Adriamycin, doxorubicin, Doxil, Caelyx, liposomal doxorubicin, pegylated doxorubicin.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance

Olaparib therapy is administered orally, on a daily basis, making treatment compliance potentially difficult to assess. The FDA assessment of dose intensity on SOLO2 is shown in Table 23. The FDA analysis differs from the Sponsor because the FDA included periods of dose interruption (daily dose

equal to 0 mg) in calculating the mean dose intensity, while the Sponsor excluded periods of interruption in their calculation, inflating the perceived mean daily dose. As a result, the numbers reported in the table are lower than are shown in the Sponsor study report.

Table 23 SOLO2 Treatment compliance by dose intensity

	Olaparib 300 mg BID (600 mg daily)	Placebo 300 mg BID (600 mg daily)
Median dose intensity mg/d (range)	590 (41-600)	596 (300-600)
Mean dose intensity mg/d	542	582

The estimated treatment compliance in the Study 19 was reviewed previously but excluded days of dose interruption. Given that the current application deals with the tablet formulation, which involves patients needing to take far fewer tablets than with the capsule formulation, compliance with the capsule formulation on Study 19 will not be described here.

Concomitant medications

Overall, the use of disallowed concomitant medications during SOLO2 was low. Six patients were documented to have received disallowed medications while taking olaparib/ placebo while on-study. This included 4 patients (2%) on olaparib and 1 (1%) on placebo who took clarithromycin. There was also 1 (0.5%) patient in the olaparib group who received anastrozole while taking olaparib. The use of these medications in these patients is unlikely to have impacted the study results for SOLO2.

Similar to SOLO2, the use of disallowed concomitant medications during the course of Study 19 was also low. It included 2 olaparib patients receiving clarithromycin, 1 olaparib patient receiving ketoconazole, and 1 placebo patient receiving rifampin. No patients received any contraindicated anticancer therapies while on Study 19.

Efficacy Results

The efficacy results from SOLO2 will be presented first, followed by the results for Study 19.

Primary Endpoint- SOLO2

From August 6, 2013 to the data-cut-off (DCO) date of September 19, 2016, the trial accrued and randomized 295 patients. A total of 187 (63.4%) patients were deemed to have progressed by investigator by the DCO date.

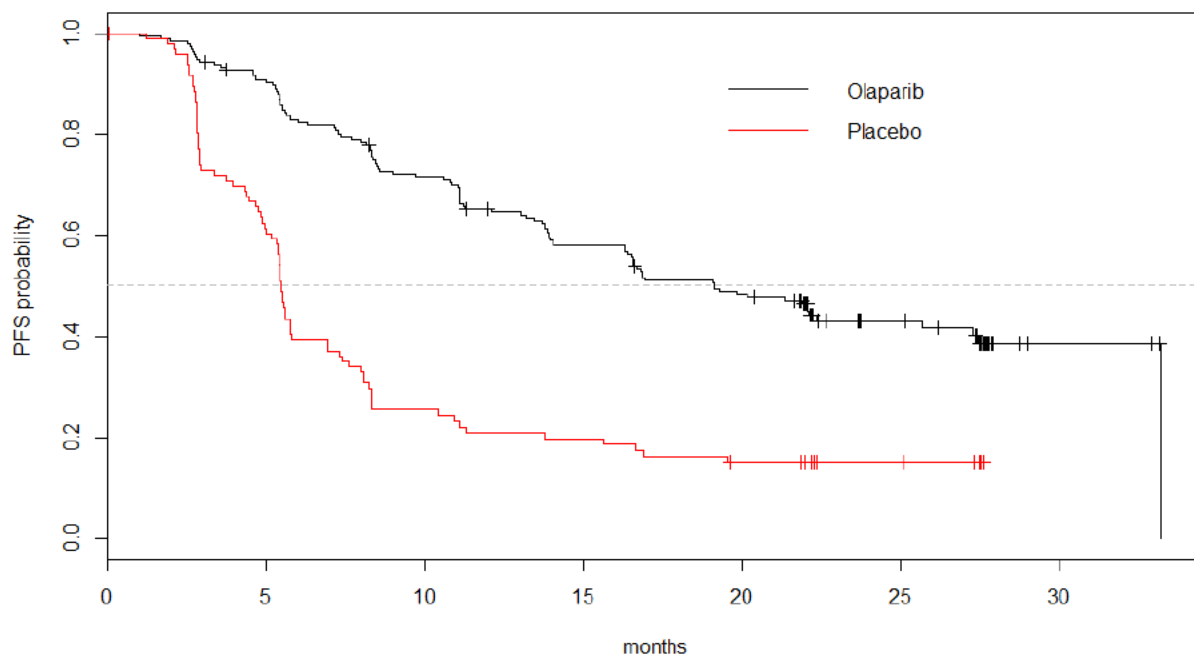
Efficacy results shown in Table 24 indicate a PFS-Inv advantage in median PFS of 13.6 months on the olaparib arm which corresponds to a 70% risk reduction. The p-value from the stratified log-rank test yielded a p-value < 0.0001 indicating the difference in PFS distributions was statistically significant. The

PFS advantage of olaparib is illustrated in Figure 4. The separation in the Kaplan-Meier curves between the arms occurs by the third month and is maintained to 20 months from randomization.

Table 24 SOLO2 Primary PFS efficacy results

	Olaparib (N=196)	Placebo (N=99)	All
PFS-Inv Results			
PD	107	80	187
%PD	54.6	80.8	63.4
Median months (95% CI)	19.1 (16.3, 27.2)	5.5 (5.3, 6.9)	
HR (95% CI)	0.30 (0.22, 0.41)		
p-value	<0.0001		

Figure 4 SOLO2 Kaplan-Meier survival curves for Primary Endpoint PFS-Inv



SOLO-2 Secondary and other relevant endpoints

PFS2:

The number of PFS2 events at the DCO date was 150. The estimated median time to the second progression event was not reached on the olaparib arm and was 18.4 months on the placebo arm. The estimated hazard ratio and p-value from the stratified log-rank test shown in Table 25 indicate a significant reduction in risk to the second progression in the olaparib arm.

Reviewer comment: If a patient had not had a second progression or death they were censored at the latest of the PFS-Inv or PFS2 assessment date. Patients who had not progressed and were censored (PFS-Inv) at last follow-up were PFS2-censored, so were patients who had progressed (PFS-Inv) but had not experienced a second progression event. Consequently, the PFS2 analysis does not differentiate between observations censored without progression and those censored after first progression. In addition, the magnitude of the PFS2 effect is difficult to interpret as the analysis does not account for the effect of other post-progression therapies. In addition, the method of assessment of PFS2 was not constant; scan intervals as well as progression type (clinical/radiologic/CA-125 elevation) depended on local clinical practice.

OS:

The number of OS events at the DCO was 72. The estimated median survival on both arms was not reached. The p-value from the stratified log-rank test exceeded the allocated alpha of 0.0001, and as a result, efficacy with respect to OS could not be claimed. Further analysis will be performed with 60% deaths.

ORR:

The response rates, estimated as the proportion of complete and partial responses, were 19.4% and 9.1% in the olaparib and placebo arms, respectively. Response was not confirmed. The median duration of response on the olaparib arm was 13.6 months, 8 months longer than the duration in the placebo arm.

Reviewer comment: No alpha was allocated to the analysis of response rate, so this analysis is considered as exploratory.

Table 25 SOLO2 Summary results for OS, PFS2, ORR

	Olaparib (n=196)	Placebo (n=99)
PFS2		
Number of events: total number of patients (%)	70/196 (35.7%)	80/99
Median, months	NR	18.4
Hazard ratio (95% CI)	0.50 (0.34, 0.72)	
p-value	0.0004 (two-sided)	
OS		
Number of events: number of patients in arm (%)	45/196 (23.0%)	27/99 (27.3%)
Median, months	NR	NR
Hazard ratio (95% CI)	0.80 (0.50, 1.29)	
p-value	0.86 (two-sided)	
Overall Response		
Response (CR+PR)	38 (17+21)	9 (5+4)
Response rate	19.4%	9.1%
Duration of Response		
Median in months* (Range)	13.6 (0+, 30.0+)	5.6 (2.8, 24.7+)

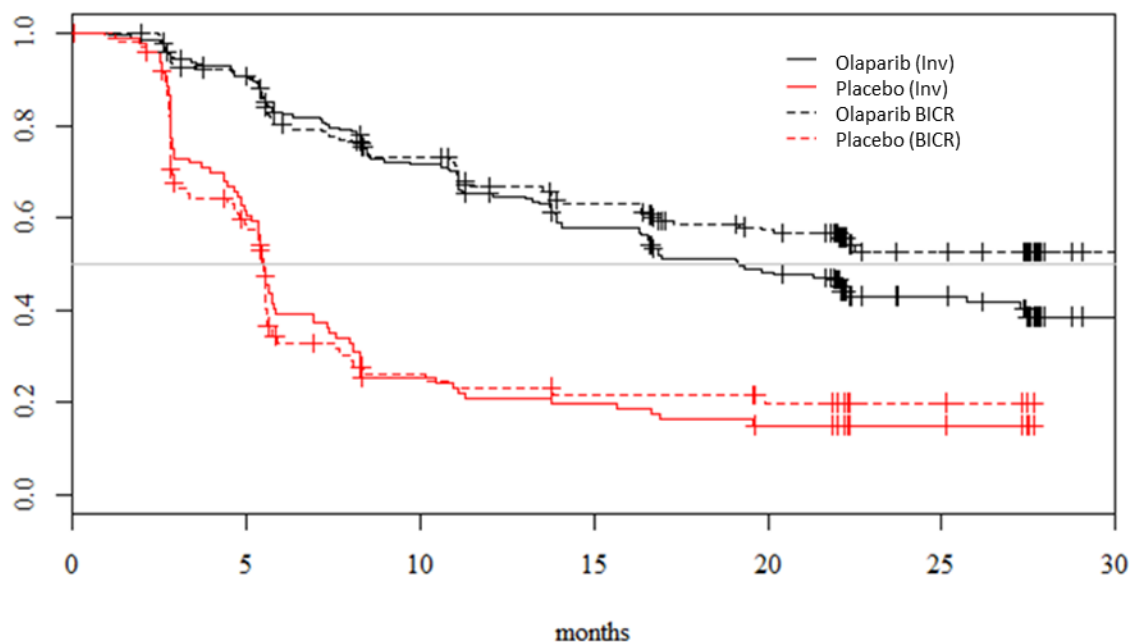
*Median from Kaplan-Meier curves, '+' denotes censored value

SOLO-2 Additional Analyses Conducted on the Individual Trial

Analysis of BICR Assessed PFS

Analysis of the BICR assessed PFS was to be used as both a supportive and a sensitivity analysis. The number of patients who were deemed to have progressed or died following BICR assessment was 151, with 81 on the olaparib arm and 70 on the placebo arm. The results of BICR analysis indicate a 75% risk reduction in the olaparib arm (HR 0.25, 95% CI: 0.18, 0.35). The p-value from the log-rank test was < 0.0001. See Figure 5.

Figure 5: SOLO2 Kaplan Meier Survival Curve for Comparison of PFS by INV and BICR



Reviewer Comment: Although the PFS-BICR results could be considered as supportive evidence of olaparib efficacy, when taken together with the primary PFS-Inv results, the 24.7 median PFS advantage on olaparib (30.2 months median PFS on the olaparib arm versus 5.5 months median PFS on the placebo arm) is not robust due to informative censoring (see Section 7.2.2.1). As a result, the PFS-BICR median advantage of olaparib was determined to be unreliable by the statistical and clinical review team.

Concordance between BICR and investigator assessment is summarized in

Table 26. There was agreement between BICR and investigator on the progression status of 249 (84.4%) patients. Prior to amendment 3, scans of patients were sent for central review on an ongoing basis. The review of a patient's scan by BICR was not initiated until they were deemed to have progressed by the investigator. Following amendment 3, sites stopped forwarding scans of patients who progressed (investigator) for central review. Following data cut-off, all scans of patients who had not progressed were sent for central review.

Reviewer comment: Given the methods for reporting and censoring by BICR, censoring of 41 patients deemed to have progressed by investigator is likely due to informative censoring. We conducted sensitivity analyses to assess the effect of informative censoring on the BICR assessments. Refer to the section on sensitivity analyses.

Version date: February 1, 2016 for initial rollout (NME/original BLA reviews)

Table 26 Concordance between investigator and central reviews

	Olaparib (N=196)	Placebo (N=99)	
PD on both	80 (40.8)	66 (66.7)	
Censored on both	88 (44.9)	15 (15.2)	
PD only by Investigator	27 (13.8)	14 (14.1)	
PD only by BICR	1 (0.5)	4 (4.0)	
			Difference
Early discrepancy rate	30.8%	17.3%	13.6%
Late discrepancy rate	51.5%	65.9%	-14.4%

Sensitivity Analyses to assess BICR/Investigator results prior to primary endpoint change

In addition to the analysis of BICR assessed PFS, the sponsor performed sensitivity analyses to assess the evaluation time bias and attrition bias. Assessment of impact of evaluation time bias involved assigning the progression date to the mid-point of the time between the detection date and the prior scan's date. Assessment of impact of attrition bias analysis involved assigning progression date to the scan date for patients who progressed following two or more missed scans. The estimated hazard ratio for impact of evaluation time bias was 0.30 (95% CI: 0.23, 0.41), while the estimated hazard ratio for impact of attrition bias was 0.28 (95% CI: 0.18, 0.38). Both analyses support the primary efficacy results.

Sensitivity analysis to assess efficacy results prior to change of endpoint

FDA initiated analysis to compare the PFS-BICR and PFS-Inv results prior to Amendment 3. By April 12, 2016, there were 143 BICR events, the estimated HR = 0.24 (95% CI: 0.35, 0.17) was evidence of olaparib efficacy. The number of investigator assessed events was 166, and the estimated HR = 0.26 (95% CI: 0.36, 0.19) suggests parity between BICR and investigator assessed results prior to the amendment.

Sensitivity analysis to assess effect of informative censoring in BICR

The results of a sensitivity analysis to assess the effect of informative censoring in the BICR assessment are shown in Table 27. Of 41 patients who had progressed based on investigator but were deemed to be censored by BICR, we re-analyzed BICR results after assuming

- (a) The 41 patients progressed at their next scheduled assessment
- (b) The 14 patients on the placebo arm were censored and the 27 patients on the olaparib arm progressed at their next scheduled assessment

In analysis (a), all 41 patients have worse PFS-BICR times compared to the PFS-BICR times in the primary analysis. In analysis (b), only the patients in the olaparib arm have worse PFS-BICR compared to the PFS-BICR times in the primary analysis. The results from both analyses indicate a survival advantage on the olaparib arm and also indicate a reduction in the BICR assessed median PFS of patients of the olaparib arm. This change in the median PFS is evidence of informative censoring having an effect on the BICR results.

Table 27 SOLO2- Sensitivity analysis of PFS-BICR results to assess informative censoring in BICR assessment

Analysis	Olaparib #PD	Placebo #PD	Olaparib Median	Placebo Median	HR 95% CI
2(a)	108	84	19.6	5.5	0.27 (0.20, 0.36)
2(b)	108	70	19.6	5.5	0.31 (0.22, 0.42)

Sensitivity analysis to assess the effect of changing scan windows

We conducted the following sensitivity analysis to examine the robustness of the results following the change in scan interval 72 weeks after randomization.

1. Censored at week 72 for events that occurred after 72 weeks from randomization.
2. Censored at weeks 72 for events that occurred after 72 weeks only in the placebo arm. This analysis favors the placebo arm.
3. Assign progression dates to the earlier scan for events that occurred 72 weeks after randomization.
4. Assign progression dates to the earlier scan if the event occurred 72 weeks after randomization on the olaparib arm. This analysis favors the placebo arm.

The results are shown in Table 28. A total of 23 patients in the olaparib arm progressed after 72 weeks from randomization. Only 3 patients in the placebo arm progressed 72 weeks from randomization. The HRs from all of the analyses support the primary results and indicate a PFS advantage in the olaparib arm.

Table 28 SOLO2- Results of analyses to assess effect of changing scan windows

Sensitivity Analysis	Treatment	PD	Censored	%Cens	Median (months)	HR	95% CI	
1	Olaparib	84	112	57.14	NR	0.27	0.20	0.37
	Placebo	77	22	22.22	5.49			
2	Olaparib	107	89	45.41	19.14	0.32	0.23	0.43
	Placebo	77	22	22.22	5.49			
3	Olaparib	107	89	45.41	16.32	0.30	0.22	0.40
	Placebo	80	19	19.19	5.49			
4	Olaparib	107	89	45.41	16.32	0.31	0.23	0.42
	Placebo	80	19	19.19	5.49			

Sensitivity analysis to assess the effect of eCRF Stratification variables

We confirmed the sponsor's sensitivity analysis using stratification variables from the eCRF. The estimated HR of 0.29 (95% CI: 0.22, 0.40) with median survival of 19.1 and 5.5 months on the olaparib and placebo arms, respectively, are supportive of primary results.

We performed an additional analysis where we used eCRF stratification and excluded patients misclassified by IVRS. Data from 237 patients yielded a HR of 0.31 (95% CI: 0.22, 0.43), with medians of 19.1 and 5.5 months on the olaparib and placebo arms, respectively. These results offer no evidence of an effect of IVRS misclassification on the primary efficacy results.

Subgroup Analyses for SOLO2

Subgroup analyses were conducted comparing PFS between treatments to assess consistency across potential prognostic factors. In the protocol, the following subgroups of the full analysis set (FAS) were also to be analyzed as part of the PFS analysis:

- Response to last platinum chemotherapy (CR or PR)
- Time to disease progression in the penultimate platinum based chemotherapy prior to enrollment (> 6 -12 months or > 12 months)
- gBRCAm status confirmed by Myriad BRACAnalysis CDx® test or gBRCA wild type or gBRCA variant of uncertain significance (VUS) or missing by Myriad BRACAnalysis CDx® test (some patients unable to be tested using the Myriad BRACAnalysis CDx® test due to sample availability. Additionally, some mutations identified at screening were unable to be confirmed by the BRACAnalysis CDx® test)
- Mutations observed in SOLO2 that were not reported in the previously approved companion diagnostic submission (novel mutation subgroup)

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- ECOG performance status at baseline (normal or restricted activity)
- Prior cytoreductive surgery for most recent progression (Y or N)
- Lines of prior platinum (2, 3, or 4+)
- Baseline CA-125 value ($\leq$ ULN or $>$ ULN)
- BRCA mutation type (BRCA1, BRCA2, or both)
- Age at randomization (< 65 or ≥ 65 y)
- Prior use of bevacizumab (Y or N)
- Region 1 (North America or Rest of World)
- Region 2 (Brazil, Poland, Russia, Japan, Korea or Rest of World)
- Race (white, black/ African American or Asian or Native Hawaiian/ Pacific Islander or American Indian/ Alaska Native or Other)

Table 29 gives the results of subgroup analyses of a subset of factors which include: the stratification factors, age, number of prior lines of platinum therapy, race and region. The results indicate a risk reduction in the olaparib arm of at least 50%. In addition, the upper limit of all the HR confidence limits (except one) is less than 1 which is evidence of lower risk of progression in the olaparib group.

Reviewer comment: There was no alpha allocated to any of the subgroup analyses, so these analyses are therefore considered exploratory.

Table 29 SOLO2 PFS (Investigator assessed subgroup analyses)

Variable	Group	Olaparib			Placebo			HR		
		N	PD	%PD	N	PD	%PD	Estimate	95% CI	
Tim to PD from	>12 mnth	117	51	43.6%	59	42	71.2%	0.32	0.21	0.49
	6 - 12 mnt	79	56	70.9%	40	38	95.0%	0.30	0.19	0.46
Resp to last plat.	CR	91	34	37.4%	47	35	74.5%	0.27	0.16	0.43
	PR	105	73	69.5%	52	45	86.5%	0.37	0.25	0.54
Age	<65	156	83	53.2%	77	62	80.5%	0.31	0.22	0.43
	>=65	40	24	60.0%	22	18	81.8%	0.44	0.24	0.83
Prior plat. lines	2	110	57	51.8%	62	44	71.0%	0.39	0.26	0.58
	3	60	34	56.7%	20	19	95.0%	0.23	0.13	0.41
	4+	25	16	64.0%	17	17	100.0%	0.22	0.10	0.48
Prior bev.	N	163	89	54.6%	79	61	77.2%	0.39	0.28	0.55
	Y	33	18	54.5%	20	19	95.0%	0.10	0.04	0.25
BRCA	BRCA1	134	74	55.2%	61	51	83.6%	0.30	0.21	0.44
	BRCA2	59	31	52.5%	35	27	77.1%	0.37	0.22	0.62
Race	ASIAN	22	11	50.0%	7	6	85.7%	0.26	0.09	0.72
	WHITE	173	95	54.9%	91	73	80.2%	0.35	0.25	0.47
Region	N. Amer	36	23	63.9%	13	10	76.9%	0.35	0.16	0.76
	ROW	160	84	52.5%	86	70	81.4%	0.33	0.24	0.46
ECOG	Normal	162	89	54.9%	77	64	83.1%	0.29	0.21	0.40
	Restricted	32	17	53.1%	22	16	72.7%	0.53	0.27	1.05

SOLO2 Review of Patient-Reported Outcomes

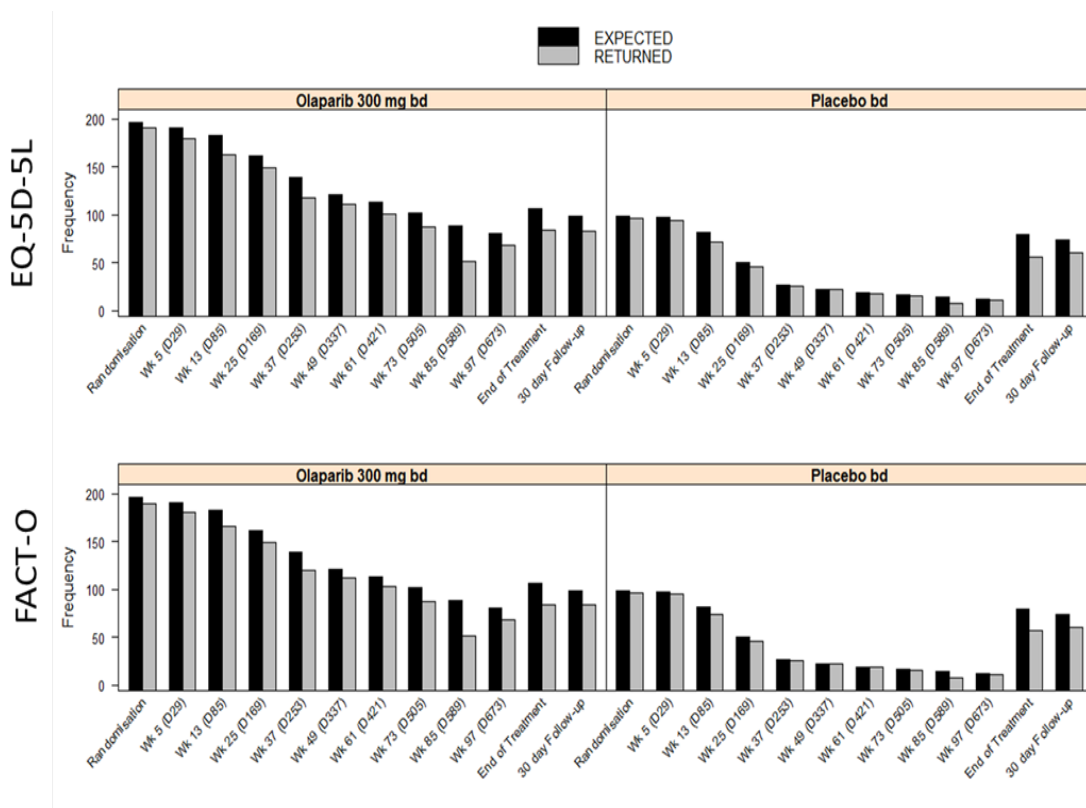
Patient reported outcomes were evaluated by two instruments, the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) and the EuroQoL Five Dimension, Five Level health state utility index (EQ-5D-5L). The FACT-O questionnaire (Given in Appendix 6) is composed of the following subscales: physical, social/family, emotional, and functional well-being as well as the “additional concerns” scales, which consists of specific ovarian cancer symptoms. The total FACT-O score was calculated from the individual subscale scores with scores derived from the FACT-O scoring manual. The health-related quality of life analysis endpoint from the FACT-O questionnaire was assessed by the Trial Outcome Index (TOI). TOI is composed of the sum of the scores from the FACT-O scales: physical well-being, functional well-being and "additional concerns".

The EQ-5D-5L index (See Appendix 6) comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on the evaluation day from five possible options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems). Each unique EQ-5D health state is assigned a five digit code allowing for a total of 3125 health states. These codes are then converted into a weighted health state index (WHSI) by applying scores from EQ5D value sets elicited from general population samples (the base case in this application was the UK valuation set, other country value sets were applied in scenario analyses).

Questionnaires were administered at baseline, at Day 29, then every 12 weeks (+/- 7 days), or 24 weeks (after 72 weeks) until objective radiological disease progression or data-cutoff, whichever occurred first. Following amendment 2 of the protocol, HRQOL questionnaires were to be administered post-progression. Quality of Life questionnaire were also to be administered at the discontinuation of study treatment visit and then 30 days post last dose.

Figure 6 shows the frequencies of the returned questionnaires by visit. The figure also includes a table of the completion rates (returned/expected) within the first 37 weeks of treatment. Unscheduled visits were excluded in this analysis. Completion rates within each arm were approximately more that 85%.

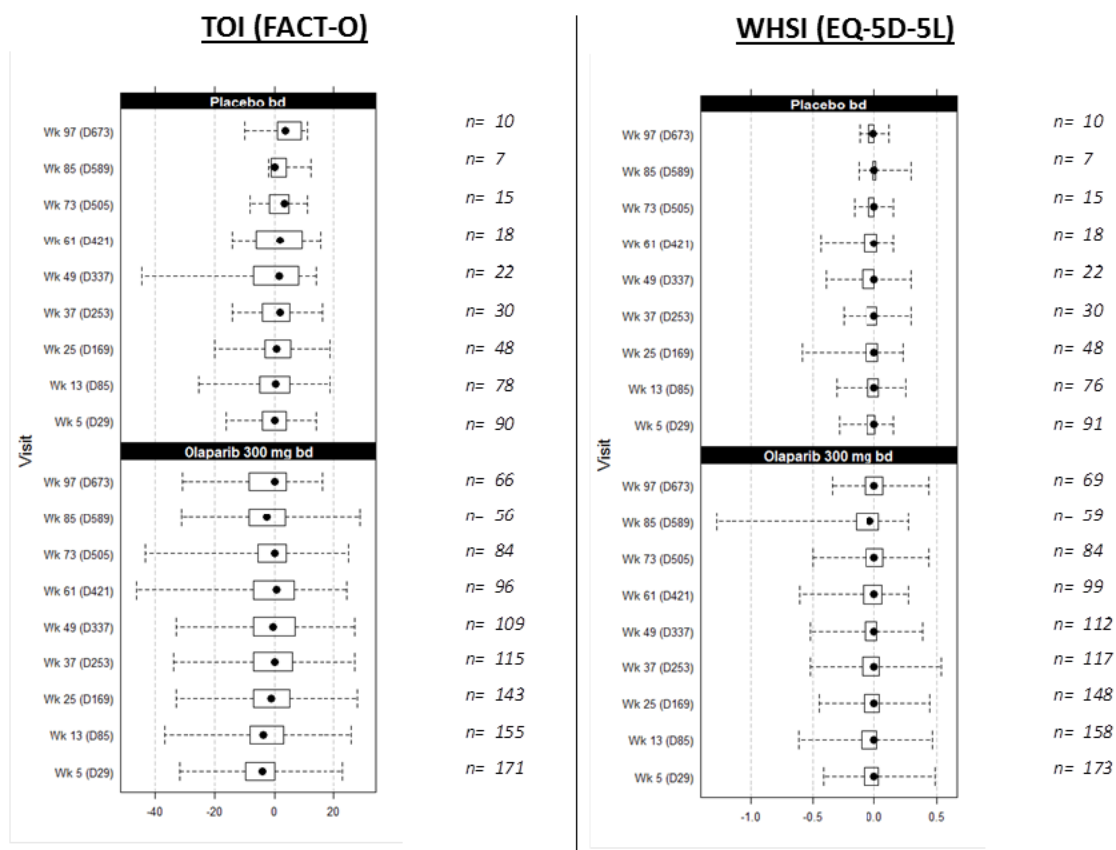
Figure 6: Frequencies of returned questionnaires for SOLO2



Olaparib				Placebo			
Visit	Expected	Completion Rates		Visit	Expected	Completion Rates	
		FACT-O	EQ-5D-5L			FACT-O	EQ-5D-5L
Baseline	196	96.9%	97.4%	Baseline	99	97.0%	98.0%
Wk 5	191	94.8%	93.7%	Wk 5	98	96.9%	95.9%
wk 13	183	90.7%	89.1%	wk 13	82	90.2%	87.8%
Wk 25	162	92.0%	92.0%	Wk 25	50	92.0%	92.0%
Wk 37	139	86.3%	84.9%	Wk 37	27	96.3%	96.3%

The boxplots in Figure 7 summarize the medians, quartiles (first and third) and range of the change from baseline of the Trial Outcome Index (TOI-DIFF) and the WHSI. An increase in the TOI score indicates worsening physical and functional outcomes and is reflected by positive values in TOI-DIFF. The lower the WHSI the better a patient's overall quality of life, a negative value in Figure 7 indicates a better quality of life compared to baseline. The summary statistics in Figure 7 offer no strong evidence of any compelling and consistent changes in patients' quality of life from baseline scores in subsequent visits, regardless of treatment.

Figure 7 Boxplots of change from baseline of TOI with five number summaries



Reviewer comment: In the figure, this analysis includes only patients on treatment, with questionnaires administered at scheduled visits.

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The proposed model for analysis of TOI-DIFF was a mixed model for repeated measures (MMRM) with TOI-DIFF as the response and the following covariates: treatment, visit, treatment by visit interaction, baseline TOI score, and baseline TOI score by visit interaction. Patients were included as a random effect by allowing for correlated TOI-DIFF across patients' visits. Only data up to and including week 37 was used (excluding visits with >75% of ITT missing data per arm). The results are given in Table 30. The negative values in adjusted mean change from baseline for olaparib and in the treatment difference indicate an observed improvement in TOI from baseline.

Table 30: Least squares means estimates of TOI change from baseline

	Olaparib N=196	Placebo N=99
N	185	94
Adjusted mean	-2.64	0.19
Standard error	0.56	0.84
95% CI	(-3.74, -1.53)	(1.47, 1.84)
Estimated difference	-2.82	
95% CI for difference	(-4.81, -0.83)	

Table 31 shows the adjusted mean TOI-DIFF estimates by visit from the MMRM model. A negative value in adjusted mean indicates an improvement in TOI from baseline. The results suggest that the initial improvement in QOL in the olaparib arm relative to placebo disappears after week 13.

Reviewer comment: No multiplicity adjustments were made. These analyses are considered exploratory. We have the following concerns about the MMRM model used. Model assumptions such as the linear relationship between the response and the covariates or the correlation structure indicating the dependence of TOI-DIFF across a patient's visits were not justified. In addition, the model assumes constant variation in TOI-DIFF, but evidence from Figure 17 invalidates this assumption.

Table 31: Least squares means estimates of TOI change from baseline by study visit

		Olaparib	Placebo
N	Wk 5 (D29)	171	90
Adjusted mean		-4.87	0.6
Standard error		0.587	0.811
95% CI		-6.021, -3.711	-0.993, 2.200
Estimated difference		-5.47	
95% CI for difference		-7.440, -3.498	
N	Wk 13 (D85)	155	78
Adjusted mean		-3	1.07
Standard error		0.643	0.906
95% CI		-4.269, -1.737	-0.715, 2.855
Estimated difference		-4.07	
95% CI for difference		-6.261, -1.885	
N	Wk 25 (D169)	143	48
Adjusted mean		-1.63	-0.49
Standard error		0.777	1.254
95% CI		-3.165, -0.103	-2.965, 1.977
Estimated difference		-1.14	
95% CI for difference		-4.046, 1.766	
N	Wk 37 (D253)	115	30
Adjusted mean		-1.05	-0.44
Standard error		0.773	1.347
95% CI		-2.573, 0.476	-3.094, 2.218
Estimated difference		-0.61	
95% CI for difference		-3.674, 2.454	

Study 19- Primary Analysis

The data cut-off date for the PFS analysis was 06/30/10. At that time, 153 total events had occurred. The events included 1 death in the absence of RECIST PD on the olaparib arm, with the remainder being progression events by RECIST criteria. The results are shown in Table 32.

Table 32 PFS results Study 19 (ITT population- Investigator Assessment)

	Olaparib (N=136)	Placebo (N=129)
Median PFS in months (95% CI)	8.4 (7.4, 11.5)	4.8 (4.0, 5.5)
Hazard Ratio (95% CI)	0.35 (0.25, 0.49)	
p-value (Cox proportional hazards) ¹	<0.00001	

¹ The analysis was performed using a Cox proportional hazards model with factors for treatment (olaparib vs. placebo), time to disease progression (>6-12 months and > 12 months, in the penultimate platinum therapy prior to enrollment), objective response (CR or PR, in the last platinum therapy prior to enrollment), and Jewish descent (yes or no).

The PFS results in the ITT population for Study 19 were statistically significant, as shown in Table 32.

Reviewer comment: In Study 19, the HR of 0.35 (95% CI: 0.25, 0.49) in the ITT population was significant and suggests a clinically meaningful treatment effect. The observed difference in median PFS was 3.6 months, but the magnitude of this difference only examines one aspect of the PFS distributions. The HR incorporates information from the entire PFS distribution and is a more reliable indicator of the significance of the treatment effect. Nevertheless, the 3.6 month difference in median PFS and HR of 0.35 are similar to the results from the SOLO2 trial and are in keeping with the HRs of recent approvals in this space, including bevacizumab and niraparib.

Study 19 Secondary and other relevant endpoints

OS:

The number of deaths in the final OS analysis for Study 19 was 210, with 98 deaths on the olaparib arm and 112 deaths on the placebo arm. The OS distributions were not significantly different, after adjusting for multiplicity, because the p-value from the stratified log-rank test exceeded the pre-specified boundary. The estimated HR of 0.73 (95% CI: 0.55, 0.95), but this CI is not adjusted for multiplicity so no claim of statistical significance can be made based on it. The median survival estimated from the Kaplan-Meier probabilities was 29.9 months and 27.8 months in the olaparib and placebo arms, respectively.

Study 19 Additional Analyses Conducted on the Individual Trial

Subgroup Analyses Study 19

In addition, as has been previously noted, the original proposed indication under NDA 206162 was for olaparib as a maintenance treatment for patients with platinum-sensitive relapsed ovarian cancer with gBRCA mutation who were in response to platinum-based therapy. The proposal stemmed from a pre-specified analysis of the retrospectively identified subgroup of 96 patients with gBRCAm ovarian cancer who were enrolled onto Study 19. This analysis of Study 19 was the subject of an Oncologic Drugs Advisory Committee (ODAC) meeting which occurred on June 25, 2014. During that meeting, the committee considered the statistical pitfalls associated with the retrospective identification of the gBRCAm subgroup that the Sponsor conducted, including that it led to loss of randomization for patients in this subgroup. The committee also expressed that the way in which the gBRCAm subgroup from Study 19 was analyzed made it impossible to estimate the true treatment effect of olaparib in these patients, and they were concerned whether the results would be reproducible in a larger trial. The Committee voted 11-2 that the safety and efficacy data from Study 19 in the gBRCAm population were insufficient to support an accelerated approval at that time, and recommended that the FDA await the results of the SOLO2 study to consider approval in the maintenance setting. Also refer to the ODAC Section 8 of the multireview. The breakdown of the 96 patients by study arm is shown in Table 33 and the Forest Plot is shown in Figure 8.

Table 33 Study 19 BRCA status

	Olaparib (N=136)	Placebo (N=129)
gBRCA (Rand) ¹	24%	22%
wtBRCA (Rand)	13%	16%
gBRCA (retro) ²	15%	12%
wtBRCA (retro)	24%	34%
gBRCA (CRF+retro)³	N=53	N=43
	39%	33%

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wtBRCA (CRF+retro)	37%	50%
tBRCA ⁴	6%	8%

¹ BRCA mutation status known at the time of randomization

² Retrospectively identified BRCA mutation status

³ Total number of patients with identified gBRCA deleterious mutation

⁴ Total number of patients with confirmed germline wtBRCA but with somatic BRCA mutations as detected by a different platform.

Subgroups by BRCA status are presented in Table 34.

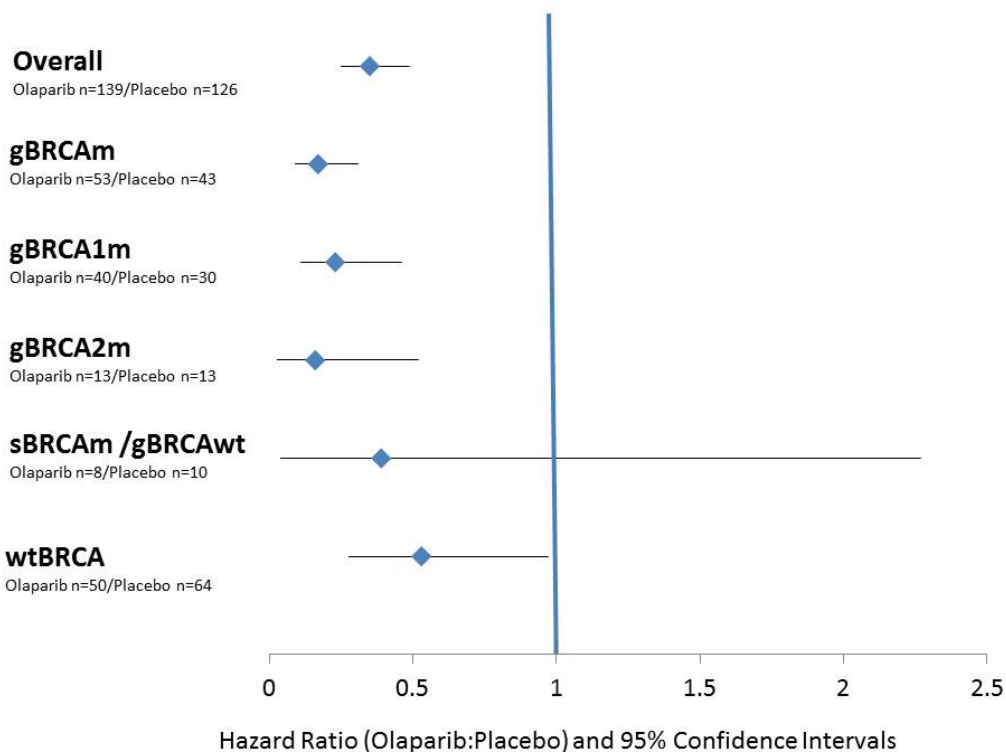
Table 34 Study 19 PFS analysis in the gBRCA subpopulations

	gBRCAm		gBRCAwt		gBRCA unk/missing	
	Olaparib N=53	Placebo N=43	Olaparib N= 50	Placebo N=64	Olaparib N=33	Placebo N=22
Median PFS in months (95% CI)	11.2 (8.4, NA*)	4.1 (2.8, 5.1)	8.3 (5.5, NA)	5.5 (3.7, 5.9)	7.4 (5.3, 12.4)	4.5 (2.7, 5.3)
HR (95% CI)	0.17 (0.09, 0.32)		0.51 (0.30, 0.84)		0.43 0.21, 0.86)	

*NA= Not estimable

Reviewer Comment: The real treatment effect of olaparib, in terms of PFS, could not be reliably ascertained in the gBRCA subgroups due to the retrospective nature of identification of these populations and suggestion of non-proportional hazards. This analysis is considered exploratory.

Figure 8 Study 19 Forest Plot of PFS Hazard Ratios by Subgroup



Analysis of patients who remain on olaparib for extended time

The review team analyzed by subgroup and by arm the time patients remained on therapy as another way to support potential clinical benefit. These results are shown in Table 35.

