CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 206,162
Drug Name:	Lynparza® (Olaparib)
Indication(s):	Monotherapy 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
Applicant:	AstraZeneca
Date(s):	Receipt: 2/3/2014 PDUFA: 1/2/2015
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Hui Zhang
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Keywords: Objective response rate, duration of response, K-M curve

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1 EXECUTIVE SUMMARY

In this original New Drug Application (NDA), the applicant is seeking an accelerated approval of olaparib as monotherapy 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 pivotal phase 2 trial D0810C00042 (referred to as Trial 42 in this review) to support the application was a non-randomized, open-label, non-comparative multicenter study evaluating the efficacy and safety of olaparib in patients with advanced cancers who had a confirmed genetic BRCA1 and/or BRCA2 mutation. The primary efficacy endpoint was tumor response rate in the all treated population. The secondary endpoints included objective response rate (ORR) in the measurable disease population, progression free survival (PFS), overall survival (OS), duration of response (DoR), and disease control rate (DCR). Due to the nature of the disease, the efficacy evaluation was based on response data from patients with measurable, germline *BRCA* mutation (g*BRCA*m) associated ovarian cancer. At the time of data-cut-off (July 31, 2012), a total of 137 patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy were enrolled in Trial 42.

In Trial 42, the objective response rate (ORR) for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy was 33.6% (95% CI: 25.7%, 42.1%) with median duration of response (DoR) of 7.9 months (95% CI: 5.6, 9.6).

Trial 42 was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed.

Whether the data and analyses from the current submission demonstrated an overall favorable benefit versus risk profile is deferred to the clinical team reviewing this application.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Lynparza® (olaparib) is an oral inhibitor of polyadenosine 5' diphosphoribose polymerase (PARP). This original New Drug Application (NDA) submission provided the clinical efficacy and safety data that intended to support the use of olaparib as monotherapy 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. This submission was primarily supported by results from a non-randomized, open-label, multicenter phase 2 trial D0810C00042 (referred to as Trial 42 in this review) under Investigational New Drug (IND) 75,918.

2.1.2 Regulatory History

The NDA submission was initially based on a randomized trial D0810C00019 (referred to as Trial 19 in this review) of olaparib as the maintenance treatment in patients with platinum sensitive relapsed ovarian cancer with germline *BRCA* mutation (g*BRCA*m) who are in response to platinum-based chemotherapy. Trial 19 was discussed at the Oncologic Drug Advisory Committee (ODAC) meeting held on June 25, 2014. The ODAC voted 2 "Yes", 11 "No" and 0 "Abstain" in response to the question of whether results from Trial 19 in the g*BRCA*m population support an accelerated approval of olaparib in the platinum-sensitive maintenance setting. After the ODAC meeting, the applicant submitted a major amendment and revised the indicated population to patients with g*BRCA*m-associated ovarian cancer treated with more than three lines of chemotherapy. The revised indication was based on results from Trial 42. Therefore, this review is now based primarily on Trial 42 with the related data pertaining to the indicated population.

Reviewer's Comments:

Trial 19 is summarized in Section 3.2.5. Detailed statistical evaluation for Trial 19 is provided in Section 6: ***Appendix: Statistical review and evaluation for Trial D0810C00019****.*

2.1.3 Studies Reviewed

The current NDA submission is based primarily on a phase 2 trial, Trial 42, as outlined in Table 1. This reviewer will focus on Trial 42 for efficacy evaluation.

Trial 42 was entitled "A phase II, open-label, non-randomized, non-comparative, multicenter study to assess the efficacy and safety of olaparib given orally twice daily in patients with advanced cancers who have a confirmed genetic *BRCA*1 and/or *BRCA*2 mutation". In Trial 42,

the primary endpoint was tumor response rate based on investigator assessments, defined as the percentage of patients who had a confirmed complete response (CR) or partial response (PR) prior to progression in the all treated population. Secondary endpoints were objective response rate (ORR) as defined by RECIST 1.1 based on investigator assessments in the measurable disease population, progression-free survival (PFS), overall survival (OS), duration of response (DoR), and disease control rate (DCR).

A total of 317 patients were enrolled from 13 centers in 6 countries in Trial 42. The data cut-off date was July 31, 2012. Among the enrolled 317 patients, 298 received olaparib. Of these 298 patients, 193 patients were in the ovarian cancer group, and 105 patients in other cancer groups including breast cancer group, pancreatic cancer group, prostate cancer group, and other cancer group. Among the 193 patients in the ovarian cancer group, 137 patients with measurable disease at baseline had received three or more prior lines of chemotherapy.

Table 1: Overview of Trial 42

Trial	**D0810C00042**
Critical Design Features	Phase 2, non-randomized, open-label, multicenter (13 centers in 6 countries)
Study Population (Number of Patients)	Patients with advanced cancers who have a confirmed genetic *BRCA*1 and/or *BRCA*2 mutation (n=298)
Treatment Arms (Number of Patients)	— Olaparib orally twice daily at 400 mg bd (n=298)
Enrollment Period	— First patient enrolled: February 21, 2010 — Last patient last visit: July 31, 2012
Efficacy Endpoints	
Primary	Tumor response rate in all treated population
Secondary	ORR in measurable disease population, PFS, OS, DoR, DCR
Sample Size Determination	Single arm trial, no formal sample size calculation
Interim Analyses	NA
***BRCA* mutation Status**	Identification of patients considered to have a deleterious or suspected deleterious *BRCA* mutation were determined based on local germline *BRCA*1/2 testing

Reviewer's Comments:

1. *The all treated population included all enrolled patients who received at least one dose of olaparib. The measurable disease population was a subset of the all treated population. It included patients who had measurable disease at baseline.*
2. *In this review, analyses of ORR and DoR in Trial 42 were based on patients with measurable, gBRCAm-associated ovarian cancer treated with three or more prior lines of chemotherapy.*

In addition, there are 5 trials with supportive data on ORR. The overview of these trials is shown in Table 2.

Table 2: Overview of supportive trials

Trial	Design	Endpoint	N [a]
D0810C00002 (Trial 2)	Phase 1, First time in human with efficacy expansion	ORR	3
D0810C00009 (Trial 9)	Phase 2, non-comparative, proof-of-concept study of olaparib monotherapy in ovarian cancer patients with *gBRCA* mutations	ORR	26
D0810C00012 (Trial 12)	Phase 2, randomized, open-label study of olaparib monotherapy vs PLD in *gBRCA* mutated ovarian cancer patients who had failed previous platinum therapy	PFS	16
D0810C00020 (Trial 20)	Phase 2, open-label, non-randomized study of olaparib monotherapy in patients with known hereditary *gBRCA* mutated or non-hereditary ovarian cancer and patients with known *gBRCA* mutated or triple-negative breast cancer	ORR	12
D0810C00024 (Trial 24)	Phase 1, comparative bioavailability of two different oral formulations of olaparib (capsule and tablet) in cancer patients with advanced solid tumors with efficacy expansion in *gBRCA* mutated ovarian and breast cancer patients	ORR	11

a: Number of patients with gBRCAm who had been treated with three or more prior lines of chemotherapy.
[Adapted from Table 1 in Clinical Overview Supplement]

This NDA submission seeks an accelerated approval of olaparib as monotherapy in patients with deleterious or suspected deleterious g*BRCA* mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Since an accelerated approval requires confirmation of benefit, the applicant is conducting a confirmatory trial D0816C00010 (referred to as Trial 10 in this review), which planned to enroll the first patients in the fourth quarter of 2014 and the last patient was estimated to be enrolled in the second quarter of 2017. Trial 10 was designed to demonstrate the superiority of olaparib compared with physician's choice single agent chemotherapy as a monotherapy in patients who have received more than 2 lines of platinum-based chemotherapy for g*BRCA*m-associated ovarian cancer. The primary endpoint of Trial 10 was PFS based on blinded independent central review (BICR) using RECIST 1.1. Positive result from Trial 10 would confirm the benefit of olaparib in the proposed indication and support conversion from an accelerated approval of olaparib to a full approval. (b) (4) , which is expected to occur approximately 3 years after the first patient is randomized in the trial. The design of the Trial 10 is summarized in Table 3.

Table 3: Study design of the confirmatory Trial 10

Trial	D0816C00010
Title	A Phase III, open label, randomized, controlled, multi-center study to assess the efficacy and safety of olaparib monotherapy versus physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying germline *BRCA*1/2 mutations
Critical Design Features	Phase 3, randomized, open label, controlled, multicenter study
Study Population	Patients who have received more than 2 lines of platinum-based chemotherapy for g*BRCA*m-associated ovarian cancer
Treatment Arms	— Arm A: Olaparib tablets 300 mg twice daily — Arm B: Investigators choice: o Weekly paclitaxel o Topotecan o Pegylated liposomal doxorubicin (PLD) o Gemcitabine
Enrollment Period	— First patients: Quarter 4 2014 — Last patient: Quarter 2, 2017
Efficacy Endpoints	
Primary	PFS based on BICR using RECIST 1.1
Secondary	— Time from randomization to second progression (PFS2) — OS — Time to earliest progression by RECIST 1.1 or CA-125 or death — (b) (4) — GCIG CA-125 response — Time to first subsequent chemotherapy or death (TFST) — Time to second subsequent chemotherapy or death (TSST) — Time to study treatment discontinuation or death (TDT) — HRQoL based on FACT-O questionnaire
Sample Size Determination	(b) (4)
Interim Analyses	

Reviewer's Comments:

The primary endpoint of PFS is acceptable in Trial 10 disease setting providing that the magnitude of effect is clinically relevant and that there is a positive risk-benefit profile of olaparib therapy in this patient population.