Table 35 Time on Treatment by Subgroup- Study 19

Time on treatment	gBRCAm n=96		gBRCAwt/VUS n=114		gBRCA unknown n=54	
	olaparib n=53 (%)	placebo n=43 (%)	olaparib n=50 (%)	placebo n=64 (%)	olaparib n=33 (%)	placebo n=21 (%)
≥ 3 years	11 (21)	2 (5)	7 (14)	0	6 (18)	1 (5)
≥ 4 years	7 (13)	1 (2)	7 (14)	0	6 (18)	0
≥ 5 years	6 (11)	1 (2)	6 (12)	0	6 (18)	0
≥ 6 years	5 (9)	1 (2)	5 (10)	0	5 (15)	0

Source: ADSL dataset NDA 208558

Reviewer comment: Taking all the subgroup and exploratory analyses together, the true magnitude of olaparib effect cannot be precisely estimated for patients who were gBRCAwt or gBRCA VUS, based upon the results from Study 19. Although the exact magnitude cannot be estimated from the results of Study 19, the fact that the HR for this subgroup was still 0.5, we are reassured that there is unlikely to be a detrimental effect in utilizing olaparib as maintenance therapy, even in patients with gBRCA wt or gBRCA VUS. It is also apparent that a percentage of patients with BRCAwt status did benefit from olaparib—likely due to aberrations in homologous recombination repair pathway proteins, and would be withheld from receiving therapy and potential benefit if the approval were restricted to the gBRCAm population. Also it would not be appropriate to separate out a subgroup from an overall positive trial unless there was a clear detrimental effect in that subgroup. Even in the BRCAwt group there are long term non-progressors which is distinct from patients on the placebo arm.

In order to provide a more precise estimate of the treatment effect of olaparib in patients with gBRCAwt, a prospectively designed trial enrolling patients known to be gBRCAwt was agreed to in order to evaluate the influence of mutations in the homologous recombination repair pathway on response to olaparib. As a result, one of the post-marketing commitments associated with the approval of this application will be to conduct a single-arm study of olaparib maintenance therapy in patients with platinum-sensitive relapsed non-germline BRCA mutation ovarian cancer who are in response to platinum-based chemotherapy (OPINION trial).

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Primary Endpoints

The primary endpoint in both SOLO2 and Study 19 was PFS. As has been noted, the SOLO2 study enrolled only patients with a documented gBRCA mutation, where this was not a prerequisite for inclusion into Study 19. As a result, Study 19 enrolled appropriate patients with ovarian cancer, regardless of BRCA mutation status.

Both studies met their predefined primary endpoints to establish the efficacy of olaparib for the maintenance treatment of patients with recurrent ovarian, fallopian tube, and primary peritoneal cancer who are in response to platinum-based chemotherapy. The results of the two studies, taken together, support the assumption that maintenance therapy with olaparib in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancers who are in response to platinum-based chemotherapy affords a prolonged PFS, when compared to placebo.

Secondary and Other Endpoints

The secondary endpoints for SOLO2 included PFS2, OS, ORR, DOR and time to earliest progression by CA-125 or death. The key secondary endpoint for Study 19 was an OS, but the difference between the olaparib and placebo arms did not reach statistical significance.

Integrated Assessment of Effectiveness

The two key trials to consider when assessing the efficacy of olaparib as a maintenance therapy in patients with relapsed ovarian cancer who are in response to platinum-based chemotherapy have been described and include Study 19 and SOLO2. Differences between the trials include the populations enrolled and the retrospective identification of the gBRCA subgroup for analysis in Study 19.

When considering the PFS analysis from the two key studies, they include a 13.6 month improvement for olaparib over placebo on SOLO2 (gBRCaM patients only), HR=0.30, and a 3.6 month improvement over placebo in the ITT population (without regard to gBRCA status) in Study 19, HR=0.35. As has been discussed, the results of Study 19 are being used to support the approval of olaparib as maintenance therapy for all patients with recurrent ovarian, fallopian tube, and primary peritoneal cancer who are in response to platinum-based chemotherapy, regardless of BRCA mutation status. This is based mainly on the fact that the improvement in PFS in the ITT population resulted in a robust hazard ratio of 0.35, which was statistically significant ($p < 0.00001$), as well as accounting for the well-known side effect profile of olaparib and its overall tolerability. Taking both SOLO2 and Study 19 together, it is clear that the gBRCA subgroup of patients benefits to a greater extent than the unselected group, however, there are some patients within the gBRCaWt group who do benefit- likely due to either somatic BRCA mutations, or HRD. At the current time there is no way to predict which of these patients within the BRCaWt population may benefit. Platinum sensitivity is also a predictor of response to olaparib and is included in the indication. Given the toxicity profile which is acceptable for the intended population and the potential for long term benefit as evidenced by 10% of gBRCaWt patients experiencing greater than or equal to 6 years on treatment without relapse, this approval is justified. In addition, the Sponsor has agreed to conduct an additional study to further assess the effect of olaparib maintenance therapy in patients with gBRCaWt to further delineate which patients within this group may benefit. One of the post-marketing commitments put forth in association with the approval of this NDA is for the Sponsor to conduct the OPINION study, which is a Phase IIIb, single-arm, open-label multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed non-germline BRCA mutated ovarian cancer patients who are in complete or partial response following platinum-based chemotherapy. The results of this trial may be used, at a later date, to further modify labeling recommendations to advise clinicians on which patients may benefit most from olaparib therapy.

7.4. Review of Safety

Safety Review Approach

The main focus of the safety review for this application was on the SOLO2 study, but an updated safety analysis on the ITT population for Study 19 was conducted when appropriate, particularly in order to update the product labeling.

A unique factor with this application is that the olaparib doses and formulations differed between Study 19 and SOLO2. In Study 19, patients were administered olaparib in a capsule formulation at a dose of 400 mg BID (administered as 8 x 50 mg capsules per dose). This dose and formulation is the currently approved dose for the indication of monotherapy in patients with gBRCAm ovarian cancer who have received 3 or more prior lines of chemotherapy (approved in 12/14 based on data from Study 42). In SOLO2, patients received olaparib in a tablet formulation at a dose of 300 mg BID (administered as 2 x 150 mg tablets per dose). It was determined previously that the tablet and capsule formulations are not bioequivalent, and the Sponsor's ultimate plan will be to discontinue marketing of the capsule formulation after the tablet formulation is approved.

As will be discussed below in section 7.4.2, there were 7 additional studies which enrolled patients with the olaparib tablet formulation; however, given that doses and schedules were not identical to patients treated on SOLO2, the additional studies were not included in an integrated safety analysis. Likewise, an integrated safety analysis including Study 19 and SOLO2 was also not conducted, due to the differences in olaparib formulations received by patients on the two trials. However, comparisons between safety analyses (including adverse event incidence and dose modifications) will be made in the sections below, as appropriate.

7.4.2. Review of the Safety Database

Overall Exposure

Tablet formulation (SOLO2)

The focus of the current safety review was on the safety of the tablet formulation of olaparib in patients with relapsed ovarian cancer with documented gBRCA mutation. The SOLO2 study, with a dose of 300 mg BID, comprised the primary study to support safety and efficacy in the current application. However, the Sponsor submitted supportive data from 7 additional studies, including 482 patients with solid tumors and 312 patients with ovarian cancer (including fallopian tube and peritoneal cancers). Patients on the trials, besides SOLO2, received varying doses and schedules of the tablet formulation of olaparib, and number of patients exposed to the tablet formulation on these trials is shown in Table 36.

Table 36 Tablet exposure in trials

Study	Indication	Number exposed to olaparib 300 mg BID tablets	Number of patients with ovarian cancer
SOLO2	Phase 3 advanced ovarian cancer	195	195
Study 24	Phase I bioavailability study in advanced solid tumors (groups 4 and 6)	24	14
Study 4	Phase I food effect and QT study in advanced solid tumors	57	23
Study 7	Phase I PK study with CYP inhibitor in advanced solid tumors	56	23
Study 8	Phase I PK study with rifampin in advanced solid tumors	19	6
Study D081BC00001	Phase I dose escalation study in Japanese patients with advanced solid tumors	19	5
Study D081CC00001	Phase I anti-hormonal PK study of olaparib	69	34
Study 6	Phase I renal impairment study of olaparib	43	12
Total		482	312

Capsule formulation (Study 19)

Study 19 comprised the single study, in this application, to support the expanded indication for olaparib as maintenance treatment for patients with relapsed ovarian cancer in response to platinum-based chemotherapy, regardless of BRCA mutation status (all-comers). A total of 264 patients were treated on Study 19, but only 136 received olaparib capsules at 400 mg twice daily (129 patients received placebo). The safety database for the capsule formulation included 735 patients with advanced solid tumors (in 11 studies) who were treated with olaparib capsules 400 mg twice daily.

Relevant characteristics of the safety population:

As has been described, the primary source of safety data for the current indication in patients with relapsed ovarian, peritoneal, and fallopian tube cancers includes the SOLO2 study, however data from Study 19 is supportive, given that safety data in patients without underlying gBRCA mutation comes only from this study. All patients enrolled on SOLO2 had relapsed ovarian cancer and a documented gBRCAm. The baseline characteristics for patients on SOLO2 were shown in Table 18 and the characteristics for patients on Study 19 were shown in Table 19.

Adequacy of the safety database:

The SOLO2 included 195 ovarian cancer patients with underlying gBRCA mutation who received the olaparib tablet at 300 mg BID, and these patients comprised the primary focus of the safety review. In addition, safety data analyses from the ITT population of Study 19 (including 136 olaparib treated patients) are referenced as appropriate. The overall safety database was considered to adequate.

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The NDA submission contained all required components of the eCTD. The overall quality and integrity of the application was adequate for substantive review to be completed.

Categorization of Adverse Events

A safety overview of key adverse events on SOLO2 is shown in Table 37.

Table 37 SOLO2 Safety Overview

	Olaparib N=195 (%)	Placebo N= 99 (%)
Grade 1-4 AEs	192 (99)	94 (95)
Grade 3-4 AEs	72 (37)	18 (18)
Serious AEs	35 (18)	8 (8)
AEs leading to death within 30 days	0	0
AEs leading to discontinuation	21 (11)	2 (2)

Routine Clinical Tests

SOLO2

The schedule of assessments on the SOLO2 study, as outlined in the protocol, is shown above in Figure 2. The figure depicts the frequency of laboratory testing, vital signs, physical exam, and adverse event monitoring. Hematology parameters were monitored weekly during Cycle 1, due to the high prevalence of hematologic adverse events with olaparib. After one month, monitoring could be extended to monthly, but if any events of hematological toxicities occur, monitoring should be increased as appropriate.

Study 19

Monitoring for safety parameters was similar to SOLO2 and has been described previously in the clinical review of olaparib at initial approval, dated 12/4/14. The only difference is that on Study 19, hematologic parameters were monitored at least weekly throughout the duration of the study. This was appropriate, given that less was known about the hematologic toxicities and MDS/AML signal at the time when Study 19 was conducted.

7.4.4. Safety Results

Deaths

SOLO2

There were no deaths due to adverse event within 30 days of study drug on either arm in SOLO2. Deaths due to underlying ovarian cancer, as well as other deaths outside of 30 days, are shown in Table 38 . Narratives for five patients designated in the table are discussed below.

Table 38 SOLO2 Deaths

	Olaparib N=196	Placebo N=99
Death related to disease under investigation only (> 30 days after last treatment dose)	42	25
AE resulting in death < 30 days after last treatment dose	0	0
AE resulting in death ≥ 30 days after last treatment dose ¹	1	1
Deaths > 30 days “unrelated to AE or disease under investigation”	2 ²	0
Death due to unknown reason	0	1 ³

¹Olaparib patient E7001507, Placebo patient E2307506.

²Olaparib patients E2312502 and E2805504

³Placebo patient E7007504

Narratives for notable patient deaths on SOLO2

- 1) Patient E7001507- Olaparib- 71 y/o female with BRCA2 mutation and fallopian tube cancer diagnosed 3/24/10. She was treated with 4 platinum-containing regimens. These included:

carboplatin + paclitaxel in 2010; carboplatin + paclitaxel in 2012; carboplatin + paclitaxel + catumaxomab in 2012; carboplatin + doxorubicin in 2013. She also had a prior history of breast cancer, which was treated with surgery, XRT, hormonal therapy with tamoxifen and letrozole. The patient started on olaparib (b) (6) and stayed on until (b) (6). Olaparib treatment was interrupted on Day 504 due to anemia. Therapy was discontinued due to the diagnosis of acute myeloblastic leukemia (AML), which was on day 526. According to the narrative, the bone marrow biopsy was performed to make the diagnosis on (b) (6). No details on the pathology report or cytogenetics are provided. Subsequent to the diagnosis of AML, she initiated treatment with cytarabine and fludarabine. She subsequently died on (b) (6) (176 days after discontinuing olaparib). Death was said to also be related to the underlying fallopian tube cancer, but elsewhere in the narrative, G5 AML is reported as being causally related to olaparib.

Reviewer comment: No information was provided on cytogenetics from the bone marrow biopsy, however, based upon the duration of treatment with olaparib and the timing of the diagnosis of AML in a patient with a known BRCA2 mutation, a causal relationship between the olaparib and the occurrence of AML cannot be excluded. This patient's history fits a more typical course for patients diagnosed with AML after therapy with a PARP inhibitor.

- 2) Patient E2307506- Placebo- 44 y/o female with ovarian cancer first diagnosed 12/21/12. Treated with 2 prior platinum containing regimens, as well as bevacizumab. She began placebo on SOLO2 on (b) (6) and continued till (b) (6) (226 days). She came off study due to progressive disease. After SOLO2, she started on doxorubicin + carboplatin (days 275-433), which was followed with olaparib maintenance (outside of clinical trial, days 478-568). She next received experimental Navitoclax (ABT-263, and anti-BCL2 agent) from days 610-638. On day 659 (433 days after discontinuing placebo therapy), she was diagnosed with acute myeloid leukemia when she was hospitalized for thrombocytopenia. She was started on azacitadine on day 666 and died the next day (day 667) on (b) (6). Investigator considered the AML to not be related to study treatment.

Reviewer comment: Although this patient received placebo on the SOLO2 clinical trial, she did go on to receive olaparib outside of the context of a trial, after study discontinuation. Exposure to olaparib was for 90 days. No information on bone marrow aspirate, biopsy, or cytogenetics is provided. However, she was exposed later to olaparib, followed by other experimental agents. Given the obvious exposure to olaparib, and the timing of onset of AML, the contribution of olaparib to this adverse event cannot be ruled out.

- 3) Patient E2312502- Olaparib- This death occurred > 30 days after olaparib discontinuation, and was listed by the Sponsor as not being related to an AE or the disease under investigation. 67 year old white female with primary peritoneal cancer diagnosed 11/4/09. She had previously received therapy with 3 platinum-containing regimens. Treatment history was as follows: carboplatin + paclitaxel in 4/10, investigational agent 7/21/10, carboplatin + doxorubicin 1/4/12, cyclophosphamide 12/4/13, carboplatin + paclitaxel 3/20/14. She started on therapy with olaparib on (b) (6) and continued until (b) (6) (D 128), when she had disease progression. While on therapy, she experience 2 SAEs, including G2 creatinine elevation starting study D15 with no report of resolution. She was hospitalized on Day 63 with SAE of hematuria (G3). Olaparib was not interrupted or dose reduced, but she required PRBC transfusion. She also experienced G2 renal colic during this hospital stay. The event resolved after 6 days. Treatment was subsequently stopped on D128, as noted) due to disease progression. Following study discontinuation, she went on to receive subsequent anticancer therapy with doxorubicin + carboplatin (Days 130- 298), gemcitabine (days 325-430), carboplatin (days 452-536) and olaparib (days 564-601).
- 4) Patient E7007504- Placebo patient- This patient discontinued placebo due to disease progression on Day 213. She died on Day 810 due to an unknown cause. It is also unknown what intervening therapy she received between the time of study discontinuation and death.

Study 19

The deaths on Study 19 are summarized in Table 21 of the primary clinical review under NDA 206162 dated 12/2/14. There were 3 deaths within 30 days due to adverse event on olaparib and no deaths on placebo. The 3 deaths due on olaparib were due to hemorrhagic stroke, cholestatic jaundice, and myelodysplastic syndrome. The deaths from stroke and MDS were likely to be related olaparib therapy. In addition, the patient who died from the hemorrhagic stroke had life-threatening thrombocytopenia at the time of death; it was suspected that she may have had underlying MDS/ AML that was not formally diagnosed prior to her death.

Serious Adverse Events

On SOLO2, there were 43 patients with 43 serious adverse events (SAEs) including thirty-five patients on olaparib (18%) and 8 patients on placebo (8%). The events are listed in Table 39. The most common SAE for olaparib treated patients on SOLO2 was anemia, occurring in eight patients. The majority of these cases were considered serious because they necessitated hospital admission for transfusion, and all of the cases occurred in patients treated outside of the US.

Table 39 SOLO2 Serious Adverse Events

Adverse Event	Olaparib N= 195 (%)	Placebo N=99 (%)
Patient with ANY AE	192	94
Patients with SAE	35 (18)	8 (8)
Blood and lymphatic system disorders		
Anemia	8	0
Neutropenia/ febrile neutropenia	2	0
Cardiac disorders		
Pericarditis	1	0
Gastrointestinal disorders		
Intestinal obstruction	3	3
Abdominal pain	3	0
Ascites	1	0
Dysphagia	1	0
Nausea	1	0
Vomiting	1	0
Constipation	0	2
Abdominal hernia	0	1
General disorders and administration site disorders		
Fatigue/ malaise	2	0
Peripheral edema	1	0
Pyrexia	1	0
Hepatobiliary disorders		
Cholecystitis	1	0
Immune system disorders		
Allergic reaction/ anaphylaxis	2	0
Infections and Infestations		
Urinary tract infection	1	1
Neutropenic sepsis	1	0
Epiduritis	1	0
Injury, poisoning, procedure		
Incisional hernia	1	0
Post-procedural fistula	0	1
Investigations		
Blood creatinine increased	1	0
Blood CPK increased	1	0
Serum amylase increased	0	1
Metabolism and nutrition disorders		
Hypokalemia	0	1
Musculoskeletal and connective tissue disorders		

Muscular weakness	1	0
Back pain	0	1
Neoplasms*		
AML/MDS	2	0
Multiple myeloma	1	0
Lymphoma	1	0
Gastric cancer	1	0
Breast cancer	0	1
Renal and urinary disorders		
Hematuria	1	0
Respiratory, thoracic, and mediastinal disorders		
Pneumonitis	1	0
Dyspnea	1	0
Cough	1	0
Vascular disorders		
Deep vein thrombosis	2	1

Study 19

On Study 19, there were patients with 53 serious adverse events (SAEs), including 25 patients (18%) who experienced 34 SAEs on olaparib and 13 (10%) patients who experienced 19 SAEs on placebo. These events have been described previously, but the breakdown of serious adverse events on Study 19 is shown in Table 40.

Table 40 Study 19 Serious adverse events ITT population

Serious Adverse Events	Olaparib n=136 N (%)	Placebo n=128 N (%)
Patient with any SAE	25 (18.4)	13 (10.2)
Blood and lymphatic system disorders		
Anemia	3	0
Pancytopenia	1	1
Thrombocytopenia	1	0
Cardiac disorders		
Cardiac insufficiency	1	0
Gastrointestinal disorders		
Intestinal obstruction (small or large)	3	4
Constipation	1	0
Diarrhea	1	0
Vomiting	1	0
Melena	1	0
Intra-abdominal hemorrhage	1	0
Gastritis	0	2
Abdominal pain	0	1

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Impaired gastric emptying	0	1
Nausea	0	1
General disorders and administration site conditions		
Hernia pain	1	0
Pyrexia	1	0
Immune system disorders		
Iodine allergy	1	0
Infections and infestations		
Pneumonia	1	1
Urinary tract infection	1	1
Upper respiratory tract infection	1	0
Appendicitis	1	0
Liver abscess	1	0
Endophthalmitis	0	1
Influenza	0	1
Injury, poisoning, procedural complications		
Femur fracture	1	0
Post-procedural hematoma	1	0
Metabolism and nutrition disorders		
Dehydration	0	1
Musculoskeletal and connective tissue disorders		
Osteoporosis	1	0
Neoplasms benign, malignant and unspecified		
Breast cancer in situ	1	0
Myelodysplastic syndrome	1	0
Bladder cancer	0	1
Nervous system disorders		
Syncope	1	0
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	2	0
Pulmonary embolism	1	0
Cough	1	0
Vascular disorders		
Deep vein thrombosis	1	0
Vena cava thrombosis	1	0
Essential hypertension	0	1

Reviewer comment: The overall incidence of serious adverse events on Study 19 was similar to that of SOLO2. Likewise, the breakdown of specific serious adverse events was also similar between the studies. An exception is that there were more serious events of anemia in olaparib-treated patients on SOLO2, compared with Study 19. This is likely related to the increased bioavailability of the tablet formulation. The majority of all hematologic events, including anemia, can be managed by dose interruption and/or reduction, as well as supportive care therapies. Guidance for clinicians on the management of hematologic events is described in the product labeling.

Version date: February 1, 2016 for initial round (NME/Original BLA reviews)

Dropouts and/or Discontinuations Due to Adverse Effects

SOLO2

On SOLO2 dose discontinuations and modifications due to adverse event are shown in Table 41. Dose discontinuations due to adverse event were common on olaparib (11%) than on placebo (2%). The most common specific adverse events leading to permanent discontinuation of olaparib included anemia (n=6), neutropenia (n=3), thrombocytopenia (n=2), and MDS/AML (n=2). On placebo, two patients discontinued therapy due to adverse events of thrombocytopenia (n=1) and diagnosis of invasive breast cancer (n=1).

Table 41 Dose discontinuations and modifications due to adverse event on SOLO2

	Olaparib N=195 (%)	Placebo N= 99(%)
Any AE leading to discontinuation	21 (11)	2 (2)
AE leading to dose interruption	84 (44)	17 (17)
AE leading to dose reduction	53 (27)	3 (3)

A breakdown of the most common adverse events leading to dose reduction, interruption, or both on SOLO2 are shown in Table 42.

Table 42 Specific adverse events leading to dose modification SOLO2

	Olaparib N= 195 (%)	Placebo N=99 (%)
AEs leading to dose reduction		
Anemia	17 (9)	0
Fatigue / asthenia	10 (5)	0
Neutropenia	5 (3)	0
AEs leading to dose interruption		
Anemia	34 (17)	0
Vomiting	14 (7)	1 (1)
Nausea	11 (6)	2 (2)
Neutropenia (including neutropenic sepsis)	10 (5)	3 (3)
Thrombocytopenia	7 (4)	0
AEs leading to dose reduction or interruption		
Anemia	42 (22)	0
Neutropenia	17 (9)	3 (3)

Fatigue/ asthenia	16 (8)	1 (1)
Vomiting	14 (7)	1(1)
Nausea	12 (6)	4 (4)
Thrombocytopenia	8 (4)	0

Reviewer comment: Overall, the same specific adverse events were responsible for dose reductions and interruptions on SOLO2 and included cytopenias, fatigue and nausea/vomiting. The majority of these adverse events were managed with dose modifications and patients were able to continue with therapy. As noted above, there were some patients who experienced prolonged cytopenias (with or without MDS/AML) that did not recover, and resulted in permanent study drug discontinuation. Guidance to clinicians, on when permanent study drug discontinuation may be appropriate is described in the product labeling.

Adverse events leading to dose modifications on Study 19 are shown in Table 43. The specific adverse events leading to discontinuation from olaparib included hemorrhagic stroke (which also lead to death, and was mentioned above), palpitations, myalgia, herpes zoster infection, pancytopenia, pharyngitis, nausea, and rash (two of the olaparib patients had 2 separate adverse events listed as resulting in discontinuation). On placebo, the adverse events that lead to treatment discontinuation included nausea and rash. Specific adverse events leading to dose modifications on Study 19 are depicted in Table 44.

Table 43 Dose discontinuations and modifications due to adverse event on Study 19

	Olaparib N=136	Placebo N=128
AEs leading to discontinuation	6 (4)	2 (2)
AEs leading to dose interruption	41 (30)	12 (9)
AEs leading to dose reduction	31 (23)	6 (5)
AEs leading to dose reduction or interruption	71 (52)	15 (12)

Reviewer comment: The proportion of patients on olaparib who had dose reductions or dose modifications (which included reduction and/or interruption) was roughly the same between the SOLO2 study and Study 19. There were overall more olaparib treated patients who required dose interruptions on SOLO2, compared with Study 19 (44% vs. 30%). The reason for this may be related to the enhanced bioavailability of the tablet formulation compared to the capsule, although fewer patients on both studies necessitated dose reductions compared with interruptions. In addition, more patients on SOLO2 discontinued olaparib due to an adverse event compared to Study 19 (11% vs. 4%). The majority of the adverse events leading to any kind of modification of olaparib were either hematologic events or nausea, all of which are fairly easily managed with dose interruption and less frequently with dose reduction.

Table 44 Specific adverse events leading to dose modification Study 19

	Olaparib N= 136 (%)	Placebo N=129 (%)
AEs leading to dose reduction		
Anemia	7 (5)	1 (1)
Fatigue	6 (4)	1 (1)
Nausea	5 (4)	0
AEs leading to dose interruption		
Vomiting	10 (7)	1 (1)
Nausea	9 (7)	1 (1)
Fatigue	6 (4)	2 (2)
Anemia	4 (3)	0
Thrombocytopenia	3 (2)	0
AEs leading to dose reduction or interruption		
Nausea	14 (10)	1 (1)
Vomiting	14 (10)	2 (2)
Fatigue	12 (9)	3 (2)
Anemia	11 (8)	1 (1)

Significant Adverse Events

MDS and AML

MDS and AML are now a well-known safety signal associated with olaparib therapy. At the time of the initial approval of olaparib under NDA 206162, there had been 22 documented cases in the olaparib safety database. With submission of the current NDA, more cases have been documented, for a total of 34 cases in 6558 patients exposed to olaparib (including 3 patients on blinded study treatment, where the study arm was not known).

Reviewer: This reviewer points out that the denominator of 6,558 is taken from the Sponsor report of "all patients" exposed to olaparib across all trials. See next comment below, regarding assessment of the likely overall risk to patients.

Of the 34 cases, 29 were confirmed in patients known to have received olaparib and 1 case was an unconfirmed case from Study 19. Five cases were in patients treated on SOLO2, including 4 on olaparib and 1 on placebo. Thirty of the 34 patients had underlying ovarian cancer, with two cases occurring in patients with breast cancer and two inpatients with prostate cancer. Seventeen of the 34 cases were in patients with documented gBRCA mutation, and 10 additional cases were in patients with BRCA

mutation which was not specified as germline. At the time of data cutoff, 20 of the 34 patients have died, and 14 are listed as ongoing. Four patients originally diagnosed with MDS progressed to AML, and all four have died. Ten of the 34 patients had documented cytogenetic abnormalities including abnormalities of chromosome 5 or 7, which is consistent with treatment-related MDS/AML. For the 34 patients, the median duration of exposure to olaparib/placebo was 361.5 days, but the range varied widely from 28 days to 1,773 days, indicating that there may not necessarily be a specific exposure duration needed to increase a patient's risk of developing MDS/AML after receiving olaparib. It is notable that in all cases, patients were exposed to other chemotherapy regimens, including anthracyclines, and some patients had also had prior radiation exposure for their underlying cancer.

Reviewer comment: Considerable debate has occurred between the Sponsor and the review team regarding the exact number of cases of MDS/AML that should be counted and described in patient labeling. The debate has revolved around issues including whether patients exposed to olaparib as part of a combination regimen should be counted, whether patients who crossed over to receive olaparib after progression on a clinical study should be counted, and whether patients who are still blinded as to study arm should be counted. Although including or excluding certain cases does not change the overall numerator substantially, the Sponsor has argued (b) (4)

For the purpose of labeling, it has been agreed that only 21 of the cases described in the table below (including 2 of 3 cases from Study 19, 4 cases from SOLO2, and 5 cases from Study 42) will be described in section 5 of the label. This will equate to an incidence of approximately 1.5% (21 out of 1680 patients treated with olaparib monotherapy) on clinical trials. When considering the incidence of MDS/AML with similar products, and given the difficulty with estimating the real incidence of MDS/AML due to the confounding factors involved, it is likely that this estimate (of 1.5%) provides a reasonable assessment of risk. This reviewer thinks that in the general population, approximately 1-2% of patients treated with olaparib will experience this devastating side effect. The current label provides guidance to clinicians on when and how to monitor for this possible event.

Table 45 presents key details on all 34 cases documented, including study, patient age, underlying tumor, prior therapy, BRCA status, diagnosis and outcome. The narratives for the 34 cases are discussed after the table.

Table 45 Cases of MDS and AML in olaparib database

No.	Study	Patient ID/ Age	Arm	Cancer under treatment	BRCA stat.	Days on study drug	diagnosis	Prior chemo received for cancer in quesiton	Cytogenetics	outcome
1	19	E1801002 77y	Olaparib	Primary peritoneal-	Wild	313	MDS- RAEB	Carboplatin+ paclitaxel; carboplatin+ gemcitabine; anastrozole	5q-, 17p-, abn 7q	Death
					gBRCA wild					
2	19	E0801001 53 y	Olaparib	Ovarian	Mut	1728	AML	Carboplatin + paclitaxel x 2 courses	-	Ongoing
					gBRCA mut					
3	19	E1808004 49 y/o	olaparib	Ovarian	Mut	205	AML unconfirmed	Carboplatin + paclitaxel; tamoxifen; bevacizumab + cisplatin + gemcitabine	none	Death
					gBRCA mut					
4	41	E1405004 78y	Olaparib + carbo/ taxol→ olaparib	Ovarian	wild	547	MDS	Carboplatin + paclitaxel	-	Death
					Tumor wild type- retrospectively defined; Found Med					
5	41	E1503001 61y	Olaparib + carbo/ taxol→ olaparib	Primary peritoneal	mut.	805	MDS	Carboplatin + paclitaxel x 3 separate regimens	-	Death
					Tumor mutant Prosp. Found Med					
6	12	E7001010 71y	olaparib	Ovarian	Mut.	126	AML	Cisplatin + doxorubicin + paclitaxel; tamoxifen; carboplatin + marimistat; carboplatin; topotecan; carboplatin + paclitaxel	Abn chromo 5 and 7; IDER	Death
					gBRCA mut					

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7	12	E6007014 63 y	olaparib	Fallopian tube	Mut. gBRCA mut	744	AML	Carboplatin + paclitaxel; letrozole; carboplatin + docetaxel	5q del; monosomy 7	Death
8	42	E0302009 63y	olaparib	Primary peritoneal	Mut. Myriad BRCA (germline)	188	AML	Carboplatin + paclitaxel; carboplatin + gemcitabine; Doxil	Abn chr 5 and 7	Death
9	42	E4007006 63y	olaparib	Ovarian	Mut. Not myriad used (other)	155	AML	Carboplatin + paclitaxel; carboplatin + paclitaxel; cisplatin	-	Death
10	42	E4003003 45y	olaparib	Ovarian	Mut. Not myriad (other)	298	MDS	Carboplatin + paclitaxel; cisplatin; carboplatin → cisplatin; doxorubicin; cyclophosphamide; cisplatin + doxorubicin	-	Death
11	42	E7802003 55y	olaparib	Ovarian	Mut. Myriad-gBRCA	152	MDS	Carboplatin + paclitaxel; cyclophosphamide + doxorubicin; carboplatin + gemcitabine → maint. Paclitaxel; cyclophosphamide + bevacizumab	-	Death
12	42	E7802029 61 y	olaparib	Ovarian/ Peritoneal	Mut.- Myriad-gBRCA	764	MDS progressed to AML	Carboplatin + paclitaxel; possibly bevacizumab and topotecan	-	Death
13	42	E4001012 51 y	olaparib	Breast (also had prior h/o ovarian cancer)	Mut -other-not myriad	1252	MDS	Cyclophosphamide, Adriamycin, 5FU; cisplatin + gemcitabine;	Del 5 q 31	Ongoing

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14	9	E0017011 68 y	olaparib	Ovarian	Mut. -Myriad mutate (gBRCA)	231	AML	Carboplatin + paclitaxel; cisplatin + topotecan	-	Death
15	9	E0613008 63 y	olaparib	Ovarian	Mut. (other lab, unclear if germline)	1759	MDS progressed to AML	Cisplatin + paclitaxel; pazopanib	-	Death
16	2	001-0078 70 y	olaparib	Ovarian	Mut. (brca2)	981	MDS progressed to AML	Carboplatin + paclitaxel; carboplatin x 3 separate regimens	Complex karyotype; +13, 17p-	Death
17	4	003-2117 64 y	olaparib+ C/P	Breast	Mut.	580	MDS/RAE	Carboplatin + paclitaxel	-	Death
18	98	E8348038 67 y	olaparib + cediranib	Ovarian	Unk.	373	MDS	Platinum + taxane; carboplatin + gemcitabine + iniparib;	-	Death
19	59	0810C000 59/008 60 y	Olaparib+ carboplatin + paclitaxel	Ovarian	Unk.	91	MDS	Carboplatin + paclitaxel+ bevacizumab ; topotecan + bevacizumab ; carboplatin+ paclitaxel + bevacizumab ; carboplatin + paclitaxel + bevacizumab (again); carboplatin; Adriamycin	2 clones: 5q-; monosomy 6p and monosomy 7q	Ongoing
20	24	E0008004 50 y/o female	Olaparib 400 mg bid	Ovarian	Mut.	733	MDS	Carboplatin +paclitaxel; doxil; carboplatin + paclitaxel; carboplatin + paclitaxel	-	Death
21	IN V (55)	D0810C00 55/JH001 67 y/o male	Olaparib 100 bid intermit- tent (w/ irino/cis/	Pancreatic	Mut.	693	MDS	Capecitabine ; XRT	-	Ongoing

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			mito-C)							
22	IN V (55)	D0810C00 55/JH004 67 y/o male	Olaparib 100 mg bid intermitte nt (w/ irino/cis)	Pancreatic	Unk.	350	MDS	Gemcitabine; capecitabine; XRT	- (5-6% blasts)	Ongoing
23	SO LO 2	E2804503 56 y/o female	Olaparib 300 mg BID tablet	Fallopian tube cancer	gBRCA mut	218	MDS		5q del	Ongoing
24	SO LO 2	E7001507 71 y/o female	Olaparib 300 mg BID tablet	Fallopian tube cancer (prior breast cancer also)	gBRCA mut	526	AML		-	Death
25	SO LO 2	E2309503 42 y/o female	Olaparib 300 mg BID tablet	Ovarian	gBRCA mut	287	CMML		-	Ongoing s/p allogeneic SCT
26	SO LO 2	E2601508 53 y/o female	Olaparib 300 mg BID tablet	Ovarian	gBRCA mut	763	AML		-	Ongoing/ unknown
27	SO LO 2	E2307506 44 y/o female	Placebo→ Olaparib open- label after PD on placebo	Ovarian	gBRCA mut	90	AML		-	Death
28	24	E0008002 80 y/o female	Olaparib capsule 400 mg bid	Ovarian cancer	BRCA1 Mut	1773	MDS		Complex karyotype	Ongoing
29	SO LO 3	E5701001 68 y/o female	Olaparib tablet 300 mg bid (open- label)	Ovarian cancer	Mut	28	MDS		-	Ongoing
30	D4 19 1N	2016SE64 767	Olaparib tablet 300 mg bid +	Ovarian cancer	wild	120	MDS		-	Ongoing

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	00 01 2	66y/o female	durvalum ab							
31	Ma na ge d acc ess pro gra m	2015SE12 340 66 y/o female	Olaparib capsule 400 mg bid	Ovarian cancer	mut	84	Both-.MDS and AML		45, XX, del 5 (q13q32), -17, del 5, - 7	Death 20 Died due to MDS and AML
32	D0 81 7C 00 00 3	03322- 0332205 58 y/o female	Blinded- olaparib or placebo + Bevacizu mab	Ovarian cancer	Unkn.	234	MDS		-	Ongoing
33	SO LO 1	E1003004 66 y/o female	Blinded study treatment - olaparib tablet vs placebo 150 mg bid	Ovarian cancer	Mut	571	AML		-	Ongoing
34	SO LO 1	E5001006 54 y/o female	Blinded study treatment - olaparib tablet vs placebo 150 mg bid	Ovarian cancer	Mut	436	Myeloprolif erative neoplasia (hypocellul ar marrow with fibrosis and incr. blasts)		-	Ongoing

1. E1801002- Study 19- olaparib. 77 y/o white female diagnosed on 4/3/07 with Stage IV, poorly differentiated, primary peritoneal cancer, wildtype BRCA, with metastases to the liver, gall bladder, genitourinary system, and lymph nodes. She was treated with carboplatin and paclitaxel from 5/4/07- 9/27/07. She then received gemcitabine + carboplatin 7/21/08- 3/9/09. Also received arimidex 7/21/08- 8/25/08. She also had a distant history of melanoma. She enrolled on Study 19 and was randomized to olaparib arm on (b) (6). On study day 226, she had a serious adverse event of grade 3 pancytopenia, considered possibly related to olaparib and resulting in dose reduction to 200 mg BID olaparib. She discontinued therapy with olaparib on (b) (6) due to disease progression. According to the patient's CRF, CT scan from (b) (6) showed new ascites, consistent with progressive disease. She was diagnosed with grade 3 myelodysplastic syndrome (MDS) on (b) (6), which was approximately 6 weeks after discontinuing olaparib. Bone marrow biopsy was performed and revealed refractory anemia

with excess blasts (RAEB). Cytogenetics showed loss of chromosome 5q and loss of 17p, as well as abnormalities of chromosome 7q, consistent with therapy-related MDS.

2. E0801001- Study 19- olaparib. 53 y/o white female with BRCA mutated ovarian cancer diagnosed 2/12/07. Prior chemotherapy included carboplatin/ taxol first-line and second-line. She began on study 19 on olaparib 400 mg bid on (b) (6) and was still on therapy on (b) (6) (data cutoff). On (b) (6) (D1728 of olaparib) she was found to have pancytopenia (WBC 2.3, Hgb 7.1, platelets 84K) and was hospitalized. Olaparib was stopped. She was transfused. She was subsequently readmitted to the hospital on (b) (6) with grade 4 acute leukemia. Bone marrow biopsy on (b) (6) (D1750, 21 days post olaparib discontinuation) revealed acute myelogenous leukemia (AML) with 20-25% blasts, considered possible leukemic transformation from therapy-related MDS. She subsequently initiated therapy with daunorubicin + AraC. Therapy with this regimen was ongoing at the time of study report.
3. E1808004- Study 19. olaparib. Adverse event of death due to hemorrhagic stroke. 48 y/o female with a history of BRCAm, stage IIIC poorly differentiated ovarian cancer diagnosed 6/20/07. She enrolled on study on (b) (6). She had initiated cycle 8 of therapy with olaparib and was found to have grade 2 thrombocytopenia (starting 7/27/10), which worsened to grade 3, then grade 4. On Day 205 of therapy, she was noted to have grade thrombocytopenia, grade 4 neutropenia, and grade 2 anemia, all considered non-serious. The grade 4 thrombocytopenia, in particular, led to interruption of olaparib therapy. On Day 209 (b) (6), she suffered a hemorrhagic stroke on (b) (6) and subsequently died on (b) (6). The adverse event of hemorrhagic stroke was said to be related to the study drug.

Reviewer comment: Based upon the persistent thrombocytopenia, and the fact that no etiology was ever determined for the thrombocytopenia before the patient died of a hemorrhagic stroke, this case was considered by the review team to be highly suspicious for an underlying case of MDS, and she was included as a documented case.

4. E1405004- Study 41- olaparib with carboplatin/ paclitaxel. 78 y/o female with BRCA wildtype ovarian cancer. Treated with olaparib. Originally diagnosed with non-BRCA mutated primary peritoneal cancer with lung mets on 2/4/09. She had surgery followed by carboplatin + taxol and completed this therapy 1 year prior to study 41 entry. On study 41, she received more carboplatin + taxol+ olaparib. She received olaparib 200 bid for 10 of 21 days each cycle starting (b) (6). Olaparib was stopped/held on (b) (6) (study Day 547) due to a diagnosis of MDS. It was noted that she had anemia at study baseline. On study Day 50, she was noted to have grade 2 neutropenia which worsened to grade 3 on Study days 62 and 73. She was hospitalized study day 73 with a grade 3 urinary tract infection. Her white blood cell count remained persistently decreased (grade 1-2) after this event. On day 150 she suffered a grade 3 femoral neck fracture. On day 338, she was noted to have grade 3 thrombocytopenia and olaparib therapy was

interrupted. On day 561 she was diagnosed with grade 3 disseminated intravascular coagulopathy (DIC). At that time olaparib had been interrupted again for 2 weeks. She was treated for the DIC with clotting factors, platelet transfusions, anti-thrombin III. On day 570 (roughly (b) (6)) the diagnosis of MDS was reported and olaparib discontinued permanently (event said to be “unrelated” to olaparib). The patient was treated with azacitadine on day 602 ((b) (6)). She died on (b) (6). The primary cause of death was said to be cerebral hemorrhage, and secondary- DIC. No cytogenetics had been reported for the MDS.

5. E1503001- Study 41- olaparib with carboplatin/ paclitaxel. 61 y/o female with BRCAm primary peritoneal cancer with pleural metastases diagnosed on 9/11/01. She had debulking surgery followed by 3 prior carboplatin/paclitaxel regimens over prior 7 years—(100 months prior to study enrollment, 60 months prior, and 20 months prior). She enrolled on Study 41 on (b) (6) and was randomized to carboplatin+ paclitaxel+ olaparib 200 mg twice daily for 10 days per 21 day cycle. She had grade 2 thrombocytopenia starting on day 129 of therapy, but was able to continue treatment, although olaparib was temporarily interrupted. On study day 805, the diagnosis of MDS was made. Olaparib was permanently discontinued at that point. At time of data cut off, patient was alive and MDS had not resolved.
6. E7001010- Study 12. olaparib. 71 y/o female with BRCA mutated ovarian cancer. Originally diagnosed 5/16/96 with metastatic disease and ascites. She had surgery followed by chemotherapy with cisplatin/doxorubicin/paclitaxel. She was then treated with tamoxifen, after which she progressed. Subsequently, she received carboplatin + marimistat, then 3 cycles carboplatin, then topotecan, then 4 cycles carbo/taxol. She was treated on Study 12 with olaparib 200 mg twice daily from (b) (6) till (b) (6) (D126). During treatment with olaparib, the patient had complications including grade 4 CVA and grade 3 syncope. On study day 42 of olaparib, she was noted to have grade 3 anemia, treated with erythropoietin and red cell transfusion. On day 125, she was found to have grade 4 neutropenia and grade 4 thrombocytopenia and olaparib was discontinued. On (b) (6) (Day 152) the patient was diagnosed with MDS /secondary AML. There were 45% blasts on peripheral blood smear and peripheral blood cytogenetics included abnormalities in chromosomes 5 and 7 + IDER (11). She died on (b) (6) from MDS.
7. E6007014- Study 12. olaparib. 63 y/o female with BRCA mutated fallopian tube cancer diagnosed 6/11/05. She had metastases to the liver, gall bladder, and peritoneum. She also had prior history of benign and malignant tumors including breast cancer, bladder cancer, basal cell carcinoma, and colon adenomas. Prior treatment treatment for breast cancer included surgery and XRT followed by tamoxifen. The breast cancer relapsed and was treated with further XRT to the axilla and chemotherapy with adriamycin, cyclophosphamide, followed by paclitaxel. A relapse in the contralateral breast was then treated with XRT and more chemotherapy with adriamycin and cyclophosphamide. Treatment for the fallopian tube cancer included surgery, carboplatin/taxol leading to complete remission. She subsequently received letrozole, then more therapy with carboplatin and docetaxel. Olaparib 200 mg bid was started (b) (6) and was

ongoing on (b) (6), the date of data cut-off. The total treatment on-study with olaparib was 585 days, but she also continued taking olaparib after the data cutoff date. On day 744 (b) (6), she was diagnosed with grade 4 MDS/ AML with 11% blasts in the bone marrow. Cytogenetics: 5q deletion and monosomy 7. Olaparib was discontinued at that time. The investigator thought that the AML was related to olaparib therapy. Thirty-five days later, the patient began induction chemotherapy with topotecan and ARA-C. She experienced a complete remission. She then went on to reduced-intensity double umbilical cord blood transplant. She died 15 months post-transplant (b) (6) of complications of GVH and pneumonia. The cause of death was listed as transplant-related mortality.

8. E0302009- Study 42. olaparib. 63 y/o female with BRCA mutated peritoneal cancer diagnosed on 9/12/07, with metastases to the spleen, liver, GB, pleura. She also had a previous history of breast cancer, treated with lumpectomy and XRT, followed by cyclophosphamide, 5FU, and MTX, approximately 15 years prior to study. She also received epirubicin and cyclophosphamide for the breast cancer diagnosis, approximately 4 years before entering Study 42. For the peritoneal cancer, she received carboplatin + paclitaxel (3 years before study 42 start). She also received carboplatin + gemcitabine, and most immediately prior to Study 42, she received Doxil for 5 months, ending about 2 months prior to study enrollment. She was on olaparib 400 mg BID from (b) (6) until (b) (6) (188 days). It was noted that myelodysplastic syndrome (MDS) was probably present at the time of entry on Study 42, but was not identified as such until later. On Day 37 of olaparib she was “reported to have a serious AE of worsening of MDS leading to acute leukemia”. Olaparib was temporarily stopped, but was restarted 21 days later. Olaparib was stopped again, 2 months later, for approximately 4 weeks, and then was restarted at a reduced dose of 200 mg BID. She received blood transfusions for myelodysplasia on days 107, 136, and 188. Her course was complicated by grade 1 hemorrhage (bleeding into her sinus) on day 129 and “grade 1 sepsis” requiring IV antibiotics on D189. She ultimately died on (b) (6), which was day 205- she had only stopped olaparib 17 days prior. The primary cause of death was AML. Analysis of the AML revealed abnormalities in chromosomes 5 and 7, consistent with therapy-related AML. It is also noted that a retrospective review of this patient’s blood films indicated that abnormalities indicative of MDS had been present at study baseline, but were not identified till later.
9. E4007006- Study 42. olaparib. 63 y/o female with BRCA mutated ovarian cancer with peritoneal involvement diagnosed 10/18/07. She underwent surgery followed by carboplatin + paclitaxel leading to a complete remission; this therapy was completed approximately 3 years prior to study entry. She had disease progression approximately 1 year later, and received further therapy with carboplatin + paclitaxel. Her disease relapsed again, at which point she received therapy with cisplatin (starting approximately 7 months prior to entry onto Study 42). She began olaparib 400 mg twice daily on (b) (6), and continued for 155 days until (b) (6). She was diagnosed with grade 2 “bone marrow toxicity” on day 141, and discontinued olaparib therapy on day 155. The event was considered to be possibly related to olaparib. On day 179, she was diagnosed with AML. She underwent therapy for AML including hydroxycarbamide and

methylprednisolone. She died one day after commencing chemotherapy for AML, on (b) (6). This was 79 days after discontinuing olaparib. The primary cause of death was listed as AML, with ovarian cancer as the secondary cause.

10. E4003003- Study 42. olaparib. 45 y/o female with BRCA mutated ovarian cancer with metastases to the liver, gall bladder, and peritoneum diagnosed 1/3/05. Therapies for ovarian cancer included surgery, nephrostomy tube placement, and XRT to the para-aortic nodes. She also received chemotherapy including carboplatin, cisplatin, and paclitaxel, approximately 5 years prior to study entry. At relapse, she received further carboplatin followed by cisplatin, then doxorubicin, approximately 2 years prior to study entry. She next received cyclophosphamide. She finally received cisplatin with doxorubicin starting nine months prior to study entry. She started olaparib 400 mg twice daily on (b) (6) and continued until (b) (6) (Day 296). The reason for stopping at that time was a “study-specific discontinuation criterion”. On Day 593 (297 days after stopping olaparib), she was found to have grade 3 myelodysplastic syndrome. A bone marrow exam showed 40% myeloid blasts. A bone marrow biopsy showed a hypercellular (90%) trilineage marrow. There were markedly increased number of immature megakaryocytes (approximately 15%) and abnormal location of immature precursors. This patient died 51 days later, on (b) (6). The primary cause of death was listed as “multi-organ disorder”, with MDS as the secondary cause.
11. E7802003- Study 42. olaparib. 55 y/o female with BRCA mutated ovarian cancer with abdominal metastases originally diagnosed in 10/06. She was treated with surgery followed by carboplatin+ paclitaxel, four years prior to enrollment on Study 42. She also received cyclophosphamide + adriamycin, followed by carboplatin + gemcitabine with maintenance paclitaxel prior to enrollment on Study 42. She then finally received therapy for another relapse with cyclophosphamide + bevacizumab prior to enrollment. She started olaparib 400 mg twice daily on (b) (6) and permanently stopped on (b) (6) (day 152) due to thrombocytopenia (which was thought possibly related to olaparib). Prior to this, she had grade 2 anemia on day 140 and grade 3 leukopenia. On D156, (4 days after stopping olaparib), she was found to have grade 3 neutropenia. She required transfusions, G-CSF, and antibiotics. On day 308, she was diagnosed with the grade 4 bone marrow failure. One bone marrow biopsy in (b) (6) showed serous atrophy. A second bone marrow biopsy showed a significantly hypocellular marrow (grade 4) with serous atrophy and multifocal fibrosis. Reticulin fibrosis and peripheral blood morphology were consistent with MDS. The diagnosis of grade 3 MDS was ultimately made on day 531 and was considered to be related to olaparib. She died on (b) (6), and the primary cause of death was said to be ovarian cancer. Further information on treatment for MDS was not provided.
12. E7802029- Study 42- olaparib. 61 y/o female diagnosed with BRCA mutated peritoneal cancer with metastases to the gall bladder and omentum in 2007. Prior therapies for ovarian cancer included surgery followed by carboplatin + paclitaxel, with a complete response. This therapy was completed 4 years prior to entry onto Study 42. Therapy with olaparib 400 mg twice daily began on (b) (6). On day 310, she experienced grade 2 neutropenia; no action was taken with

regard to olaparib therapy. She was still taking olaparib therapy at the data cut off on (b) (6) (Day 520), and she continued therapy after the cutoff date. On day 762, she permanently discontinued therapy with olaparib, although the reason for discontinuation is not given. On Day 774, a serious adverse event of pancytopenia was reported; platelet count was 23 K/uL, hemoglobin was 9.5 g/dL and white blood cell count was 3.0 K/uL. She received transfusion with red cells and platelets. On Day 786, a serious adverse event of MDS was reported. No further details were provided.

Reviewer comment: It is noted that the cases of MDS/ AML in patients treated on Study 42 were diagnosed after more prolonged durations of cytopenias than for more recent studies. This may be due to the increased awareness of the association of MDS and AML with olaparib that developed over time, and may not have been as widely known when Study 42 was ongoing. Likewise, in current practice, patients with confirmed MDS/ AML would be immediately taken off therapy with olaparib, whereas this did not occur with some of the patients on study 42.

13. E4001012- Study 42. olaparib. 51 y/o white female with BRCA mutated breast cancer. She was originally diagnosed with metastatic disease to the skin, soft tissue, bone, and locomotor systems on 11/8/07. She also had a prior history of stage 2 ovarian cancer diagnosed in 2002 for which she received 6 cycles carboplatin + paclitaxel ending July 2002. She then was diagnosed with triple negative breast cancer (T2N1) on 11/8/07. She received cyclophosphamide, adriamycin, and 5FU from January 2008 till April 2008. She had recurrent breast cancer in May 2009, at which time she received cisplatin + gemcitabine for 24 cycles (May 2009- 2/22/10). In March 2010, she received 3 cycles of single agent gemcitabine. She began on Study 42 and received therapy with olaparib 400 mg twice daily from 4/28/10 till 9/30/13 (Day 1252). On 9/30/13, she was reported to have myelodysplasia (after persistent pancytopenia for several months leading up to the diagnosis of myelodysplasia), and therapy with olaparib was permanently discontinued at that time. Bone marrow aspirate and biopsy on 9/30/13 revealed hypercellular marrow with immature red and white cells. The differential diagnosis was MDS versus MDS with excess blasts and erythroleukemia. Although blasts were increased in the marrow, CD34 and C-kit failed to support the diagnosis. FISH was performed and showed: Deletion 5q31. A definitive diagnosis of erythroleukemia could not be made, and MDS was probable diagnosis. No information on therapy for MDS or outcome was provided.
14. E0017011- Study 9. olaparib. 68 y/o female with BRCA mutated ovarian cancer with metastases to the liver, soft tissue, lymph nodes originally diagnosed on 3/30/04. She also had a history of breast cancer treated with modified bilateral mastectomy. Therapy for ovarian cancer included surgery followed by carboplatin + paclitaxel. At the time of relapse, she received cisplatin + topotecan. She enrolled on Study 9. She started treatment with olaparib 400 mg twice daily on (b) (6) and continued until (b) (6) (231 days). Therapy was temporarily stopped due to neutropenia. On day 252, she was noted to have grade 2 anemia, fatigue, and thrombocytopenia, and grade 3 neutropenia. Olaparib was permanently discontinued at that

point. The only further information provided is that the patient died on (b) (6), with a primary cause of death listed as AML. No details of the diagnosis of AML were described. The death occurred 265 days after therapy with olaparib was discontinued.

15. E0613008- Study 9. olaparib. 63 y/ female diagnosed with BRCA mutated ovarian cancer on 1/16/06. She underwent surgery followed by chemotherapy with cisplatin + paclitaxel and achieved a complete remission. This was followed by therapy with pazopanib, which was stopped 32 days before starting olaparib. She began on Study 9, receiving olaparib 400 mg twice daily starting on (b) (6). She continued olaparib until (b) (6) (Day 1759), and the reason for discontinuation was grade 2 thrombocytopenia. She received no further therapy for ovarian cancer thereafter. On D1807 she was diagnosed with myelodysplastic syndrome (MDS) and was treated with 3 cycles of azacytidine. Transformation to AML occurred 158 days later, on D1965. Bone marrow biopsy confirming this transformation occurred on (b) (6). The marrow showed prominent infiltrate of primitive cells with myeloid features. Megakaryocytes were present in moderate to significantly reduced numbers. Erythropoiesis was decreased with scanty residual forms. Maturation was normoblastic. Granulopoiesis was significantly reduced but with normal maturation. The outcome of the diagnosis AML was death (Grade 5), but the exact date of the patient's death is not given.
16. E001-0078- Study 2. olaparib. 70 y/o female with BRCA2 mutated breast cancer originally diagnosed on 2/5/85. She also developed BRCA-2 mutated ovarian cancer on 1/22/02. Therapy for breast cancer included XRT to the chest wall and axilla, followed by chemotherapy with CMF and Tamoxifen for 5 years. Therapy for ovarian cancer included surgery followed by carboplatin + paclitaxel, leading to a complete remission. The ovarian cancer relapsed three times in the next 5 years, and was treated each time with carboplatin (i.e. 3 separate courses of carboplatin)-dates or exact number of cycles not specified. The disease progressed during the last course of carboplatin. She began Study 2 and therapy with olaparib 200 mg twice daily on (b) (6), and continued on therapy after the data cutoff date of (b) (6). On (b) (6), she was diagnosed with grade 4 MDS, after receiving a total of 976 days of olaparib. Olaparib was discontinued at that time. Bone marrow cytogenetics revealed a complex karyotype including +13 and 17p-, consistent with the diagnosis of therapy-related MDS. No therapy was administered for MDS, and no further therapy for ovarian cancer was given. The patient died 10 months after the MDS diagnosis. The primary cause of death was listed as acute myeloid leukemia. Details of when the MDS was considered to have transformed to AML are not provided.
17. 003-2117- Study 4. olaparib. 64 y/o female with a history of BRCA mutated breast cancer treated with XRT and ovarian cancer treated with carboplatin and paclitaxel. She enrolled on Study 4 on 3/18/10. On this study, she received therapy with carboplatin + paclitaxel in combination with olaparib 100 mg twice daily. She experienced grade 4 neutropenia necessitating treatment delay starting 6/16/10. Therapy with single agent olaparib was resumed on 8/24/10. Olaparib was then permanently discontinued on 10/10/11, after 580 days of therapy with olaparib. The reason for therapy discontinuation was "bone marrow toxicity". On

10/28/11, grade 4 therapy-related MDS was reported. Bone marrow biopsy showed 7.5% blasts, possibly RAEB1. She received multiple transfusions as a result of the diagnosis. She began therapy with azacytidine on 12/12/11. Further follow-up on the outcome was not available.

18. E83480380- Study 98. olaparib and cediranib. 67 y/o female with ovarian cancer diagnosed in 3/08. Therapy included platinum + taxane (adjuvant). Upon disease recurrence, she received treatment with carboplatin + gemcitabine + iniparib. She began therapy on Study 98, with olaparib (initial dose unspecified) and cediranib (20 mg daily) on 12/12/11. On 12/10/12, the patient was noted to have grade 1 thrombocytopenia, requiring delay of therapy with olaparib and cediranib. Treatment with olaparib was restarted on 1/7/13, at a reduced dose of 150 mg twice daily and the cediranib dose was reduced to 15 mg daily. On 1/14/13, patient had grade 2 thrombocytopenia. Olaparib and cediranib were discontinued 1/18/13. On (b) (6), she had a bone marrow aspirate which revealed 4% blasts, 50% myeloid cells, 37 % erythroid cells (dysplastic, left-shifted) with M:E ratio of 1.3:1. The diagnosis of MDS was made. One month later, on 4/3/13, patient had progression of ovarian cancer and began therapy with paclitaxel. This was then discontinued on 4/29/13, and palliative care was begun. At last follow up, on 5/21/13, patient was still alive.
19. 0810C00059/008. Study 59. olaparib with carboplatin/ paclitaxel. 60 y/o female originally diagnosed with ovarian cancer 9/07. She received carboplatin, taxol, and Avastin from 1/15/08 till 5/25/08. She then received topotecan + Avastin from 6/09 till 8/09. She then received low-dose carboplatin + Taxol+ Avastin from 8/08 till 2/10. Next, she received carboplatin + taxol+ Avastin from 11/10 till 2/11, followed by single agent carboplatin from 3/11 till 9/11 and from 12/11-1/12. She began Adriamycin in 3/12 and continued till 6/12. She enrolled on Study 59 on 12/10/12 and received olaparib 150 mg twice daily with weekly carboplatin and paclitaxel. She was on this therapy for 91 days. She was noted to have pancytopenia on 12/29/12. In addition, on 1/25/13, the patient was seen by a hematologist for pancytopenia. On 3/12/13, she was diagnosed with MDS bone marrow biopsy. Cytogenetic analysis showed two abnormal clones, each with deletion of 5q. One clone also had translocation of chromosomes 6 and 7 which resulted in monosomy 6p, partial monosomy 7q. This is consistent with therapy-related MDS. No further information was provided.
20. E0008004. Study 24. olaparib. 50 y/o white female with BRCA mutated ovarian cancer originally diagnosed 10/26/02. Prior chemotherapy included carboplatin + paclitaxel until 4/8/03. Upon initial relapse, she received Doxil, followed by carboplatin + paclitaxel again until 7/3/06, and another course of carboplatin + paclitaxel ending 3/15/10. She enrolled on Study 24 and received olaparib 400 mg twice daily from (b) (6) (data cutoff date). She was deemed to have progressive disease on 1/11/12. However, she continued on olaparib until (b) (6) (Day 233). She was noted to have grade 3 anemia on 5/29/13, at which time olaparib therapy was interrupted. She was transfused and restarted olaparib on 6/4/13. Grade 2 anemia persisted, so she was hospitalized on (b) (6) and received Vitamin B12 and folic acid. Olaparib was permanently discontinued on (b) (6) due to the anemia. On 7/5/13, she was noted to

have grade 4 thrombocytopenia. A diagnosis of MDS was suspected, but initial bone marrow biopsy was a “dry tap”. Repeat bone marrow on 8/27/13 was suspicious for MDS. She continued to have persistent anemia and thrombocytopenia. She was treated with azacytidine for 1 cycle on 10/28/13 without benefit. She subsequently died on (b) (6). Her cause of death was listed as being MDS, gross hematuria, and lung failure.

21. D0810C00055/JH001- Study 55 (Inv-sponsored trial). 67 y/o male with metastatic BRCA positive pancreatic cancer diagnosed originally in March 2011. He had a family history of breast, prostate, and ovarian cancer, as well as leukemia. He had previously received capecitabine and XRT for the pancreatic cancer. He began on study 55 and received olaparib 100 mg twice daily on days 1-8, in combination with cisplatin and irinotecan from 6/7/11 till 4/30/13. He experienced grade 4 neutropenia on study day 36, though details are not provided. He had therapy held on day 693 (4/30/13) due to failure of blood counts to recover. Additional testing was done and he was diagnosed with MDS on 6/19/13 (Day 744). He began therapy with azacitadine. He was noted to still have stable pancreatic cancer on 10/29/13. Description of bone marrow biopsy from 10/13 showed hypercellular marrow (70-80%) with trilineage hematopoiesis. M:E ratio increased >5:1. Megakaryocytes were decreased. Aspirate showed myeloid shift. Myeloblasts 5-6%. Peripheral blood smear showed cytopenias with abnormal, lobulated, hypogranular neutrophils. Flow cytometry revealed abnormal maturation and borderline increased blast count.
22. D0810C00055/JH004- Study 55 (Inv-sponsored trial). 67 y/o male with BRCA unknown pancreatic cancer diagnosed in 8/11. Comorbidities included alcoholism, GI hemorrhage, splenectomy, diabetes, prior smoker. He received chemotherapy with gemcitabine and capecitabine and XRT. He began on study 55 and initiated olaparib 100 mg twice daily on days 1-8 in combination with cisplatin and irinotecan on 3/20/12. He was on this therapy for 350 days until 3/5/12, when had progression of pancreatic cancer. He necessitated red blood cell transfusions during olaparib therapy for anemia. He was eventually diagnosed with MDS on 10/4/13 (Day 563). Bone marrow on 10/16/13 revealed “therapy-related myeloid neoplasm”. Marrow was hypercellular (70-80%) with trilineage hematopoiesis. M:E ratio increased (>5:1). Megakaryocytes decreased in number. Aspirate showed myeloid left shift and “megablastic” changes in erythroid and myeloid lineages. Myeloblasts 5-6%. Flow cytometry shows abnormal maturation and borderline increased myeloblasts.
23. E2804503- SOLO2- olaparib 300mg BID tablet arm- 56 year old white female (BRCA2 mut) with a history of hereditary spherocytosis (s/p splenectomy) and previous right breast cancer (ER/PR+, HER2+) treated in 2009 with surgery followed by adjuvant docetaxel, epirubicin, cyclophosphamide, trastuzumab, and letrozole. She was diagnosed with Stage IIIB serous papillary fallopian tube cancer 2/18/11. She received 3 lines of platinum-containing chemotherapy as follows: carboplatin + paclitaxel x 6 cycles 3/11- 6/12, carboplatin + gemcitabine + bevacizumab x 6 cycles 7/12- 11/12 followed by bevacizumab continuation until 7/13 (18 cycles total). She also received Doxil x 6 cycles 11/13- 4/14. She initiated therapy with

olaparib (b) (6) on SOLO2. Therapy was interrupted 6/27/14 due to an unknown AE, and restarted 8/5/14. On 1/2/15 she had white cell count $20.8 \times 10^9/L$ and leucoerythroblastic blood film, suspicious for myelodysplasia. Bone marrow biopsy 1/8/15 confirmed G4 MDS with marked dyserythropoiesis. Cytogenetics revealed del(5)(q13q33)[11]. Study drug was initially interrupted on (b) (6) (D218), and permanently discontinued on study D241 due to the MDS. At the time of study report, the MDS was ongoing. No treatment for the MDS had been reported. The patient was alive as of the data cutoff date (9/19/16).

Reviewer comment: This case is fairly typical of a treatment-related MDS, including other cases diagnosed in olaparib treated patients. The cytogenetic abnormality involving chromosome 5 is characteristic of diagnosis, and this patient had fairly long exposure (~241) to olaparib. Her prior exposure to Doxil may also have been a contributing factor in this case. In addition, this patient had a prior history of breast cancer, for which she was treated with additional chemotherapy, including anthracyclines. Given the entire clinical picture, a causal relationship between the MDS and olaparib exposure remains likely.

24. E7001507- SOLO2- olaparib 300mg BID tablet arm- 71 y/o female gBRCAm fallopian tube cancer diagnosed 3/24/10. She also had a prior history of breast cancer treated with surgery, XRT, hormonal therapy including tamoxifen and letrozole. Previous chemotherapy included carboplatin/ paclitaxel from 4/10-8/10, carboplatin/ paclitaxel from 8/11- 1/12, carboplatin/ paclitaxel from 8/12-11/12, catumaxomab 12/12-1/13, carboplatin/ caelyx 7/13-12/13. She required GCSF treatment during therapy with carboplatin and caelyx. Concurrent medical history included cutaneous xerosis, vitreous detachment, and anemia. She initiated therapy with olaparib on SOLO2 (b) (6). She received blood transfusions in (b) (6) during therapy. She had epistaxis in 5/15. She had G3 anemia resulting in dose interruption in (b) (6). And discontinuation on (b) (6) (study day 504). She was referred to a hematologist and bone marrow biopsy in (b) (6) revealed acute myeloblastic leukemia (Study day 526); cytogenetics were not reported. She initiated therapy with cytarabine and fludarabine (Days 540-679). She died on (b) (6), Day 680, which was 176 days after treatment discontinuation. The cause of death was AML.

Reviewer comment: This patient had history of two cancers, including breast and ovarian cancer, with prior exposure to anthracyclines and XRT. However, she was on olaparib therapy for 504 days, which is considerable exposure duration. Although no information on cytogenetics is reported, the clinical picture including the underlying BRCA2 mutation, and prolonged exposure to olaparib make a causative relation between olaparib exposure and the diagnosis of AML likely.

25. E2309503- SOLO2- olaparib 300mg BID tablet arm- 42 y/o female gBRCAm ovarian cancer diagnosed 11/3/11. She underwent initial cytoreductive surgery in 2011. She was treated with carboplatin + paclitaxel from 12/11- 5/12, and this was followed with maintenance bevacizumab until 5/13. She then received carboplatin + Doxil from 4/14 till 8/14. She had an additional history of

a well differentiated appendiceal neuroendocrine carcinoma. She began therapy with olaparib in the SOLO2 study (b) (6). She experienced grade 2 neutropenia starting day 272. This became a serious adverse event of grade 4 neutropenia starting on day 295, which lasted 7 days and resulted in dose interruption of olaparib. Olaparib therapy remained on hold until a diagnosis of CMML was made on day 324. This was grade 3 at the time of diagnosis. Hematologic parameters were within the normal range by CTC criteria. Olaparib therapy was permanently discontinued on study day 343. The patient went on to undergo allogeneic stem cell transplantation of CMML on day 644.

Reviewer comment: CMML is a less typical leukemia to be seen in the setting of olaparib therapy or other prior chemotherapy agents. However, similar to MDS, CMML has a propensity to progress to AML and is associated with features of both a myeloproliferative neoplasm and MDS at presentation. There also is overlap in the genetic mutations observed with MDS and CMML, particularly chromosome 7 abnormalities. Although an association with CMML and prior cytotoxic chemotherapy or XRT exposure is less clear, many consider the same exposures to be risk factors for the development of CMML. Given this information, it is feasible that PARP inhibitor exposure could also be a causative agent in the development of CMML, and a relationship between the exposure to olaparib and the development of CMML in this patient cannot be excluded.

26. E2601508- SOLO2- olaparib 300 mg BID tablet arm- 53 y/o female with gBRCAm ovarian cancer first diagnosed 5/8/08; she had ascites and peritoneal metastases at diagnosis. She underwent cytoreductive surgery followed by carboplatin/ paclitaxel ending 9/15/08. She then received immunotherapy with abagovomab ending 5/15/10. She received 2 subsequent lines of therapy with carboplatin/ gemcitabine ending 1/15/11 and 2/8/13. She also received cisplatin ending 4/9/14. (She underwent a total of 4 lines of platinum containing therapy prior to on-study date). She initiated therapy with olaparib (b) (6). She remained on therapy till (b) (6). While on study, she experienced 2 adverse events of neutropenia, one on day 450 and one on day 510. Both events led to dose interruption; the first event led to dose reduction to 200 mg BID. The second event ultimately was dose discontinuation (b) (6) day 616). Subsequent anticancer therapy with commercially available olaparib was initiated on day 687. The patient then underwent a bone marrow analysis on an unknown date, and the pathology was consistent with chemotherapy-related AML. At the time of data cutoff, the outcome of AML was unknown. No further details are provided.

Reviewer comment: Given that AML is a known safety signal associated with olaparib therapy, the lack of details on this patient's specific diagnosis (namely, the lack of reporting on bone marrow biopsy or cytogenetic analyses) is disappointing. Nevertheless, given the known association of olaparib with AML and the fact that this patient was on therapy for > 700 days, it is likely that the diagnosis of AML was causally related to olaparib therapy.

27. E2307506- SOLO2- placebo → received open-label olaparib after progression- 44 y/o female BRCAm ovarian cancer diagnosed 12/21/12. She received 2 prior lines of anticancer therapy with platinum-containing regimens and bevacizumab ending 1/9/14. She initiated therapy with placebo on the SOLO2 study (b) (6) and remained on until (b) (6) (226 days), when she had disease progression. She

subsequently received therapy with doxorubicin and carboplatin (days 275-393), followed by maintenance therapy with olaparib (days 478-568). She also received experimental therapy with oral Navitoclax (days 610-638). On day 659 she was hospitalized and was transfused 2U PRBCs, as well as platelets and plasma. She was diagnosed with acute myeloid leukemia at this time (day 659), which was (b) (6). Bone marrow biopsy confirmed the diagnosis, but no details of the report or cytogenetics are provided. On day 666, therapy with azacitadine was initiated. The patient died the next day, day 667. The primary cause of death was said to be AML, the secondary cause of death was cardiac arrest. Autopsy was not performed.

Appears this way on original

28. E0008002- Study 24- ovarian cancer- BRCA1 mut – 80 y/o female ovarian cancer. She received carboplatin/paclitaxel x 6 cycles 11/03- 2/04, carboplatin/ paclitaxel x 4 cycles from 4/04- 7/04, and carboplatin/ paclitaxel x 6 cycles from 3/08- 9/09. She began therapy with olaparib (b) (6) and continued for almost 5 years until (b) (6), when she was found to have grade 2 anemia. Olaparib was stopped. Bone marrow analysis revealed MDS including megakaryopoeisis with dysplastic forms; myelofibrosis WHO grade 1. Myeloid precursors were noted with 10.5% blasts. Genotype findings were consistent with myelodysplasia and lymphoproliferative neoplasia. There was a complex karyotype (> 3 anomalies) on cytogenetics and FISH, consistent with unfavorable prognosis. She initiated therapy with azacytidine on 4/11/16. The MDS was ongoing at the time of data cutoff.

Reviewer comment: This case is consistent with other cases of therapy related MDS, including those associated with olaparib. This particular patient was on therapy with olaparib for almost 5 years, which is longer than many patients, but this duration makes a relation to olaparib to be highly likely.

29. E5701001- SOLO3- olaparib 68 y/o female with ovarian cancer and unspecified gBRCAm was previously treated with carboplatin/paclitaxel from 4/11- 9/11, then second line therapy with carboplatin/paclitaxel from 6/14- 2/14, third-line carboplatin from 7/14-11/14, therapy with Caelyx from 10/15- 2/16. She began therapy with olaparib 300 mg twice daily on (b) (6), and discontinued one month later on (b) (6) when she had disease progression. She had had normal platelets at the time of starting olaparib. One month after discontinuing therapy, she had grade 2 thrombocytopenia, which worsened to grade 4 in (b) (6), and was associated with grade 3 neutropenia. Bone marrow biopsy on

11/24/16 revealed severe myelodysplastic syndrome. No cytogenetics information was reported, nor was information on whether the patient received therapy for MDS. The MDS was thought to be related to olaparib therapy by the investigator and was ongoing at the time of data cutoff.

Reviewer comment: Agree with the Sponsor assessment that there is likely a causal relationship between olaparib and the development of MDS in this patient.

30. D4191N00012- 66 y/o female with BRCA wild type serous ovarian cancer diagnosed 7/12. She received treatment with carboplatin/ paclitaxel, carboplatin/ gemcitabine, bevacizumab/ Doxil, docetaxel and cyclophosphamide from 12/15- 3/16. She also had a history of breast cancer diagnosed 10/14 and treated with partial mastectomy, as well as history of thalassemia and anemia. She began therapy on study D4191N00012 with durvalumab (PD1 inhibitor) and olaparib. She was on this therapy from (b) (6), when it was discontinued. She developed grade 3 thrombocytopenia 3/15/16 while she was on oral Cytosan (which may have been for the thalassemia). Bone marrow biopsy revealed hypercellular marrow with atypical megakaryocytes, suspicious for MDS. She began therapy with azacitidine and stopped the Cytosan. The MDS was ongoing at the time of data cutoff. The investigator determined that the MDS was possibly related to olaparib and probably related to Cytosan.

Reviewer comment: I agree with the investigator assessment that the diagnosis of MDS in this particular case may have been related to both olaparib and/or Cytosan. The definitive underlying cause cannot be determined with certainty, but the contribution of olaparib cannot be excluded. It is notable that although she is said to be BRCA wt, her overall history, including diagnoses of breast and ovarian cancers, are suspicious for an underlying mutation in a less common pathway, possibly HRD.

31. Managed access program- 2015SE123- 66 y/o French female ovarian cancer- BRCA2 mut, she was enrolled in the Olaparib French Named Patient Temporary Authorization for US program for patients with platinum-sensitive relapsed ovarian cancer. She had prior history of breast infiltrating lobular carcinoma treated with surgery, XRT, and chemotherapy (not specified), as well as hormonal therapy. She was diagnosed with high grade serous ovarian cancer 8/9/11. She also was on tamoxifen for breast cancer at the time. She had recurrent ovarian cancer in 3/14, treated with carboplatin/ Doxil for 8 cycles (3/14-10/14) and then initiated therapy with olaparib (b) (6). Her platelet count was not normal at baseline. After ~ 2 months, she developed grade 2 anemia and elevated LFTs. She also developed thrombocytopenia and neutropenia. Olaparib was discontinued (b) (6). Her count had not recovered by 4/15, so bone marrow was performed and revealed myelodysplasia. She subsequently was found to have AML (27% blasts) on 6/8/15 with unfavorable cytogenetics 45, XX, del5; q13, -17, del 5, -7. She started azacitidine, but developed worsening pleural progression of ovarian cancer which required initiation of Caelyx. On (b) (6), she was admitted to palliative care unit. She died due to MDS/ AML and left "pleurisy" on (b) (6). The investigator thought the MDS was related to olaparib.

Reviewer comment: This patient had exposure to both olaparib and anthracyclines as possible etiologies for her AML/MDS diagnosis. The association between anthracyclines and abnormalities of chromosome 5 and 7 do make a contribution of prior Caelyx/ doxorubicin notable in this case, but an underlying association with olaparib therapy can also not be ruled out. Whether this patient's risk was enhanced due to exposure to both agents is also unknown, but possible.

32. D0817C00003- blinded olaparib vs. placebo + bevacizumab- 58 y/o with ovarian cancer and family history including colon, breast, and peritoneal cancers. It is said that her BRCA mutation status was unknown. She received frontline therapy for ovarian cancer with carboplatin-based therapy for 9 cycles from 4/15- 10/15. She began therapy with olaparib on the current study (standard first-line carboplatin/paclitaxel and bevacizumab with concurrent and maintenance olaparib vs. placebo). She began study drug (olaparib vs. placebo) (b) (6). Dose of olaparib was reduced due to anemia. Anemia was G3 in 3/16. Her last dose of bevacizumab was 7/16 and of olaparib was (b) (6). She was diagnosed with MDS on 8/2/16 with G3 anemia at the time. Olaparib was discontinued on (b) (6) but bevacizumab was continued. Information on bone marrow analysis or cytogenetics was not provided. A causal relationship with olaparib could not be ruled out. MDS was ongoing at the time of data cutoff.

Reviewer comment: As with other cases, a causal relationship with (blinded) olaparib therapy cannot be excluded.

33. E1003004 (SOLO1)- blinded olaparib vs. placebo in patients in response to first line platinum. 66 y/o female with BRCA2m ovarian cancer who had completed first line platinum and enrolled on a blinded study of olaparib vs. placebo maintenance. Prior therapy had included carboplatin/paclitaxel from 2/14- 6/14. She then began on the randomized study on (b) (6). It is not specified how long she remained on study therapy, but was diagnosed with secondary AML on 2/18/16. She began therapy for the AML, and this was ongoing at the time of data cutoff.

Reviewer comment: Although details, including cytogenetics, are missing from this patient's narrative, a causal association of olaparib/placebo with the onset of AML cannot be ruled out.

34. E5001006 (SOLO1)- blinded olaparib vs. placebo in patients in response to first line platinum. 54 y/o female with BRCA1m ovarian cancer who was treated with first-line platinum based chemotherapy and then enrolled into the SOLO1 maintenance study. She began blinded therapy (olaparib vs. placebo) on (b) (6). Study drug was discontinued (b) (6) (reason not clear). She was found to have pancytopenia in 7/16. Bone marrow samples revealed hypocellular marrow with fibrosis and increased blasts. Myeloproliferative neoplasm (hypocellular marrow with fibrosis and increased blasts) was the diagnosis. The investigator felt that the diagnosis of MDS was related to study therapy. No further testing results were provided. The MDS was ongoing at the time of data cutoff.

Reviewer comment: Although it is not known whether this patient received olaparib or placebo, she was not as heavily pretreated as other cases of MDS/AML after olaparib therapy since she had only received first-line platinum. If she did receive olaparib, she was on that therapy for approximately 18 months, and therefore it is reasonable to suspect a causal relationship with the development of MDS, based upon the timing.

Secondary malignancies other than MDS/AML

Another safety signal associated with olaparib has been the development of secondary solid tumors, other than MDS/AML. An analysis of events was conducted for the SOLO2 study and other studies in the tablet formulation pool. A total of 8 cases of solid tumors in 7 patients, excluding MDS/ AML, were identified in patients treated with olaparib tablets, as well as one case in a placebo patient on SOLO2. A summary of the diagnoses in patients treated with the tablet formulation of olaparib are shown in Table 46. Available narratives for these cases were reviewed and are discussed below the table.

Reviewer comment: There appear to have been fewer diagnoses, overall, of secondary solid tumors in the tablet safety database, compared with the capsule. The reason for this is difficult to interpret, although there was only 1 report of a skin cancer in the tablet database, compared with 9 reports under NDA 206162 (including 1 case of melanoma). It is possible that reporting of skin cancers (basal cell and squamous cell) simply was not done with the tablet formulation, given the commonness of these tumors in the general population, regardless of other factors. Regardless, the incidence of secondary solid tumors was not described in the original olaparib label, and no changes will be made to the current label, based upon these updated assessments.

Table 46 Secondary solid tumor malignancies with tablet formulation (SOLO2 included)

No.	Study	Patient ID	Age	Race	Treatment arm	BRCA status and/or primary cancer	Secondary cancer	Time to onset (study day)
1	SOLO2	E4304505	57	Asian	olaparib	BRCA1mut Ovarian cancer	Gastric cancer Lymphoma unspecified	513

2	SOLO2	E6002502	59	Asian	olaparib	BRCA2mut ovarian	Gastric cancer	156
3	SOLO2	E5702504	60	White	olaparib	BRCA1mut ovarian	Hepatic neoplasm (focal lesion)	344
4	SOLO2	E2803503	65	white	olaparib	BRCA1mut ovarian	Meningioma	109
5	SOLO2	E2307511	56	white	olaparib	BRCA1mut ovarian	Plasma cell myeloma	714
6	SOLO2	E2302503	56	white	placebo	BRCA1mut ovarian	Invasive ductal breast carcinoma	596
7	DC081CC00001 (anti-hormonal PK study)	E0501006	67	white	Olaparib + letrozole (fasted) Part B	Prostate	Transitional cell carcinoma bladder	289
8	DC0816C00006 (Phase I renal impairment study)	E2368002	72	white	Olaparib Part A + Part B	Renal cell	Basal cell carcinoma skin	216

- 1) E4304505- SOLO2 study- Olaparib- Gastric cancer and Lymphoma- 57 y/o Asian female (from Japan) with BRCA1 mut ovarian cancer. She received 2 prior platinum regimens for ovarian cancer and started olaparib (b) (6) on SOLO2 study. Study D501 had G2 intestinal obstruction. Gastroscopy was performed revealing swollen gastric wall. Olaparib was interrupted (b) (6). She underwent debulking surgery and pathology (b) (6) revealed G3 moderate gastric cancer (SAE also). Olaparib was interrupted, but restarted (b) (6). At the time of DCO 1/27/16, the event of gastric cancer was resolved. The same patient was subsequently diagnosed with lymphoma on study day 908 of olaparib therapy. Treatment was interrupted as a result of this diagnosis, and was subsequently discontinued on treatment day 965.