2.1.4 History of Protocol Amendments for Trial 42

The original protocol for Trial 42 was dated November 2, 2009, and the last version was Amendment 3 dated August 8, 2011. The protocol amendments are summarized in Table 4.

Table 4: Trial 42 – History of protocol amendments

Protocol Amendment	Date	Major Statistical Amendment
Original protocol	November 2, 2009	Planned to recruit up to approximately 150 patients with a *BRCA* mutation
Protocol Amendment 1	March 31, 2010	No major statistical amendment
Protocol Amendment 2	August 26, 2010	— Sample size increased to 300 patients to allowed a more precise estimate of tumor response rate in patients across a variety of *BRCA* tumor types — Included an additional blood sample collection to enable confirmation of genetic *BRCA* mutation status by a central laboratory — New requirement added to ensure retention of the CT/MRI source data in the study sites. Scans would be retained at site to allow possible retrospective central analysis of tumor evaluations — Patients who received subsequent anticancer therapy prior to progression would not be censored in PFS analysis
Protocol Amendment 3	August 8, 2011	Data cut-off was changed from "6 months after the last patient has commenced study treatment" to "12 months after the last patient started study treatment or the date when no patient remains on study treatment, whichever is the earlier" to allow longer follow up of patients and collection of more safety data

2.2 Data Sources

The electronic submission for Trials 42 and 19, including protocols, statistical analysis plan, study reports, and analysis datasets are located on the network with network path: \\CDSESUB1\EVSPROD\NDA206162\0000\M5.

Clinical overview supplement of Trial 42 for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy is located on the network with network path:
\\CDSESUB1\EVSPROD\NDA206162\0043\m2\25-clin-over.

The SAS dataset to support the analyses of ORR and DoR for Trial 42 and the pooled analysis is located on the network with network path:
\\CDSESUB1\EVSPROD\NDA206162\0035\m5\datasets\pooled-data\analysis\legacy\datasets.

Updated analysis datasets for Trial 19 are located on the network with network path:
\\CDSESUB1\EVSPROD\NDA206162\0020\m5\datasets\d0810c00019amend\analysis\adam\datasets.

3 STATISTICAL EVALUATION

Part of the text, tables, and figures presented in this review were adapted from the following documents:

- For Trial 42: Clinical overview supplement_Study 42, and Clinical overview supplement,
- For Trial 19: Clinical study report (CSR), CSR addendum 1, and CSR errata.

3.1 Data and Analysis Quality

The data and analysis quality of the submission was acceptable for the reviewer to be able to perform the statistical review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Overall Study Design

Trial 42 was a phase 2, non-randomized, open-label, multicenter study evaluating the efficacy and safety of olaparib in patients with deleterious or suspected deleterious g*BRCA*m advanced cancers. The primary objective of Trial 42 was to assess the efficacy of oral olaparib by assessment of tumor response in the all treated population. The patient population for this trial consisted of patients with ovarian cancer, breast cancer, prostate cancer, and pancreatic cancer.

Olaparib was self-administered orally twice daily at 400 mg continually until objective disease progression (determined by RECIST 1.1) as long as in the investigator's opinion patients were benefiting from treatment and they do not meet any other discontinuation criteria.

Baseline radiological tumor assessments were performed no earlier than 28 days before the start of study treatment. Subsequent tumor assessments according to RECIST were performed at the end of every 8 weeks (+/-1 week) up to 6 months after starting treatment and then every 12 weeks thereafter according to the planned study schedule up to objective progression by RECIST 1.1. Patients were required to be followed until RECIST disease progression.

Patients were followed for survival, unless they withdrew consent, up to the point at which the study database was closed.

No formal sample size calculation was performed. Approximately 300 patients were planned to be recruited to the trial. It was intended that, approximately 220 patients with breast and ovarian cancer would be recruited; approximately 30 patients with pancreatic cancer and 10 patients with prostate cancer would be recruited.

3.2.1.2 Efficacy Endpoints

Per the SAP and the protocol, the primary efficacy endpoint was tumor response rate, defined as the percentage of patients who achieved a confirmed complete response (CR) or partial response (PR) prior to progression based on RECIST 1.1, as assessed by the investigator in the all treated population.

The secondary efficacy endpoint included:

- Objective response rate (ORR): defined as the percentage of patients who achieved a CR or PR in the measurable disease population.
- Progression-free survival (PFS): defined as the time from start of treatment until the date of objective disease progression as defined by RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the subject withdraws from study treatment or receives another anticancer therapy prior to progression.
- Overall survival (OS): defined as the time from the date start of study treatment until death due to any cause.
- Duration of response (DoR): defined as the time from the date of first documented response (CR/PR) until date of documented progression (as defined by RECIST 1.1) or death (by any cause) in the absence of disease progression. DoR was summarized in the 'measurable disease' population only.
- Disease control rate (DCR): defined as the percentage of patients who have at least one visit response of CR or PR or who have demonstrated SD for a minimum interval of 16 weeks (-3 days, i.e. 109 days) following start of treatment.

Reviewer's Comments:

1. *The all treated population included all enrolled patients who received at least one dose of olaparib. The measurable disease population was a subset of the all treated population. It included patients who had measurable disease at baseline.*

2. *ORR is very similar to tumor response rate except that they are based on different analysis populations.*
    - *Tumor response rate was based on the all treated population.*
    - *ORR was based on the measurable disease population.*

3.2.2 Statistical Methodologies

3.2.2.1 Sample Size Consideration

Trial 42 is a single-arm trial. No formal sample size calculation was performed.

3.2.2.2 Efficacy Analysis Population

The all treated population included all enrolled patients who received at least one dose of olaparib.

The measurable disease population was a subset of the all treated population. It included patients who have measurable disease at baseline.

Reviewer's Comments:

Due to the nature of the disease, the efficacy evaluation was based on response data from measurable disease population.

3.2.2.3 Efficacy Analysis

The ORR was summarized with denominator of measurable disease population, and corresponding 95% confidence interval (CI) was calculated using a binomial distribution with Clopper-Pearson method.

The DCR analysis method was identical to tumor response rate analysis except that it was based on both all treated population and the measurable disease population.

All time-to-event endpoints were summarized using Kaplan-Meier approach.

Reviewer's Comments:

In this submission, the proposed indication is monotherapy in patients with measurable, gBRCAm-associated ovarian cancer treated with three or more prior lines of chemotherapy. Therefore, this review will focus on efficacy evaluation in this indicated population (i.e. measurable disease population) in Trial 42. Tumor response rate will not be evaluated since this endpoint is based on all treated population, which included non-measurable disease population.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

This review will focus on the efficacy evaluation in the measurable disease population in Trial 42.

3.2.3.1 Patient Disposition

In Trial 42, at the time of data cut-off of July 31, 2012, a total of 137 patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. Of the 137 patients, 15 remained on treatment in the trial (Table 5). The most common reason for discontinuation was development of study specific discontinuation criteria (50.4%). The second most common reason for treatment discontinuation was disease progression (22.6%).

Table 5: Trial 42 – Patient disposition for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy

Disposition	**Olaparib N=137 n (%)**
Receiving Treatment	137
Ongoing on Treatment at Data Cut-off	15 (10.9)
Discontinued from Treatment	122 (89.1)
Adverse event	9 (6.6)
Development of study specific discontinuation criteria	69 (50.4)
Severe non-compliance to protocol	2 (1.5)
Patient decision	8 (5.8)
Subjective disease progression	31 (22.6)
Other	3 (2.2)
Discontinued from Study	122 (89.1)
Death	81 (59.1)
Eligibility criteria not fulfilled	1 (0.7)
Patient decision	7 (5.1)
Other	33 (24.1)

3.2.3.2 Demographic and Baseline Characteristics

Table 6 presents the baseline demographics for ovarian cancer patients with 3 or more prior lines of chemotherapy and measurable disease at baseline in Trial 42.

Table 6: Trial 42 – Baseline demographics for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy

Characteristic	Olaparib N=137
Age (years)	
n	137
Mean (SD)	57.5 (9.0)
Median	58.0
Range	35.0 – 79.0
Age Group, n (%)	
n	137
< 50	26 (19.0)
≥ 50 to < 65	83 (60.6)
≥ 65	28 (20.4)
Race, n (%)	
n	137
White	129 (94.2)
Black or African American	1 (0.7)
Asian	6 (4.4)
Other	1 (0.7)
ECOG PS, n (%)	
n	137
0	76 (55.5)
1	52 (38.0)
2	8 (5.8)
Missing	1 (0.7)
Region, n (%)	
n	137
US	40 (29.2)
Non-US	97 (70.8)
***BRCA* Status, n (%)**	
n	137
*BRCA*1	106 (77.4)
*BRCA*2	30 (21.9)
Both	1 (0.7)
***BRCA* Test, n (%)**	
n	137
Myriad	36 (26.3)
Other (Myriad)	7 (5.1)
Other (BRCA test)	91 (66.4)
Both	3 (2.2)

ECOG PS: Eastern Co-operative Oncology Group performance score ; SD: Standard Deviation
[Source: Module 2.5 – Clinical Overview Supplement_Study 42 Table 2 and statistical reviewer's analysis]

Table 7 summarizes the important baseline disease characteristics for ovarian cancer patients with 3 or more prior lines of chemotherapy and measurable disease at baseline in Trial 42.

Table 7: Trial 42 – Baseline disease characteristics for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy

Characteristic	Olaparib N=137
Primary Tumor Location, n (%)	
n	137
Ovary	125 (91.2)
Fallopian tube	3 (2.2)
Peritoneum	7 (5.1)
Primary peritoneal	2 (1.5)
Number of Prior lines of Chemotherapy	
n	137
Mean (SD)	5.0 (2.1)
Median	5.0
Range	3.0 – 14.0
Time from Diagnosis to First Dose (Years)	
n	137
Mean (SD)	5.4 (3.6)
Median	4.0
Range	1.0 – 19.0

[Source: Module 2.5 – Clinical Overview Supplement_Study 42 Table 2]

3.2.3.3 Protocol Deviations

Table 8 shows the summary of major protocol deviations in Trial 42. A total of 15 patients (10.9%) had major protocol deviations defined in the study protocol.