Reviewer comment: It is difficult to determine attribution of olaparib in this case. This patient was from Japan, where the prevalence of gastric cancer is higher than other regions. She also had an underlying gBRCA mutation, but it is unclear whether this increases the risk of developing gastric cancer. Likewise, the details of her later lymphoma diagnosis were also lacking, and no further information was available.

- 2) E6002502- SOLO2 study- Olaparib- Gastric cancer- 59 y/o Asian female (from Korea) with BRCA2 mut ovarian cancer. She had received 2 prior lines of platinum-based chemotherapy. She started olaparib on (b) (6). While on olaparib, she experienced abdominal pain, gastritis, and decreased appetite. She underwent EGD on Day 149. Olaparib was interrupted on Day 151 due to the decreased appetite. The G3 SAE of gastric cancer was diagnosed on Day 156 (b) (6) and olaparib was permanently discontinued at that time. Prior to the diagnosis of the gastric cancer, she was found to also have progressive ovarian cancer (exact date not specified); the investigator considered the event to actually be ovarian cancer metastatic to the stomach. The event of gastric cancer was reported as resolved on Day 180, though it does not specify how it resolved (if it was treated). The patient received subsequent chemotherapy for ovarian cancer with doxorubicin from days 207-274. She died on Day 369 (b) (6), which was 218 days after stopping olaparib. The primary cause of death was said to be progressive ovarian cancer, with a secondary cause being multi organ dysfunction. Autopsy was not performed.

Reviewer comment: Although the narrative includes conflicting information, including that the diagnosis was actually ovarian cancer metastatic to the stomach rather than a second primary gastric cancer, the study report and narratives do report this throughout as a case of gastric cancer. The contribution of olaparib to the occurrence of the gastric cancer is unclear.

- 3) E5702504-SOLO2 study- Olaparib- Hepatic neoplasm- 60 y/o white female with BRCA1 mutated ovarian cancer. She had received 2 prior platinum containing regimens and started on olaparib (b) (6). She experienced AEs of abdominal pain, nausea/vomiting, and asthenia while on olaparib. On study day 344 she was reported to have a hepatic neoplasm (liver focal lesion-tumor). The patient was hospitalized on Day 345 for this event. She remained hospitalized till day 347, and the event of hepatic neoplasm was said to have resolved by Day 349. Treatment with olaparib was interrupted from Day 344-350 due to this event. Olaparib was resumed on Day 351 and continued until day 715 when progressive ovarian cancer was diagnosed and treatment was discontinued.

Reviewer comment: The details of the hepatic neoplasm are not well described. It is noted in the study report that the investigator actually considered this event to be disease progression of the underlying ovarian cancer, rather than a primary hepatic neoplasm. However, a biopsy did not appear to have been performed and the patient remained on olaparib therapy for an additional year after the hepatic neoplasm was "diagnosed". If the lesion represented progressive ovarian cancer, it seems that this may have been an isolated area of metastasis, which would be unusual. Otherwise there is not an explanation for why the investigator continued olaparib therapy if he/she thought the patient had progressed on therapy.

- 4) E2803503- SOLO2 study- meningioma- olaparib- Narrative not provided, given that this was a benign tumor.
- 5) E2307511- SOLO2 study- plasma cell myeloma- olaparib- 56 y/o white female with Stage IV serous ovarian cancer diagnosed 6/16/11. Underwent debulking surgery followed by carboplatin + paclitaxel ending 10/11 with PR. She then received carboplatin + paclitaxel again for 3 cycles in 1/12-2/12, followed by bevacizumab for 16 cycles until 1/13. She then received carboplatin + Doxil for 9 cycles from 2/14- 9/14 and achieved a CR. She began olaparib therapy on SOLO2 on (b) (6). Discontinued study on (b) (6) when she had a fall and was diagnosed with epiduritis (which resulted in discontinuation of olaparib therapy). She was subsequently diagnosed with multiple myeloma from bone biopsy on (b) (6) (study day 714).

Reviewer comment: The details of this case are lacking due to missing narrative. Given that myeloma is a hematologic malignancy, it is interesting to consider whether there may be an association between this event and olaparib. It seems that a possible association cannot be ruled out.

- 6) E2302503- SOLO2 study- breast- placebo- 56 y/o white female with BRCA1m ovarian cancer diagnosed 2/8/11. She received two prior lines of platinum, as well as XRT. She was randomized to the placebo arm on the SOLO2 study on (b) (6). On study D 596 (b) (6), she was diagnosed with infiltrating ductal carcinoma of the R breast. She was discontinued from placebo at that time (b) (6). She was treated for the invasive breast cancer and was listed as having recovered on D135 (b) (6).

Reviewer comment: Given that this patient was randomized to placebo and had not exposure to olaparib, there is no causality that can be associated between olaparib and the diagnosis of breast cancer.

- 7) E0501006- antihormonal study- olaparib- 67 y/o male with a history of prostate cancer diagnosed 2/10. Previous therapies included XRT in 2011, casodex, docetaxel/ prednisone (2012), and abiraterone/ prednisone and cabazitaxel in 2013. He then received docetaxel/ prednisone in 2014, LHRH agonist with enzalutamide in 2014. He began on a Phase I, open-label study to assess effect of olaparib on PK antihormonal agents including anastrozole, letrozole, and tamoxifen. He received olaparib tablet 300 mg BID with letrozole 2.5 mg daily beginning on (b) (6) and ending (b) (6) (D329); treatment was stopped due to disease progression. While

on study, on D289, he was diagnosed with transitional cell carcinoma of the bladder. He underwent surgical therapy (curettage) on Day 278 (for diagnostic purposes). He subsequently began chemotherapy for both the diagnosis of bladder cancer and the prostate cancer on D332; therapy consisted of oxaliplatin and gemcitabine. The investigator thought that the new diagnosis of transitional cell carcinoma of the bladder was unrelated to olaparib therapy.

Reviewer comment: Although the patient may have had risk factors for the development of bladder cancer (including a previous diagnosis of prostate cancer), he was on olaparib therapy for over 1 year. It seems that a causative association between olaparib and the onset of bladder cancer cannot be ruled out, given that olaparib therapy has been thought to be associated with development of other tumors (mainly MDS/AML, but possibly other solid tumors). The contribution in this particular case, however, is unclear.

8) E2803503- DC0816C00006- olaparib- (Phase I renal impairment study)- basal cell skin cancer- no narrative provided.

In the safety database with the capsule formulation (including patients treated on Study 19), there were reports of 21 secondary malignancies in 19 patients treated with the olaparib capsule, excluding cases of MDS and AML. The majority of those tumors was skin cancers, and occurred mostly in patient with documented BRCA mutations (17 of the 19 patients). There appeared to be confounding factors in all cases, making definitive determination of the contribution of olaparib difficult, but a risk of developing secondary malignancies other than MDS/ AML appears to be present. The cases of secondary malignancies in patients receiving the capsule formulation of olaparib are shown in *Table 47*.

Table 47 Secondary malignancies in patients receiving olaparib (capsule formulation)

No.	Study #	Patient ID	Study Treatment	BRCA status	Secondary cancer diagnosed	Time to onset (days)
1	19	E1701005	olaparib	mutated	Breast	469
2	19	E0106003	olaparib	mutated	Colon cancer	145
3	19	E1203002	Placebo	negative	Bladder cancer	44
4	12	E8001045	olaparib	mutated	Plasma cell myeloma	Post-tx. 784
5	12	E8001062	olaparib	mutated	Lung cancer	1085
					Lung carcinoma cell not specified, "recurrent"	1507
6	20	E0101044	olaparib	negative	Squamous cell	836

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					skin	
					Basal cell	787
7	24	E0004006	olaparib	mutated	Breast	204
8	42	E4001075	olaparib	mutated	Breast	504
9	42	E4004011	olaparib	mutated	Gastric cancer	Post-tx D359
10	42	E7801020 Male- pancreatic	olaparib	mutated	Squamous cell skin	361
11	42	E4001012	olaparib	mutated	Basal cell	448
12	42	E4001077	olaparib	mutated	Basal cell	14
13	42	E4001080	olaparib	mutated	Basal cell	176
14	42	E4001005	olaparib	mutated	Basal cell	366
15	42	E4001055	olaparib	mutated	Basal cell	208
16	42	E7801032	olaparib	mutated	Skin cancer	41
17	42	E2601008	olaparib	mutated	Skin (nos)	1
18	63	TN04 Male- CLL primary	olaparib	Not tested	Melanoma	90
19	4	002-01- 2109	Olaparib + carbo and taxol—then olaparib mono	mutated	Precursor T- lymphoblastic lymphoma/ leukemia	(b) (6) (died D (b) (6))
20	21	E0002986	Olaparib + cisplatin	mutated	Malignant muscle neoplasm	16

Pneumonitis

A previously described event found to be associated with olaparib therapy is pneumonitis. On review of the safety database for the capsule formulation of olaparib, there were 10 olaparib treated patients (including 1 on Study 19) who experienced pneumonitis during or after therapy with olaparib. The event was particularly concerning because five of the ten patients (50%) died as a result of the pneumonitis.

In the current submission, an analysis of cases of pneumonitis associated with the tablet formulation of olaparib was also conducted. A total of 6 cases were identified, including 3 patients receiving olaparib on SOLO2 and 3 additional cases on other studies in the safety database. In contrast to the cases seen with the capsule formulation, there were no cases with an outcome of death, and 4 of the 6 cases were considered to be grade 1 by the Sponsor (radiographic findings only). Several cases with the tablet formulation occurred in patients with history of prior chest radiation therapy, including one patient who had experienced radiation pneumonitis in the past. Based upon the new cases described with this application, pneumonitis remains one of the adverse events of interest in the product label.

Brief pneumonitis narratives:

SOLO2 cases

- 1) SOLO2- E7005505- olaparib- 55y/o white female with BRCA2m ovarian cancer diagnosed 5/14/12. Previously received two lines of platinum therapy. She had a prior smoking history. She began therapy with olaparib (b) (6). On study D83, she was diagnosed with G1 pneumonitis. She did not receive therapy and olaparib was not interrupted. No duration for the AE was noted. At the time of data cutoff (9/19/16) the event was not resolved.
- 2) SOLO2- E7005505- olaparib- 55y/o white female with BRCA2m ovarian cancer diagnosed 5/14/12. Previously received two lines of platinum therapy. She had a prior smoking history. She began therapy with olaparib (b) (6). On study D83, she was diagnosed with G1 pneumonitis. She did not receive therapy and olaparib was not interrupted. No duration for the AE was noted. At the time of data cutoff (9/19/16) the event was not resolved.
- 3) SOLO2- E7808501- olaparib- 70 y/o white female with BRCA1m ovarian cancer diagnosed 9/09. Previously received 3 lines of anticancer therapy with platinum-containing regimens. She also received XRT to the mediastinum in 2013, and had experienced radiation pneumonitis at that time. She began olaparib therapy on the SOLO2 study on (b) (6). She experienced G1 pneumonitis first noted on study D 29. She was treated for this adverse event with prednisone from study days 46-123. The olaparib dose was not interrupted or changed. The adverse event of pneumonitis was said to have resolved by study day 95.

Reviewer comment: This adverse event of pneumonitis should be considered a grade 2 event (rather than grade 1) based upon the fact that the patient was treated with steroids (G2, by CTCAE). Although this patient had received prior radiation therapy and had experienced radiation pneumonitis, a causal association between olaparib and the event described cannot be ruled out. It has also been suggested that prior chest radiation therapy is an additional risk factor for the development of pneumonitis during olaparib therapy, and that may have been the case with this patient.

Version

Safety database cases

- 4) D0816C0004- E2841001- 77y/o male with lung cancer on Study 4, experienced a serious adverse event of G3 pneumonitis beginning study day 174. Olaparib therapy (300 mg BID tablet) was withdrawn as a result of the diagnosis. The event was considered to be related to olaparib. It is not known whether the patient had received prior radiation therapy.
- 5) D0816C0004- E5043001- 37 y/o female with breast cancer on Study 4 (olaparib tablet 300 mg BID) experienced G2 pneumonitis beginning on study day 9, which was not considered serious. The dose of olaparib was not changed, as a result of the event. The investigator did not think this event was related to olaparib. The event was not resolved at the time of data cutoff.
- 6) D081CC00001- E0502005- 57 y/o female with ovarian cancer on study 1, received olaparib (tablet 300 mg BID) + letrozole on clinical trial. She experienced G1 pneumonitis (not serious) beginning on study day 109; olaparib dose was reduced as a result.

Reviewer comment: Based upon the cases reviewed in the current application, it appears that although the possibility of developing pneumonitis still exists with the tablet formulation, there seem to have been fewer cases reported compared to the capsule formulation and no cases resulting in death with the tablet. Given that pneumonitis is admittedly a rare event associated with olaparib use, it is difficult to draw too many conclusions from the new cases. The review team recommended that pneumonitis remain in the Warnings and Precautions section (5.2) of the label, and the Sponsor agreed. No changes were made to the overall wording of the warning to prescribers, which includes advising that some cases of pneumonitis associated with olaparib have been fatal.

Treatment Emergent Adverse Events and Adverse Reactions

Common Adverse Events

The most common grade 1-4 adverse reactions in > 10% of patients in either arm on SOLO2 are shown in Table 48. The adverse events that are most notable include cytopenias and gastrointestinal disorders. In particular, cytopenias of all types are the most predominant reason for dose modifications of olaparib. Likewise, many patients on both arms experienced various gastrointestinal adverse events, including nausea, vomiting, and abdominal pain. Although olaparib is certainly associated with these various gastrointestinal adverse events, it is notable that many of these events are symptoms that patients with advanced ovarian cancer experience based upon the nature of the underlying disease.

Table 48 SOLO2 Grade 1-4 Adverse Reactions in >10%

Adverse reactions by SOC and PT	Olaparib N=195 (%)		Placebo N= 99 (%)	
	G1-4	G3-4	G1-4	G3-4
Any adverse reaction	192 (98)	72 (37)	94 (99)	18 (18)
Blood and lymphatic system disorders				
Anemia	85 (44)	38 (20)	9 (9)	2 (2)
Neutropenia	38 (19)	10 (5)	6 (6)	4 (4)
Leukopenia	31 (16)	5 (3)	2 (2)	0
Thrombocytopenia	27 (14)	2 (1)	3 (3)	1 (1)
Gastrointestinal disorders				
Nausea	148 (76)	5 (3)	33 (33)	0
Abdominal pain	85 (44)	5 (3)	47 (47)	4 (4)
Vomiting	73 (37)	5 (3)	19 (19)	1 (1)
Diarrhea	65 (33)	3 (2)	22 (22)	0
Constipation	40 (21)	0	23 (23)	3 (3)
Stomatitis	39 (20)	2 (1)	16 (16)	0
Dyspepsia	34 (17)	0	10 (10)	0
General disorder and administration site conditions				
Fatigue/ Asthenia	128 (66)	8 (4)	39 (39)	2 (2)
Pyrexia	27 (14)	1 (0.5)	6 (6)	0
Infections and infestations				
Nasopharyngitis/ URI/ sinusitis/ rhinitis/ influenza	70 (36)	0	29 (29)	0
Urinary tract infection	28 (14)	2 (1)	11 (11)	0
Investigations				
Blood creatinine increased	23 (12)	0	3 (3)	0
Metabolism and nutrition disorders				
Decreased appetite	43 (22)	0	11 (11)	0
Hypomagnesemia	31 (16)	0	13 (13)	0
Musculoskeletal and connective tissue disorders				
Arthralgia/ myalgia	58 (30)	0	28 (28)	0
Back pain	22 (11)	0	13 (13)	2 (2)
Nervous system disorders				
Dysgeusia	52 (27)	0	7 (7)	0
Headache	50 (26)	1 (0.5)	14 (14)	0
Dizziness	30 (15)	1 (0.5)	8 (8)	0
Respiratory disorders				
Cough	35 (18)	1 (0.5)	5 (5)	0
Dyspnea	27 (14)	2 (1)	1 (1)	0
Skin and subcutaneous tissue disorders				
Rash	36 (18)	0	15 (15)	0
Edema	21 (11)	1 (0.5)	7 (7)	0

The common grade 1-4 adverse events on Study 19 were reviewed previously, however the focus had been in only patients with gBRCA mutation, at that time. Based upon the intention to expand the approval indication to include all patients with relapsed ovarian cancer in response to chemotherapy, without regard to gBRCA status, an updated analysis of adverse events in the ITT population from Study 19 was conducted. The common grade 1-4 adverse events in the ITT population from Study 19 are depicted in Table 49.

Table 49 Study 19 Grade 1-4 Adverse Reactions

AE category SOC/ Preferred term	ITT safety population n=265			
	Olaparib 400 mg N=136		Placebo N=128	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Blood and Lymphatic disorders				
Anemia	34 (25)	3 (2)	9 (7)	1 (1)
Neutropenia	9 (7)	4 (3)	7 (5)	2 (2)
Thrombocytopenia	5 (4)	0	3 (2)	0
Gastrointestinal disorders				
Nausea	98 (72)	1 (1)	47 (37)	0
Abdominal pain	67 (49)	2 (1)	55 (43)	4 (3)
Vomiting	46 (34)	3 (2)	18 (14)	1 (1)
Diarrhea	38 (28)	3 (2)	32 (25)	2 (2)
Constipation	28 (21)	0	16 (13)	0
Decreased appetite	28 (21)	0	17 (13)	0
Dyspepsia	24 (18)	0	11 (9)	0
Dysgeusia	22 (16)	0	8 (6)	0
General disorders				
Fatigue + Asthenia	84 (62)	2	60 (47)	1 (1)
Pyrexia	13 (10)	1	4 (3)	0
Edema (peripheral edema)	12 (9)	0	8 (6)	0
Infections and infestations				
Nasopharyngitis/URI/Pharyngitis	39 (29)	0	24 (18)	0
Investigations				
Blood creatinine/ BUN increased	7 (5)	0	2 (2)	0
Hypomagnesemia	9 (7)	1	15 (12)	0
Metabolism and nutrition disorders				
Decreased appetite	28 (21)	0	17 (13)	0
Hyperglycemia	3 (2)	0	5 (4)	0
Musculoskeletal and Connective tissue disorders				
Arthralgia/Musculoskeletal pain	41 (30)	1	35 (27)	0
Myalgia	19 (14)	1	16 (13)	0
Back pain	22 (16)	2	16 (13)	0

Nervous system disorders				
Dizziness	21 (15)	0	12 (9)	0
Headache	28 (21)	0	17 (13)	0
Peripheral neuropathy	19 (14)	1	14 (11)	0
Memory impairment	5 (4)	1	6 (5)	0
Dysgeusia	22 (16)	0	8 (6)	0
Psychiatric disorders				
Anxiety	9 (7)	0	8 (6)	0
Depression	12 (9)	0	11 (9)	0
Insomnia	8 (6)	0	9 (7)	0
Renal and Urinary disorders				
Dysuria	4 (3)	0	4 (3)	0
Urinary incontinence	5 (4)	0	2 (2)	0
Vulvovaginal disorder	4 (3)	0	5 (4)	0
Respiratory, Thoracic, Mediastinal disorders				
Cough	29 (21)	0	13 (11)	0
Dyspnea	19 (14)	2	8 (6)	0
Skin and Subcutaneous Tissue disorders				
Dermatitis	3 (2)	0	5 (4)	0
Dry skin/ eczema	3 (2)	0	8 (6)	0
Rash	22 (16)	0	17 (13)	0
Pruritis	7 (5)	0	7 (5)	0
Vascular disorders				
Hypertension	9 (7)	1	9 (7)	0
Venous thrombosis (includes PE and vena cava thrombus)	3 (2)	1	3 (2)	1
Hot flush	8 (6)	0	17 (13)	0

Reviewer comment: The main difference, with regard to common adverse events, between the SOLO2 study and Study 19 appears to be in the hematologic adverse events, such that more events in every category (anemia, neutropenia, and thrombocytopenia) occurred in olaparib treated patients on SOLO2 when compared to Study 19. This is most likely due to the different formulations (tablet vs. capsule) used in each trial, and supports the proposed labeling claims, advising clinicians to be aware of the different formulations and instructions that the two formulations are not interchangeable. In addition, it is notable that the overall plan for the marketing of olaparib is that the capsule formulation will be discontinued and only the tablet formulation will be available for all patients.

Laboratory Findings

The laboratory abnormalities seen in patients treated on SOLO2 are shown in Table 50 and those for the ITT population on Study 19 are shown in Table 51. The incidence for these abnormalities was calculated using the respective laboratory datasets for each study. The results analyzed were the standard

reference laboratory values, including only on-study (post-baseline) values. Grading utilized was according to CTCAE v.4.03.

Table 50 Laboratory abnormalities SOLO2

	Olaparib N=195 (%)		Placebo N=99 (%)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Decrease in lymphocytes (10 ⁹ /L)	167 (86)	19 (10)	67 (68)	1 (1)
Increase in mean corpuscular volume (fL)	168 (86)	-	45 (45)	-
Decrease in hemoglobin (g/dL)	165 (85)	34 (17)	72 (73)	1 (1)
Decrease in leukocytes (10 ⁹ /L)	160 (82)	12 (6)	67 (68)	2 (2)
Decrease in absolute neutrophil count (10 ⁹ /L)	117 (60)	17 (9)	45 (45)	5 (5)
Decrease in platelets (10 ⁹ /L)	88 (45)	4 (2)	24 (24)	2 (2)
Increase in serum creatinine (μmol/L)	86 (44)	0	29 (29)	0

Table 51 Study 19 Laboratory abnormalities ITT

Laboratory parameter	Olaparib N= 136		Placebo N=129	
	Grades 1-4 N (%)	Grades 3-4 N (%)	Grades 1-4 N (%)	Grades 3-4 N (%)
Decrease in hemoglobin (g/dL)	116 (85)	9 (7)	83 (64)	1 (1)
Decrease in leukocytes (10 ⁹ /L)	103 (78)	4 (3)	68 (53)	1 (1)
Increase in mean corpuscular volume	101 (74)	-	45 (35)	-

(fL)				
Decrease in absolute neutrophil count (10 ⁹ /L)	62 (46)	6 (4)	45 (35)	3 (2)
Increase in serum creatinine (μmol/L)	60 (44)	1 (1)	18 (14)	0
Decrease in platelets (10 ⁹ /L)	41 (30)	1 (1)	24 (19)	0
Decrease in lymphocytes (10 ⁹ /L)	28 (21)	0	13 (10)	0

Reviewer comment: During labeling negotiations, (b) (4)

Vital Signs

The on-study vital sign deviations for SOLO2 and Study 19 (ITT) are shown in Table 52 and Table 53, respectively. It is notable that there were not marked differences between study arms in most parameters, which may indicate that assessment of individual vital signs in this application may not be as reliable as assessing adverse events (which may include abnormalities in vital signs). No definitive conclusions can be made on vital sign analyses that will affect labeling recommendations.

Table 52 SOLO2 On-study vital sign abnormalities

	Olaparib		Placebo	
	N=196		N=99	
	G1-4 N (%)	G3-4 N (%)	G1-4 N (%)	G3-4 N (%)
Temperature (fever)	6 (3)	0	2 (2)	0
High systolic BP	166 (85)	16 (8)	86 (87)	2 (2)

Low systolic BP	16 (8)	-	5 (5)	-
High diastolic BP	129 (66)	6 (3)	79 (80)	1 (1)
Low diastolic BP	7 (4)	-	3 (3)	-
High pulse rate (>100 bpm)	36 (18)	-	13 (13)	-
Low pulse rate (< 60 bpm)	35 (18)	-	13 (13)	-

Table 53 Study 19 On-study vital sign abnormalities (ITT)

	Olaparib		Placebo	
	N= 136		N= 129	
	G1-4 N (%)	G3-4 N (%)	G1-4 N (%)	G3-4 N (%)
Temperature (fever)	1 (1)	0	1 (1)	0
High systolic BP	129 (95)	16 (12)	121 (94)	18 (14)
Low systolic BP	7 (5)	-	2 (2)	-
High diastolic BP	94 (69)	4 (3)	96 (75)	5 (7)
Low diastolic BP	6 (4)	-	3 (2)	-
High pulse rate (>100 bpm)	26 (19)	-	12 (9)	-
Low pulse rate (< 60 bpm)	27 (20)	-	19 (15)	-

Electrocardiograms (ECGs)

See QT section below.

QT

See the QT-IRT Interdisciplinary review in DARRTs dated 5/11/17 from Christine Garnett and Dhananjay Marathe. Based upon data submitted in the current NDA and upon data previously reviewed, there is no clinically relevant effect of olaparib in QT interval. Language in Section 12.2 of product labeling reflects that no effect of olaparib in QTc interval was noted from analysis of pooled data.

Immunogenicity

An assessment of reactions that may indicate immunogenicity or allergy to olaparib on SOLO2 was done. The safety dataset for the SOLO2 study was the focus and an analysis of the following adverse event terms was conducted:

Anaphylactic reaction, dermatitis, dermatitis allergic/contact, drug hypersensitivity, hypersensitivity, inflammation, pruritis, rash, sneezing, urticaria, wheezing.

On the SOLO2 study, there were 36 patients on the olaparib arm with such an event (8%). All events were grade 1-2 in severity with the exception of one grade 4 event. Two events were considered serious. In addition, only one of the events (a grade 2 event on study day 18) resulted in permanent study drug discontinuation. Details regarding the grade 4 event are as follows:

Patient E4308502 (olaparib)- experienced a G4 anaphylactic reaction while on study, which was serious. However, further information indicated that the event occurred following IV contrast injection for CT scan, and it was determined that she suffered an IV contrast reaction. No action was taken with regard to olaparib therapy, and the event was considered to be unrelated to olaparib.

An assessment was also conducted on the safety database with the capsule formulation, for patients receiving 3 or more lines of therapy. It was found that in that population, on 16% of patients experienced an adverse event that may have interpreted as a potential allergic/ hypersensitivity reaction. It was concluded that the risk of reactions such as this is low with olaparib.

7.4.5. Analysis of Submission-Specific Safety Issues

Specific safety issues related to olaparib (including MDS/AML, secondary malignancies other MDS/AML, and pneumonitis) have been addressed in Section 7.4.4.

7.4.6. Safety Analyses by Demographic Subgroups

An analysis of common grade 1-4 adverse events by age group was conducted for the SOLO2 study and is shown in Table 54. The majority of the patients on the study fell in the 50-65 year age group, so the subgroup of patients over 65 was small. There was not large variability in the incidence of specific adverse events by age group, and there was no definite trend to suggest that older patients experienced more adverse events than the other age groups. There were a few exceptions, including anemia and thrombocytopenia, where the overall incidence of these events were reported with a higher frequency in patient >65 years of age. However, given the relatively small number of patients in this subgroup, it is difficult to draw any definitive conclusions about this observation. In the product labeling, it is appropriate to say that there were no major differences in the safety profile of patients treated with olaparib based upon age group.

Table 54 SOLO2 Common adverse events by age

Adverse event by PT (Grades 1-4)	N=196 (FAS)		
	Age < 50 N=38 (%)	Age 50- <65 N=118 (%)	Age ≥ 65 N=40 (%)
Anemia	15 (39)	45 (38)	25 (63)
Neutropenia	10 (26)	22 (19)	11 (28)
Thrombocytopenia	6 (16)	15 (13)	10 (25)
Nausea	28 (74)	94 (80)	26 (65)
Vomiting	17 (45)	46 (39)	10 (25)
Diarrhea	13 (34)	41 (35)	11 (28)
Fatigue/ Asthenia	25 (66)	74 (63)	30 (75)
Nasopharyngitis	12 (32)	32 (27)	10 (25)
Arthralgia/ myalgia	8 (21)	39 (33)	15 (38)

7.4.7. Specific Safety Studies/Clinical Trials

As was described in section 7.4.4, the potential for QTc prolongation was assessed previously. Overall, there is no clinically relevant effect of olaparib in QT interval. This language is included in product labeling.

A dedicated hepatic impairment study was conducted (discussed in the Clinical Pharmacology Section 6.2.2 of the combined olaparib NDA review); no dose adjustment for olaparib is required for patients with mild hepatic impairment (Child-Pugh A). A study (b) (4) is ongoing.

A dedicated renal impairment study was also conducted (discussed in the Clinical Pharmacology Section 6.2.2 of the combine olaparib NDA review). Based upon this study, it is recommended that olaparib tablet dose be reduced to 200 mg BID for patients with moderate renal impairment (CrCl 31-50 ml/min). No dose adjustment is required for patients with mild renal impairment (CrCl 51-80 ml/min).

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Specific carcinogenicity studies have not been conducted with olaparib (in animals), however all patients in the clinical trials discussed in this review had cancer prior to study entry. As has been described in section 7.4.5 of this review, there have been cases of myelodysplastic syndrome and acute leukemia (MDS/ AML) diagnosed in patients treated with olaparib. The duration of therapy in patients who developed MDS/AML after olaparib therapy varied widely from < 6 months to longer than 2 years, so it is unclear that there is a minimal exposure need to increase a given patient's risk. In the product labeling, there are recommendations to prescribers on how to monitor patients, during and after olaparib therapy, for this potential adverse event. The Sponsor has also been required to submit annual updates to the NDA, describing the new and existing cases of MDS/AML.

An association between olaparib and the development of other solid tumor malignancies has also been described (in section 7.4.5). Most of these tumors are skin cancers, but a variety of solid tumors have been reported. The contribution of olaparib in the development of these tumors is more difficult to ascertain as many cases had confounding factors, including other exposures (XRT, smoking, sun exposure).

Pediatrics and Assessment of Effects on Growth

As is noted in section 8.4 of the product labeling, the safety and efficacy of olaparib have not been established in pediatric patients. The Sponsor submitted a request for waiver of pediatric studies (associated with IND 75918) at the time of NDA submission on 2/22/17. The PerC met on 7/19/17 and agreed to grant a full waiver, as requested.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This drug does not have drug abuse potential.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No new safety signals have been identified through postmarket experience. The previously identified signal for the occurrence of MDS and AML after olaparib therapy has continued to be monitored for new cases. It seems that the risk among all patients exposed to olaparib, regardless of duration or other risk factors, is around 2% overall. This 2% estimate seems to vary, depending upon the denominator for the pool of patients included, but it is important to note that any exposure to olaparib causes an increased risk in patients, particularly those with an underlying BRCA mutation. The exact risk cannot be accurately assessed.

7.4.10. Integrated Assessment of Safety

The primary analysis relevant to the indication of olaparib as a maintenance therapy came from SOLO2 and Study 19. This includes 295 patients on the SOLO2 trial (196 treated with olaparib) and 265 patients treated on Study 19 (136 treated with olaparib). The safety analyses from the two trials were reported separately in this review, but “side by side” in each respective section. This was done for several reasons, including the differences in formulation between the 2 trials, and the fact that the results from Study 19 were previously reported and analyzed in a separate application, but were reassessed for the current review.

The key adverse event of interest with olaparib is the occurrence of MDS and AML, which can occur during or after therapy. This analysis was described under Significant Adverse Events in this review. It was noted that the overall risk of developing MDS/AML to all patients treated with olaparib is likely to be in the range of 1-2%. Patients with an underlying BRCA mutation are likely to have an increased risk, compared to those without a BRCA mutation, but it is difficult to approximate the magnitude of that increase in risk. The development of other secondary malignancies, primarily skin cancers, is also a risk associated with olaparib therapy, but this risk is even more difficult to quantify than the MDS/AML risk, as the number of documented events has been lower and the actual tumor types have varied. Finally, pneumonitis has been described in patients treated with olaparib. Although this adverse event is uncommon, and the occurrence may be confounded by other factors including history of prior chest XRT, several cases have resulted in death. Therefore, this adverse event continues to be described in patient labeling, so that clinicians can monitor patients appropriately.

An analysis of common grade 1-4 adverse events was conducted using the combined ISS dataset, including 482 patients with advanced solid tumors (shown in Table 32 above) who had received the tablet formulation of olaparib as monotherapy (including 195 patients from SOLO2 who received olaparib). The results of this analysis are shown in Table 55.

Table 55 Common Grade 1-4 adverse events in ISS including ovarian cancer monotherapy patients

Adverse event	N=482	
	Grade 1-4 N (%)	Grade 3-4 N (%)
Any adverse event	476 (99)	194 (40)
Anemia	188 (39)	71 (15)
Leukopenia (includes neutropenia)	78 (16)	22 (5)
Neutropenia	67 (14)	21 (4)
Thrombocytopenia	44 (9)	8 (2)
Nausea	332 (69)	10 (2)
Abdominal pain	188 (39)	10 (2)
Vomiting	186 (39)	11 (2)
Diarrhea	159 (33)	7 (1)

Constipation	112 (23)	0
Nasopharyngitis/ Upper respiratory infection/Sinusitis	100 (21)	0
Fatigue	255 (53)	21 (4)
Decreased appetite	144 (30)	4 (1)
Arthralgia/ myalgia	145 (30)	4 (1)

Reviewer comment: When comparing the incidence of these common adverse events between SOLO2 and the pooled dataset, they are generally comparable. A few differences include a lower incidence of all grades of thrombocytopenia in the pool compared to SOLO2 (9% vs. 14%), as well as lower incidence of nausea in the pooled set (69% vs. 76%). Abdominal pain and fatigue were overall also higher on SOLO2. Finally, grade 3-4 adverse events were overall similar when comparing the incidence between SOLO2 and the pooled dataset.

Third-line and beyond indication for tablet formulation

During review of the current application, there was substantial discussion between the review team and the Applicant regarding the applicability of available safety data to support granting the indication for use of the tablet formulation in patients with ovarian cancer who have received 3 or more prior lines of therapy. This was a potentially problematic issue, since it is known that the capsule and tablet formulations are not bioequivalent, and the original indication in the third-line setting was based upon data with the capsule formulation. Reference is made to the Clinical Pharmacology review by Dr. Runyan Jin for discussion of the issue. In addition, as part of the effort to compare the safety of the two formulations in the more refractory setting, a safety analysis was done to compare the adverse events in the 223 patients from the capsule database (n=223) and a similar set of advanced (3+ line) ovarian cancer patients (n=90) treated on 6 different trials with the tablet formulation. Table 56 depicts which trials were included in this tablet formulation dataset, and Table 57 shows results of the adverse event analysis in the ovarian cancer patients treated on these 6 trials (n=90) in a side-by-side comparison with the 223 ovarian cancer patients (3+ lines) treated with the capsule formulation.

Table 56 Tablet formulation ovarian cancer pool with 3+ lines

Study # and description	gBRCAm	Non-gBRCA (includes VUS, wt, unk)	Total Number patients with ovarian cancer treated with 3 or more lines of chemotherapy
24	10	1	11
8	0	3	3
1	8	21	29
6	1	9	10
7	1	19	20
4	3	14	17
Total	23	67	90

Table 57 Adverse event comparison between tablet and capsule ovarian cancer pool 3+ lines of therapy

Adverse Event by PT	300 mg BID Tablet pool 3+ line Ovarian cancer patients n=90		400 mg BID Capsule pool 3+ line ovarian cancer patients N=223	
	Grade 1-4 (%)	Grade 3-4 (%)	G1-4 (%)	G3-4 (%)
Blood and Lymphatic disorders				
Anemia	41 (46)	18 (20)	77 (35)	41 (18)
Neutropenia	7 (8)	2 (2)	17 (8)	9 (4)
Thrombocytopenia	8 (9)	3 (3)	18 (8)	5 (2)
Gastrointestinal disorders				
Abdominal pain/discomfort	47 (52)	4 (4)	100 (45)	19 (9)
Constipation	25 (28)	0	38 (17)	3 (1)
Decreased appetite	37 (41)	1 (1)	51 (23)	2 (1)
Nausea	63 (70)	2 (2)	145 (65)	5 (2)
Vomiting	41 (46)	5 (6)	96 (43)	8 (4)
Diarrhea	33 (37)	2 (2)	69 (31)	2 (1)
Dyspepsia	14 (16)	0	61 (27)	0
Dysgeusia	17 (19)	0	35 (16)	0
Stomatitis	13 (14)	1 (1)	31 (14)	0
General disorders				
Fatigue/lethargy/asthenia	63 (70)	6 (7)	151 (68)	17 (8)
Edema peripheral	16 (18)	1 (1)	35 (16)	2 (1)
Infections and infestations				
Nasopharyngitis/ URI/pharyngitis	21 (23)	0	52 (23)	1 (0.5)
Investigations				
Blood creatinine/ BUN increased/ renal impairment	4 (4)	0	13 (6)	0
Hypomagnesemia	12 (13)	1 (1)	15 (7)	1 (0.5)
Metabolism and nutrition disorders				
Hyperglycemia	1 (1)	1 (1)	11 (5)	1 (0.5)
Musculoskeletal and Connective tissue disorders				
Back pain	21 (23)	0	33 (15)	2 (1)
Nervous system disorders				
Dizziness	10 (11)	0	26 (12)	2 (1)
Headache	19 (21)	0	37 (17)	0
Peripheral neuropathy	15 (17)	0	36 (16)	1 (0.5)
Renal and Urinary disorders				

Urinary tract infection	14 (16)	3 (3)	32 (14)	2 (1)
Respiratory, Thoracic, Mediastinal disorders				
Cough	20 (22)	0	44 (20)	0
Dyspnea	28 (31)	3 (3)	39 (17)	8 (4)
Skin and Subcutaneous Tissue disorders				
Dry skin/ eczema	1 (1)	0	16 (7)	0
Rash	13 (14)	0	27 (12)	0
Pruritis	2 (2)	0	10 (5)	0
Vascular disorders				
Hypertension	5 (6)	0	7 (3)	1 (0.5)
Venous thrombosis (includes PE and vena cava thrombus)	3 (3)	2 (2)	15 (7)	5 (2)
Hot flush	6 (7)	1 (1)	15 (7)	0

Reviewer comment: From this analysis, it was determined that based on incidence of adverse events between the 2 groups (formulations), there appeared to be a similar safety profile. There were a few differences, including more grade 1-4 anemia, gastrointestinal AEs, back pain, and dyspnea in the tablet cohort. However, the grade 3-4 adverse events were comparable between the formulations. Although this analysis may indicate that there may be slightly lower tolerability of the tablet formulation (in the more advanced setting patients), it seems overall safe and reasonable to conclude that patients with gBRCA ovarian cancer who have received 3 or more lines of chemotherapy can be treated with the tablet formulation of olaparib once the capsule formulation is no longer available.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

This application features data from two studies: SOLO2 and Study 19. The results from SOLO2 were meant to support the efficacy of olaparib in gBRCA mutated patients while results from Study 19 were meant to support the efficacy of olaparib in all comers (adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy). Study 19 was designed to detect a significant PFS effect in all comers hence the true magnitude of the olaparib effect in the gBRCA subgroups cannot be estimated. The clinical team

concluded that all gBRCA subgroups derived some benefit from olaparib, an in depth discussion is given in Section 7.3.2.

Another major issue was informative censoring in PFS-BICR results. In the late stages of the trial, the agency agreed to the sponsor's request to a change in primary endpoint from PFS-BICR to PFS-Inv. The agency however recommended that all patient scans be subjected to blinded independent central review. Some post-progression scans of patients who had progressed (as assessed by the investigator) were not sent for BICR review. This caused informative censoring. Furthermore, the statistical analysis plan for the change in endpoints (dated April 22, 2016) was not submitted to the agency for evaluation; the Agency was therefore not able to provide important feedback on the statistical analysis plan.

The statistics reviewers had issues confirming the sponsor's investigator and BICR assessed PFS results. It took several requests and a teleconference to help resolve data quality issues and verify the PFS efficacy results. Table 58 gives details on the communication between the agency and the sponsor.