Table 8: Trial 42 – Summary of major protocol deviation for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy

Number of Patients	Olaparib N=137 n (%)
Major Protocol Deviation	15 (10.9)
Deviation from inclusion criteria	6 (4.4)
Medication stoppled when AE worsened	1 (0.7)
RECIST performed more than 28 days	3 (2.2)
Received prohibited medication	5 (3.6)

3.2.4 Results

3.2.4.1 Results of Objective Response Rate in Trial 42

ORR per investigator assessments was used to evaluate efficacy in the measurable disease population. ORR was 33.6% with median duration of response of 7.9 months (Table 9).

Table 9: Trial 42 – Objective response rate results for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy

	Olaparib N=137
Objective response rate (CR + PR), n (%)	46 (33.6)
Complete response (CR), n (%)	2 (1.5)
Partial response (PR), n (%)	44 (32.1)
95% CI [a]	(25.7, 42.1)
Duration of response (DoR)	n=46
Number of patients progressed or died, n (%)	30 (65.2)
Median DoR (Months) (95% CI)	7.9 (5.6, 9.6)

[a] 95% CI for one sample binomial using Clopper-Pearson method

3.2.4.2 Results for Other Efficacy Endpoints in Trial 42

Table 10 presents the efficacy analysis results for PFS, OS.

Table 10: Trial 42 – Results for other efficacy endpoints for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy

	Olaparib N=137
PFS (Months)	
Number of patients progressed/died	111 (81.0%)
Number of patients censored	26 (19.0%)
Median (95% CI)	7.0 (5.5, 8.7)
OS (Months)	
Number of patients died	81 (59.1%)
Number of patients censored	56 (40.9%)
Median (95% CI)	14.4 (12.2, 18.4)

Reviewer's Comments:

The efficacy analyses presented in Table 10 are considered exploratory because PFS and OS analyses are not interpretable in a single-arm trial without a control group.

3.2.4.3 Results from Pooled Data

In the 5 supportive Trials 2, 9, 12, 20, and 24, there are 68 patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy. Pooled analyses of ORR and DoR were performed based on 205 patients: 137 from Trial 42 and 68 from 5 supportive trials.

Table 11 presents the results of ORR and DoR based on the pooled analysis.

Table 11: Pooled analysis – Objective response rate results for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy

	Olaparib N=205
Objective response rate (CR + PR), n (%)	64 (31.2)
Complete response (CR), n (%)	4 (2.0)
Partial response (PR), n (%)	60 (29.3)
95% CI [a]	(25.0, 38.1)
Duration of response (DoR)	N=64
Number of patients progressed or died, n (%)	41 (64.1)
Median DoR (Months) (95% CI)	7.8 (5.6, 9.5)

[a] 95% CI for one sample binomial using Clopper-Pearson method

Reviewer's Comments:

The results from the pooled analysis support the primary efficacy findings in Trial 42.

3.2.5 Other Trial – Trial 19

The applicant initially sought an accelerated approval of olaparib as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with g*BRCA*m who are in response (complete response or partial response) to platinum-based chemotherapy. The efficacy of olaparib for this indication is based on the subgroup analysis of the single efficacy trial D0810C00019 (Trial 19) in 96 patients with deleterious g*BRCA*m-associated platinum-sensitive ovarian cancer.

A brief overview of Trial 19 and a summary of major statistical issues and findings are presented in this section (Section 3.2.5). Detailed description on Trial 19 and statistical evaluations can be found in Section 6: **Appendix: Statistical review and evaluation for trial d0810c00019** of this review.

Table 12 shows the overview of Trial 19.

Table 12: Overview of Trial 19

Trial	D0810C00019
Critical Design Features	Phase 2, randomized, double-blind, placebo-controlled, multicenter (82 sites in 16 countries)
Study Population (Number of Patients)	Patients with platinum-sensitive serous ovarian cancer following treatment with ≥2 platinum-containing regimens (n=265) Note: Patients must have achieved a CR or PR to the platinum-based chemotherapy immediately preceding the maintenance therapy
Treatment Arms (Number of Patients)	— Olaparib 400 mg bd capsule (oral) (n=136) — Matching placebo (n=129)
Enrollment Period	— First patient enrolled: August 28, 2008 — Last patient enrolled: February 9, 2010
Efficacy Endpoints	
Primary	PFS (investigator assessments)
Secondary	OS, BOR by RECIST, DoR, time to progression by CA-125 or RECIST, CA-125 response, tumor size, and health-related quality of life (QoL) measured by the FACT-O scale
Sample Size Determination	— 1:1 randomization ratio — 1-sided alpha of 0.2 — 80% power — HR = 0.75 (median PFS of 9 months for the placebo arm and 12 months for the olaparib arm) — 250 patients with 137 PFS events
Interim Analyses	**PFS:** No interim analysis **OS:** Two interim analyses o First interim OS analysis: at the time that 100 deaths occurred o Second interim OS analysis: at the time that 137 deaths occurred o Final analysis of OS: at the time that ~222 deaths occurred
***BRCA* mutation Status**	Knowledge of *BRCA* mutation status was not required at study entry, but was determined during the study

Reviewer's Comments:

1. *For Trial 19, this review will focus on the efficacy evaluation in the gBRCAm subgroup.*
2. *In Trial 19, all available archived blood samples were tested for BRCA status (gBRCA) by the Myriad laboratory developed test. The retrospective identification of gBRCA mutation status resulted in 210/265 (79%) of the study population having a known gBRCA status as defined by either the Myriad test or other local testing.*

The following major statistical issues need to be considered in evaluating olaparib in the platinum-sensitive maintenance setting:

1. The primary efficacy analysis was based on the ITT population. No adjustments for multiplicity were planned for multiple subgroup comparisons as well as multiple analyses for secondary endpoints. Therefore, the p-values from these analyses are not interpretable.
2. The subgroup of gBRCAm population was identified retrospectively based on convenience samples. Randomization as executed in the ITT population does not hold in the subgroup.
3. The sample size in the gBRCAm subgroup is small; therefore, the estimate of magnitude of treatment effect may be unstable.

The submission of olaparib in the maintenance setting based on results in Trial 19 was discussed at the Oncologic Drug Advisory Committee (ODAC) meeting held on June 25, 2014. The question posed to the Committee was "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?", where SOLO-2 was designed to assess the efficacy of olaparib maintenance monotherapy in relapsed gBRCAm high-grade serous ovarian cancer (HGSOC) patients or high-grade endometrioid cancer who have responded following platinum-based chemotherapy. Trial SOLO2 design largely mimics the design of Trial 19, and approximately 264 patients will be recruited (2:1 olaparib:placebo ratio). The ODAC voted 2 "Yes", 11 "No" and 0 "Abstain" in response to the question due to concerns with the statistical issues, the occurrence and duration of adverse effects, including rare occurrence of secondary cancers, and the impact of accelerated approval of the drug on the accrual of the ongoing confirmatory trial.

Reviewer's Comments:

Appendix: Statistical review and evaluation for trial d0810c00019 *was prepared for the ODAC meeting to discuss whether the accelerated approval of olaparib was acceptable in the platinum-sensitive maintenance setting.*

3.2.5.1 Objective

The primary efficacy objective of Trial 19 was to compare the PFS based on investigator assessments when treated with olaparib versus placebo as maintenance treatment in patients with platinum-sensitive relapsed ovarian cancer who were in response to platinum-based chemotherapy. The secondary efficacy objectives included comparisons for OS, BOR by RECIST, DoR, time to progression by CA-125 or RECIST, CA-125 response, tumor size, and health-related quality of life (QoL) measured by the FACT-O scale.

3.2.5.2 Study Design and Endpoints

Trial 19 was a randomized, double-blinded, placebo-controlled, multicenter phase 2 study comparing the efficacy and safety of olaparib to placebo as maintenance treatment in patients

with platinum-sensitive relapsed ovarian cancer who were in response to platinum-based chemotherapy.

Treatment was administered in 4 week cycles until objective disease progression (RECIST) or as long as in the investigator's opinion that patients were benefiting from treatment and they did not meet any other discontinuation criteria, patients should continue with therapy to RECIST progression despite rises in CA-125. Olaparib or matching placebo were administered orally twice daily at a dose of 400mg bid on Days 1 through to 28 for all cycles. There was no maximum duration of treatment with olaparib or matching placebo. No cross over to olaparib was permitted.

Tumor assessments were performed every 12 weeks (3 cycles) after randomization, up to 60 weeks (15 cycles) then every 24 weeks (6 cycles) until objective disease progression by RECIST, death without evidence of progression, or withdrawal of consent. If patients fulfilled the CA-125 GCIG criteria for progression, they may have an unscheduled tumor assessment to assess radiological progression by RECIST. If the unscheduled assessment did not confirm RECIST progression, patients continued on treatment and continued to be assessed for RECIST progression per the protocol schedule. Disease progression was only determined by RECIST and not by CA-125. Tumor response in all cases was assessed according to the RECIST.

Patients were followed for survival unless they withdrew consent, regardless of whether study treatment was discontinued or delayed and/or protocol violations.

Approximately 250 patients were planned to be randomized via Interactive Voice Response System (IVRS) system in a 1:1 ratio. Randomization was stratified by time to disease progression (>6-12 months vs. >12 months, in the penultimate platinum therapy prior to enrolment), objective response (CR vs. PR, in the last platinum therapy prior to enrolment) and whether a patient is of Jewish de**s**cent (yes vs. no).