Table 58 Communication with Sponsor regarding inability to verify PFS results

Date of request	Description of request	Response to request
4/4/2017	The reviewer had a problem verifying PFS-BICR as lesion measurement as they could not locate lesion measurement for some patients. The reviewer was also unclear on adjustments made to lesion measurements by the sponsors. The reviewer requested that the sponsor submit a dataset that provides individual lesion measurements by both IRC and INV assessment at each visit in one dataset.	The sponsor's response (Dated April 6, 2017) was that the data was in the original submission but was located in various files. The sponsor also clarified what the adjustment in lesion measurements was in reference to very small tumors and baseline measurement. The sponsor provided SAS pseudocode and instruction on how to access the data.
4/17/2017	The reviewers still had problems verifying BICR assessment using the multiple datasets. This was largely due to missing baseline BICR assessments in some patients. It was also unclear whether all patient scans had been sent for blinded central review. There were also challenges in working with the multiple datasets and the ability of the reviewer being able to identify missingness in tumor attributes. The reviewers expressed these concerns in the IR and asked the sponsor to submit a file indicating which patients had BICR	The sponsor's response on (April 20, 17) stated that all baseline scans were sent for BICR review on an ongoing basis, however blinded review was initiated by investigator assessed progression. The sponsor submitted a file indicating which patients scans were sent for review. The sponsor provided a dataset with IRC scan dates and CRF dates and a flag for when both dates matched. In some patients the CRF dates and IRC dates. The sponsor provided an explanation when scans did

	reviews performed.	not match.
5/19/2017	This reviewer was still unable to verify the sponsor's BICR results with the provided information. Despite the sponsor's assertion that all patients had a BICR review, A total of 41 (approximately 14%) of patients who had an investigator assessed event were censored according IRC assessment. In addition, a total of 187 (63%) had no investigator assessed baseline tumor measurements. Among these 187 patients, 62 were described as having had a partial response (PR) following their last platinum treatment prior to study entry, making it unclear why these patients had no baseline tumor measurements recorded. The reviewer identifying missing tumor attributes in the datasets, it was unclear whether missing values were because measurements were not performed. In the IR, the reviewer asked the sponsor to clarify that all patients' scans were reviewed by BICR. In addition the reviewer requested that the sponsor provide one dataset for investigator lesion evaluations where specific tumor attributes per patient per visit were indicated, any missing values were to be marked as missing.	In a tele-conference with the review team on May 25th, 2017. The sponsor informed the review team that all the scans were sent for review by BICR at the data cut-off. Of the 187 patients who had missing investigator assessed baseline lesion measurements, 127 had no evidence of (measurable) disease at baseline (see Figure 3). Patients with NED had their lesion measurements/attributes in a separate dataset. The sponsor also addressed the issue of IVRS and CRF stratification and provided additional sensitivity analysis (Please see the section on sensitivity analysis). The sponsor submitted a dataset with all patients BICR lesion assessments including patients with NED at baseline. With this dataset this reviewer was able to replicate the PFS-BICR results.

7.6. Conclusions and Recommendations

The review team recommends regular approval for olaparib 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 a complete or partial response to platinum-based chemotherapy.
- Lynparza is indicated 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.

The recommendation is based upon review of the results from the SOLO2 study which was a double-blind, placebo-controlled trial in which patients with gBRCAm ovarian, fallopian tube, or primary peritoneal cancer were randomized (2:1) to receive olaparib or placebo (twice daily) until disease progression or unacceptable toxicity. All patients had received at least two prior platinum-containing regimens and were in response (CR or PR) to their most recent platinum regimen. All patients had a deleterious or suspected deleterious germline BRCA mutation (gBRCA), which was confirmed by the BRACAnalysis CDx. The trial demonstrated a statistically significant improvement in investigator-assessed PFS for patients treated with olaparib, as compared to placebo. The estimated median PFS for patients treated with olaparib was 19.1 months, compared with 5.5 months on placebo (HR 0.30 [95% CI: 0.22, 0.41], p-value <0.0001). The results of multiple sensitivity analyses, including assessment of the PFS endpoint by blinded independent central review (BICR), were considered to be supportive of the primary analysis, despite issues with informative censoring.

Additional support of the efficacy of olaparib in the proposed setting came from Study 19, which enrolled patients regardless of BRCA status and demonstrated a 3.6 month improvement favoring olaparib (HR 0.35 [95% CI: 0.25, 0.49]). An issue at the time that the results of Study 19 became available was that although it was unclear what margin of PFS improvement for a maintenance therapy would be considered clinically meaningful, a general consensus was that OS would be required. Although there were never explicit discussions between the Sponsor and FDA to corroborate this assumption, it is one of the reasons that the indication pursued by the Sponsor, at the time of submission of the Study 19 results, was for the gBRCA subset, rather than the ITT population. As further development of olaparib has occurred in recent years, and a better understanding of the risk-benefit ratio has been gained, as well as approval of other agents with similar treatment effect in the maintenance setting, the indication for patients regardless of BRCA status is warranted. It is likely that investigators will make treatment decisions with their individual patients based on the current knowledge of the differential efficacy, based upon BRCA status, as well as consideration of the risks of therapy.

The safety profile of the olaparib tablet was adequately assessed in the submitted database. The primary data in support of the olaparib tablet as maintenance therapy for patients in response to platinum-based chemotherapy came from the results of the SOLO2 study, but data from the ITT population on Study 19 was also considered. The most serious potential adverse event associated with olaparib therapy is the development of MDS/AML, which can occur at any time during or after olaparib therapy. As has been noted, there is debate as to the exact number of documented cases there have

been, but using a conservative estimate, there have been approximately 34 potential cases in patients exposed to olaparib on trials conducted to date (including blinded trials). This equates to an approximate 0.5% incidence, when considering all patients who have been exposed to olaparib. It is likely that this is an underestimate of the precise number of cases, due to underreporting that occurs in certain types of trials, such as investigator initiated (research) trials. When considering the incidence in only the randomized trials, the numbers are also skewed depending upon the timeframe considered for diagnosis (eg, within 30 days of trial participation, vs. longer-term follow-up, including subsequent exposure to olaparib after trial participation). On Study 19, there were 3 patients on olaparib (2.2%) and 1 patient on placebo (0.7%) who developed MDS/AML. On SOLO2, there 4 cases in patients randomized to olaparib (2.1%), however there were also 4 cases (4%) in patients randomized to placebo. One of the placebo patients had documentation of receipt of olaparib after discontinuing placebo on SOLO2 and prior to developing AML, but this was outside of the 30-day window on SOLO2. In addition, it is not known if the other 3 placebo patients on SOLO2 received olaparib post-progression on study, as there is no explicit documentation of this. Considering these factors, it is acknowledged that it is difficult to approximate the exact incidence of MDS/ AML, as well as the exact risk to patients after exposure. There are clearly multiple factors at play, in addition to exposure to olaparib, including other prior therapies and radiation exposure, the presence of an underlying BRCA mutation, and other contributors that may not yet be understood. As was noted previously in this review, it is likely that the risk of the occurrence of MDS/AML after therapy with olaparib is approximately 1-2%.

The common adverse events include cytopenias, nausea, and fatigue and are mostly managed with dose interruptions, and less frequently, dose reductions. Analysis of safety data for both the capsule and tablet formulations was conducted, and although there were some differences in tolerability, the two are basically comparable, with regard to adverse event profiles. There was initial concern about whether the safety information for the tablet formulation was adequate to support imparting the 3+ line indication for the capsule to the tablet formulation. It has been determined that this will be acceptable based on available data including patient efficacy and safety comparison data and PK information, given that the capsule will eventually be phased out and only the tablet formulation will be commercially available. Therefore the team also recommends approval of olaparib tablets for the treatment of patients with deleterious or suspected deleterious germline BRCA mutated (based on an approved test) advanced ovarian cancer who have been treated with three or more prior lines of therapy.

Overall, olaparib is considered by the review team to have a favorable risk-benefit profile when considering its use in both indications described.

X

X

Primary Statistical Reviewer
Stella Karuri

Statistical Team Leader
Jason Schroeder

X

X

Primary Clinical Reviewer
Gwynn Ison

Clinical Team Leader
Sanjeeve Balasurbramaniam

8 Advisory Committee Meeting and Other External Consultations

No ODAC was convened for this application, however for the initial NDA submission of olaparib capsules an ODAC was convened on June 25, 2014. At that time, the proposed indication under discussion was the use of olaparib capsules as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA mutation as detected by an FDA-approved test, who are in response (complete response or partial response) to platinum-based chemotherapy. Study 19 was the trial discussed in the context of supporting the proposed indication at that time.

The committee voted as follows:

VOTE: Do the safety and efficacy results from Study 19 in the gBRCAm population support an accelerated approval, or should consideration for marketing approval be delayed until the results of SOLO-2 are available?

Vote Result: Yes: 2 No: 11 Abstain: 0

Importantly, no question was posed to ODAC regarding the approval of the ITT unselected population inclusive of gBRCAm and gBRCAwt.

Those committee members who voted “no” expressed several concerns with the data and interpretation of the data from study 19:

1. Many committee members described a strong preference for a demonstrated improvement in overall survival to support approval in the setting of maintenance therapy rather than progression-free survival (PFS). Some committee members also acknowledged the practical challenges with use of overall survival in certain settings, and these members expressed a comfort with use of PFS, provided a sufficient magnitude was demonstrated. In discussing the appropriate magnitude to provide a favorable risk-benefit profile in this population, most committee members were unable to state a specific magnitude that was felt to be acceptable. In 2014, these ODAC members felt that the 3.6 month improvement that was demonstrated in the intent-to-treat population from Study 19 was not sufficient to demonstrate clinical benefit.

Reviewer Comment: While the desire for OS is noted from the prior ODAC, since the time of ODAC, the thinking on this disease setting has changed and there have been two approvals in this space based on PFS (Avastin [two trials] and niraparib [one trial]) as noted above in Table 1. Therefore, the current application for olaparib in the maintenance setting needs to be viewed in this context and with demonstration of a similar HR to the other approvals in this setting from Study 19 in the unselected population, thus supporting olaparib's approval for the broader indication despite the prior ODAC discussion.

2. Many of those members who voted negatively described concerns with the occurrence and duration of adverse effects, including rare occurrence of secondary cancers, in a setting where patients would otherwise not receive drug therapy and its attendant adverse effects.

Reviewer Comment: These concerns have been further explored with additional follow-up data, and the overall safety of olaparib is now felt to be acceptable in the intended patient population. In addition, the extension of the indication to an unselected population is supported by both a lower rate of MDS/AML in the gBRCAwt population as well as a strong scientific rationale for this being a lesser risk in the gBRCAwt population, which, given the expected lower magnitude of benefit in this population, still provides for a favorable risk-benefit profile.

3. Additional discussion revolved around the post-hoc and retrospective nature identifying gBRCAm and the ensuing subgroup analysis of the gBRCAm subgroup as not being statistically valid. Specifically, discussion centered on the fact that results in the gBRCAm subgroup constituted an exploratory analysis where statistical integrity was compromised through loss of randomization.

Reviewer Comment: We agree with this opinion. In fact, the question voted on by the previous ODAC asked specifically for the members to separate out this subgroup, which accounted for approximately half of the patients enrolled on the trial. Ultimately, Study 19 was statistically significant for the overall population, and as described above represents a result within the PFS range of prior approvals in the maintenance setting. The magnitude of benefit of the gBRCAm group is more than the unselected group, but still gBRCAwt patients could benefit from therapy, including those likely with tBRCAm and those with HRR pathway aberrations.

9 Pediatrics

As is described in section 8.4 of product labeling, the safety and efficacy of olaparib have not been established in pediatric patients. The Sponsor submitted a request for waiver of pediatric studies (associated with IND 75918) at the time of NDA submission on 2/22/17. The PerC met on 7/19/17 and agreed to grant a full waiver, as requested.

10 Labeling Recommendations

10.1. Prescribing Information

The table below summarizes significant changes to the proposed prescribing information made by FDA. The Applicant also made additional labeling revisions based on the previously approved Lynparza capsules to describe the new Lynparza tablet formulations in the applicable labeling sections. This labeling was under negotiation at the time of this review. See the final approved prescribing information for Lynparza (tablets) accompanying the NDA 208558 approval letter for more information.

Summary of Significant Labeling Changes (As of July 26, 2017)		
Section	Proposed Labeling	Approved Labeling
Highlights		
Indications and Usage	<i>See Full Prescribing Information, 1 Indications and Usage.</i>	<i>See Full Prescribing Information, 1 Indications and Usage for corresponding revisions.</i>
Dosage and Administration	(b) (4)	To increase prominence and better characterize this information, FDA revised this statement to: “To avoid substitution errors and overdose, do not substitute Lynparza tablets with Lynparza capsules on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. (2.1)”
Full Prescribing Information		
1. Indications and Usage	(b) (4)	The indication statement (and headings) were revised to: “Lynparza is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.” This indication statement was revised to clarify “adult” patients to be consistent with OND best

	...	labeling practices.
2. Dosage and Administration	(b) (4)	FDA moved this to subsection to 2.1 consistent with the FDA Dosage and Administration Guidance (III.A.) when lack of knowledge can have serious consequences to patients. This statement was revised to “DO NOT substitute Lynparza tablets (100 mg and 150 mg) with Lynparza capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation.”
5. Warnings and Precautions	5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia (b) (4)	FDA agreed with the Applicant’s pooled methodology for MDS/AML across Lynparza monotherapy trials. FDA added the number of cases identified and total number of patients treated with Lynparza (i.e., “21/1680”). FDA added the following: “Additional cases of MDS/AML have been documented in patients treated with Lynparza on combination studies.” FDA added statements to clarify the duration of Lynparza therapy for patients developing MDS/AML and to clarify the BRCA mutational status of patients who developed MDS/AML (i.e., 19/21 had documented BRCA mutation).
5. Warnings and Precautions	5.2 Pneumonitis (b) (4)	FDA revised this section to be more accurate and concise; and to make the risk of fatal pneumonitis and pneumonitis management more prominent as follows: “Pneumonitis, including fatal

	(b) (4)	cases, occurred in < 1% of patients treated with Lynparza. 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.”
6. Adverse Reactions	6.1 Clinical Trial Experience ... <u>Maintenance Treatment of Recurrent Ovarian Cancer</u> <i>SOLO-2</i> ...	FDA removed the following unqualified general statement: “(b) (4) FDA added the clinical trial names (i.e., SOLO-2 and Study 19) throughout labeling to be consistent with current best labeling practices. FDA added the following: “The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anemia (22%), neutropenia (9%), and fatigue/asthenia (8%).” FDA added ARs for stomatitis, infections, and arthralgia/myalgia to the most common AR table based on the FDA safety review findings. FDA revised the ARs reported in

	<i>Study 19</i> ...	SOLO-2 in <20% of patients to add rash, cough, hypomagnesemia, and edema. FDA replaced (b) (4) to an “on study” laboratory abnormality table. (b) (4) Use of the “on study” laboratory abnormalities provides the most relevant, precise, and accurate clinical experience for patients in the SOLO-2 (and Study 19) trial(s). FDA removed the following statement: (b) (4) ” FDA added the following statement: “Adverse reactions led to dose interruptions in 35% of those receiving Lynparza and 10% of those receiving placebo; dose reductions in 26% of Lynparza and 4% of placebo; and discontinuation in 6% of Lynparza and 2% in placebo.” FDA added constipation and respiratory tract infections to the most common ARs table for Study 19; and added dyspnea, pyrexia and edema to the list of ARs occurring in <20% of the patients treated with Lynparza.
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		The corresponding revisions made for the laboratory abnormalities table for the SOLO-2 trial were also made for the Study 19 laboratory abnormalities table (see above comments).
12. Clinical Pharmacology	12.3 Pharmacokinetics ...	FDA added the following to better describe the differences in the capsule and tablet formulations of Lynparza: “Lynparza is available as a tablet and capsule formulation. The oral bioavailability of the tablet formulation is higher than the capsule formulation. Population pharmacokinetic analyses have shown that the steady state exposure (AUC) following 300 mg tablet twice daily was 77% higher compared to that following 400 mg capsule twice daily. The olaparib geometric mean AUC and Cmax following a single 300 mg tablet dose were 42.0 µg*h/mL (n = 204) and 5.8 µg/mL (n = 204), respectively, and the steady state geometric mean AUC and Cmax following 300 mg tablet twice daily were 49.0 µg*h/mL (n = 227) and 7.7 µg/mL (n = 227), respectively. Olaparib showed time-dependent PK that the steady state clearance decreased by 15% after multiple dosing.”
14. Clinical Studies	14.1 Maintenance Treatment of Recurrent Ovarian Cancer ... (b) (4)	FDA added the study names and NCT#s to be consistent with current best labeling practices. To be consistent with FDA Guidance and best labeling practices, FDA replaced this information with the following to adequately describe the SOLO-2 trial design characteristics,

	(b) (4) ...	enrolled patient population, and key study eligibility criteria: “SOLO-2 (NCT01874353) was a double-blind, placebo-controlled trial in which patients (n=295) with germline BRCA-mutated (gBRCAm) ovarian, fallopian tube, or primary peritoneal cancer were randomized (2:1) to receive 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. 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).” The major efficacy outcome was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Additional endpoints included overall survival (OS). ... FDA added patient demographic and baseline disease information to better describe the progression-free intervals since
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	penultimate platinum treatment and to describe the prior therapies received by the patients enrolled in the SOLO-2 trial. ... FDA removed (b) (4) FDA added the following statement: "Results from an independent review were consistent." (b) (4) (b) (4) (b) (4) were removed from the labeling (b) (4) was removed (b) (4) (b) (4) <u>Study 19</u> (b) (4)	penultimate platinum treatment and to describe the prior therapies received by the patients enrolled in the SOLO-2 trial. ... FDA removed (b) (4) FDA added the following statement: "Results from an independent review were consistent." (b) (4) (b) (4) (b) (4) were removed from the labeling (b) (4) was removed (b) (4) (b) (4) FDA replaced this information with the following: "Study 19 (NCT00753545) was a double-blind, placebo-controlled trial in which patients (N=265) with platinum-sensitive ovarian cancer who had received 2 or more previous platinum-containing regimens were randomized (1:1) to receive Lynparza capsules 400 mg orally twice daily or placebo until unacceptable toxicity or
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	(b) (4) ...	progressive disease. Randomization was stratified by response to last platinum chemotherapy (CR versus PR), time to disease progression in the penultimate platinum-based chemotherapy (6-12 months versus > 12 months), and descent (Jewish versus non Jewish).” ... FDA made revisions to the patient demographic and baseline disease information similar to those made for the SOLO-2 trial labeling above. ... FDA removed (b) (4)
17. Patient Counseling Information	<u>Administration Instructions</u> ...	FDA added the following: ... • Inform patients not to substitute Lynparza tablets (100 mg and 150 mg) with Lynparza capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation [see <i>Dosage and Administration</i> (2.1)] ...

10.2. Patient Labeling

A medicaion guide is included with labeling.

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

For detailed discussion of the safety issue (capsule-to-tablet transition) that was discussed as potentially warranting a REMS, see the DRISK review by Dr. Naoimi Redd checked into DARRTs on 7/28/17. Ultimately, however, the sponsor's plan was acceptable to facilitate transition, and assure all new capsules will be provided through specialty pharmacies. Therefore, no REMS was required.

An important issue with the current application was the formulation change from the currently approved capsule to a newer tablet formulation. (b) (4)

(b) (4) the capsule dose is 400 mg twice daily (administered as eight 50 mg capsules with each dose) and the tablet dose is 300 mg twice daily (administered as two 150 mg tablets with each dose). Due to difference in bioavailability of the two formulations, the tablets and capsules are not interchangeable. At the time of approval of the tablet, the capsule formulation will still be on the market. The Sponsor plans to discontinue marketing of the capsule (b) (4) after the tablet is approved, which will mean that both formulations will be commercially available during that time. After consultation among the review divisions, and after discussions with the Sponsor, an acceptable risk mitigation plan was adopted without requirement for a REMS. The plan will include restricting distribution of the olaparib capsule formulation to two specialty pharmacies in the US, so that the dispensation of the capsules will be closely monitored. Likewise, the tablets will also only be distributed by 5 specialty pharmacies in the US. All new patients prescribed olaparib after the approval of the current NDA will only dispensed tablets and only patients already taking capsules at the time of the tablet approval will be allowed to continue on capsules, if they choose to do so. Patients already on capsules will also have the option to switch to tablets. Education materials will be provided to healthcare providers (prescribers and pharmacists) which will highlight the differences between the formulations and their lack of interchangeability. Finally, prior authorization will be required before olaparib can be dispensed to a patient. If a pharmacy inadvertently attempts to dispense an excess quantity of olaparib tablets (using the capsule dose instead), the prior authorization will deny coverage. The review team ultimately concluded that the Sponsor's proposed strategy was adequate, and it was determined that a REMS is not needed.

11.2. Conditions of Use to Address Safety Issue(s)

See section 11.1 above.

11.3. Recommendations on REMS

No REMS was instituted at the time of approval of this application.

12 Postmarketing Requirements and Commitments

PMC 3238-1

Submit the progression-free survival (PFS) and molecular characteristics (patient and tumor) final report, labeling, and datasets from clinical trial D0816C00020, entitled, “OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non- Germline BRCA mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy.”

Draft protocol submission:	08/2017
Final protocol submission:	11/2017
Trial completion:	12/2020
Final report submission:	06/2021

PMC 3238-2

Submit the overall response rate (ORR) and duration of response (DOR) analyses with datasets from clinical trial D0816C00010: (SOLO3), entitled “ a randomized trial establishing the superiority of olaparib over physician’s choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline BRCA1/2 mutations.”

Draft protocol (amendment) submission:	10/2017
Draft statistical analysis plan submission:	11/2017
Final protocol submission:	12/2017
Trial completion:	02/2019
Final report submission:	08/2019

PMC 3282-3

Submit the overall survival (OS) analyses with datasets from clinical trial D0818C00002, SOLO-2, the ongoing randomized double-blind, placebo-controlled, multi-center trial to assess the efficacy of olaparib maintenance monotherapy in relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations (documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)) who have responded following platinum-based chemotherapy.

Trial completion	06/2019
Final report submission	12/2019

13 Appendices

13.1. References

1. Howlader, N, et al (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to SEER web site, April 2017.
2. Kim, G. (2015). FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy. *Clin Cancer Res*, 21 (19), 4257-4261.
3. Pal, T.P.-W. (2005). BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer*, 104 (12), 2807-2816.
4. Siegel R. (2014). Cancer statistics, 2014. CA: A Cancer Journal for Clinicians, 9-29.
5. Travis, L.B. (1999). Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med*, 340(5), 351-357.
6. Zhang, S.R. (2011). Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecologic oncology*, 121(2), 353-357.

13.2. Financial Disclosure

Disclosure of financial interests for Study 19 was described previously in Section 3.3 of the Clinical Review NDA 206162 in DARRTS on 12/4/14. There were no significant financial interests reported under that NDA.

Disclosure of financial interests of the investigators who conducted the SOLO2 study described in NDA 208558, including statements of due diligence in cases where the applicant was unable to obtain a signed form from the investigator, was submitted in the FDA forms 3454.

Covered Clinical Study (Name and/or Number): SOLO2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>755</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
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: _____ Significant payments of other sorts: <u>2</u> (b) (6) Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
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) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. OCP Appendices (Technical documents supporting OCP recommendations)

Pharmacometrics Analyses

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

Key Review Questions

The purpose of this review is to address the following key questions.

Q1. What is the impact of switching the 400 mg capsule BID to 300 mg tablet BID for 4th line patients in the treatment setting?

The patients are expected to have same or better efficacy outcome and increased hematological adverse events after switching to 300 mg tablet BID from 400 mg capsule BID. However, these adverse events are manageable according the exposure safety analysis.

Based on the population PK analysis using pooled data, the relative bioavailability of tablet formulation is 236% relative to the marketed 400 mg capsule. The patients at treatment setting was expected to have >70% increase olaparib exposure by switching the from 400 mg capsule BID to 300 mg tablet BID.

Exposure-response relationship for PFS in SOLO-2 study is not conclusive due to the potential confounding effect. However, based on the data from Study D0810C00012, the 400 mg capsule showed numerically better progression free survival experience as compared with 200 mg capsule, suggesting a trend of greater efficacy with increasing exposure. On the other hand, the exposure safety analysis showed a negative correlation between olaparib exposure and longitudinal hemoglobin level: higher olaparib exposure would lead to greater hemoglobin reduction over time. However, the simulation showed that the predicted mean decrease in hemoglobin is relatively small and the absolute values were >10 g/dL, even at 100% higher geometric mean AUC for 4th line ovarian cancer patients following ≥6 months olaparib 400 mg BID capsule treatment. Thus, taking the totality of evidence and clinical convenience, it is acceptable to switch the olaparib from 400 mg capsule to 300 mg tablet for 4th line treatment patients.

Q2. Is the relevant labeling regarding the description of olaparib pharmacokinetics adequately supported by population PK analysis?

Yes. The population PK model using pooled data based on FDA reviewer's analysis were employed to inform the labeling language on the description of olaparib PK at section 12.3.

The model predicted olaparib geometric mean AUC and C_{max} following a single 300 mg tablet dose were 42.0 µg·h/mL (n = 204) and 5.8 µg/mL (n = 204), respectively, and the steady state geometric mean AUC and C_{max} following 300 mg tablet twice daily were 49.0 µg·h/mL (n = 227) and 7.7 µg/mL (n = 227), respectively. The mean bioavailability of the 300 mg tablet formulation relative to the 400 mg capsule formulation was estimated to be 236%.

Olaparib showed slightly time-dependent PK with different estimates of apparent clearance after a single dose and at steady-state after a multiple repeated dose administration (~15% decrease over time). For all covariates including demographic factors, renal and hepatic function, disease status, line treatment and tablet strength evaluated, only tablet strength and disease status, evaluated by ECOG status were identified as significant covariates impacting olaparib PK. However, the impact of these covariates on olaparib exposure was not clinically meaningful based on exposure-response relationships.

Results of Applicant's Analysis

Population PK Analysis

The applicant initially conducted population PK analysis separately with different populations and formulations (capsule PK [MS-01], tablet PK excluding study SOLO-2 [MS-02] and tablet PK from study SOLO-2 [MS-03]). To compare the relative bioavailability between tablet and capsule, increase the power for covariate detection, and unify the PK parameter description in terms of distribution and metabolism/elimination between tablet and capsule formulations, FDA issued an information request asking the applicant to develop a population PK model including all available PK data from these two formulations (Appendix A).

Per FDA's request, the applicant developed a population PK analysis using pooled data from collected from both capsule and tablet formulation. Eleven clinical studies included in the current submission and previous application (NDA206162). And this model was employed to inform the labeling language. This review will mainly focus on the population PK model with the pooled data.

The primary objectives of this analysis were to:

To characterize olaparib PPK in cancer patients following the administration of capsule and tablet formulations with potential distinct absorption between capsule and tablet formulations

To estimate PPK parameters of the PPK model, including typical values and random between subject variability

To estimate the relative bioavailability between tablet and capsule formulations

To evaluate the potential impact of treatment line, disease severity, tumor types and other covariates including demographic, renal and hepatic function on olaparib PK

To predict exposure measured by area under olaparib concentration curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}) following a single dose and multiple doses at steady-state during a dose interval for 400 mg capsule and 300 mg tablet in relevant studies using individual empirical Bayes estimates (EBE) of olaparib PK parameters

Data

This analysis utilized pooled data from 11 phase I/II/III clinical studies with olaparib monotherapy, 5 studies for capsule formulation only (D0810C00001 [Study 11], D0810C00002 [Study 92], D0810C00008 [Study 44], D0810C00009 [Study 58], D0810C00012 [Study 12]), 5 studies for tablet formulations only (D081BC00001 [Study 1], D0816C00004 [Study 4], D0816C00007 [Study 7], D0816C00008 [Study 8], D0816C00002 [SOLO2]) and 1 study for both capsule and tablet formulations (D0810C00024 [Study 24]). An overview of those clinical studies including phase of studies and number of subjects is shown in **Table 59**.

Table 59 Summary of Studies included in Population PK Analysis

Formulation	Study number	Study phase and patient population	Dose regimen	Number of patients
Capsule	D0810C00001 (Study 11)	Phase I: Japanese patients with solid tumour	100, 200, 400 mg qd or bid	12
Capsule	D0810C00002 (Study 92)	Phase I: Patients with advanced Tumours	10, 20, 40 and 80 mg qd, or 60, 100, 200, 400 and 600 mg bid	89
Capsule	D0810C00008 (Study 44)	Phase II: Patients with advanced BRCA1 or BRCA2 associated breast cancer	100, 400 mg bid	41
Capsule	D0810C00009 (Study 58)	Phase II: Patients with advanced BRCA1 or BRCA2 associated ovarian cancer	100, 400 mg bid	48
Capsule	D0810C00012 (Study 12)	Phase II: Patients with advanced BRCA1 or BRCA2 associated Ovarian cancer who have failed previous platinum based chemotherapy	200, 400 mg bid	61
Tablet	D081BC00001 (Study 1)	Phase I: Patients with advanced solid tumours	200, 300 mg qd or bid	11
Tablet	D0816C00004 (Study 4)	Phase I: Patients with advanced solid tumours	300 mg qd or bid	60
Tablet	D0816C00007 (Study 7)	Phase I: Patients with advanced solid tumours	100 mg qd, 300 mg bid	59
Tablet	D0816C00008 (Study 8)	Phase I: Patients with advanced solid tumours	300 mg qd	22
Capsule/Tablet	D0810C00024 (Study 24)	Phase I: Patients with advanced solid tumours	200, 250, 300, 350, 400, 450 mg, qd or bid	162
Tablet	D0816C00002 (SOLO2)	Phase III: Patients with PSR BRCA mutated ovarian cancer patients	300 mg bid	94

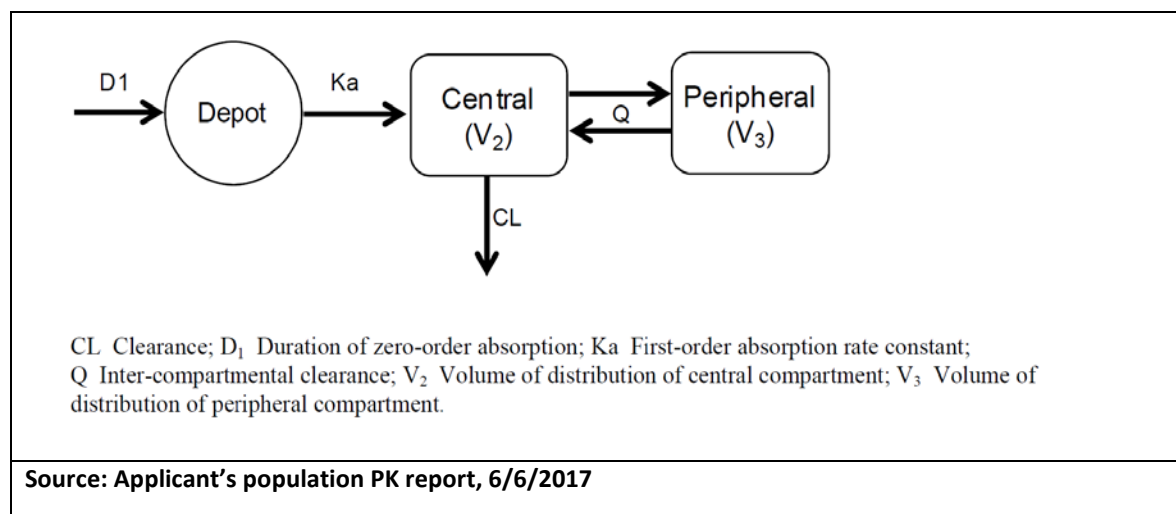
qd once daily; bid twice daily; PSR Platinum sensitive relapse; BRCA Breast cancer susceptibility gene.

Source: Applicant's population PK report, QS-CLV-006

Results

Olaparib PK was well described by a two-compartment model with sequential zero-order and first-order absorption and first-order elimination (**Figure 9**).

Figure 9: Diagram of Olaparib Model Structure



The following findings are listed based on the population PK model with pooled data from MS-01, MS-02 and MS-03:

Olaparib PK for both capsule and tablet formulations was described by a linear 2-compartment disposition model with consecutive zero- and first-order absorption.

Olaparib showed slightly time-dependent PK with different estimates of apparent clearance after a single dose and at steady-state after a multiple repeated dose administration.

For all covariates including demographic factors, renal and hepatic function, disease status, line treatment and tablet strength evaluated, only tablet strength and disease status, evaluated by ECOG status were identified as significant covariates impacting olaparib PK. However, the impact of these covariates on olaparib exposure was predicted to be small or moderate.

Model predicted geometric mean steady-state olaparib AUC_{ss} and C_{max,ss} following 400 mg capsule BID from studies using commercial capsule formulation were 44.6 µg.h/mL and 6.37 µg/mL, respectively.

Model predicted geometric mean steady-state olaparib AUC_{ss} and C_{max,ss} following 300 mg tablet BID using commercial tablet formulation were 49.1 µg.h/mL and 7.65 µg/mL, respectively.

The mean bioavailability of the 300 mg tablet formulation relative to the 400 mg capsule formulation was estimated to be 147%.

Parameter estimates and corresponding 95% CI for the final covariate model are summarized in **Table 60** and Table 61.

Table 60 Parameter Estimates (95% CI) for Olaparib Final PK Model (Part 1)

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NDA/BLA Multi-disciplinary Review and Evaluation NDA 208558
Lynparza™ (Olaparib)

Parameter	Description	Final model		Shrinkage (%)	Bootstrap		
		Estimate	RSE ^a (%)		Median	2.50%	97.50%
θ3	Clearance for single dose, CL1 (L/h)	4.81	17.5		4.97	4.30	5.79
θ4	Scaling factor for steady state CL2, with CL2 calculated as $\theta3 \cdot \exp(\theta4) = 4.10$ (L/h)	-0.161	3.40		-0.161	-0.217	-0.102
θ5	Volume of distribution of central compartment for single dose, V ₂ (L)	2.94	18.5		2.91	2.46	3.46
θ6	Volume of distribution of peripheral compartment, V ₃ (L)	21.0	18.5		21.6	17.4	26.6
θ7	Inter-compartmental clearance, Q (L/h)	1.150	17.4		1.19	0.944	1.55
θ8	Relative bioavailability F1 for capsule > 100 mg ^b	0.376	17.1		0.387	0.330	0.458
θ9	Relative bioavailability F1 for tablet formulation ^b	0.711	17.5		0.731	0.633	0.855
θ10	Absorption rate constant for capsule, Ka (h ⁻¹)	0.239	2.9		0.234	0.206	0.280
θ11	Absorption rate constant for tablet, Ka (h ⁻¹)	0.194	2.7		0.197	0.181	0.214
θ12	Duration of zero-order absorption for capsule, D ₁ (h)	0.961	8.0		0.932	0.804	1.063
θ13	Duration of zero-order absorption for tablet, D ₁ (h)	0.461	3.6		0.467	0.421	0.531
θ14	Disease severity (ECOG=1) on CL	-0.229	15.7		-0.237	-0.307	-0.153
θ15	Disease severity (ECOG=2) on CL	-0.598	8.5		-0.596	-0.713	-0.490
θ16	Tablet strength (100 mg) on Ka, Ka*(1+θ16)	0.879	4.4		0.877	0.683	1.095
θ17	Tablet strength (100, 200, 300, 125, 225 mg) on Ka, Ka*(1+θ17)	0.334	17.6		0.317	0.224	0.415
^a The RSE (%) for correlation parameters were based on the estimates of the covariance							
^b Relative to <100 mg capsule formulation.							
θ Typical parameter estimate; ω Omega*100=IIV in CV%; BSV Between subject variability; CL Clearance; CV% Coefficient of variation; D1 Duration of zero-order absorption; F1 Bioavailability; IIV Inter-individual variability; IOV Inter-occasion variability; OFV Objective function value; Q Inter-compartmental clearance; RSE Relative standard error from NONMEM output.							
Source: Applicant's population PK report, 6/6/2017							

Table 61 Parameter Estimates (95% CI) for Olaparib Final PK Model (Part 2)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 208558
Lynparza™ (Olaparib)

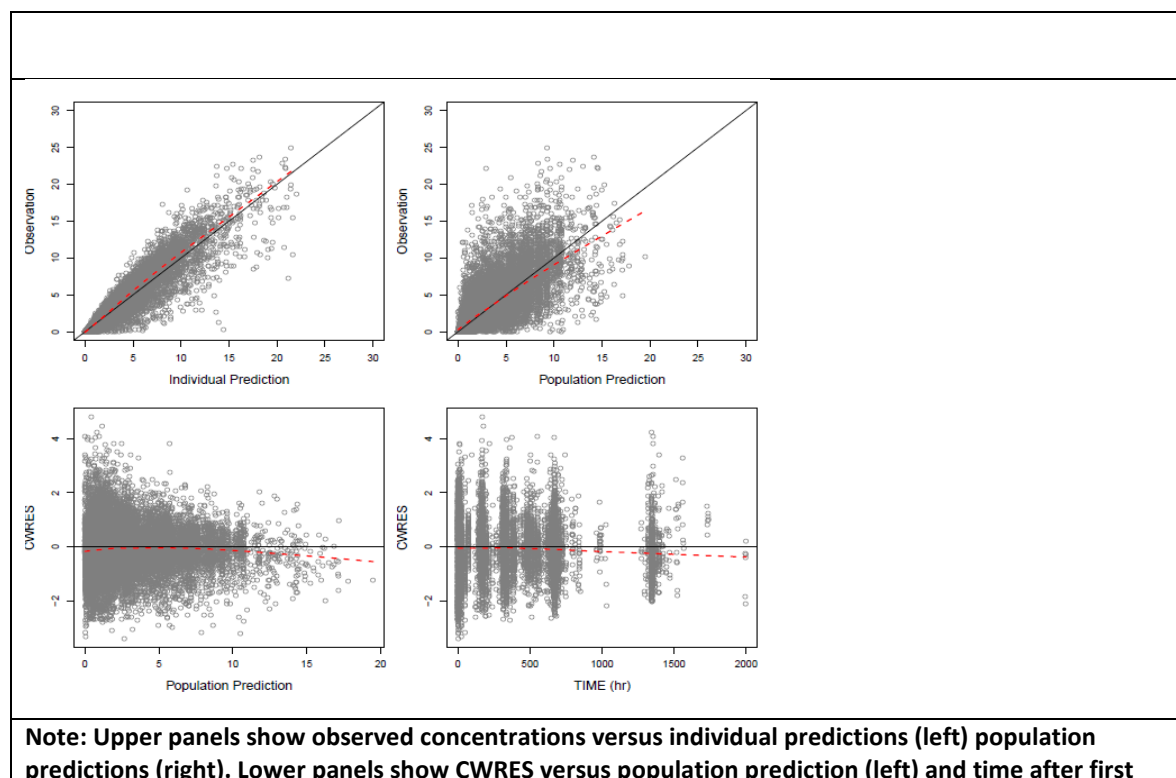
Parameter	Description	Final model			Bootstrap		
		Estimate	RSE ^a (%)	Shrinkage (%)	Median	2.50%	97.50%
ω_1	BSV in CL for single dose (CV%)	59.0	5.2	2.79	58.8	54.8	63.5
ω_2	BSV in V_2 for single dose (CV%)	72.0	12.0	35.6	70.6	60.6	77.9
ω_3	BSV in V_3 (CV%)	120	9.1	23.1	123	103	141
ω_4	BSV in Q (CV%)	80.0	11.0	26.0	77.6	64.4	94.5
ω_5	BSV in D1 (CV%)	77.0	8.7	29.5	74.8	64.9	83.1
ω_6	BSV in Ka (CV%)	27.0	12.0	28.5	27.5	21.1	32.7
Residual variability							
θ_1	Proportional error	0.35	0.55		0.35	0.30	0.37

^a The RSE (%) for correlation parameters were based on the estimates of the covariance
^b Relative to <100 mg capsule formulation.
 θ Typical parameter estimate; ω Omega*100=IIV in CV%; BSV Between subject variability; CL Clearance; CV% Coefficient of variation; D1 Duration of zero-order absorption; F1 Bioavailability; IIV Inter-individual variability; IOV Inter-occasion variability; OFV Objective function value; Q Inter-compartmental clearance; RSE Relative standard error from NONMEM output.

Source: Applicant's population PK report, 6/6/2017

The goodness-of-fit plots for the final covariate model for all data are shown in **Figure 10**.

Figure 10 Goodness-of-fit plots for final covariate model

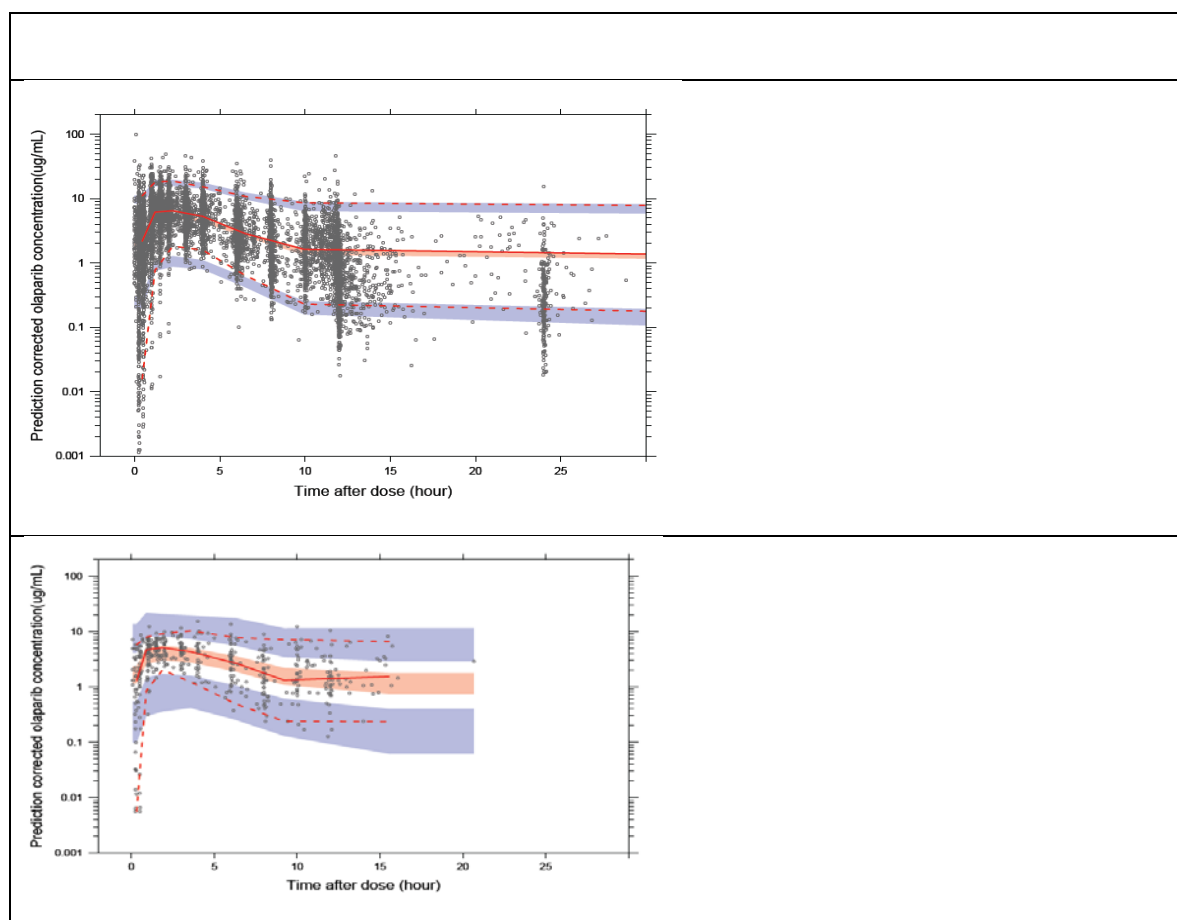


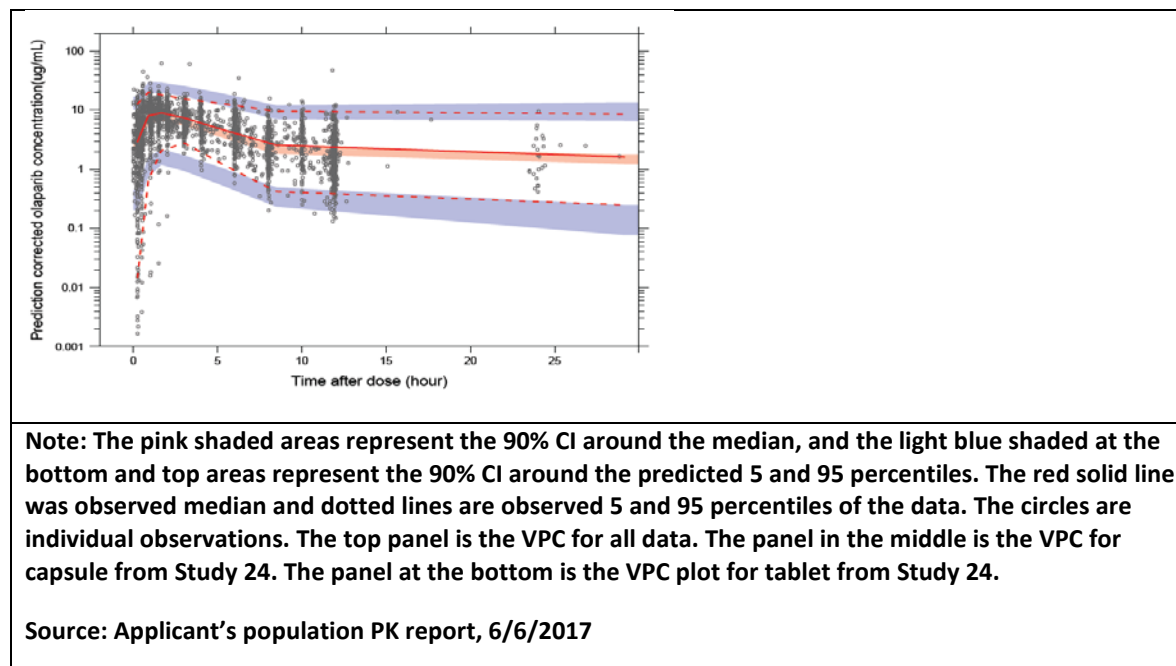
dose (right).

Source: Applicant's population PK report, 6/6/2017

The VPC plot for the final covariate model with all data is shown in **Figure 11**. The VPC plots for representative Study 24 with olaparib dosed by capsule and tablet formulation are also shown in **Figure 11**. All these model diagnostic plots suggest that the final olaparib PPK model adequately describe the observed olaparib concentrations.

Figure 11 VPC plots for final covariate model





The final olaparib PPK model was used to predict single dose and steady-state exposure of AUC, Cmax and Cmin for subjects dosed by 100, 200 and 400 mg olaparib single or multiple (BID) capsule formulation from two studies using commercial olaparib capsule formulation (Studies 12 and 24), and for subjects dosed by 200, 250 and 300 mg olaparib single or multiple (BID) tablet formulation. The results are shown in **Table 62**.

Table 62 Summary of model predicted AUC and Cmax after single or multiple dose administrations of olaparib 100, 200 and 400 mg capsule formulation BID and 200, 250 and 300 mg tablet formulation BID.

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NDA/BLA Multi-disciplinary Review and Evaluation NDA 208558
Lynparza™ (Olaparib)

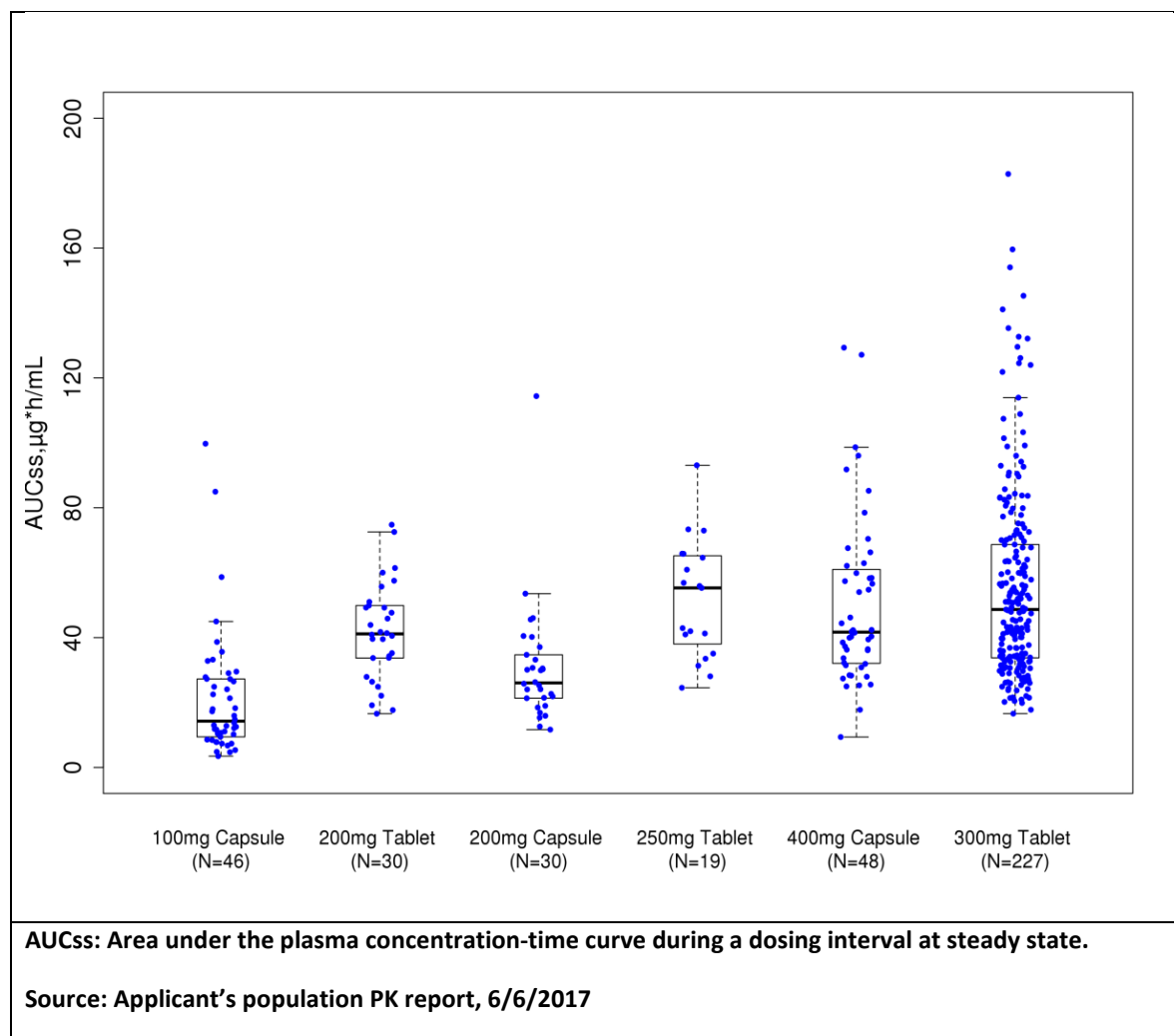
	Exposure parameter	Geometric mean	Geometric CV%	Min	Max
Capsule 100 mg (N=48) single dose	AUC (µg.h/mL)	14.0	91.7	2.96	85.2
	C _{max} (µg/mL)	1.67	50.7	0.42	5.98
Capsule 100 mg (N=46) steady-state	AUC _{ss} (µg.h/mL)	16.0	87.3	3.48	99.7
	C _{max,ss} (µg/mL)	2.45	63.2	0.56	9.63
	C _{min,ss} (µg/mL)	0.57	154	0.09	7.26
Capsule 200 mg (N=30) single dose	AUC (µg.h/mL)	23.2	49.3	9.93	97.7
	C _{max} (µg/mL)	2.48	31.2	1.20	4.26
	AUC _{ss} (µg.h/mL)	27.2	49.3	11.7	114
Capsule 200 mg (N=30) steady-state	C _{max,ss} (µg/mL)	3.86	36.9	2.12	11.6
	C _{min,ss} (µg/mL)	1.15	79.7	0.29	7.76
Capsule 400 mg (N=48) single dose	AUC (µg.h/mL)	38.0	53.5	7.98	110
	C _{max} (µg/mL)	4.18	30.1	1.72	10.5
	AUC _{ss} (µg.h/mL)	44.6	53.5	9.36	129
Capsule 400 mg (N=48) steady-state	C _{max,ss} (µg/mL)	6.37	36.7	2.12	14.7
	C _{min,ss} (µg/mL)	1.87	85.2	0.19	8.11
Tablet 200 mg (N=32) single dose	AUC (µg.h/mL)	36.7	64.2	14.1	379
	C _{max} (µg/mL)	5.56	42.2	2.82	19.6
	AUC _{ss} (µg.h/mL)	39.0	41.2	16.6	74.8
Tablet 200 mg (N=30) steady-state	C _{max,ss} (µg/mL)	6.96	33.9	3.36	14.0
	C _{min,ss} (µg/mL)	1.15	78.0	0.21	3.42
Tablet 250 mg (N=27) single dose	AUC (µg.h/mL)	44.4	40.6	20.9	85.7
	C _{max} (µg/mL)	6.65	26.7	4.15	12.2
	AUC _{ss} (µg.h/mL)	48.7	38.1	24.5	93.1
Tablet 250 mg (N=19) steady-state	C _{max,ss} (µg/mL)	8.41	22.6	5.71	12.8
	C _{min,ss} (µg/mL)	1.43	70.2	0.58	4.47
Tablet 300 mg	AUC (µg.h/mL)	42.0	50.5	14.1	186
	C _{max} (µg/mL)	5.78	36.3	2.08	14.7
	AUC _{ss} (µg.h/mL)	49.1	51.6	16.6	183
Tablet 300 mg (N=227) steady-state	C _{max,ss} (µg/mL)	7.65	40.5	3.21	23.5
	C _{min,ss} (µg/mL)	1.56	86.2	0.25	10.0

Note: Exposure estimation for capsule only applies to patients in study 12 and study 24. with commercial formulation, while the estimation for 100 mg capsule was from patients dosed by non-commercial formulation; AUC Area under concentration curve; AUC_{ss} Area under concentration curve at steady-state; C_{max} Maximum concentration, C_{max,ss} Maximum concentration at steady-state; C_{min,ss} Minimum concentration at steady-state; N number of subjects

Source: Applicant's population PK report, 6/6/2017

The steady-state AUC for different doses are also presented in **Figure 12**.

Figure 12: Boxplots of Trough Observations Stratified by Concomitant Medication



Reviewer comment: The applicant conducted population PK analysis per FDA's request by pooling all available data from both capsule and tablet formulations. The PPK model was able to adequately describe the time course of the olaparib concentration following multiple dose levels with both capsule and tablet formulations. Based on this model, FDA reviewer performed independent analysis by employing a more accurate function to describe the absorption of capsule olaparib. More details will be discussed in the later part.

For 2 clinically relevant doses, 400 mg capsule (Studies 12 and 24) and 300 mg tablet, the average relative F of 300 mg tablet compared with the 400 mg capsule can be derived as the ratio of dose normalized AUCss of 300 mg tablet over that of 400 mg capsule, i.e., $F = (49.1/300)/(44.6/400) = 147\%$.

Reviewer comment: One objective for the population PK analysis in this submission is to compare the relative bioavailability between capsule and tablet formulation, so as to address the clinical relevant question that how much exposure increase would be expected for a subject who switch from capsule to tablet. Thus, a comparison of model predicted exposure based on empirical Bayesian estimate (EBE) was inappropriate because other covariates affecting PK could not be adjusted under this scenario. Instead, the model estimated fixed effect on the relative bioavailability should be employed to describe the extent of absorption between these two formulations. In the applicant's final PPK model with pooled data, only 2 groups of olaparib doses were evaluated for F: one was for all capsule formulations with dose >100 mg and the other was for all tablet formulations, with reference to a capsule dose <100 mg. This was inadequate to differentiate the F for dose levels above 100 mg capsule, and may potentially underestimate the difference in bioavailability between these two formulations. FDA reviewer performed a population PK analysis by employing a more accurate function to describe the extent of absorption for the capsule formulation above 100 mg (see more details in Section 4). Based on FDA reviewer's analysis, the relative bioavailability between tablet and 400 mg capsule is 236%.

Per the FDA's request, the potential impact of treatment line, disease severity (ECOG status), tumor types, together with other covariates including demographics factors (age, weight, race, sex), hepatic and renal function and tablet strength on olaparib PK, were evaluated for the pooled data set. While the previously identified tablet strength covariate (Olaparib-MS-02) remained statistically significant with a similar magnitude of impact on the absorption rate constant, ECOG score of 0, 1 and 2 were found to be statistically significant on impacting olaparib CL. Patients with ECOG=1 and 2 were estimated to decrease olaparib CL by 22.9% and 59.8%, respectively, when compared to patients with ECOG=0. Conceptually, lower exposure in SOLO2 study (Olaparib-MS-03) compared to pooled tablet Phase I studies (Olaparib-MS-02) could be partially related to the lower percentage of patients with ECOG=1 (22%) and no patients with ECOG=2 in SOLO2 compared to 45% and 3.7%, respectively in pooled tablet Phase I studies.

Reviewer comment: In study SOLO-2, subjects who took 300 mg tablet olaparib showed ~50 % lower steady-state AUC as compared with pooled tablet phase I studies. To address this observation, FDA recommended the applicant to conduct the population PK analysis using pooled data to explore the potential reasons. Although the applicant initially made efforts to do so based on the PPK models developed separately (MS-02 and MS-03), that method was not sensitive because such analysis may not be powered enough to detect the covariates which had distinct distribution between MS-01 and MS-03. Thus, the population PK analysis using pooled data should be more appropriate. According to the applicant's PPK model using pooled data, the greater disease severity (ECOG>0) was associated with lower drug clearance. This could partially explain the lower exposure at Study SOLO-2, where 78% of the subject had ECOG=0, as compared with 51.3% at pool tablet phase I studies as the applicant mentioned. The potential mechanism for the association between disease severity and drug clearance could due to the possible reduced enzyme activity of CYP3A in oncology patients [1].

Exposure-Response Analysis

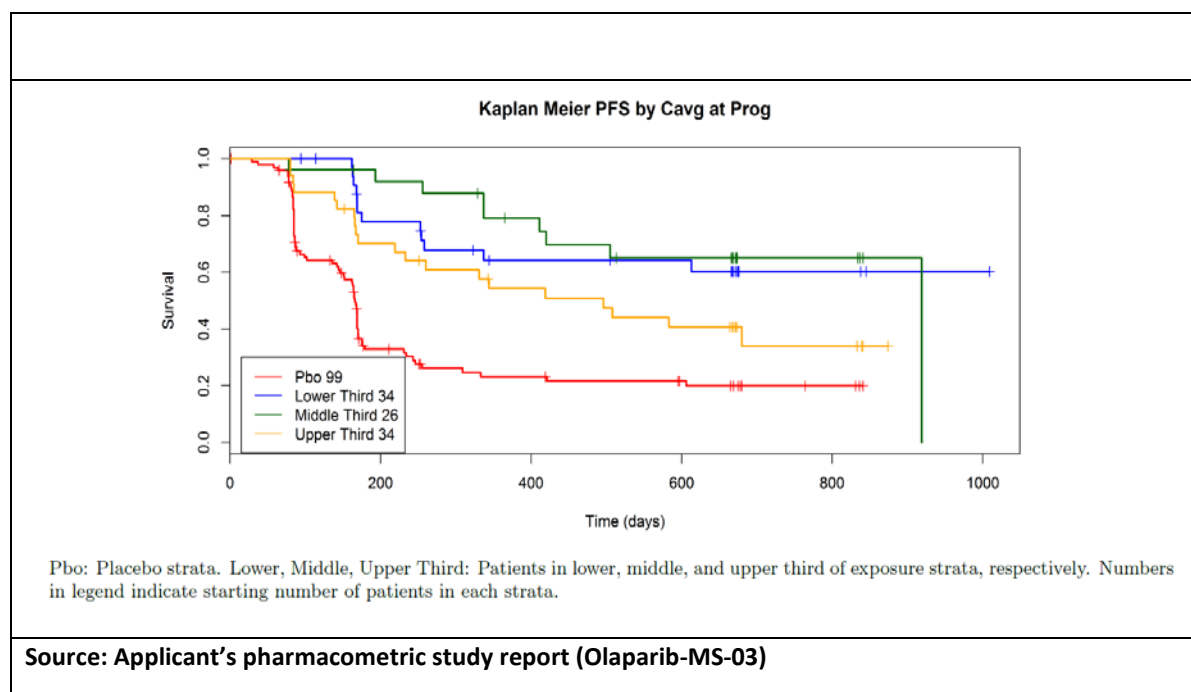
Based on the data from pivotal study SOLO-2, the applicant conducted exposure response analysis to explore and model (if applicable) the relationship between olaparib plasma exposure and selected efficacy and safety variables.

Exposure-efficacy Analysis

Exposure-PFS analysis

Sponsor explored exposure-PFS relationship by performing the graphical exploratory analysis. Olaparib treated patients were divided into tertiles based on average cumulative C_{avg} at the time of progression (n=26 to 34), and the placebo arm (n=99) was included. A Kaplan-Meier graph with PFS stratified on exposure is found **Figure 13**. It indicates no clear relationship to olaparib exposure, with the lowest third and middle tertiles overlapping greatly.

Figure 13 Kaplan Meier plot for PFS vs average cumulative C_{avg} at the time of progression



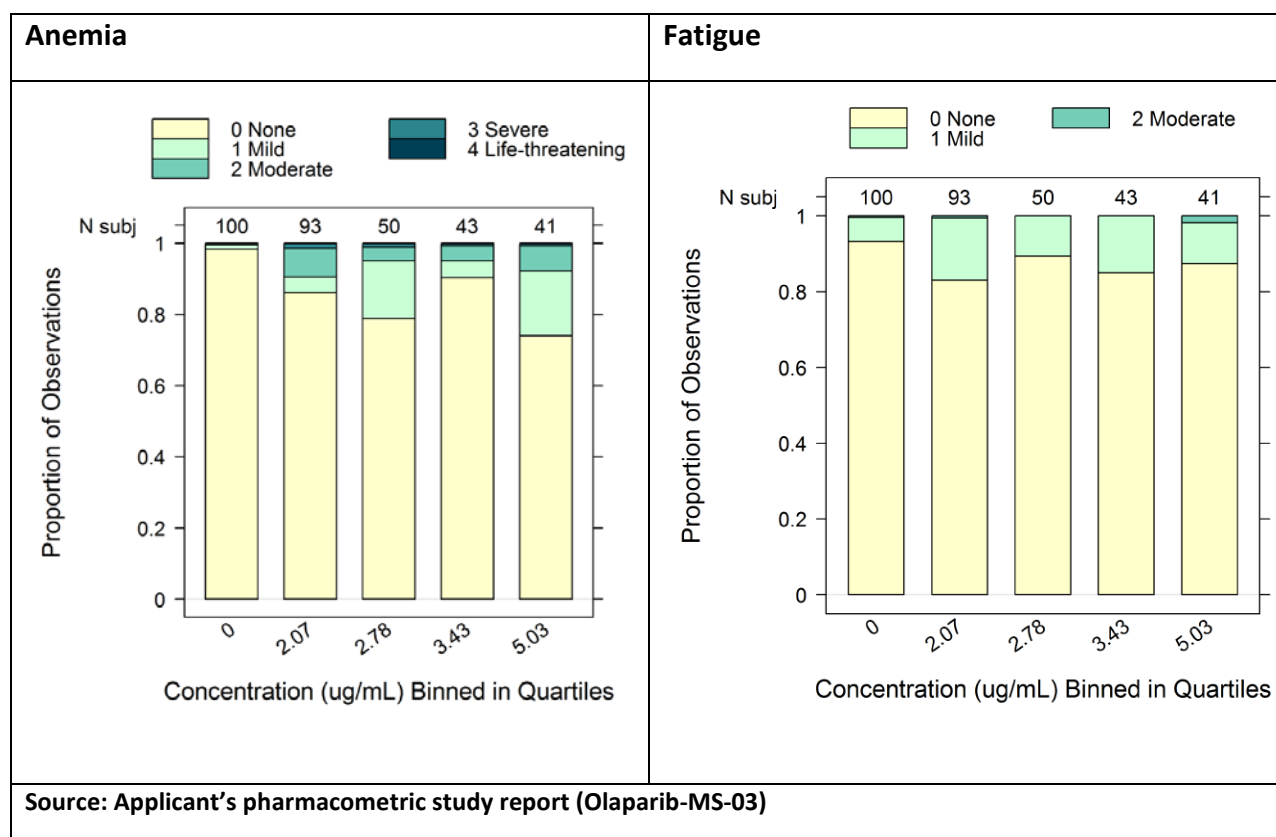
Reviewer comment: The result from exploratory KM plot for exposure-PFS analysis could be biased; even average cumulative C_{avg} was used as the exposure metrics. Due to dose reduction/interruption in the trial, exposure showed a downward trend in a general manner and subjects who had longer time to progressive disease or death could have greater chance to experience dose interruption/reduction. Thus, the C_{avg} tends to be lower in the patients with longer PFS, which made the exposure-PFS relationship look flat.

Exposure-safety analysis

Graphical Exploratory Analysis of Safety Exposure-Response

A potential relationship between proportion of observed anemia grades and olaparib exposure can be seen in **Figure 14**. An examination of the commonality between anemia and fatigue outcomes showed higher incidence of fatigue in patients who had grade 1 or higher of anemia, and higher incidence of fatigue at higher grades of anemia as well. The same applied when viewing this as incidence of anemia given fatigue outcomes. Cumulative Cavg is the average cumulative concentration of olaparib up until the observation.

Figure 14 Boxplots of Proportion of Observed AE Grades vs. Olaparib Cumulative Cavg.



Exposure-Response Model - Hemoglobin

A placebo model was developed based on the placebo patient data. Hemoglobin levels appeared to change over time and thus time-dependent models were evaluated. The change in hemoglobin over time was described by an Emax type function: a maximum effect (Emax) function to describe the time course was used. The predicted observation (y_i at time i) is given by:

$$y_i = y_0 + \frac{Emax_{Time} * day_i}{ET50 + day_i}$$

where $Emax_{Time}$ denotes the maximum the observation will grow to, $ET50$ denotes the time where half of full effect is observed, day_i is a given time point and y_0 is baseline.

An indirect response (IDR) model for Hb with olaparib exposure AUC impacting the synthesis rate of Hb as follows was examined:

$$\frac{dHb}{dt} = K_{in} \times (1 - SLOPE \bullet AUC) - K_{out} \times Hb$$

Where K_{in} is synthesis rate constant of hemoglobin, K_{out} is the elimination rate constant of hemoglobin, and $SLOPE$ represents the slope of AUC impacting K_{in} as a linear relationship. AUC is average cumulative AUC on day of measurement. The parameter estimates of the final model are given in **Table 63**.

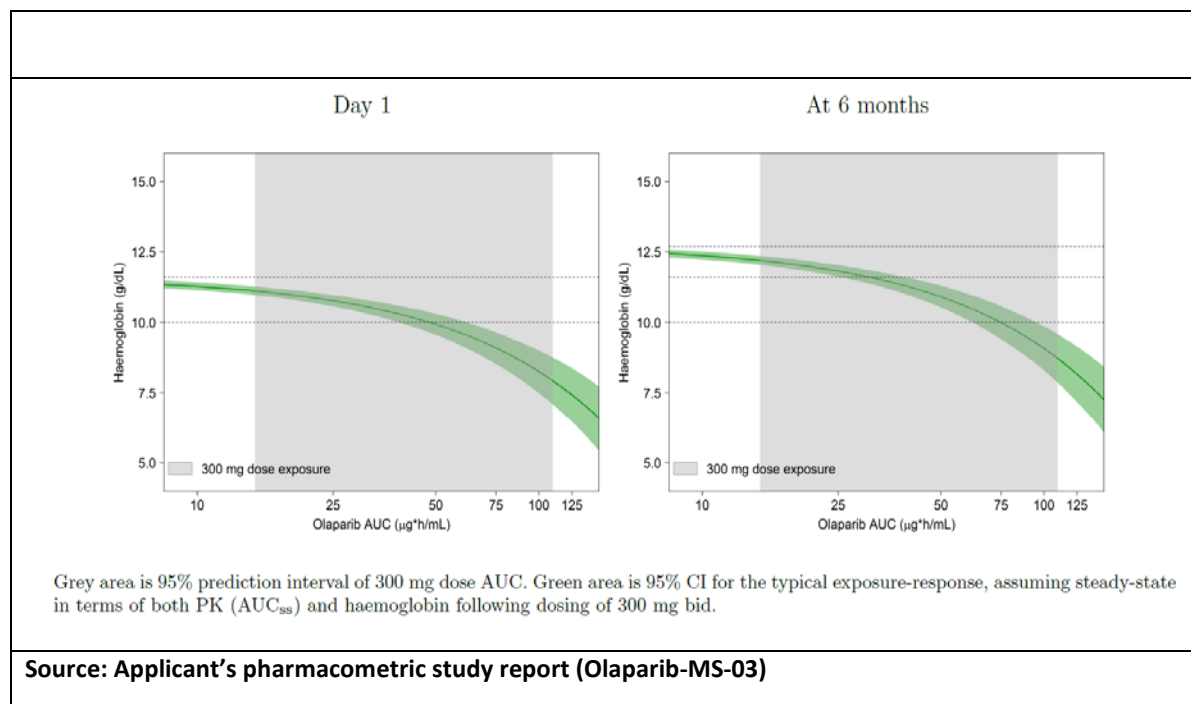
Table 63 Parameter Table - Final Hemoglobin Model

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Baseline haemoglobin (g/dL)	11.6	0.6	(11.5 - 11.8)
θ_2	Kin ((g/dL)/h)	0.0117	6.2	(0.0103 - 0.0132)
θ_3	Slope for the drug effect (g/dL/h)/(μ g·h/mL)	0.00287	11.7	(0.00221 - 0.00352)
θ_4	Additive residual variability (g/dL)	0.732	1.3	(0.714 - 0.751)
θ_5	$ET50$ (days)	42.4		NC
θ_6	$Emax_{Time}$ (g/dL)	1.39		NC
$\omega_{1.1}$	$\omega_{Baselinehaemoglobin}^1$	0.935	11.5	(0.724 - 1.15)
$\omega_{2.1}$	$\omega_{Corr}^{1,2}$	1.15	29.9	(0.475 - 1.82)
$\omega_{2.2}$	ω_{Slope}^2	9.95	16.8	(6.68 - 13.2)

Parameter values for the final haemoglobin model. ω_X^2 : Variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega_X^2 \cdot 100 \cdot \omega_{X,Y}^2}$: Covariance of the IIV of parameters X and Y. Corr: Correlation. NC: Not Calculated. CI: Confidence Interval. SE: Standard error. $Emax$: maximum effect. $ET50$: time where half of full effect is observed. Kin: synthesis rate constant of haemoglobin

The model shows predicted typical ER curve for hemoglobin concentrations. At the time of day 1 and 6 months, the predicted mean baseline hemoglobin concentrations with the placebo model are 11.6 and 12.7 g/dL, respectively. At a baseline hemoglobin concentration of 11.6 g/dL, hemoglobin is predicted to decrease to 10.3 g/dL (95% CI: 9.98-10.6 g/dL) at predicted steady-state median olaparib exposure (assuming 300 mg bid dosing), while if the exposure is doubled, hemoglobin is predicted to decrease to 8.93 g/dL (95% CI: 8.33-9.52 g/dL).

Figure 15 Typical Hemoglobin Exposure-Response Plot



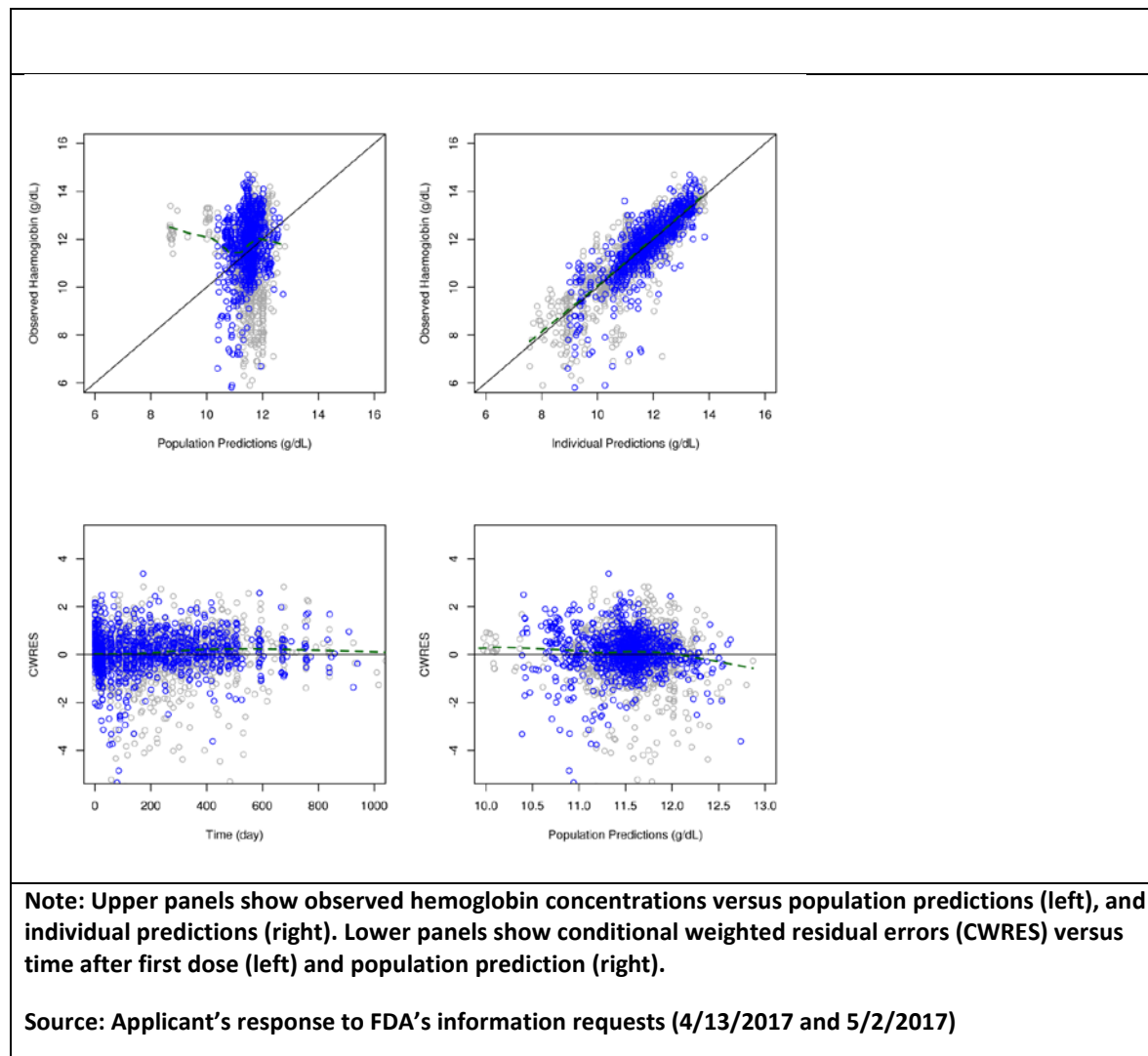
Reviewer comment: The applicant's IDR model describing the time course of the hemoglobin was able to describe the data reasonably well.

Evaluation of the impact upon hemoglobin level by switching capsule to tablet formulation at 4th line patients in the treatment setting.

Per FDA's request, the applicant evaluated the potential hemoglobin profile at exposure level 50%, 70% and 100% higher than 400 mg BID capsule in 4th line treatment setting in ovarian cancer patients with gBRCA mutation. The E-R model for hemoglobin as described above was employed.

The goodness-of-fit plots of hemoglobin exposure and response model for 4th line ovarian cancer patients overlaid with all patients as shown in **Figure 16**. It indicates that the final E-R model of hemoglobin from SOLO2 study (Olaparib-MS-03) adequately described the observed hemoglobin concentration profile for 4th line ovarian cancer patient.

Figure 16 Goodness-of-fit plots of hemoglobin exposure and response model for patients with 4th line treatment overlaid with all patients in the final hemoglobin E-R data set (Olaparib-MS-03)

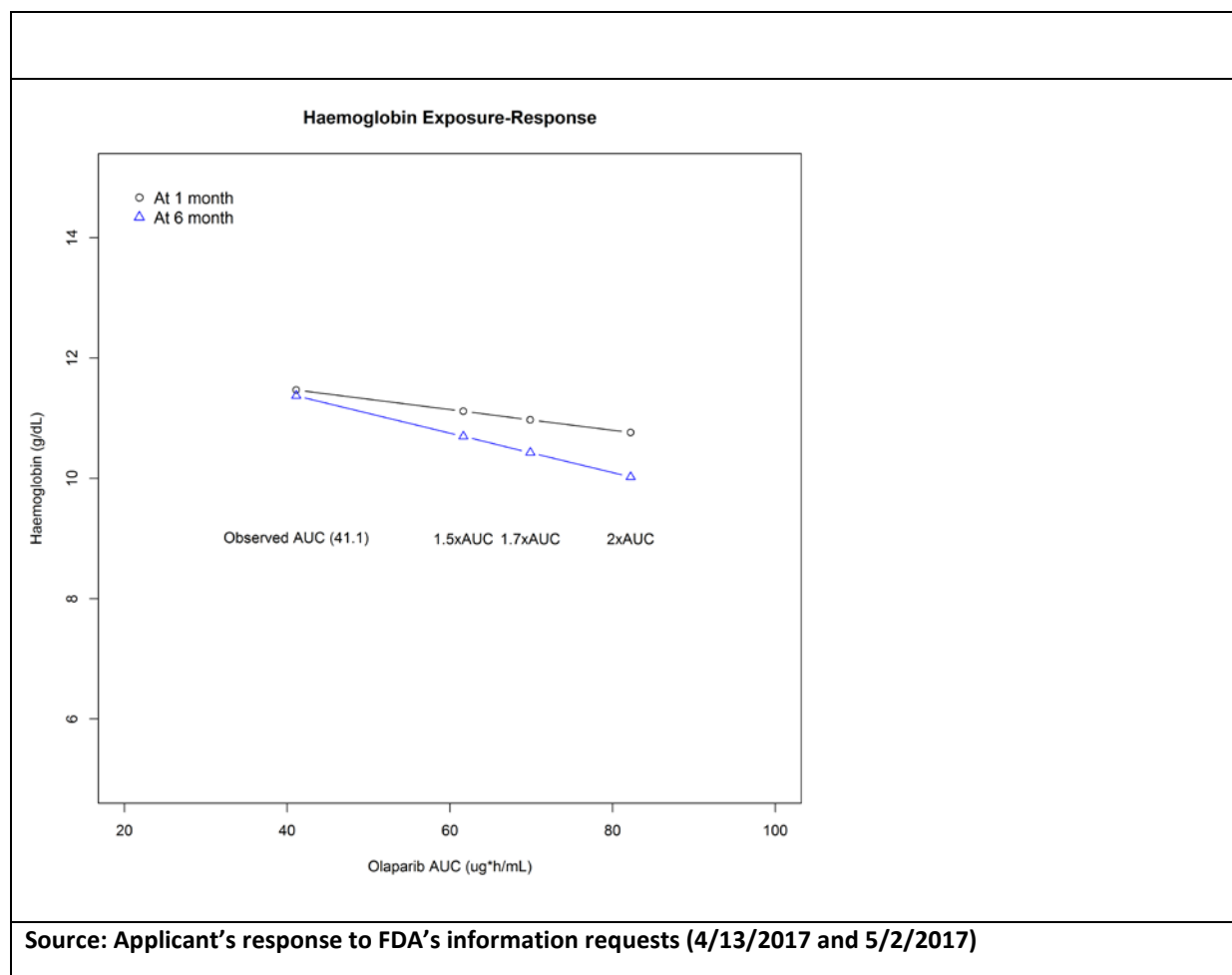


Reviewer comment: The final E-R model for hemoglobin from SOLO2 study is able to describe the time course of hemoglobin level at treatment setting reasonably well. Thus this model is acceptable for evaluation of the impact of formulation switch at hemoglobin 4th line patients in the treatment setting.

There were 52 4th line ovarian cancer patients in the capsule pooled population. The predicted geometric mean steady-state AUC for the 52 patients using the individual EBE estimates of olaparib PK parameters from the capsule pooled population PK model (Olaparib- MS-01) was 41.1 ug.h/mL. The predicted mean hemoglobin response for exposure level at 50%, 70% and 100% higher than the geometric mean AUC for 4th line ovarian cancer patients following 1 and 6 months of 400 mg capsule

BID, are shown in **Figure 17**. The predicted mean hemoglobin response >6 months were similar to those for 6 months and are therefore not shown. The figure indicates that the predicted mean decrease in hemoglobin concentration is small and the absolute values were >10 g/dL, even at 100% higher geometric mean AUC for 4th line ovarian cancer patients following ≥6 months olaparib 400 mg BID capsule treatment.