The primary endpoint **PFS** was defined as the time from randomization to the earlier date of radiological progression or death by any cause in the absence of objective progression. Disease progression was based on the tumor assessment by investigator assessment using RECIST 1.0.

The secondary endpoint **OS** was defined as the time from randomization to the date of death from any cause. Patients who had not died at the time of analysis were censored at the last date the patient was known to be alive.

Other secondary endpoints included ORR, BoR, DoR, time to CA-125 or RECIST progression, CA-125 response, tumor size, and health-related quality of life (QoL) measured by the FACT-O scale.

Reviewer's Comments:

1. *Patients were in either complete or partial response to platinum-based chemotherapy prior to randomization. There were few additional responses, which occurred on both treatment*

arms. No meaningful conclusions can be drawn from analysis of ORR, BOR and DoR. Therefore, this review does not cover these endpoints.

2. *The endpoints of time to CA-125 or RECIST progression and tumor size are not clinically meaningful endpoints; therefore, this review does not cover these endpoints.*
3. *PRO analyses were based on a subset of the ITT population that included patients with evaluable quality of life (QoL)/Symptom endpoints at baseline.*

3.2.5.3 Statistical Methodologies

3.2.5.3.1 Sample Size Consideration

Per the SAP, Trial 19 was designed to have 80% power to detect a hazard ratio (HR) of 0.75 with a 1-sided alpha of 0.2 and 1:1 randomization ratio, assuming a median PFS of 9 months for the placebo arm and 12 months for the olaparib arm. No interim efficacy analysis of PFS was planned. It was estimated that 137 PFS events were needed for the PFS analysis, which could be expected from a total of 250 patients.

3.2.5.3.2 Interim Analyses

No interim efficacy analysis was planned for the primary endpoint PFS.

Per the SAP (dated November 2, 2011), an interim efficacy analysis was planned for the secondary endpoint OS after approximately 100 deaths had occurred. Final OS analysis was planned to be conducted when 137 deaths occurred. However, per Protocol Amendment 6 (dated October 17, 2012), the first interim analysis of OS was performed when approximately 100 deaths had occurred; a subsequent interim analysis of survival was performed when approximately 137 deaths had occurred. The final survival analysis was to be performed when approximately 222 deaths had occurred. The alpha allocation was based on Peto et al (1976) and Haybittle (1971) method. In the CSR, the OS interim analyses were performed per protocol.

<u>Reviewer's Comments:</u>

1. *Per the final version of the protocol (Version 7, dated May 30, 2013), additional analyses of survival data may be performed to meet Regulatory Agency requests or the applicant planning requirements.*
2. *Per the protocol, statistical significance in favor of olaparib, would be declared at the first interim analysis in the ITT population for OS if the observed p-value was <0.001 (2-sided) and at the second interim analysis if the observed p-value was <0.03 (2-sided). At each subsequent analysis half the remaining alpha was planned to be spent, unless it was the final analysis where all the remaining alpha would be spent. This allows the overall alpha to be controlled at 5% (2-sided).*

3.2.5.3.3 Efficacy Analysis Method

The Full Analysis Set (FAS) population consisted of all randomized patients. Following the Intent-to-Treat (ITT) principle, patients were analyzed according to the treatment and stratum they were assigned to at randomization. Per the protocol and the SAP, this population was the primary population for evaluating efficacy results.

The analysis for PFS 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 enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no). The treatment effect was estimated by the adjusted hazard ratio (HR) and its corresponding 80% and 95% CIs. The median OS with corresponding 95% CIs and survival curves were estimated using the Kaplan-Meier (K-M) method.

The stratified log-rank test, stratified by the same stratification factors as used for randomization, was planned as a supportive analysis.

The OS analysis method was identical to that of PFS analysis.

Reviewer's Comments:

1. *The primary efficacy analyses of Trial 19 were based on the ITT population.*
2. *No adjustments for multiplicity were planned for multiple analyses of the secondary endpoints. Therefore, p-values in these analyses are uninterpretable.*
3. *Subgroup analysis based on the gBRCAm population was not defined in the protocol but was prospectively defined in the SAP (dated May 28, 2011) that was finalized prior to unblinding of the data for analysis. No adjustments for multiplicity were planned for multiple subgroup comparisons. Therefore, all p-values in the analyses based on the gBRCAm population are uninterpretable.*

3.2.5.4 Results and Conclusions

3.2.5.4.1 Primary Efficacy Endpoint – Progression Free Survival

Table 13 presents the applicant's efficacy analysis for PFS for the g*BRCA*m population. There were a total of 50 PFS events. There was a demonstrated difference in PFS comparing olaparib with the placebo based on the adjusted Cox proportional hazards model with a nominal p-value <0.0001. The median PFS was 11.2 months (95% CI: 8.3, NE) for the olaparib arm and 4.1 months (95% CI: 2.8, 5.1) for the placebo arm. The stratified Cox HR was 0.17 with 95% CI (0.09, 0.32).

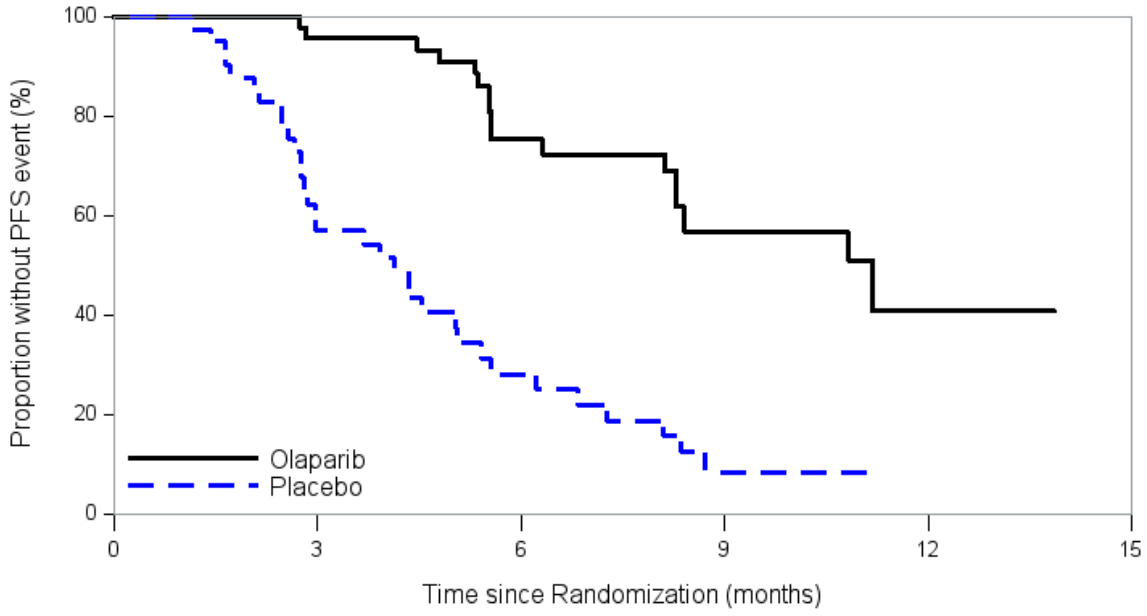
Table 13: Trial 19 – Progression Free Survival results in g*BRCA*m population

	Olaparib (N=53)	Placebo (N=43)
Patients randomized	53	43
Events	17 (32%)	33 (77%)
Censored	36 (68%)	10 (23%)
PFS (months) [a]	11.2	4.1
Median (95% CI)	(8.3, NE)	(2.8, 5.1)
p-value [b]	<0.0001[c]	
Hazard ratio (95% CI) [b]	0.17 (0.09, 0.32)	

[a] Progression free survival time is calculated as months from date of randomization to earlier date of radiological progression or death by any cause in the absence of objective progression.
[b] p-value and HR are from 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 enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no). Hazard ratio < 1 favors olaparib.
[c] This is a nominal p-value.
Note: data cut-off date June 30, 2010.
[*Adapted from Trial 19 Clinical Study Report Addendum 1 Tables 4 and 5*]

Figure 1 presents the Kaplan-Meier (K-M) curves for PFS for gBRCAm population.

Figure 1: Trial 19 – Kaplan-Meier survival curves for Progression Free Survival in g*BRCA*m population



Reviewer's comments:

1. *Olaparib demonstrated superior PFS over placebo in the gBRCAm population.*

2. *The results from exploratory sensitivity analyses conducted by the Applicant and this reviewer were consistent with the results from the primary analysis of PFS in the gBRCAm population. (Sensitivity analyses results are available in the Appendix.)*

3.2.5.4.2 Secondary Efficacy Endpoint – Overall Survival

Table 14 summarizes the applicant's efficacy analysis results for the second interim analysis of OS in the g*BRCA*m population.

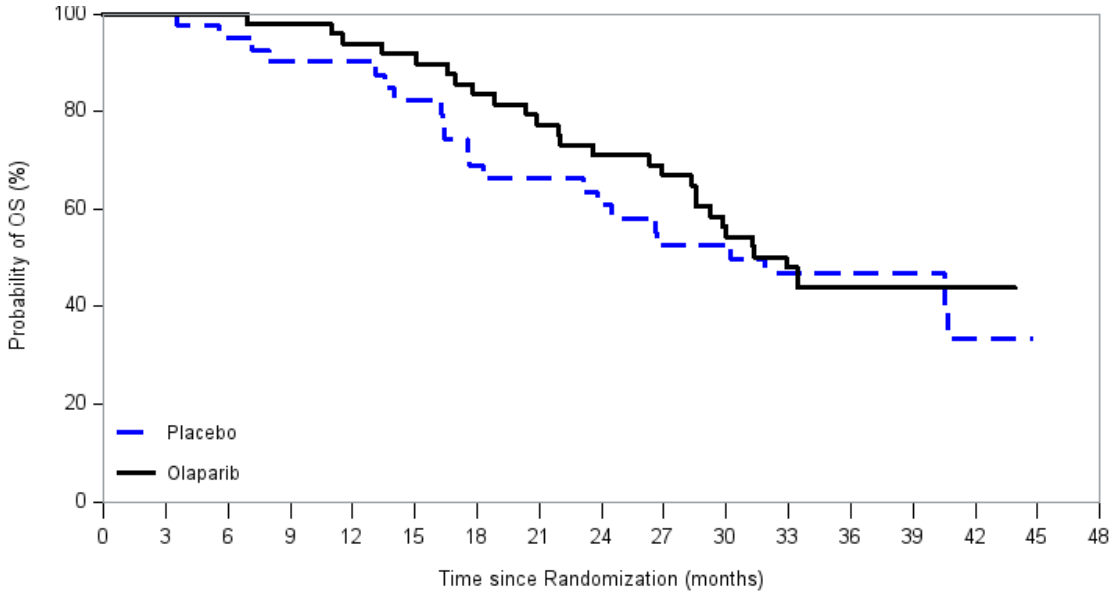
Table 14: Trial 19 – Interim analyses of Overall Survival in g*BRCA*m population

	Olaparib (N=53)	**Placebo (N=43)**
Patients randomized	53	43
Deaths	27 (50.9)	22 (51.2)
Censored	26 (49.1)	21 (48.8)
OS (months) [a]	32.9	30.2
Median (95% CI)	(28.4, NE)	(18.3, NE)
p-value [b]	0.58	
Hazard ratio (95% CI) [b]	0.85 (0.48, 1.51)	

Note: data cut-off date November 26, 2012.

Figure 2 presents the K-M curves for the second interim analysis of OS in the g*BRCA*m population.

Figure 2: Trial 19 – Kaplan-Meier survival curves for Overall Survival in g*BRCA*m population



Reviewer's comments:

This interim analysis of OS shows that there is no improvement of OS with treatment of olaparib compared to placebo.

3.2.5.4.3 Conclusion for Trial 19

Trial 19 shows that olaparib demonstrated an improvement in the primary endpoint PFS in both ITT population and g*BRCA*m population. However, based on the Oncology Drug Advisory Committee votes, the results from Trial 19 in the platinum-sensitive maintenance setting do not support granting accelerated approval due to concerns with the statistical issues, the occurrence and duration of adverse effects, including rare occurrence of secondary cancers, and the impact of accelerated approval of the drug on the accrual of the ongoing SOLO-2 trial.

3.2.6 Conclusions for Efficacy

The pivotal trial, Trial 41, demonstrated durable treatment benefit of olaparib as monotherapy for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy, with an ORR of 33.6% and median duration of response of 7.9 months.

3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

3.4 Benefit-Risk Assessment

Since the pivotal trial supporting this NDA application was a sing-arm trial, the benefit/risk cannot be assessed based on comparative analyses. Whether the submission demonstrated an overall favorable benefit vs. risk profile for olaparib is deferred to the clinical team reviewing this submission.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 15 summarizes ORR subgroup analysis results by age and geographic region for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy in Trial 42.

Table 15: Trial 42 – Objective response rate subgroup analyses by age and geographic region for patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy

	Olaparib N=137
Age	
< 50	5/26 (19.2%)
≥ 50 to < 65	32/83 (38.6%)
≥ 65	9/28 (32.1%)
Region	
US	14/40 (35.0%)
Non-US	32/97 (33.0%)

Reviewer's Comments:

All ovarian cancer patients with 3 or more prior lines of chemotherapy and measurable disease at baseline were female and most of them (94%) were white in Trial 42. Therefore, subgroup analyses of ORR by gender and race were not performed.

5 SUMMARY AND CONCLUSIONS

In this original NDA, the applicant is seeking an accelerated approval of olaparib as monotherapy in patients with deleterious or suspected deleterious g*BRCA* mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy based on the pivotal single-arm phase 2 Trial 42.

5.1 Statistical Issues

The pivotal trial, Trial 42, was a single-arm study; therefore, no comparative evaluation of treatment effect of olaparib can be performed.

5.2 Collective Evidence

Based on the objective response data from Trial 42, olaparib provided durable treatment effect for patients with deleterious or suspected deleterious g*BRCA* mutated advanced ovarian cancer who had been treated with three or more prior lines of chemotherapy. However, because Trial 42 was a single-arm study, the treatment effect of olaparib can only be descriptively summarized.

This original NDA submission seeks an accelerated approval of olaparib as monotherapy in patients with deleterious or suspected deleterious g*BRCA* mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The confirmatory trial, Trial

10, is a randomized phase 3 trial which was designed to demonstrate the superiority of olaparib compared with physician's choice single agent chemotherapy as a monotherapy in patients who have received more than 2 lines of platinum-based chemotherapy for g*BRCA*m-associated ovarian cancer. The primary endpoint of the Trial 10 is PFS based on blinded independent central review (BICR) using RECIST 1.1. Positive result from Trial 10 would confirm the benefit of olaparib in the proposed indication and support conversion from an accelerated approval of olaparib to a full approval.

5.3 Conclusions and Recommendations

This NDA submission was based on a pivotal phase 2 trial, Trial 42, to evaluate the treatment effect of olaparib as a monotherapy for patients with deleterious or suspected deleterious g*BRCA* mutated advanced ovarian cancer who had been treated with three or more prior lines of chemotherapy.

Trial 42 demonstrated durable treatment effect of olaparib for patients with deleterious or suspected deleterious germline *BRCA* mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The final decision on the benefit versus risk profile for olaparib is deferred to the clinical team reviewing this submission.

5.4 Labeling Recommendations

The results of the ORR and DoR analyses for Trial 42 will be included in the label.

6 APPENDIX: STATISTICAL REVIEW AND EVALUATION FOR TRIAL D0810C00019

Reviewer's Comments:

The applicant initially sought an accelerated approval of olaparib as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed ovarian cancer with gBRCAm who are in response to platinum-based chemotherapy. This document was prepared for the Oncologic Drug Advisory Committee (ODAC) meeting held on June 25, 2014 to discuss the question of whether results from D0810C00019 (Trial 19) in the platinum sensitive maintenance settings support granting accelerated approval.

6.1 EXECUTIVE SUMMARY

This NDA submission initially sought an accelerated approval of olaparib as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline *BRCA* mutation (g*BRCA*m) who are in response (complete response or partial response) to platinum-based chemotherapy.

Trial 19 to support the indication of platinum sensitive maintenance setting was a randomized, double-blinded, placebo-controlled multinational phase 2 study evaluating the efficacy and safety of olaparib relative to placebo in patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens. The primary efficacy endpoint was progression free survival (PFS) based on investigator assessments using RECIST 1.0 criterion. The secondary efficacy endpoints included overall survival (OS), best objective response (BoR) by RECIST, duration of response (DoR), time to progression by CA-125 or RECIST, CA-125 response, tumor size, and health-related quality of life (QoL) measured by the Functional Assessment of Cancer Therapy Ovarian (FACT-O) scale. A total of 265 patients were randomized in a 1:1 allocation (Olaparib: 136; placebo: 129).

The data and analyses from Trial 19 demonstrated that patients on olaparib had a statistically significant improvement in PFS when compared with placebo in the ITT population. The p-value for PFS comparison was < 0.0001. The median PFS was 8.4 (95% CI: 7.4, 11.5) months for olaparib and 4.8 (95% CI: 4.0, 5.5) months for placebo. The adjusted Cox proportional hazard ratio (HR) was 0.35 with 95% CI (0.25, 0.49). The second interim analysis of OS with 154 deaths numerically favored olaparib arm but did not reach a statistical significance (adjusted HR = 0.88, 95% CI: 0.64, 1.21, p-value 0.44).

The subgroup analyses from Trial 19 demonstrated that olaparib had an improvement in the PFS when compared with placebo in the g*BRCA*m population. The nominal p-value for PFS comparison was <0.0001. The median PFS was 11.2 (95% CI: 8.3, NE) months for olaparib and 4.1 (95% CI: 2.8, 5.1) months for placebo. The adjusted Cox proportional hazard ratio (HR) was 0.17 with 95% CI (0.09, 0.32). The second interim analysis of OS with 49 deaths numerically favored olaparib arm but did not reach a statistical significance (adjusted HR = 0.85, 95% CI: 0.48, 1.51).

However, the following major statistical issues need to be considered in evaluating olaparib in platinum-sensitive maintenance setting:

1. The primary efficacy analysis was based on the ITT population. No adjustments for multiplicity were planned for multiple subgroup comparisons as well as multiple analyses for secondary endpoints. Therefore, the p-values from these analyses are not interpretable.

2. The subgroup of g*BRCA*m population was identified retrospectively based on convenience samples. Randomization as executed in the ITT population does not hold in the subgroup.
3. The sample size in the gBRCAm subgroup is small; therefore, the estimate of magnitude of treatment effect may be unstable.

In the Oncologic Drug Advisory Committee (ODAC) meeting held on June 25, 2014, one of the questions was whether results from Trial 19 in the platinum sensitive maintenance settings support granting accelerated approval. The ODAC voted 2 “Yes”, 11 “No” and 0 “Abstain” in response to this question due to concerns with the statistical issues, the occurrence and duration of adverse effects, including rare occurrence of secondary cancers, and the impact of accelerated approval of the drug on the accrual of the ongoing confirmatory trial.