Figure 17 Predicted mean hemoglobin response for exposure levels 50%, 70% and 100% higher than the geometric mean AUC for 4th line ovarian cancer patients following 1 and 6 months of 400 mg BID capsule



Reviewer comment: Based on the FDA reviewer's PPK analysis, the exposure (eg. AUCss) would increase by 77% when olaparib was switched from 400 mg capsule to 300 mg tablet. And, the predicted mean hemoglobin level would not be lower than 10 g/dL when 300 mg tablet was used for 4th line ovarian cancer patients.

Results of Reviewer's Analysis

Objectives

The reviewer initiated an independent population PK analysis to investigate the relative bioavailability between capsule and tablet formulations.

Software

NONMEM version 7.3 was used for all the simulations. R version 3.2.3 was used for data handling, visualization, and post-processing.

Results and Discussions

Population PK analysis using pooled data

The FDA reviewer performed a PPK analysis based on the applicant's PPK model to describe the distinct bioavailability at different doses of capsule formulation. In the applicant's PPK model with pooled dataset, the relative bioavailability for capsule formulation (>100 mg) was represented lumped as one fixed effect. As the 400 mg dose is mostly relevant for clinical usage, different capsule dose levels above 100 mg were treated as continuous variable. The relative bioavailability to capsule dose <100 mg in FDA reviewer's PPK model is described using the following equation:

$$\text{Relative bioavailability for capsule} = 1 + \theta_8 \times \log_{10}(\text{Dose})$$

Parameter estimates and corresponding 95% CI for the PPK model are summarized in **Table 64**.

Table 64 Parameter estimates and corresponding 95% CI for the PPK model

Parameter	Description	Value	RSE
OFV	Objective function value	11151.865	–
θ_3	Clearance for single dose (L/h)	4.22	7.6%
θ_4	Scaling factor for steady state CL (L/h)	-0.159	3.6%
θ_5	Central Volume of Distribution (L)	2.57	9.4%
θ_6	Peripheral Volume of Distribution (L)	19.2	10.1%
θ_7	Inter-compartmental clearance (L)	1.11	8.4%
θ_8	Effect of dose on Bioavailability	-0.282	3.0%
θ_9	Relative bioavailability of tablet to capsule (<100 mg)	0.628	7.6%
θ_{10}	Absorption rate constant for capsule, K_a (h ⁻¹)	0.247	2.9%
θ_{11}	Absorption rate constant for tablet, K_a (h ⁻¹)	0.201	2.7%
θ_{12}	Duration of zero-order absorption for capsule, D1 (h)	0.901	7.7%
θ_{13}	Duration of zero-order absorption for tablet, D1 (h)	0.477	5.9%
θ_{14}	Disease severity (ECOG=1) on CL	-0.239	15.7%
θ_{15}	Disease severity (ECOG=2) on CL	-0.585	8.9%
θ_{16}	Tablet strength (100 mg) on K_a , $K_a^*(1+\theta_{16})$	0.86	4.6%
θ_{17}	Tablet strength (100, 200, 300, 125, 225 mg) on K_a , $K_a^*(1+\theta_{17})$	0.325	17.2%
ω_1	BSV in CL for single dose (CV%)	58.3%	2.7%
ω_2	BSV in V2 for single dose (CV%)	66.9%	5.9%
ω_3	BSV in V3 (CV%)	124.1%	4.4%
ω_4	BSV in Q (CV%)	77.3%	5.4%
ω_5	BSV in D1 (CV%)	73.3%	4.3%

ω6	BSV in Ka (CV%)	25.1%	6.7%
Source: FDA reviewer's analysis			

Reference

[1] Schwenger E, Moorthy G, Masson E, Tomkinson H, Vishwanathan K. harnessing PBPK to better understand disease drug interactions in cancer patients. The American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2017 Annual Meeting, Washington D.C.

Appendix

Information Requests (IR) to the Applicant (4/13/2016)

Reference is made to your MS-01, MS-02 and MS-03 in the NDA208558 submission for olaparib.

- I. Submit the datasets and control stream for the PPK and E-R analysis in MS-03.
- II. Combine all available PK data from different patient populations and healthy subjects in your integrated population PK model to evaluate the impact of formulations, treatment lines, disease severity, tumor types or other relevant factors on the PK of olaparib:
 - a. Data for PPK analysis of MS-01, MS-02 and MS-03 should all be included.
 - b. If necessary, the absorption process could be described by distinct functions based on the formulations (capsule vs. tablet).
 - c. The drug distribution and elimination of capsule and tablet should be described by the same set of functions
 - d. Estimate the relative bioavailability for tablet as compared with capsule; if the extent of drug absorption is dose dependent with capsule formulation, take dose<100 mg, fast/unknown release capsule as the reference.
 - e. Assess if the treatment line, disease severity, tumor types, or other factors may potentially impact the olaparib PK profile by evaluating them as covariates.

Please use this mega-PPK analysis to:

- 1) Evaluate the exposure profile changes (C_{max}, C_{min}, AUC_{ss}, etc.) at the treatment group (4th line ovarian cancer patients) by switching from the 400 mg capsule into 300 mg tablet formulation. In addition, please also compare the exposure profiles at the treatment group for the secondary dose levels (200 mg capsule vs. 250 mg tablet, 100 mg capsule vs. 200 mg tablet). This comparison will be simulation based.
 - 2) Evaluate the reason that the exposure at SOLO2 study was lower as compared with the tablet pooled population.
- III. Conduct the exposure response analysis for safety, especially myelosuppressive adverse events at 2nd + line treatment setting in ovarian cancer patients with gBRCA mutation. Predict and compare the safety profile following 300 mg tablet BID and 400 mg capsule BID in these 2nd + line treatment setting in ovarian cancer patients. In addition, provide prediction of safety profile at exposure level 50%, 70% and 100% higher than 400 mg BID capsule in 2nd + line treatment setting in ovarian cancer patients with gBRCA mutation.

For the item 4(I), please respond by COB of April 17, 2017. For the rest of items, please provide responses with relevant datasets and programs to the corresponding items by COB of April 25, 2017.

PBPK Analysis

Objectives

The main objective of this review is to evaluate the adequacy of sponsor's olaparib physiologically-based pharmacokinetic (PBPK) model to 1) predict the effect of moderate and weak CYP3A inhibitors/ inducers on the exposure of olaparib; 2) predict the DDI potential of olaparib as a perpetrator in various drug-drug interaction (DDI) mechanisms including UGT1A1 metabolism; 3) provide a dosing recommendation based on the predicted DDI potential.

To support its conclusions the sponsor provided the following PBPK modeling and simulation reports and updates:

Simulating the Drug-Drug Interaction Potential of Olaparib Tablet Formulation as a Victim and Perpetrator, using Simcyp® (V15 R1), Based on Data from in vitro and Clinical Studies [1]

Response to FDA information request regarding PBPK (Email). [2]

Background

Olaparib (AZD2281 or KU-0059436) is a poly (ADP-ribose) polymerase (PARP) inhibitor developed as monotherapy in patients with platinum-sensitive relapsed (PSR) breast cancer susceptibility gene mutated (BRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy [3]. The capsule formulation of olaparib (brand name Lynparza) was approved under NDA 206162 in 2014. Olaparib's approved dosing regimen is 400 mg (eight 50 mg capsules) taken twice daily (bid) [3]. In the current submission (NDA 208558), the applicant proposed a new dosing regimen, 300 mg twice daily (bid), for tablet formula.

Applicant's olaparib PBPK models were reviewed during original and its supplement NDA submission. Applicant has used olaparib PBPK models to predict the DDI effect of olaparib as a victim (with CYP3A moderators) and a perpetrator of CYP3A and P-gp mediated pathway [4, 5]. In this submission, the applicant updated previous reviewed PBPK models to predict olaparib as a victim (with CYP3A moderators) and a perpetrator (on probe CYP3A substrates, a probe P-gp substrate and UGT1A1 inhibitor). **Table 65** summarizes the use of olaparib PBPK model to support olaparib dosing recommendations with various CYP3A modulators, P-gp and CYP3A probe substrates in current and past submissions.

Table 65 Summary of the use of olaparib PBPK model to support olaparib labeling

		PBPK review table 2017 Current Submission		PBPK review table 2014	PBPK review Capsule 2016	olaparib dosing recommendation and labeling indication
		AUC ratio	Cmax ratio			

NDA/BLA Multi-disciplinary Review and Evaluation NDA 208558
Lynparza™ (Olaparib)

Inhibitors (Olaparib as a victim drug)	itraconazole	3.55	1.2	√	√	reduce dose to 150mg
	fluconazole	2.21	1.14	√	√	reduce dose to 200 mg
	fluvoxamine	1.02	1.01		√	No dose adjustment
Inducer(Olaparib as a victim drug)	rifampicin	0.25	0.56	√	√	Not Recommended
	efavirenz	0.4	0.69	√	√	Not Recommended
	dexamethasone	1.0	1.0			No dose adjustment
Olaparib as a perpetrator						
As a CYP3A inhibitor	midazolam	1.61	1.18		√	support labeling statement on olaparib is a weak CYP3A inhibitor
	simvastatin	1.54	1.33		√	
As a p-gp inhibitor	digoxin	1.02	1.05		√	(b) (4)
As an UGT1A1 inhibitor	raltegravir	1.07	1.04			(b) (4)

Based on the PBPK analysis, the applicant proposed the following changes in the proposed prescription information (USPI) Section 12.3 [6].

“Simulations suggested that olaparib is a weak CYP3A inhibitor in humans.”

(b) (4)

(b) (4)

This review summarized the previous PBPK reviews and evaluated the adequacy of PBPK modeling to support the above labeling changes.

Methods

Previous Submission and FDA review

Applicant first submitted the olaparib PBPK in NDA 206162 submission in 2013. There have been multiple updates in the applicant's olaparib PBPK modeling given the newly available in-vitro and in-vivo dataset.

In the original NDA 206162 submission, the applicant submitted two versions of PBPK models of olaparib using Simcyp software [4]. The newer version of the two submitted models (Model 3) [7] was developed using Simcyp Version 13.1, which includes a mechanistic absorption model and a full PBPK distribution model. Model 3 was verified by comparing the simulated olaparib tablet DDI potential with clinically observed DDI with strong CYP3A inhibitor or inducer (itraconazole and rifampin). Applicant also used Model 3 to predict the DDI potential with a moderate CYP3A inhibitor fluconazole or inducer efavirenz. PBPK model predicted an approximately 2-fold increase in olaparib exposure with a moderate inhibitor, fluconazole [4]. The effect of a moderate CYP3A inducer efavirenz was predicted to decrease olaparib exposure by approximately half [4]. FDA reviewer concluded that the applicant's olaparib tablet PBPK model (Model 3) is adequate to support the dosing recommendations of olaparib on the effect of moderate CYP3A modulators on olaparib PK. See "Physiological-based Pharmacokinetic Modeling Review" by Dr. Ping Zhao [4]

In September 2015, the applicant submitted updated olaparib PBPK models for tablets and capsule (Model 4) using Simcyp Version 14 [8]. These PBPK models took the capsule and tablet formulation characteristics into consideration. Applicant noted the oral clearance was 6.07 and 6.35 L/hr. for capsule and tablet respectively (pg. 70, Model 4 PBPK report [8]). The models also incorporated CYP3A inhibition/induction and P-gp inhibition parameters from in vitro studies. The models were used to predict olaparib as a victim (with CYP3A moderators) and a perpetrator (net effect of olaparib on probe CYP3A substrates and a probe P-gp substrate). In the Addendum 1 of Olaparib Simcyp Model 4 [9], the applicant updated the renal clearance rate from 1.09 L/hr. to 1.48 L/hr based on new measured renal clearance data (Study D0816C00006). In the Addendum 2 of Olaparib Simcyp Model 4 [10], the applicant executed Model 4 in Simcyp V15. No model parameters were modified. FDA reviewer concluded that the final olaparib Model 4 (Model 4 in Simcyp V15 [10]) is sufficient to predict olaparib PK in patients co-administered with CYP3A modulators including a weak inhibitor fluvoxamine [5]. The effect of a weak inhibitor fluvoxamine was predicted to have no impact on olaparib exposure. FDA reviewer also concluded that olaparib is not predicted to have time dependent effect on CYP3A4 for two reasons [5]. First, the simulation with no net time dependent effect on CYP3A4 provided better descriptions of olaparib plasma exposures than those simulated using the original Model 4 parameters (Appendix Figure A1). Second, there is no clinically significant time-dependent PK profiles observed after multiple dosing of both olaparib capsule and tablet. The capability of the PBPK model to predict olaparib as a P-gp perpetrator was not evaluated because the predictive performance of PBPK for P-gp inhibition has not been established. See "Physiological-based Pharmacokinetic Modeling Review" by Dr. Wentao Fu for more detail [5]

Current Submission

In the current submission (NDA 208558), the applicant updated the final olaparib Model 4 by incorporated UGT1A1 inhibition parameters from in vitro studies. The oral clearance (CL/F) was updated from 6.35 to 7.6 L/h [1]. Applicant noted the difference on CL/F is due to large inter-individual variability observed clinically and a switch between CL_{po} and CL/F used in the current model (pg 87, Model 6 PBPK report [1]). The updated olaparib PBPK models (Model 6) were used to predict olaparib as a victim (with weak CYP3A inducer dexamethasone) and as a perpetrator (effect of olaparib on a probe UGT1A1 substrate such as raltegravir). Development of dexamethasone and raltegravir PBPK model is

summarized in Appendix B and C. Appendix Table A1 listed the description of in vitro data and in vivo PK studies used to support the input parameters of olaparib PBPK model in the current submission. Table 66 listed the update PBPK parameters between Model3, Model 4 and Model 6.

Table 66 List of updated PBPK model parameters from 2014 to the current model (only parameters are different among models are listed)

	Model 3, SimcypV13	Model 4, Simcyp V14	Model 4-add, SimcypV15	Model 6, Simcyp V15
Elimination				
Clearance Type	Enzyme Kinetics	Enzyme Kinetics	Enzyme Kinetics	Enzyme Kinetics
Pathway	Pathway 1	Pathway 1	Pathway 1	Pathway 1
Enzyme	CYP3A4	CYP3A4	CYP3A4	CYP3A4
CLint (μL/min/pmol of isoform)	0.057	0.057	0.057	0.057
Additional HLM CLint	0.22	0.17	0.16	0.22
CL R (L/h)	1.10	1.10	1.48	1.48
CYPs and/or UGTs Interaction				
Enzyme		CYP3A4	CYP3A4	CYP3A4
Ki (μM)		59.500	59.500	59.500
Kapp (μM)		72.200	72.200	72.200
Kinact (1/h)		4.050	4.050	4.050
Ind max		48.100	48.100	48.100
Ind C50 (μM)		17.650	17.650	17.650
Enzyme				UGT1A1
Ki (μM)				48.350
fu mic				0.892
Transporters Interaction				
Organ/Tissue		Gut	Gut	Gut

Transporter		ABCB1 (P-gp/MDR1)	ABCB1 (P-gp/MDR1)	ABCB1 (P-gp/MDR1)
Ki (μM)		73.910	73.910	73.910
Organ/Tissue		Liver	Liver	Liver
Transporter		ABCB1 (P-gp/MDR1)	ABCB1 (P-gp/MDR1)	ABCB1 (P-gp/MDR1)
Ki (μM)		73.910	73.910	73.910
Organ/Tissue		Kidney	Kidney	Kidney
Transporter		ABCB1 (P-gp/MDR1)	ABCB1 (P-gp/MDR1)	ABCB1 (P-gp/MDR1)
Ki (μM)		73.910	73.910	73.910

DDI Simulations

Perpetrator models (itraconazole ("itraconazole_Fasted Soln.cmpz"), fluconazole ("SV-fluconazole.cmpz"), fluvoxamine ("SV-fluvoxamine.cmpz"), rifampicin ("SV-rifampicin-MD.cmpz") and efavirenz ("SV-Efavirenz.cmpz")) and victim models (midazolam ("Sim-midazolam.cmpz"), simvastatin ("SV-simvastatin.cmpz"), and digoxin ("SV-digoxin.cmpz")) from the Simcyp V15.1 drug model library were directly used.

Applicant also developed PBPK models of dexamethasone and raltegravir to predict olaparib as a CYP3A victim and as a UGT1A1 inhibitor respectively. Appendix B and C describe the development of PBPK model for dexamethasone and raltegravir respectively.

Model Applications

Table 67 summarizes the design of simulations and clinical studies for each interacting drug.

Table 67 Trial designs for PBPK simulations used in the PK and DDI simulations

	Sub. (n) × Trail (n)	Perpetrator Drug	Dose Regimen	Treatment day	Victim Drug	Dose Regimen	Treatment day	Analysis
1	10×10	olaparib	300 mg sd	Day1	NA	NA	NA	Pred-vs Obs
2	10×10	olaparib	300 mg bid	1-5 day	NA	NA	NA	Pred-vs Obs
3	10×10	itraconazole	200 mg	1-7 day	olaparib	100 mg	Day 5	Pred-vs

			qd			sd		Obs
4	10×10	rifampin	600 mg qd	1-13 day	olaparib	300 mg sd	Day 10	Pred-vs Obs
5	10×10	fluconazole	200 mg qd	1-7 day	olaparib	100 mg sd	Day 5	Pred only
6	10×10	fluvoxamine	50 mg qd	1-7 day	olaparib	100 mg sd	Day 5	Pred only
7	10×10	efavirenz	600 mg qd	1-13 day	olaparib	300 mg sd	Day 10	Pred only
8	10×10	dexamethasone	8 mg qd	1-13 day	olaparib	300 mg sd	Day 10	Pred only
9	10×10	olaparib	300 mg bid	1-7 day	midazolam	5 mg sd	Day 5	Pred only
10	10×10	olaparib	300 mg bid	1-7 day	simvastatin	40 mg sd	Day 5	Pred only
11	10×10	olaparib	300 mg bid	1-7 day	digoxin	0.5 mg sd	Day 5	Pred only
12	10×10	olaparib	300 mg bid	1-8 day	raltegravir	400 mg sd	Day 5	Pred only

*Data source: PBPK report table 6-14 [1]

Results

Q1. Can olaparib PBPK model provide a reasonable description of the observed DDI effects of olaparib as a victim (with CYP3A moderators) and a perpetrator (net effect of olaparib on probe CYP3A substrates and a probe P-gp substrate)?

Olaparib PBPK models have been reviewed by other FDA's reviewers [4, 5] and were used to support dosing recommendations of olaparib in the label [3]. The current olaparib PBPK model (Model 6) reasonably described the plasma concentration-time profile for olaparib tablet following single and multiple dosing as shown in **Table 68**. Applicant verified Model 6 using clinical DDI studies with strong CYP3A inhibitor or inducer (itraconazole and rifampin) as shown in **Table 69**. The final olaparib Model 6 (Model 6 in Simcyp V15 [1]) is sufficient to predict olaparib PK in patients co-administered with CYP3A modulators. Appendix Table A2 present the observed and simulated effect of olaparib as a victim (with CYP3A moderators) and a perpetrator (net effect of olaparib on probe CYP3A substrates, a probe P-gp substrate, and UGT1A substrate) using the Model 6.

Table 68 Comparison of simulated and observed PK of olaparib following single and multiple oral dosing of olaparib

Olaparib Dose		Observed <i>in vivo</i> clinical data	PBPK predicted (n=100)
Single dose 300 mg tablet	AUC _(0-∞) (μg.h/mL)*	43.6 (15.7 to 144) [54.3]	59.6 (24.2 to 191) [48]
	GMean (range) [%CV], n	n = 52 ^a	
	C _{max} (μg/mL)	7.00 (2.63 to 19.1) [35.1]	7.97 (5.47 to 14.2) [19]
	GMean (range) [%CV], n	n = 55 ^a	
Multiple doses 300 mg twice daily tablet	AUC _{ss} (μg.h/mL)	58.32 (25.5 to 189) [44.5]	80.9 (9.82 to 240.8) [51]
	GMean (range) [%CV], n	n = 49 ^b	
	C _{max} (μg/mL)	9.17 (4.82 to 24.9) [37.1]	11.6 (3.22 to 24.3) [34]
	GMean (range) [%CV], n	n = 49 ^b	
^a Data taken from fasted arm Table 14 study D0816C00004 CSR			
^b Data taken from Table 16 study D0816C00004 CSR			
AUC _(0-∞) area under curve from zero to 72hours post-dose; AUC _{ss} area under curve at steady state; C _{max} maximum plasma concentration; CV% coefficient of variation; GMean geometric mean; n number of subjects; PK pharmacokinetic.			

Extracted: Table 4 of applicant's PBPK report [1]

Applicant verified Model 6 using clinical DDI studies with strong CYP3A inhibitor or inducer (itraconazole and rifampin) as shown in **Table 69**. The final olaparib Model 6 [1] is sufficient to predict olaparib PK in patients co-administered with CYP3A modulators. Simulated effect of olaparib as a victim (with CYP3A moderators) and a perpetrator (net effect of olaparib on probe CYP3A substrates, a probe P-gp substrate, and UGT1A substrate) using the Model 6 is presented in **Table 66**.

Table 69 Summary of observed and simulated effects of olaparib as a victim (with CYP3A moderators) and a perpetrator

		Observed ^a ratio with/without a CYP3A modulator		Simulated ^b ratio with/without a CYP3A modulator	
		Geomean AUCR	Geomean CmaxR	Geomean AUCR	Geomean CmaxR
Strong CYP3A inhibitor	itraconazole	2.7 (2.44 to 2.97) ¹	1.42 (1.33 to 1.52) ¹	3.55 (3.46 to 3.65)	1.20 (1.20 to 1.21)
Strong CYP3A inducer	rifampin	0.13 (0.11 to 0.16) ²	0.29 (0.24 to 0.33) ²	0.25 (0.24 to 0.27)	0.56 (0.54 to 0.58)

¹Itaconazole clinical data (Study D0816C00007); ²Rifampicin clinical data (Study D0816C00008)

^aGeometric mean (90% confidence interval). ^bGeometric mean (95% confidence interval)

In vitro studies have shown that olaparib can inhibit CYP3A via reversible and non-reversible mechanisms; and only one of the two in-vitro studies indicated that olaparib is a non-reversible CYP3A inhibitor. In vitro studies also have shown that olaparib is a potential CYP3A inducer; however, the induction parameters (Emax, EC50) could not be estimated experimentally due to low activity and cytotoxicity. The applicant did not include any inhibition or induction parameters in their original PBPK (Model 3) submission [4]. In the updated model (Model 4) and current submission (Model 6), with a worst-case assumption for inhibition/induction potency, the applicant included in-vitro derived inhibition and induction parameters to evaluate the effect of olaparib as a CYP3A perpetrator. The final olaparib PBPK model (Model 6) predicted 61% and 54% increase in AUC of midazolam and simvastatin, respectively, when the drugs are co-administered with olaparib 300 mg bid (**Table 66**).

In addition, the applicant presented additional clinical DDI data to support olaparib as a weak CYP3A inhibitor. Study D081CC00001 investigated the DDI between olaparib and the anti-hormonal agents anastrozole, letrozole and tamoxifen at steady state. Tamoxifen is metabolized mainly via CYP3A4 and CYP2D6. When olaparib was combined with tamoxifen, tamoxifen Cmax increased by 13% and AUC at steady state increased by 16%. Based on the updated PBPK modeling and the new clinical data submitted by the applicant, FDA reviewer agrees that olaparib is a weak CYP3A inhibitor in human.

The PBPK modeling of olaparib as a P-gp inhibitor or substrate is not evaluated in this review, given the lack of systematic validation of both P-gp inhibitor and substrate PBPK models.

Q2. Can olaparib PBPK model use to predict the effect of olaparib on a sensitive UGT1A1 substrate?

Yes, the current PBPK models are adequate to predict effect of olaparib on the PK of a sensitive UGT1A1 substrate such as raltegravir.

In vitro studies have shown that olaparib can inhibit UGT1A1 and the IC50 was 96.7 µM. To evaluate UGT1A1 inhibition by olaparib, the applicant developed a PBPK model for raltegravir, a probe UGT1A1 substrate based on Hartmann *et al* 2012. See Appendix B for the development of raltegravir PBPK model. The raltegravir PBPK model reasonably describes the PK of raltegravir following a single IV dosing and single oral dosing at multiple dosing levels [11]. Applicant conducted a sensitivity analysis to evaluate the effects of uncertainties in the in-vitro UGT1A1 inhibition parameter on the in vivo DDI prediction. By assigning a 10-fold lower Ki (4.8 µM) than the Applicant's Ki value (48.4 µM, IC50/2), the model predicted a 60% increase in raltegravir AUC by olaparib as showed in Appendix Figure C2. Applicant stated this sensitivity analysis is sufficient to represent a worst-case scenario. FDA reviewer identified two limitations on applicant's proposed use of PBPK modeling to evaluate the DDI between olaparib and raltegravir.

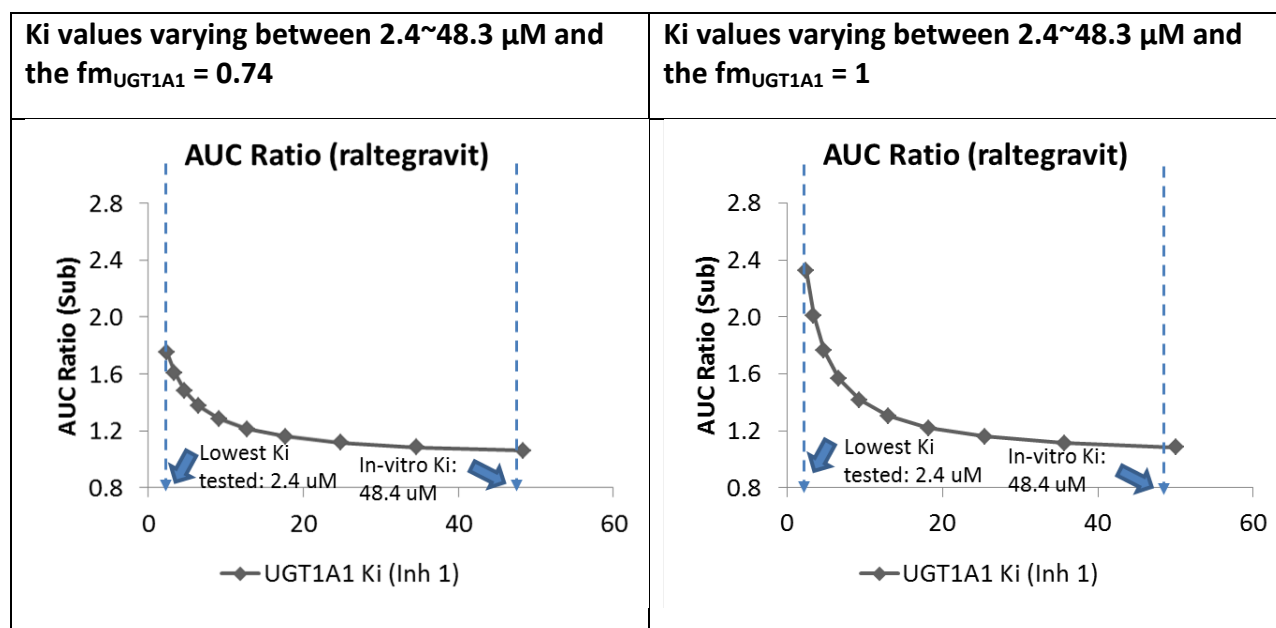
First, there is lack of quantitative determination to verify the contribution of the UGT pathways to the hepatic clearance of raltegravir. Applicant assigned the contributions of UGT1A1 (74%) and UGT1A9 (26%) enzyme to the hepatic clearance based on in-vitro microsomal data. There is no additional information such as in-vivo DDI study to confirm the contribution of the UGT pathways (fmUGTs). In addition, genetic polymorphism of human UGT1A1 has been reported. Therefore, additional sensitivity analysis on fmUGTs should be conducted to evaluate the effect of UGT1A1 polymorphisms and drug-drug interactions.

Second, the sensitivity analysis of UGT1A1 inhibition parameter conducted by the applicant, within 10-fold ranges of the reported value, is insufficient to characterize the uncertainty of the in-vitro UGT1A1 inhibition parameters. In FDA's review experience, values up to 20 fold potent than the in-vitro values

has been used clinically to fit the observed inhibitory effects of an inhibitor on the enzyme-mediated pathways.

Therefore, the FDA reviewer used applicant's submitted models to conduct two additional sensitivity analyses. The FDA's first sensitivity analysis was conducted by varying the UGT1A1 inhibition K_i value up to 20-fold lower (2.4 μM) than the measured in-vitro value (48.3 μM). The model predicted a 1.8 fold increase in AUC of raltegravir when K_i value was set to 2.4 μM . The second sensitivity analysis was conducted by varying the K_i values between 2.4~48.3 μM and setting the fmUGT1A1 as 1 to represent the uncertainty over the in-vitro derived fmUGT1A1 and the UGT1A1 extensive metabolizer. The model predicted a 2.3 fold increase in raltegravir AUC with lowest K_i (2.4 μM) as shown in **Figure 18**. The FDA reviewer notes that a conservative approach should be taken when in-vitro interaction measurement were directly used as PBPK model inputs (b) (4). By using the worst-case scenario defined by FDA reviewer, the simulation results indicated that olaparib increases the exposure of UGT1A1-sensitive substrate such as raltegravir by two-fold.

Figure 18 FDA sensitivity analysis of the UGT1A1 inhibition by olaparib



Conclusion

The final olaparib Model 6 (Model 6 in Simcyp V15 [1]) is sufficient to predict olaparib PK in patients co-administered with CYP3A modulators. The PBPK model predicts an increase of 1.38-fold in the steady-state AUC of olaparib when in-vitro values of reversible, time-dependent inhibition and induction of CYP3A4 are included in the model. By using the worst-case scenario defined by the FDA reviewer, the simulation results indicated a two-fold increase in raltegravir AUC by olaparib. (b) (4)

The capability of the PBPK model to predict olaparib as a P-gp

inhibitor has not yet been evaluated as the predictive performance of PBPK for P-gp inhibition has not been established.

The FDA reviewer acknowledges the scientific inputs from Dr. Shinichi Kijima.

Appendices for PBPK Analysis

Abbreviations

bid., twice daily dosing; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; B/P, blood to plasma ratio; C_{max}, maximal concentration in plasma; C_{maxR}, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; CL_{int}, intrinsic clearance; DDI: drug-drug interaction; F, bioavailability; F_a, fraction absorbed; f_{mj}, fraction of total clearance mediated by j CYP/UGT isoform or renal elimination; f_{up}, fraction unbound in plasma; Ind_{max}, maximal fold induction; Ind₅₀, concentration causing half-maximal fold induction; k_a, first order absorption rate constant; K_i, reversible inhibition constant; K_I, inactivation constant, inhibitor concentration resulting in half maximal inactivation; K_m, Michaelis-Menten Constant; k_{inact}, maximal inactivation rate constant; LogP, logarithm of the octanol-water partition coefficient; NA, not applicable; P_{app}, apparent passive permeability; P_{eff,man}, effective passive permeability in man; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; qd, once daily dosing; Q_{gut}, a hypothetical flow term for the intestine absorption model; sd, single dosing; T_{max}: time at maximal concentration in plasma; V_{ss}, volume of distribution.

Appendix A. Supplemental Tables and Figures

Appendix Table A1. Description of parameters used in olaparib PBPK model in current submission

Model name: "Olaparib enzyme kinetics tablets v6.cmp" (SimCYP Version 15, [4])

Parameter	Value	Comment
MW (g/mole)	434.5	
LogP	1.55	As Olaparib has a basic pKa of 1.25 and acidic pKa of 12.07, the compound will be almost completely unionised at pH 7.4 so the LogP and LogD values will be almost identical. As such, the LogD value of 1.55, which was generated in study BL8475/B, was used.
B:P (Blood to plasma ratio)	0.7	Study D2281 KPJ019 reported the mean blood/plasma ratio for olaparib to be 0.60 at a concentration of 100 ng/mL and 0.74 at a concentration of 10000 ng/mL. Given the observed C _{max} and C _{min} values, it is considered that 0.7 is an appropriate value to use for the blood/plasma binding value.
f _p (fraction unbound in plasma)	0.181	Concentration dependent plasma fractions were reported in the in-vitro studies. Study D2281 KPJ019 reported the mean percentage of free fraction of olaparib at concentrations of 10, 100, 1000 and 10000 ng/mL was 8.9%, 8.8%, 9.1% and 18.1% respectively. Given the observed C _{max} and C _{min} values, it is considered that 0.181 is an appropriate value to use for the blood/plasma binding value. Applicant note that they elected to not use a concentration dependent plasma fraction unbound profile in the model. This

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		decision is because the use of concentration dependent fraction unbound would prevent the use of the full PBPK model which would prevent the possibility to model olaparib as a substrate or inhibitor of any transporter in the future.
Absorption	Advance Dissolution, absorption, and metabolism (ADAM)	
f_u, gut (apparent unbound fraction in enterocytes)	0.259	The value was assumed to be equal to free fraction in blood
Critical Supersaturation ratio	100	The value was chosen as the maximum super-saturation ratio to ensure sufficient solubility is seen at all tablet doses.
Dispersion Type	Monodisperse d	Default values predicted by the software
Radius (μm)	10.000	Default values predicted by the software
Particle density (g/mL)	1.200	Default values predicted by the software
Diffusion coeff, ionised (10^{-4} cm²/min)	3.968	Default values predicted by the software
Diffusion coeff, micelle (10^{-4} cm²/min) mean	0.780	Default values predicted by the software
Diffusion coeff. (10^{-4} cm²/min)	3.968	Default values predicted by the software
Effective diffusion layer thickness (μm)	10.0	Default values predicted by the software
Effective permeability in man: $P_{eff, man}$ (10^{-4} cm/s)	36.23	This value, 36.23×10^{-4} cm/s, was used Model 3 by fitting the data collected from 119 patients. Applicant noted that this value is unlikely to be a good estimate of the actual P_{eff} since human as it is much higher than the value of 10×10^{-4} cm/s seen for D-glucose. This value has been retained in the current submission (Model 6) as in combination with the other parameters in the model since it gives a model performance that best describes the observed data.
Distribution	Full PBPK model	Mean apparent steady state volume of distribution (V_{ss}/F) was 73.4 L from mass balance study. The human in vivo oral volume of distribution from studies D0810C00010 and DC0810C0002 suggest that the V/F is between 0.3 and 1 L/kg (assuming a body weight of about 70 kg). Sponsor chose full PBPK mode and the method of predicting tissue: plasma partitioning ratio (K_p) for each organ using methods by Rodgers et al [REF] to allow for future evaluation of potential involvement of drug transporters
Steady state Volume of Distribution: V_{ss} (L/kg)	0.39	Simcyp Method 2. Applicant noted that the human oral volume of distribution from clinical studies D0810C00010 and DC0810C0002 suggest that the V/F is between 0.37 and 1.05 L/kg (assuming a body weight of 70 kg).

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Kp values	Adipose 0.429 Bone 0.597 Brain 0.615 Gut 0.588 Heart 0.372 Kidney 0.416 Liver 0.474 Lung 0.318 Muscle 0.352 Skin 0.411 Spleen 0.476 Pancreas 0.472	Simcyp prediction
Elimination	Enzyme Kinetics module	An apparent plasma clearance (CL/F) of 6.34 L/h was to derive intrinsic clearance in Model 3. Applicant noted the value of oral clearance (CL _{po}) was 6.34 and 6.08 L/h for tablet and capsule formula respectively in Model 4. In Model 6, CL/F for tablet formula is set to 7.56 L/hr. Applicant stated this value is based on the olaparib monotherapy PK data. Studies D0810C0010 (Mass Balance study) using capsule formulation show that 15% and 6% of the dosed radioactivity were unchanged olaparib in the urine and feces, and the fraction absorbed (Fa) was estimated to be 0.941. Renal clearance (CL _R) is reported ranged from 0.206 to 1.77 L/h.
Intrinsic clearance: CL_{int}, CYP3A4 (μL/min/pmol of isoform)	0.0575	A retrograde analysis assumed CL/F of 7.56 L/h and was used to derive intrinsic clearance (CL _{int}) in the liver. The sponsor assumed that CYP3A4 and an un-identified pathway in human liver microsomes (HLM) contributed to the hepatic clearance. Fraction metabolized by CYP3A (f _{m,CYP3A}) was assumed to be 0.973 according to enzyme inhibition experiments in human liver microsomes (f _{m,CYP3A} calculated to be 0.80 according to supersome experiment).
Additional HLM CL_{int} (μL/min/mg)	0.218	
Renal clearance CL_R (L/h)	1.48	Renal clearance was 1.096 L/h in Model 3 based on renal clearance data for 6 female patients dosed with [14C]-Olaparib in study D0810C0010. Renal clearance of 1.48 L/h is used in Model 4 and Model 6; this value was determined from 4 female and 3 male patients in a more recent study (Study D0816C00006 – a renal impairment study)
Interactions		
Reversible Inhibition Ki (μM)	59.5	In vitro data for olaparib suggests that the IC ₅₀ for competitive inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 is above 100 μM and has not been accurately quantified. Additional experiment showed that olaparib inhibited the production of 1-OH-Midazolam with an IC ₅₀ value of 119 μM. The calculated Ki value of 59.5 μM was used as an input for reversible inhibition.

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Time dependent inhibition KI(μM)	72.2	Study AZD2281 KMX001 showed little or no time dependent inhibition at 10 μM of Olaparib with a range of CYP450 enzymes. In study ADME-AZS-Wave4-131106, time-dependent inhibition of CYP3A4/5 by Olaparib was observed between 2 and 200 μM and was determined to have mean inhibition parameters of 0.0675 min ⁻¹ (4.05 h ⁻¹) and 72.2 μM for kinact and KI, respectively.
Time dependent inhibition Kinact(hr⁻¹)	4.05	
Induction EC50 (μM)	17.65	Olaparib caused the concentration dependent up-regulation in CYP3A4 mRNA expression of up to 65-fold which was up to 40% of positive control response. In contrast, caused no change in CYP3A4 activity-mediated testosterone 6β-hydroxylase activity. Induction parameters (Emax, EC50 and F2) could not be estimated for CYP3A mRNA and activity due to cytotoxicity. Applicant fixed the Emax at the at the maximum data to deliver a worst-case scenario for the EC50.
Induction Emax (fold)	48.1	The final values that were used in the all the simulations were 48.1 induction Emax (fold) and Induction EC50 of 17.65 μM.
Transport		
P-gp inhibition (Ki)	73.91	Two in-vitro studies suggested that olaparib has minimal/no P-gp inhibitory potential at concentrations up to 100 μM. A third study, Study ADME-AZS-Wave 3-140714, identified inhibition of basolateral to apical transport of digoxin in MDCKII-MDR1 cells with an IC50 of 76.0 μM. Under the assay conditions Ki was predicted using Simcyp calculator and found to be 73.91 μM.
UGT1A1 (Ki =IC50/2)	48.35	Luo 2014 has determined an IC50 for UGT1A1 inhibition value of olaparib to be 96.7uM. Ki was assumed to be 48.35 μM.