6.2 INTRODUCTION

6.2.1 Overview

6.2.1.1 Class and Indication

Ovarian cancer is the fifth most common cause of cancer death in women. Ovarian cancer often goes undetected until it has spread within the pelvis and abdomen. At this late stage, ovarian cancer is difficult to treat and is often fatal. Some ovarian cancers are caused by an inherited gene mutation. The genes known to increase the risk of ovarian cancer are called breast cancer gene 1 (*BRCA*1) and breast cancer gene 2 (*BRCA*2).

Olaparib (also known as AZD2281 and KU-0059436) is a potent inhibitor of polyadenosine 5' diphosphoribose polymerase (PARP). Tumors in patients with a *BRCA* mutation would be expected to be sensitive to PARP inhibition due to the loss of function of the mutated copy of the gene and the loss of function of the second copy of the gene within the tumor (Polyak and Garber 2011).

In the initial NDA submission, the indication proposed by the applicant was for maintenance treatment of patients with platinum-sensitive relapsed ovarian cancer with g*BRCA*m who are in response to platinum-based chemotherapy. This indication was primarily supported by a pivotal Phase 2 trial D0810C00019 (referred to as Trial 19 in this review) under Investigational New Drug (IND) 75,918.

6.2.1.2 Study Reviewed

The clinical efficacy and safety evaluation that intend to support the use of olaparib as a monotherapy in the platinum-sensitive maintenance setting is primarily based on a pivotal phase 2 Trial 19 (Table 16).

Trial 19 was a randomized, double-blinded, placebo-controlled multinational phase 2 study evaluating the efficacy and safety of olaparib relative to placebo in patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens. The primary efficacy endpoint was progression free survival (PFS) based on investigator assessments using RECIST 1.0 criterion. The secondary efficacy endpoints included overall survival (OS), best objective response (BoR) by RECIST, duration of response (DoR), time to progression by CA-125 or RECIST, CA-125 response, tumor size, and patient-reported outcomes (PRO) measured by the Functional Assessment of Cancer Therapy Ovarian (FACT-O) scale. No interim efficacy analysis of PFS was planned for this trial. There were two interim analyses for OS.

Table 16: Overview of Trial 19

Trial	**D08110C00019 (Trial 19)**
Level of Evidence	Pivotal
Critical Design Features	Phase 2, randomized, double-blind, placebo-controlled, multicenter (82 sites in 16 countries)
Study Population (Number of Subjects)	Patients with platinum-sensitive serous ovarian cancer following treatment with ≥2 platinum-containing regimens (N=265) Note: Patients must have achieved a CR or PR to the platinum-based chemotherapy immediately preceding the maintenance therapy
Treatment Arms (Number of Subjects)	— Olaparib 400 mg bd capsule (oral) (N=136) — Matching placebo (N=129)
Enrollment Period	— First subject enrolled: August 28, 2008 — Last subject enrolled: February 9, 2010
Efficacy Endpoints	
Primary	PFS (investigator assessment)
Secondary	OS, BoR by RECIST, DoR, time to progression by CA-125 or RECIST, CA-125 response, tumor size, and PRO measured by the FACT-O scale
Sample Size Determination	— 1:1 randomization ratio — 1-sided alpha of 0.2 — 80% power — HR = 0.75 (median PFS of 9 months for the placebo arm and 12 months for the olaparib arm) — 250 patients with 137 PFS events
Interim Analyses	— **PFS:** No interim analysis — **OS:** Two interim analyses o First interim OS analysis: 100 deaths o Second interim OS analysis: 137 deaths o Final analysis of OS: ~222 deaths
***BRCA* mutation Status**	Knowledge of *BRCA* mutation status was not required at study entry, but was determined during the study

Trial 19 was entitled "Phase II randomized, double blind, multicenter study to assess the efficacy of ZAD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens". The original protocol was issued on June 2, 2008, and was last amended on May 30, 2013 (Version 7). The trial was blinded under protocol Version 1 through Version 3. The Statistical Analysis Plan (SAP) (Version 3) was finalized on November 2, 2011. A total of 265 patients were randomized in a 1:1 allocation (olaparib: 136; placebo: 129).

Table 17 shows the protocol amendments regarding statistical issues that were more relevant to this statistical review.

Table 17: History of Trial 19 protocol amendments

Protocol Amendments	Major Amendments	Rational
Amendment 1 (November 27, 2008)	Clarified that the study had co-primary objectives comparing PFS in both the overall study population and subpopulation of patients with Homologous Recombination Deficient (HRD) tumors	
Amendment 2 (May 14, 2009)	Added an interim efficacy analysis of PFS conducted by Independent Data Monitoring Committee (IDMC) when approximately 80 progression events occurred	Determine whether there is sufficient efficacy to trigger a Phase 3 study in the overall population. There is no intention to stop the study early on the basis of good efficacy results from the interim analysis
Amendment 3 (May 17, 2010)	Removed interim analysis of PFS Removed analysis of PFS in the HRD population as a co-primary objective	An assay to identify HRD patients not available at the time of primary analysis
Amendment 4 (November 2, 2010)	Removed the interim analysis of OS at the time of the primary PFS analysis, planned to conduct final OS analysis when 137 deaths occured	Insufficient OS events for a meaningful interim analysis at time of the primary PFS analysis
Amendment 5 (November 1, 2011)	Added an interim analysis of overall survival when approximately 100 deaths occurred	Provide sufficient confidence to be able to start a phase 3 trial in a timely manner
Amendment 6 (October 17, 2012)	Changed the final analysis of overall survival performed when 137 deaths occurred to be the second interim OS analysis Changed the timing the final OS analysis (when ~222 deaths occurred)	

Table 18 shows the timeline of pre-specified analysis populations, data unblinding, and *BRCA* mutation status determination.

Table 18: Trial 19 – Timeline of pre-specified analysis populations, data unblinding, and BRCA mutation status determination

Event	Date	Key Points
Original protocol	June 2, 2008	
Protocol Amendment 1		Clarified that the HRD subset was a co-primary analysis population
Protocol Amendment 3	June 2, 2009	Removed HRD subset as a co-primary analysis

		since an assay to identify HRD patients was not available at the time of primary analysis
SAP signed off	June 3, 2010	Signed off SAP prior to unblinding of data for the primary analysis Specified that assessment of consistency across subgroups would include the stratification factors plus *BRCA* status
Data cut-off (DCO) for primary PFS analysis	June 30, 2010	Data were unblinded following DCO and a statistically significant benefit was seen for the primary PFS analysis in the overall population. Note: investigators were not unblinded at this time There was some indication of differential benefit for the subpopulation of patients with a *BRCA* mutation (based on *BRCA* mutation status known for 37% of patients at study entry) Note: At the time of the primary PFS analysis, there were insufficient events to support OS analysis
CSR Version 2	July 26, 2011	Original primary CSR
Protocol Amendment 4	November 2, 2010	Clarified that the final analysis of OS was scheduled to take place when 137 deaths have occurred
Protocol Amendment 5	November 1, 2011	Added an interim analysis of OS when approximately 100 deaths occurred
SAP Version 3	November 2, 2011	Provided in the current NDA submission as the final SAP
First interim analysis of OS	December, 2011	No evidence of OS benefit observed in the ITT population There was a differential benefit in g*BRCA*m patients compared with g*BRCA*wt patients (based on g*BRCA* mutation status known for 37% of patients at study entry) Note: results were shared with the Principal Investigator but not the other trial investigators
g*BRCA* and t*BRCA* status determination	Throughout 2012	For patients who had provided samples and consent for optional genetic testing, all available blood samples were tested for *BRCA* status (g*BRCA*) by Myriad first and then tumor samples were tested by (b) (4) (t*BRCA*). PFS and OS were reanalyzed on the basis of the resulting larger data sets.
Regulatory interactions	September	The results of a re-analysis of PFS data (DCO

with MPA, MEB and ANSM	2012-December 2012	30 June 2010) and OS data within the expanded g*BRCA* population (CRF and/or Myriad) were shared. Tumor *BRCA* mutation status data were not available at this time. The analysis showed statistically significant benefit in PFS and a non-significant numerical advantage for OS in favor of olaparib in the g*BRCA* mutated subpopulation. No OS advantage was evident in the g*BRCA* wild type population.
Protocol Amendment 6	October 17, 2012	The original final analysis of OS with 137 deaths was changed to be the second interim analysis. The final survival analysis was planned to be performed with ~222 deaths.
Re-analysis of PFS and OS with a further expanded *BRCA* mutation status	Throughout January 2013	PFS (DCO June 30, 2010) and OS (second interim analysis DCO November 26, 2012) were reanalyzed with *BRCA* mutation status known for a total of 96% of patients, including 136 patients with a *BRCA* mutation (germline and/or tumor mutations)
Protocol Amendment 7	May 30, 2013	Final version of protocol
CSR Version 3	July 31, 2013	Final version of CSR

Reviewer's comments:

1. *Protocol Amendments 4-7 were made after data unblinding.*
2. *The final SAP (Version 3) was dated November 2, 2011. No SAP amendment incorporated further changes in Protocol Amendments 6 and 7.*
3. *The trial was not powered for overall survival. The timing of interim and final analyses of OS was amended after data unblinding.*

The initial submission sought an accelerated approval of olaparib in platinum-sensitive maintenance setting. Since an accelerated approval requires confirmation of benefit, the applicant is conducting a confirmatory trial, D0816C00002 (SOLO2), which is currently ongoing. Trial SOLO2, was designed to demonstrate the superiority of olaparib compared with placebo as a maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy. The primary endpoint of the trial SOLO2 was PFS determined by central review of RECIST data. Positive results from the SOLO2 trial in the maintenance setting would confirm the benefit of olaparib. The analysis of PFS will be performed when 158 PFS events have occurred, which is expected to occur approximately 24 months after the first subject is enrolled in the study (FSI). Overall survival (OS) is a key secondary endpoint. The final analysis of OS will be performed at approximately 158 deaths have occurred, this is anticipated to occur approximately 60 months (5 years) after FSI. The design of the trial SOLO2 is summarized in Table 19. The results of this trial are expected to be available at the end of 2015.

Table 19: Study design of the confirmatory trial SOLO2

Trial	D0816C00002 (SOLO2)
Critical Design Features	Phase 3 randomized, double blind, placebo controlled, multicenter study
Study Population	Platinum sensitive relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy
Treatment Arms	— Olaparib tablets *p.o.* 300 mg twice daily — Placebo tablets *p.o.* twice daily
Enrollment Period	Recruitment expected to be completed in the first quarter of 2015 Data expected to be available in the fourth quarter of 2015
Efficacy Endpoints	
Primary	PFS by central review of RECIST data
Secondary	— OS — Time to earliest progression by RECIST or CA-125 or death — Time from randomization to second progression (PFS2) — Time from randomization to first subsequent therapy or death (TFST) — Time from randomization to second subsequent therapy or death (TSST) — Time from randomization to study treatment discontinuation or death (TDT) — The Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian Cancer (FACT-O) will be used to determine rate: — (b) (4) — Time to deterioration
Sample Size Determination	— 2:1 randomization ratio — Sized to have sufficient precision of the estimated Hazard Ratio (HR) — 264 patients with 158 PFS events are required to give sufficient precision of the HR. If a HR of 0.2 (similar to Trial 19) was observed, the 95% CI would be 0.14-0.28; if a HR of 0.3 was observed, the 95% CI would be 0.22-0.42; if a HR of 0.4 was observed, the 95% CI would be 0.29-0.56; and if a HR of 0.5 was observed, the 95% CI would be 0.36-0.70.
Interim Analyses	— **PFS:** No interim analysis — **OS:** One interim analysis o Interim OS analysis: at the time of the PFS analysis (50 deaths) o Final OS analysis: at the time when ~60% deaths occur

Reviewer's comments:

Trial SOLO2 was sized to have sufficient precision of the hazard ratio. Therefore, the trial may be powered to detect a statistically significant but potentially clinically insignificant improvement in PFS. For example, if the median PFS in the control arm is 4 months, with a sample size of 158 PFS events, Trial SOLO2 could detect a minimum statistically significant improvement in PFS of only 1.5 months, with a corresponding HR of 0.73.

Throughout this review, subjects who were randomized to receive olaparib are referred to as "olaparib arm" in the text and as "olaparib" in the tables/figures, whereas subjects who were randomized to receive placebo are referred to as "placebo arm" in the text and as "placebo" in the tables/figures.

6.2.1.3 Oncology Drug Advisory Committee Outcomes

This application was discussed at the Oncologic Drug Advisory Committee (ODAC) meeting held on June 25, 2014. The ODAC voted 2 "Yes", 11 "No" and 0 "Abstain" in response to the question "Do the safety and efficacy results from Study 19 in the g*BRCA*m population support an accelerated approval, or should consideration for marketing approval be delayed until the results of SOLO-2 are available?" Per the ODAC meeting minutes, those committee members who voted "no" expressed several concerns with the existing data. Several committee members described a preference for a demonstrated improvement in overall survival to support approval in the setting of maintenance therapy. Some of these committee members specifically cited a lack of comfort with the available data concerning outcomes of subsequent chemotherapy, particularly in the absence of supportive overall survival data. 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. Several committee members also voiced concern regarding the impact of accelerated approval of the drug on the accrual of the ongoing SOLO-2 trial, which studies a similar area of treatment and is placebo-controlled. Some committee members also cited concern with the statistical interpretation of Study 19, specifically referencing the retrospective analysis of the data.

6.2.2 Data Sources

The electronic submission for Trial 19, including protocols, statistical analysis plan, study reports, and analysis datasets are located on the network with network path: \\CDSESUB1\EVSPROD\NDA206162\0000\M5.

Updated analysis datasets for Trial 19 are located on the network with network path: \\CDSESUB1\EVSPROD\NDA206162\0020\m5\datasets\d0810c00019amend\analysis\adam\datasets.

6.3 STATISTICAL EVALUATION

Part of the text, tables, and figures presented in this review were adapted from clinical study report (CSR), CSR addendum 1, and CSR errata.

6.3.1 Data and Analysis Quality

The data and analysis quality of the submission was acceptable for the reviewer to be able to perform the statistical review.

6.3.2 Evaluation of Efficacy

6.3.2.1 Study Design and Endpoints

6.3.2.1.1 Overall Study Design

Trial 19 was a multinational, multicenter, randomized, double-blinded, placebo-controlled phase 2 study comparing the efficacy and safety of olaparib to placebo in patients with platinum-sensitive relapsed ovarian cancer who are in response to platinum-based chemotherapy.

Treatment was administered in 4 weeks cycles until objective disease progression (RECIST) or as long as in the Investigator's opinion that patients were benefiting from treatment and they did not meet any other discontinuation criteria, patients should continue with therapy to RECIST progression despite rises in CA-125. Olaparib or matching placebo were administered orally twice daily at a dose of 400mg bid on Days 1 through to 28 for all cycles. There was no maximum duration of treatment with olaparib or matching placebo. No cross over to olaparib was permitted.

Tumor assessments were to be performed every 12 weeks (3 cycles) after randomization, up to 60 weeks (15 cycles) then every 24 weeks (6 cycles) until objective disease progression by RECIST, death without evidence of progression, or withdrawal of consent. If patients fulfilled the CA-125 GCIG criteria for progression, they may have an unscheduled tumor assessment to assess radiological progression by RECIST. If the unscheduled assessment did not confirm RECIST progression, patients continued on treatment and continued to be assessed for RECIST progression per the protocol schedule. Disease progression was only determined by RECIST and not by CA-125. Tumor response in all cases was assessed according to the RECIST.

Patients were followed for survival unless they withdrew consent, regardless of whether study treatment was discontinued or delayed and/or protocol violations.

Approximately 250 patients were planned to be randomized via Interactive Voice Response System (IVRS) system in a 1:1 ratio. Randomization were stratified by time to disease progression (>6-12 months vs. >12 months, in the penultimate platinum therapy prior to

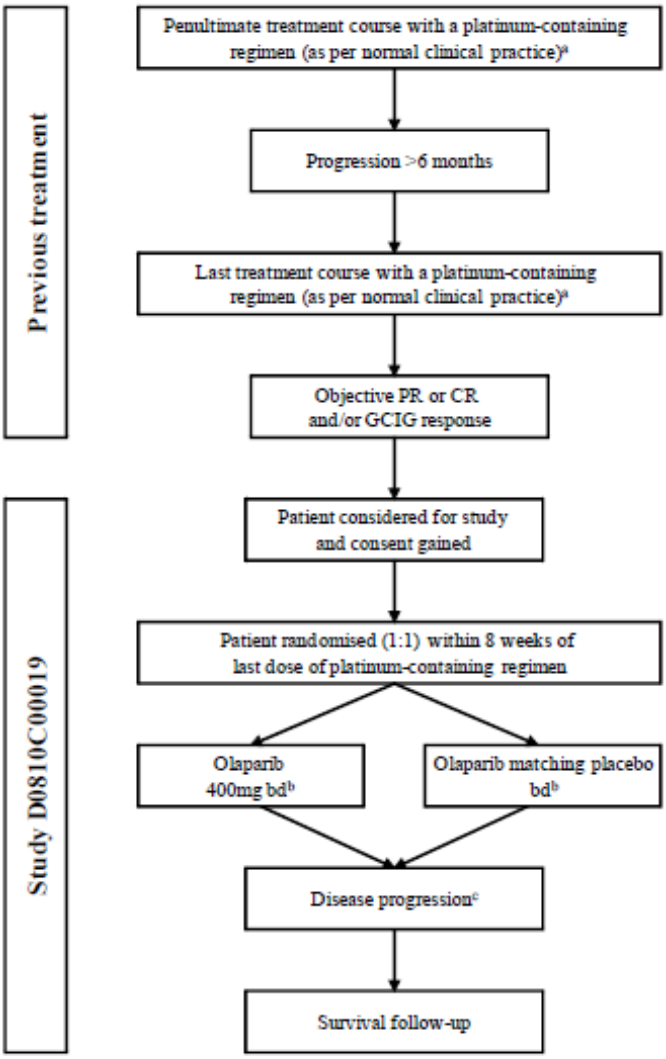
enrolment), objective response (CR vs. PR, in the last platinum therapy prior to enrolment) and whether a patient is of Jewish descent (yes vs. no).

The key inclusion criteria were:

- Patients with relapsed serous ovarian, primary peritoneal or fallopian tube cancer.
- Patients must have completed at least 2 prior courses of a platinum containing regimen.
- Patients must have disease progression greater than 6 months after the completion of their penultimate platinum regimen.
- Patients must be in partial or complete response to their last platinum regimen and patients must be treated on the study within 8 weeks of the completion of their final dose of the platinum containing regimen.
- Patients must have adequate organ function as defined by:
    - Hemoglobin $\geq$ 9.0 g/dL
    - Absolute neutrophil count $\geq$ 1.5 x 10^9/L
    - Platelet count $\geq$ 100 x 10^9/L
    - Total bilirubin $\leq$ 1.5 x institutional upper limit of normal
    - AST/ALT $\leq$ 2.5 x institutional upper limit of normal
    - Serum creatinine $\leq$ 1.5 x institutional upper limit of normal
- Patients must have an ECOG performance status $\leq$ 2

The trial design is shown in Figure 3.