Appendix Table A2. Summary of observed and simulated effect of olaparib as a victim (with CYP3A moderators) and a perpetrator

		Observed^a ratio with/without a CYP3A modulator		Simulated^b ratio with/without a CYP3A modulator	
		Geomean AUCR	Geomean CmaxR	Geomean AUCR	Geomean CmaxR
Strong CYP3A inhibitor	itraconazole	2.7 (2.44 to 2.97) ¹	1.42 (1.33 to 1.52) ¹	3.55 (3.46 to 3.65)	1.20 (1.20 to 1.21)
Strong CYP3A inducer	rifampin	0.13 (0.11to 0.16) ²	0.29 (0.24 to 0.33) ²	0.25 (0.24 to 0.27)	0.56 (0.54 to 0.58)
Moderate CYP3A inhibitor	fluconazole	NA	NA	2.21 (2.14 to 2.28)	1.14 (1.13 to 1.16)

Weak CYP3A inhibitor	fluvoxamine	NA	NA	1.02 (1.01 to 1.02)	1.01 (1.01 to 1.01)
Moderate CYP3A inducer	efavirenz	NA	NA	0.4 (0.38 to 0.43)	0.69 (0.66 to 0.71)
Weak CYP3A inducer	dexamethasone	NA	NA	1.00 (0.99 to 1.00)	1.00 (1.00 to 1.00)
CYP3A substrate	midazolam	NA	NA	1.61 (1.42 to 1.83)	1.18 (1.10 to 1.27)
CYP3A substrate	simvastatin	NA	NA	1.54 (1.33 to 1.78)	1.33 (1.18 to 1.49)
P-gp substrate	digoxin	NA	NA	1.02 (1.02 to 1.02)	1.05 (1.04 to 1.05)
UGT1A1 substrate	raltegravir	NA	NA	1.07 (1.06 to 1.08)	1.04 (1.04 to 1.04)

*Data source: PBPK report table 6-14 [Model 6]

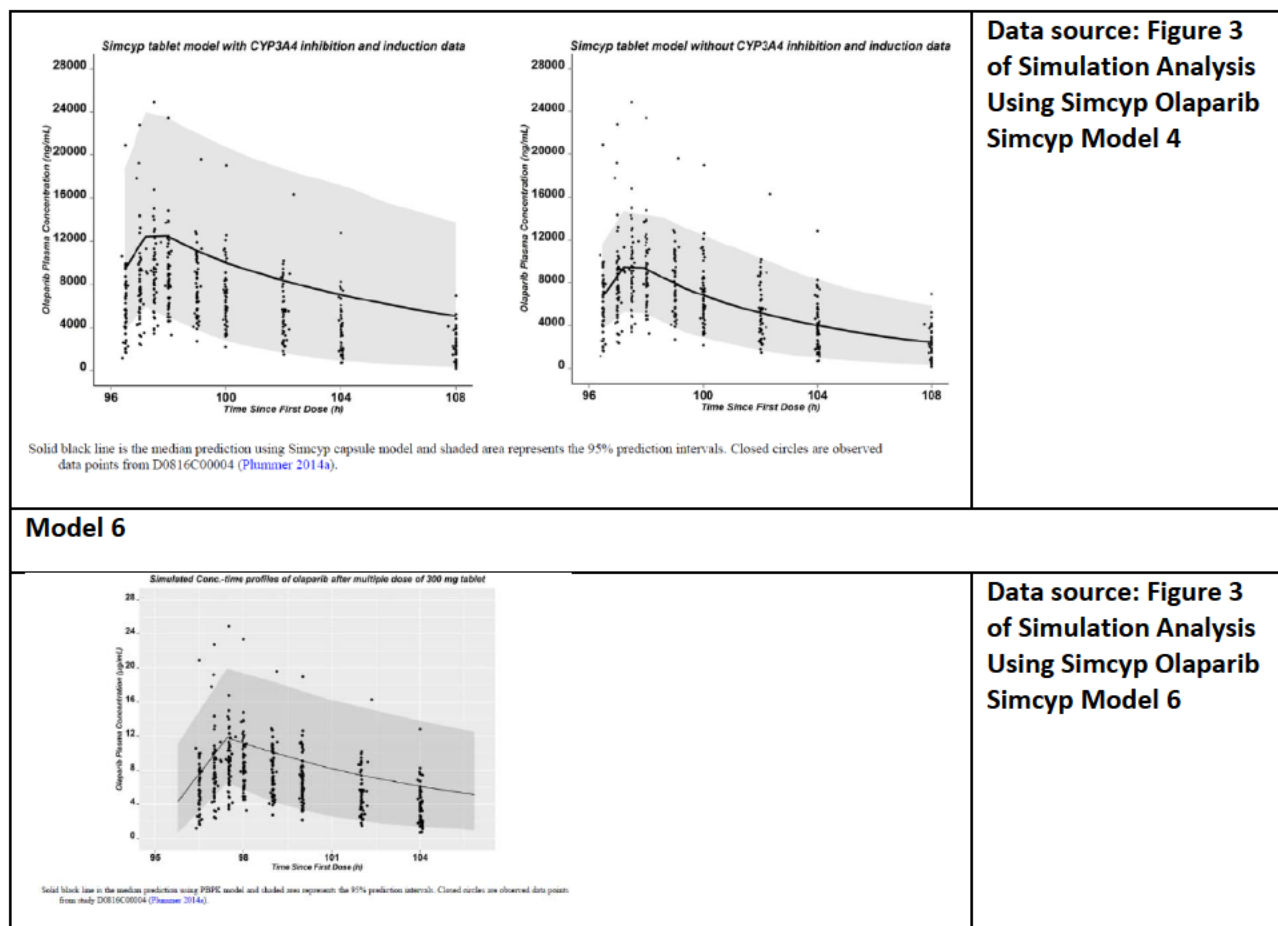
¹Itraconazole clinical data: Study D0816C00007; ²Rifampicin clinical data: Study D0816C00008

^aGeometric mean (90% confidence interval). ^b Geometric mean (95% confidence interval)

Appendix Figure A1. PBPK model simulated vs observed olaparib plasma concentration-time profiles following multiple doses of tablet (300 mg bid.) in Model 4 and Model 6

Model 4

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Appendix B. Dexamethasone PBPK model

Applicant developed a minimal dexamethasone PBPK model in Simcyp based on in vitro measurements and clinical PK observations. Dexamethasone PBPK model parameters are presented in Appendix Table B1.

Appendix Table B1. List of dexamethasone PBPK model parameters

Compound Name	Dexamethasone		
PhysChem		CYPs and/or UGTs Interaction	
Mol Weight (g/mol)	392.46	Enzyme	CYP3A4
log P	1.83	Ind max	5.00
B/P	0.93	Ind EC50 (μM)	6.40
fu	0.28	Enzyme	CYP3A5
Distribution Model	Minimal PBPK	Ind max	5.00

	Model		
Absorption Model	1st order	Ind EC50 (μM)	6.40
fa	1.00		
ka (1/h)	4.80		
fu(Gut)	0.19		
Elimination			
Clearance Type	Enzyme Kinetics		
In vitro metabolic system	HLM		
Enzyme	CYP3A4		
CLint (μL/min/mg - microsomal protein)	15.00		
fu mic	1.00		
CL R (L/h)	0.00		

Applicant verified the dexamethasone PBPK model by comparing the simulated and observed PK of dexamethasone following a single oral dose of 8mg dexamethasone as shown in Appendix Table B2. Induction parameters, Indmax and IndEC50, were assigned by the applicant based on published literature.

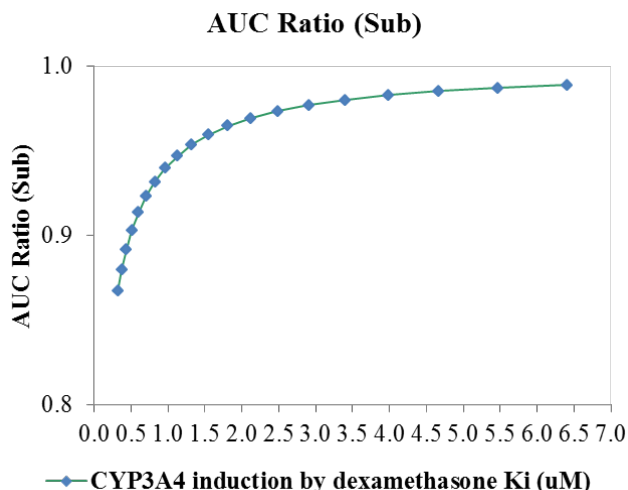
Appendix Table B2. Comparison of the predicted and observed PK parameters at 8 mg dose of dexamethasone

	Predicted (95% Confidence interval)	Observed (Marbury 2011) (95% Confidence interval)	Extracted from Table 21, Model 6 PBPK report [1]
C_{max} (ng/ml)	78 (71 to 87)	70.4	
AUC (ng/ml*h)	426 (361 to 502)	364 (308 to 430)	
T_{max} (h)	0.72 (0.7 to 0.8)	1 (1 to 3 range)	

PBPK models were used to evaluate the effect of dexamethasone on the PK of olaparib. The simulation results showed that coadministration of olaparib (300mg sd) and dexamethasone (8mg qd) resulted in no change in the olaparib exposure (<1%). Since the applicant did not verify the induction potential of dexamethasone with an additional CYP3A substrate, FDA reviewer conducted a sensitivity analysis on the reported induction parameters, Indmax and IndEC50. By doubling the value of Indmax and varying

the value of IndEC50 between 6.4 and 0.32 μM , the model predicted minimal change in the olaparib exposure as shown in Appendix figure B1.

Appendix Figure B1. Sensitivity analysis of the CYP3A induction of dexamethasone on olaparib AUC



Appendix C. Raltegravir PBPK model

A Simcyp minimal raltegravir PBPK model developed by Hartmann et al 2012 was adapted by the applicant to evaluate the effect of UGT1A1 inhibition by olaparib on raltegravir, a sensitive UGT substrate. This model was developed based on raltegravir physicochemical properties, in vitro measurements and clinical PK observations. Raltegravir PBPK model parameters are presented in Appendix Table C1.

Appendix Table C1. List of raltegravir PBPK model parameters

Compound Name	Raltegravir	Reference
PhysChem		
Mol Weight (g/mol)	444.40	
log P	0.50	Hartmann et al 2012
pKa 1	6.30	Hartmann et al 2012
B/P	0.60	Hartmann et al 2012
fu	0.17	Hartmann et al 2012
Distribution Model	Minimal PBPK Model	
Absorption Model	1st order	
fa	0.96	Simcyp predicted

ka (1/h)	1.27	fitted
fu(Gut)	0.30	
Q(Gut) Input	Predicted	
PCaco-2(10E-06 cm/s)	16.400	Moss DM et al., 2012
Clearance Type	Enzyme Kinetics	
In vitro metabolic system	Recombinant	
Enzyme	UGT1A9	
CLint (μL/min/pmol of isoform)	10.20	Rizk 2012, Gibson 2011
Enzyme	UGT1A1	
CLint (μL/min/pmol of isoform)	29.30	Rizk 2012, Gibson 2011
fu mic	1.00	
CL R (L/h)	3.60	Iwamoto 2008

It is assumed that approximately 90% of raltegravir is metabolized through UGT-mediated pathways in liver where the contributions of UGT1A1 and UGT1A9 enzyme to the total hepatic clearance are 74% and 26% respectively according to enzyme inhibition experiments in human liver microsomes. The model was verified by comparing the simulated and observed concentration-time data of raltegravir in plasma after single intravenous (50 μg) and oral dosing (50 to 400 mg). Appendix Table C2 and Figure C1 compare the predicted and observed PK parameters at 400 mg dose of raltegravir.

Appendix Table C2. Comparison of the predicted and observed PK parameters at 400 mg dose of raltegravir

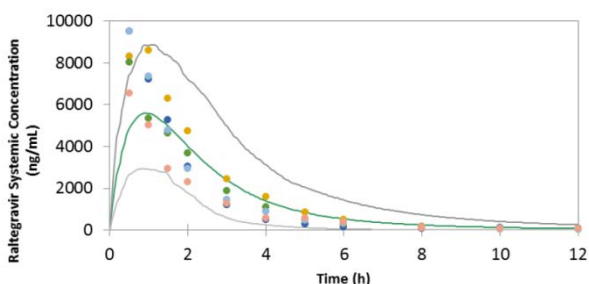
	Predicted (95% Confidence interval)	Observed (95% Confidence interval)
C _{max} (μM)	12.2 (11.4 to 13.1)	16.2 (12.9 to 22.3)
AUC (μM*h)	34.6 (31.6 to 37.9)	34.8 (28.5 to 45.7)
T _{max} (h)	0.95 (0.91 to 1.00)	0.65 (0.5 to 0.92)

Appears this way on original

Observed data : Hartmann 2012
Extracted from Table 22, PBPK

report

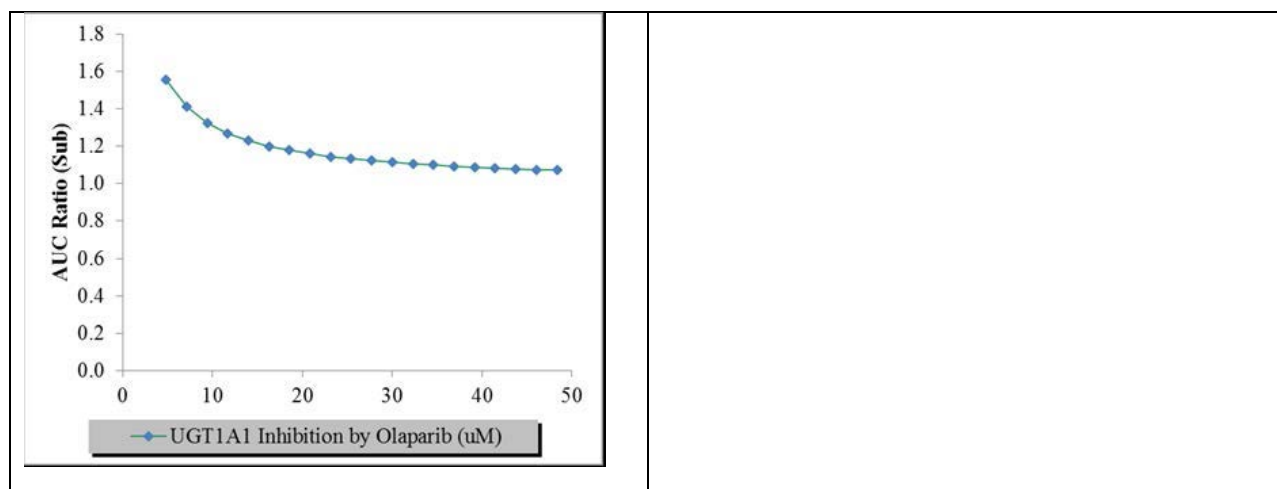
Appendix Figure C1. Overlay of simulated and observed concentration of raltegravir in plasma following a single oral dose of 400mg raltegravir



Data source: Applicant's Response to FDA information request

In-vitro reported K_i , 48.4 μM , was used in the olaparib PBPK model to predict the effect of UGT1A1 inhibition by olaparib on PK of raltegravir. The model predicted a minimal increase (less than 10%) in raltegravir C_{max} and AUC ratios with/without co-administration with olaparib. Applicant performed a sensitivity analysis on K_i by varying the value of in-vitro report K_i by 10 fold (4.84 to 48.4). The AUC ratio increased by approximately 60% with the lowest tested K_i value (4.84 μM).

Appendix Figure C2. Sensitivity analysis of the UGT1A1 inhibition by olaparib on raltegravir AUC



References for PBPK Analysis

ASTRAZENECA. (b) (4) Simulating the Drug-Drug Interaction Potential of Olaparib Tablet Formulation as a Victim and Perpetrator, using Simcyp® (V15 R1) Based on Data from in vitro and Clinical Studies. January 12, 2017

ASTRAZENECA. Response to FDA information request regarding PBPK Question. April 06, 2017

NDA/BLA Multi-disciplinary Review and Evaluation NDA 208558
Lynparza™ (Olaparib)

Current Olaparib USPI for capsule.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/206162s003lbl.pdf

FDA 206162 Clinical Pharmacology Review.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000ClinPharmR.pdf

FDA NDA 206162/SDN 279 Olaparib Clinical Pharmacology Review 1/26/2017.

<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af8041ced9>

ASTRAZENECA. Draft US Prescription Information submitted in March, 2017

ASTRAZENECA. Overview document: Response to FDA information request regarding PBPK (Email). 24-Jun-2014.

ASTRAZENECA. (b) (4) Simulating the Drug-Drug Interaction Potential of Olaparib (Capsule and Tablet Formulation) as a Victim and Perpetrator using Simcyp® (V14 R1) Based on Data from in vitro and clinical studies. September 08, 2015.

ASTRAZENECA. (b) (4) Addendum to Simcyp Model 4 Report entitled “Simulating the Drug-Drug Interaction Potential of Olaparib (Capsule and Tablet Formulation) as a Victim and Perpetrator using Simcyp® (V14 R1) Based on Data from in vitro and Clinical Studies”. January 12, 2016.

ASTRAZENECA. (b) (4) Addendum to Olaparib Simcyp Model 4 Report Entitled “Simulating Interactions with Efavirenz, a Moderate Inducer of CYP3A4”. June 15, 2016.

Hartmann G, Gibson C, Rizk M, Xu Y, Retrospective Analysis of Raltegravir (Isentress™) Oral Pharmacokinetics in Healthy Volunteers Using the SimCYP PBPK Model, Simcyp Consortium Meeting 2012

FACT-O Questionnaire

(Page 1)

FACT-O (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
Q01	I have a lack of energy	0	1	2	3	4
Q02	I have nausea	0	1	2	3	4
Q03	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
Q04	I have pain	0	1	2	3	4
Q05	I am bothered by side effects of treatment	0	1	2	3	4
Q06	I feel ill	0	1	2	3	4
Q07	I am forced to spend time in bed	0	1	2	3	4

<u>SOCIAL/FAMILY WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
Q08	I feel close to my friends	0	1	2	3	4
Q09	I get emotional support from my family	0	1	2	3	4
Q10	I get support from my friends	0	1	2	3	4
Q11	My family has accepted my illness	0	1	2	3	4
Q12	I am satisfied with family communication about my illness	0	1	2	3	4
Q13	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q14	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.					
Q15	I am satisfied with my sex life	0	1	2	3	4

(Page 2)

FACT-O (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>EMOTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
CE1	I feel sad	0	1	2	3	4
CE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
CE3	I am losing hope in the fight against my illness	0	1	2	3	4
CE4	I feel nervous	0	1	2	3	4
CE5	I worry about dying	0	1	2	3	4
CE6	I worry that my condition will get worse	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
CF1	I am able to work (include work at home)	0	1	2	3	4
CF2	My work (include work at home) is fulfilling	0	1	2	3	4
CF3	I am able to enjoy life	0	1	2	3	4
CF4	I have accepted my illness	0	1	2	3	4
CF5	I am sleeping well	0	1	2	3	4
CF6	I am enjoying the things I usually do for fun	0	1	2	3	4
CF7	I am content with the quality of my life right now	0	1	2	3	4

(Page 3)

FACT-O (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
01	I have swelling in my stomach area	0	1	2	3	4
02	I am losing weight	0	1	2	3	4
03	I have control of my bowels	0	1	2	3	4
04	I have been vomiting	0	1	2	3	4
05	I am bothered by hair loss	0	1	2	3	4
06	I have a good appetite	0	1	2	3	4
07	I like the appearance of my body	0	1	2	3	4
08/11	I am able to get around by myself	0	1	2	3	4
09	I am able to feel like a woman	0	1	2	3	4
10	I have cramps in my stomach area	0	1	2	3	4
11/1	I am interested in sex	0	1	2	3	4
12/11	I have concerns about my ability to have children	0	1	2	3	4

14 Division Director (OB)

Rajeshwari Sridhara
Director Division of Biometrics V

15 Division Director (Clinical)

The recommendation for the approval of olaparib tablets, according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), is primarily based on the efficacy and safety data from two trials, Study 19 and SOLO2, both randomized, placebo-controlled, double-blind, multicenter trials in patients with recurrent ovarian cancer who were in response to platinum-based therapy. SOLO2 enrolled 295 women with germline BRCA-mutated (gBRCAm) ovarian, fallopian tube, or primary peritoneal cancer and randomized patients 2:1 to receive olaparib tablets or placebo. Study 19 enrolled 265 women regardless of BRCA status and randomized patients 1:1 to either olaparib capsules or placebo; a retrospective analysis for germline BRCA mutation status demonstrated that 36% (n=96) of patients from the intent-to-treat (ITT) population had gBRCAm ovarian cancer. Results from SOLO2 demonstrated a statistically significant improvement in investigator-assessed PFS in patients randomized to olaparib as compared to placebo (HR: 0.30; 95% CI 0.22, 0.41; $p < 0.0001$). Results from Study 19 demonstrated a statistically significant improvement in investigator-assessed PFS in patients randomized to olaparib as compared to placebo (HR: 0.35, 95% CI: 0.25, 0.49; $p < 0.0001$). The safety appeared acceptable for the intended population and AML/MDS incidence was $< 1.5\%$ including patients with long-term follow up. All members of the review team recommended approval of this application or reported that there were no findings that would preclude approval.

There were a number of review issues encountered during the review of this NDA which are described below:

1. Approval in the Maintenance Setting for Patients Regardless of gBRCA Status:

Study 19 provided information in the maintenance setting for patients with platinum-sensitive recurrent ovarian cancer without regard to gBRCA mutations. In Study 19, in a retrospective analysis of the ITT population, 36% of patients were found to have gBRCAm ovarian, fallopian tube, or primary peritoneal cancer, 43% had germline BRCA-wild type (gBRCAwt), and 21% had unknown BRCA status. All patients on Study 19 were platinum-sensitive. Study 19 demonstrated a statistically significant improvement in investigator-assessed PFS in patients randomized to olaparib as compared to placebo (HR: 0.35, 95% CI: 0.25, 0.49; $p < 0.0001$). While the observed difference in median PFS was modest at 3.6 months, the magnitude of this difference only focuses on one aspect of the PFS distributions while the HR incorporates information from the entire PFS distribution and is a more reliable indicator of the significance of the treatment effect.

It would not be appropriate to extrapolate the efficacy of other PARP inhibitors to that of olaparib, and no extrapolation was made in this NDA review. However, the results of Study 19 should be viewed in the context of recent approvals and, thus, in the context of what FDA has recently viewed as representative of clinical meaningfulness in the maintenance setting, as an evolution of the field since the 2014 ODAC where Study 19 and the maintenance setting of ovarian cancer were discussed (see below and Section 8). Bevacizumab (a VEGF inhibitor) and niraparib (a PARP inhibitor) were previously approved in a similar patient population of platinum-sensitive recurrent ovarian cancer for maintenance treatment (bevacizumab after combination treatment with chemotherapy). No companion diagnostic was associated with the use of bevacizumab or niraparib. Niraparib was approved with a complementary diagnostic, and information regarding gBRCAm and non-gBRCAm

status was presented in the label. The efficacy results of products that have received approval in the maintenance setting are shown below in conjunction with the olaparib trial results.

Results from Olaparib Trials, and Trials of Approved Drugs, in the Platinum-Sensitive Recurrent Ovarian Cancer Maintenance Setting

	Study 19 olaparib (unselected)	SOLO2 olaparib (gBRCAm)	GOG213 bevacizumab (unselected)	OCEANS bevacizumab (unselected)	NOVA Trial niraparib (gBRCAm)	NOVA Trial niraparib (non- gBRCAm)
Median PFS improvement	3.6	13.6	3.4	4	15.5	5.4
PFS HR (95% CI) p-value	0.35 (0.25-0.49)	0.30 (0.22, 0.41)	0.61 (0.51-0.72)	0.46 (0.37-0.58)	0.26 (0.17, 0.41) <0.0001	0.45 (0.34, 0.61) <0.0001
OS HR (95% CI)	0.73 ^a (0.55-0.95)	^b	0.84 (0.69-1.01)	0.95 (0.77-1.17)	^c	^c

Source: Package inserts for niraparib (IRC PFS) and bevacizumab (INV PFS)

a: not adjusted for multiple analyses

b: OS data not mature (24% events)

c: OS data not mature (17% events)

In exploratory analyses of Study 19, olaparib appears to have a larger effect in the gBRCAm subgroup (HR 0.17: 95% CI 0.09, 0.32) compared to the ITT population. While the true magnitude of olaparib effect in patients with gBRCAwt ovarian cancer cannot be precisely estimated, the gBRCAwt subgroup (HR 0.51: 95% CI 0.30, 0.84) did not appear to experience a detrimental effect. It is also apparent that a percentage of patients in the gBRCAwt group did benefit from olaparib—likely due to aberrations in homologous recombination repair pathway proteins—and would be withheld from receiving therapy and benefit if the approval were restricted to the gBRCAm population. Supporting the benefit demonstrated in the gBRCAwt subgroup is an analysis of long-term non-progressors. Within the Study 19 ITT population, 11% of patients continued to receive olaparib for at least six years, while only one patient on placebo continued therapy for this duration. Within the gBRCAwt subgroup, 14% of patients treated with olaparib remained on therapy for four years or more and 10% of patients treated with olaparib remained on therapy for six years or more, compared to 0% of placebo treated patients remaining on therapy for three years or more. The therapy was acceptable from a safety standpoint with a mechanistic reason for a lower AML/MDS risk in patients with gBRCAwt ovarian cancer. In addition, although not adjusted for multiple analyses, the long-term overall survival data demonstrated no detriment in the unselected ITT population.

From a scientific standpoint, in high-grade serous ovarian cancer, homologous recombination deficiency is a determinant of platinum sensitivity (Fong 2009, Ledermann 2012, Scott 2015, Bowtell 2015), and sensitivity to platinum agents is reflected with sensitivity to olaparib (Fong 2010). While BRCA mutations account for the most common deficit in homologous recombination repair (HRR) pathway, aberrations in other homologous recombination genes likely also result in sensitivity to olaparib. In addition, the mechanism of action of olaparib does not require direct interaction with a mutated gene/protein. As such, while patients with gBRCAm are sensitive to PARP inhibition with olaparib, lack of a BRCA mutation (in the case of Study 19, patients classified as gBRCAwt) does not preclude sensitivity to olaparib. Along these lines, it is likely those in the gBRCAwt group who benefit most from olaparib have defects in other components of HRR pathways, but no diagnostic

technology is currently validated to adequately detect and separate the group of the gBRCAwt population that benefits from olaparib compared to those that do not. For this reason, the applicant agreed to further study the gBRCAwt cohort of patients in a post-marketing commitment, OPINION – “A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non- Germline BRCA mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy”. FDA will work with the applicant on the design of this trial to better define and describe the different subgroups within gBRCAwt that may have differential benefit to maintenance olaparib.

The ODAC in 2014 voted negatively (11-2) on the following question: “Do the safety and efficacy results from Study 19 in the gBRCAm population support an accelerated approval, or should consideration for marketing approval be delayed until the results of SOLO-2 are available?” Importantly, no question was posed to ODAC regarding the approvability of the ITT unselected population inclusive of gBRCAm and gBRCAwt. In fact, as described above in Section 8, the committee felt that OS would be needed in the maintenance setting. However, as also described above, the regulatory environment has changed since the 2014 ODAC with the approval of two other drugs in this setting based on PFS. Another concern was the risk-benefit analysis, given the occurrence of MDS/AML, but with long-term safety data it now appears the risk is similar to what was previously reported and acceptable for the proposed unselected indication with a mechanistic rationale to expect a lower incidence of AML/MDS in those with gBRCAwt who do not have defects in HRR. Also, the ODAC discussed that separating out a subpopulation that was retrospectively defined would be problematic. We agree with this and are viewing the results of the ITT population in a total unselected population.

An additional review issue was that Study 19 did not reflect the overall prevalence of BRCA mutations in U.S. patients with ovarian cancer. While the overall make-up of the trial does not mirror the exact percentages of prevalence of BRCA mutations in the general US population, from a regulatory standpoint, Study 19 results would be considered relevant to a U.S. population inclusive of patients with gBRCAwt tumors, because a substantial portion of the trial had gBRCAwt ovarian cancer (43%), the trial was statistically significant in the ITT population, and a proportion of patients with gBRCAwt status still demonstrated clinical benefit.

The totality of evidence shows a benefit of olaparib treatment in the maintenance setting in the gBRCAm subgroup as well as in an unselected population. To restrict the indication to those patients with gBRCAm cancers would be to withhold the drug and potential benefit to those in the gBRCAwt population without fully understanding the science of those with homologous recombination deficiencies and without a validated test to detect those individuals. A PMC will further explore the true benefit to this gBRCAwt subgroup. The indication for the unselected patient population includes that patients be platinum-sensitive, which may provide some prediction of benefit given current scientific understanding. In addition, the safety is acceptable for the intended population. Therefore, recommendation for approval in the maintenance setting is for the unselected population and the decision for treatment in the context of potential benefit and risk will be a discussion between the individual patient and their provider.

2. SOLO2 Blinded Independent Central Review:

Prior to the submission of the NDA and analysis of the study, the applicant requested that the primary endpoint of SOLO2 be changed from Blinded Independent Central Review (BICR)-assessed to investigator-assessed PFS. The Agency agreed to this change, but advised the applicant that all patient scans be subjected to blinded independent central review (March 3, 2016, communication). Despite FDA's recommendation, post-progression scans of patients who had progressed by investigator assessment were not sent for BICR review after the time of the change in primary endpoint.

After analysis of the submitted data, including sensitivity analyses of the submitted BICR data, the differences in median PFS seen between the investigator-assessed PFS and BICR-assessed PFS appear to be due to informative censoring (as described above in the main review document Section 7.2.2). Given the impact of informative censoring on the analysis of the BICR results, the median PFS duration from the BICR analysis cannot be considered reliable (b) (4)

3. Olaparib Capsule to Olaparib Tablet:

Clinical Data: The indication for the maintenance setting relied on information from SOLO2 (study done with olaparib tablets), and Study 19 (study done with olaparib capsules). The indication of olaparib capsules for 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 was initially granted using information with the capsule formulation. Although the two formulations—tablet and capsule—do not exhibit the same bioavailability, the tablet formulation offers significant convenience due to reduced pill burden. In addition the effectiveness of the 300mg tablet should not be inferior to that of the 400mg capsule as the steady state AUC following the tablet was higher compared to that following the capsule. Patient data comparing the 300mg BID tablet and 400mg BID capsule showed similar response rates in the later line setting as well as similar safety. For these reasons, it is appropriate to approve the fourth line advanced ovarian cancer setting indication for olaparib tablets, and to use Study 19 to support the maintenance indication for olaparib tablets.

Medication Error Concerns: Given the change in capsule to tablet formulation that do not have the same bioavailability, the review team was concerned about the potential for medication and dosing errors with both formulations on the market at the same time. Therefore, FDA requested that additional steps be taken to mitigate the potential of dosing errors. The applicant agreed to implement the following steps:

- a. 100% of the capsule formulation transitioned to two applicant network specialty pharmacies prior to the launch of the tablet formulation (which entailed the transfer of (b) (4) % of patients or (b) (4) patients). This transition occurred over a (b) (4) period, allowing time for patients to consult with their provider and make sure there were no gaps in therapy for patients. Notification of the changes to the capsule formulation distribution were sent to all sites of care. In addition the applicant agreed to conduct site visits to these sites. A timeline was agreed upon for this transition.

- b. Within the specialty pharmacies, all drugs will be dispensed by employing workflow software that verifies NDC and approved dose, attempts to dispense the wrong formulation or dose will trigger an error notice.
- c. Prior authorization limitations, such as payer requirements prevent dispensing excess quantities of drug because reimbursement must be confirmed before the prescription is filled.
- d. Modification to the product bottle label including, and modification to the PI (both tablet and capsule) to state that the capsule and tablet should not be substituted due to differences in the dosing and bioavailability of each formulation.
- e. Educate patients, inform prescribers with a communication plan.
- f. Remove capsule formulation from the market within (b) (4) months after approval

FDA, including DMEPA, felt these mitigation strategies were sufficient to prevent medication error.

4. **Fulfillment of Accelerated Approval PMR:**

Two PMRs were initiated under 21CFR 314 Subpart H at the time of the accelerated approval of olaparib capsules (NDA 206162) for “the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy”. One PMR was for the results of SOLO2, and one was for the results of SOLO3 (an ongoing clinical trial of olaparib versus physician’s choice single-agent chemotherapy for the third-line treatment of women with platinum-sensitive relapsed gBRCAm ovarian cancer). The results of SOLO2 are described above and with the review of SOLO2 PFS analyses and data the PMR and accelerated approval requirement will be fulfilled. A PMC for the final OS analyses and data from SOLO2 was agreed upon under NDA 208558. As stated in the expedited program guidance, demonstration of clinical benefit can occur in a different line of therapy than the initial accelerated approval. The other PMR for SOLO3 will be released as the accelerated approval requirement is fulfilled and a PMC for ORR from SOLO3 was agreed upon under NDA 208558 to gain additional information regarding the treatment of patients with gBRCAm ovarian cancer in the fourth line setting.

In summary, ovarian cancer is a serious and life-threatening disease, and based on the totality of evidence demonstrating statistically significant and clinically relevant effects from two trials, SOLO2 and Study 19, combined with long term follow up, clear benefit in certain patients with gBRCAwt cancer, and acceptable safety profile for the intended population, there is sufficient evidence to recommend regular approval of olaparib tablets for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy, and to grant the prior olaparib capsule indication to olaparib tablets for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

Julia Beaver
Director (acting) Division of Oncology Products 1

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/s/

RAJESH VENUGOPAL
08/15/2017

TIFFANY RICKS
08/15/2017

TODD R PALMBY
08/15/2017

RUNYAN JIN
08/15/2017

CHAO LIU
08/15/2017

JINGYU YU
08/15/2017

JINGYU YU on behalf of YANING WANG
08/15/2017

QI LIU
08/15/2017

STELLA W KARURI
08/15/2017

ROBERT J SCHROEDER
08/15/2017

WILLIAM F PIERCE
08/15/2017

SANJEEVE BALASUBRAMANIAM on behalf of GWYNN ISON
08/15/2017

SANJEEVE BALASUBRAMANIAM
08/15/2017

RAJESHWARI SRIDHARA
08/15/2017

I concur and acknowledge Dr. Shenghui Tang's contribution to the statistical review

JULIA A BEAVER
08/15/2017

NDA 208558 Clinical Team Leader Review

8/14/17

CDTL review is complete, and has been added to the NDA 208558 Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

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/s/

SANJEEVE BALASUBRAMANIAM
08/14/2017

Memo

NDA#: 208558

SN#: 0001

Date: August 12, 2017

Drug name: Olaparib

Indication: Platinum sensitive BRCA mutated ovarian cancer

Statistical team leader: Jason Schroeder

Statistical reviewer: Stella W. Karuri

Medical reviewer: Gwynn Ison

Sponsor: AstraZeneca

The statistical Secondary Review is complete. My recommendation for this application is approval.

Jason Schroeder, PhD
Supervisory Mathematical Statistician

CC:

Dr Karuri/Dr Sridhara/Dr Beaver/Dr Ison/Dr Balasubramaniam
HFD-700/ Ms. Lillian Patrician

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/s/

ROBERT J SCHROEDER
08/14/2017

Memo

NDA#: 208558

SN#: 0001

Date: August 11, 2017

Drug name: Olaparib

Indication: Platinum sensitive BRCA mutated ovarian cancer

Statistical reviewer: Stella W. Karuri

Medical reviewer: Gwynn Ison

Sponsor: Astrazeneca

The statistical review is complete, and has been added to the NDA 208558 Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

Stella W. Karuri
Mathematical Statistician

CC:

Dr. Tang/Dr Schroeder/Dr Sridhara/Dr Beaver/Dr Ison/Dr Balasubramaniam
HFD-700/ Ms. Lillian Patrician

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/s/

STELLA W KARURI
08/11/2017

MEMORANDUM

Date: August 11, 2017
From: Todd Palmby, PhD, Supervisory Toxicologist
Division of Hematology Oncology Toxicology for Division of Oncology Products 1
To: File for NDA 208558 LYNPARZA (olaparib) tablets

The nonclinical Secondary Review is complete. My recommendation for this application is approval.

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/s/

TODD R PALMBY
08/11/2017

NDA 208558 Clinical Review Memo

8/11/17

The Clinical review for this application is complete, and has been added to the NDA 208558 Multidisciplinary Review and Evaluation. The clinical team recommendation for this application is approval.

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/s/

GWYNN ISON

08/11/2017

SANJEEVE BALASUBRAMANIAM

08/11/2017

MEMORANDUM

Date: August 1, 2017
From: Tiffany Ricks, PhD
Division of Hematology Oncology Toxicology for Division of Oncology Products 1
Through: Todd Palmby, PhD
Division of Hematology Oncology Toxicology for Division of Oncology Products 1
To: File for NDA 208558 LYNPARZA (olaparib) tablets

The nonclinical review is complete and has been added to the NDA 208558 Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

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/s/

TIFFANY RICKS
08/01/2017

TODD R PALMBY
08/01/2017

Office of Clinical Pharmacology Memo

NDA or BLA Number	208558
Link to EDR	\\CDSESUB1\evsprod\NDA208558\0002
Submission Date	Rolling submission CMC and Nonclinical-12/9/2016 Clinical-2/21/2017
Submission Type	Priority
Brand Name	Lynparza
Generic Name	Olaparib
Dosage Form and Strength	Tablets: 150 mg, 100 mg
Route of Administration	Oral
Proposed Indication	Olaparib tablets as monotherapy: • For the maintenance treatment of patients with platinum-sensitive relapsed epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response (complete response or partial response) to platinum-based chemotherapy • In patients with deleterious or suspected deleterious germline BRCA-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy
Proposed Dosing Regimen	Tablet 300 mg twice daily
Applicant	Astrazeneca Pharmaceuticals LP
Associated IND	75918
OCP Review Team	Runyan Jin, Ph.D., Chao Liu, Ph.D., Yuching Yang, Ph.D., Jingyu Yu, Ph.D., Yaning Wang, Ph.D., Qi Liu, Ph.D.
OCP Final Signatory	Qi Liu, Ph.D. Team Leader Division of Clinical Pharmacology V

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the NDA Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Based on our analyses of the submitted PK, efficacy, and safety data, our recommendation for this application is approvable from a clinical pharmacology perspective.

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/s/

RUNYAN JIN
07/28/2017

CHAO LIU
07/28/2017

YUCHING N YANG
07/28/2017

JINGYU YU
07/28/2017

YANING WANG
07/28/2017

QI LIU
07/28/2017

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 208588

Supporting document/s: 1, 5

Sponsor's letter date: February 22, 2017

CDER stamp date: February 22, 2017

Product: Lynparza (olaparib)

Indication: Maintenance treatment of patients with
platinum-sensitive relapsed epithelial ovarian,
fallopian tube or primary peritoneal cancer, who
are in response to platinum-based
chemotherapy
Patients with deleterious or suspected
deleterious germline *BRCA*-mutated advanced
ovarian cancer who have been treated with
three or more prior lines of chemotherapy

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Review Division: Division of Hematology Oncology Toxicology
(Division of Oncology Products 1)

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EXECUTIVE SUMMARY

Lynparza (olaparib) is an orally bioavailable poly (ADP-ribose) polymerase (PARP) inhibitor. PARPs are a family of enzymes involved in normal cellular functions including DNA transcription and DNA repair. In vitro, olaparib inhibited several PARP enzymes, including PARP1, PARP2, and PARP3. Olaparib inhibited growth of select tumor cell lines and mouse tumor models harboring deficiencies in BRCA and other DNA repair pathways.

The US FDA previously approved Lynparza capsules under NDA 206162 for the treatment of patients with deleterious or suspected deleterious germline *BRCA*-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. To support the current NDA 208588, the Applicant submitted new clinical data for the use of Lynparza tablets in the previous indication and as maintenance treatment of patients with platinum-sensitive relapsed epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in response to platinum-based chemotherapy.

The Applicant submitted nonclinical pharmacology and toxicology data, which were reviewed previously under NDA 206162. The Applicant updated the animal to human exposure ratios in sections 8.1 and 13.1 of the prescribing information to reflect the differences in exposures with the new tablet formulation. The Applicant also updated information on the mechanism of action in section 12.1, which described olaparib activity in cell lines and mouse tumor models deficient in non-BRCA proteins involved in homologous recombination repair of DNA damage. This data also correlated with tumor response to platinum treatment.

The proposed specification limit of no more than (NMT) (b) (4) % for impurity (b) (4) is above the limit outlined in ICH Q3A and Q3B guidances. Because (b) (4) the tablet formulation leads to (b) (4) olaparib drug substance with greater solubility and bioavailability than the capsule formulation, it is likely that (b) (4) will also have greater bioavailability. The steady state exposure (AUC) following administration of 300 mg olaparib tablets twice daily (BID) was 77% higher compared to the exposure following administration of 400 mg capsules BID. The CMC review team requested an impurity assessment to determine if toxicology studies were conducted with sufficient excess of (b) (4) to justify the higher specification limit considering the higher bioavailability of the tablet formulation.

The Applicant has conducted repeat-dose toxicology studies with olaparib formulated with the previous manufacturing process. Rats have received doses up to 1000 mg/kg/day olaparib administered orally for up to 6 months. (b) (4) was detected in toxicology lots at (b) (4) %. The amount of this impurity administered to patients at the recommended clinical dose of 300 mg olaparib tablets BID would be approximately 6-fold lower than the levels of this impurity (b) (4) % given at a non-severely toxic dose of 1000 mg/kg/day in a 3-month repeat-dose toxicology study in rats.

(Study # 526803). Therefore, (b) (4) is qualified at the proposed specification limit of NMT (b) (4) % even with higher bioavailability of the new tablet formulation.

From the nonclinical perspective, Lynparza tablets are recommended for approval for the proposed indication.

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/s/

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07/05/2017

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