Figure 3: Trial 19 flow chart of study design



[a] The 2 platinum regimens determining eligibility did not necessarily have to be sequential. For example, if a patient received topotecan between the penultimate and last platinum-based chemotherapy, they could be eligible provided the criteria specified above were satisfied.

[b] Patients could continue on olaparib or matching placebo until progression or as long as they were benefiting from treatment (and they did not meet any other discontinuation criteria). Patients were followed-up until progression regardless of whether study treatment was discontinued, delayed or if there were protocol violations.

[c] All existing and new AEs and SAEs that occurred during the 30 calendar days after last dose of study medication were followed to resolution.

bd Twice daily; CR Complete response; GCIG Gynaecologic Cancer InterGroup; PR Partial response.

[Source: Trial 19 CSR Figure 1]

6.3.2.1.2 Efficacy Endpoints

The primary endpoint **Progression free survival (PFS)** was defined as the time from randomization to the earlier date of radiological progression or death by any cause in the absence of objective progression. Disease progression was based on investigator assessment using RECIST 1.0.

Overall survival (OS) was defined as the time from randomization to the date of death from any cause. Patients who had not died at the time of analysis were censored at the last date the patient was known to be alive.

Objective response rate (ORR) was defined as the number of patients with a best overall response of CR and PR (at any time up to and including the defined analysis cut-off point) divided by the number of randomized patients with a PR and measurable disease at entry.

Best overall RECIST response (BOR) was calculated based on the overall visit responses from each RECIST assessment.

Duration of response (DoR) was measured for patients who have an overall best response of PR or CR. It is defined as the time from the assessment prior to the time point where the PR or CR was confirmed.

Time to CA-125 or RECIST progression was defined as the time from randomization to the earlier date of CA-125 or RECIST progression or death by any cause in the absence of progression.

CA-125 response: A response according to CA-125 will be considered to have occurred if there is at least a 50% reduction in CA-125 levels from the last pre-treatment sample. The response must be confirmed and maintained for at least 28 days. The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.

Tumor size was defined as the sum of the longest diameters for all target lesions.

Patient-Reported Outcomes (PRO) were assessed using the FACT-O questionnaire, which was administered at baseline, every 12 weeks up to 60 weeks and then every 24 weeks until disease progression or until the patient withdrew consent.

Reviewer's Comments:

1. *Patients were in either complete or partial response to platinum-based chemotherapy prior to randomization. There were few additional responses, which occurred on both treatment arms. No meaningful conclusions can be drawn from analysis of ORR, BOR, DoR and CA-125 response. Therefore, this review does not cover these endpoints.*
2. *The endpoints of time to CA-125 or RECIST progression and tumor size are not clinically meaningful endpoints; therefore, this review does not cover these endpoints.*

3. *PRO analyses were based on a subset of ITT population that included patients with evaluable quality of life (QoL)/Symptom endpoints at baseline.*

6.3.2.2 Statistical Methodologies

6.3.2.2.1 Sample Size Consideration

Per the SAP, Trial 19 was designed to have 80% power to detect a hazard ratio (HR) of 0.75 with a 1-sided alpha of 0.2 and 1:1 randomization ratio, assuming a median PFS of 9 months for the placebo arm and 12 months for the olaparib arm. No interim efficacy analysis of PFS was planned. It was estimated that 137 PFS events were needed for the PFS analysis, which could be expected from a total of 250 patients.

6.3.2.2.2 Interim Analyses

Per SAP (dated November 2, 2011), one interim efficacy analysis and the final analysis of OS were planned when approximately 100 deaths and 137 deaths had occurred, respectively. However, per Protocol Amendment 6 (dated October 17, 2012), the first interim analysis of OS was planned to be performed when approximately 100 deaths had occurred; a subsequent interim analysis of OS was planned to be performed when approximately 137 deaths had occurred. The final survival analysis was to be conducted when approximately 222 deaths had occurred. The alpha allocation was based on the Peto et al (1976) and Haybittle (1971) method. In the CSR, the OS interim analyses were performed per Protocol Amendment 6.

Reviewer's Comments:

1. *Per the final version of the protocol (Version 7, dated May 30, 2013), additional analyses of survival data may be performed to meet Regulatory Agency requests or the applicant planning requirements.*
2. *The planned second interim analysis and final analysis of OS were amended after the primary PFS analysis and the first interim OS analysis had been performed. Therefore, the second interim analysis and final analysis of OS were considered as post-hoc analyses for hypothesis generating since the total number of events for the final OS analysis was not pre-specified but determined after analyzing available data.*

6.3.2.2.3 Efficacy Analysis Method

The Full Analysis Set (FAS) population consisted of all randomized patients. Following the Intent-to-Treat (ITT) principle, patients were analyzed according to the treatment and stratum they were assigned to at randomization. Per protocol and SAP, this population was the primary population for evaluating efficacy results.

Efficacy Analysis Method for Progression Free Survival

The analysis for PFS 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 enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no). The treatment effect was estimated by the adjusted hazard ratio (HR) and its corresponding 80% and 95% CIs. The median OS with corresponding 95% CIs and survival curves were estimated using the Kaplan-Meier (K-M) method.

The stratified log-rank test, stratified by the same stratification factors as used for randomization, was planned as a supportive analysis.

Efficacy Analysis Method for Overall Survival

The OS analysis method was identical to that of PFS analysis.

Efficacy Analysis Method for Patient-Reported Outcomes

Analyses of PRO variables derived from the FACT-O consisted of the Trial Outcome Index (TOI), the total FACT-O score, and the FACT/NCCN Ovarian Symptom Index (FOSI). For each of the TOI, FOSI and total FACT-O endpoints, the proportion of patient with best responses of 'Improved', 'No Change' and "Worsened" were compared between treatments using logistic regression with factors as for the analysis of PFS. The time to worsening was compared between treatments for each of the TOI, FOSI and total FACT-O, using a Cox proportional hazards model using the same factors as for the analysis of PFS.

Reviewer's Comments:

1. *The primary efficacy analyses of Trial 19 were based on the ITT population.*
2. *No adjustments for multiplicity were planned for multiple analyses of the secondary endpoints. Therefore, p-values in these analyses are uninterpretable.*
3. *Per the FDA Briefing document for the ODAC meeting, in 2006, a joint FDA/ASCO/AACR public workshop was held to discuss clinical trial endpoints in ovarian cancer. Overall survival was considered to be the most significant endpoint in trials of drugs for maintenance therapy; as such treatment entails additional toxicity. An improvement in PFS also was considered to be acceptable if the treatment produces "relatively few major toxicities" (Bast, 2007). Using PFS as an endpoint in trials evaluating maintenance therapy has some pitfalls, as it is difficult to recognize the magnitude of effect needed in terms of both hazard ratio and median estimates to demonstrate direct clinical benefit to the patient. In addition, the increase in the progression-free interval may not translate into the delay in the onset of symptoms, as radiographic progression most often precedes symptomatic progression of disease.*
4. *In this review, efficacy analyses were based on the gBRCAm population since this subgroup pertains to the proposed indication which showed a large and potentially clinically meaningful magnitude of treatment effect in terms of PFS.*

5. *Subgroup analysis based on the gBRCAm population was not defined in the protocol but was prospectively defined in the SAP (dated May 28, 2011) that was finalized prior to unblinding of the data for analysis. No adjustments for multiplicity were planned for multiple subgroup comparisons. Therefore, all p-values in the analyses based on gBRCAm population are uninterpretable.*

6.3.2.3 Patient Disposition, Demographic and Baseline Characteristics

6.3.2.3.1 Determination of BRCA Status

In Trial 19, BRCA mutation testing was not mandatory for patients to participate in the study. However, *BRCA* mutation status data were obtained by three approaches, as summarized below.

1. For patients with pre-existing *BRCA* test results, the sequence variants (as determined on a blood sample) and local testing laboratory classification were captured in CRFs. This was pre-specified in the protocol. The locally assessed g*BRCA* data recorded on the CRFs were collected prior to the unblinding of the study.
2. Blood samples from patients who consented to the optional genetic analysis were retrospectively analyzed and classified at Myriad in March 2012. The analyses of blood samples at Myriad were performed post unblinding of the clinical database.
3. Archival tumor samples in patients who consented to genetic analysis were retrospectively analyzed at (b) (4) for mutations in *BRCA*1 and *BRCA*2: the sequence variants were classified, by AstraZeneca Personnel, using the Breast Cancer Information Core (BIC) database on December 6, 2012 and December 7, 2012. The analyses of tumor samples at (b) (4) were performed post unblinding of the clinical database.
4. Per the CSR, scientists who performed the analyses in Approaches 2 and 3 were blinded to the treatment assignment, the clinical outcome of the patient and the assignment of *BRCA* status (g*BRCA* and/or t*BRCA* mutations) made by any other method.

Reviewer's Comments:

The proposed indication was based on germline BRCA mutation status. Tumor BRCA mutation status was not evaluated in this review.

Table 20 shows number of patients by gBRCA mutation status in Trial 19.

Table 20: Trial 19 – Number of patients by gBRCA mutation status

Number of Patients	Olaparib n (%)	Placebo n (%)	Total n (%)
ITT	136	129	265
CRF g*BRCA* Status			
Mutant	32 (23.5)	28 (21.7)	60 (22.6)

Wild Type	18 (13.2)	20 (15.5)	38 (14.3)
Missing	86 (63.2)	81 (62.8)	167 (63.0)
Myriad g*BRCA* Status			
Mutant	38 (27.9)	27 (20.9)	65 (24.5)
Wild Type / VUS	40 (29.4)	55 (42.6)	95 (35.8)
Missing	58 (42.7)	47 (36.4)	105 (39.6)
CRF + Myriad g*BRCA* Status			
Mutant	53 (39.0)	43 (33.3)	96 (36.2)
Wild Type / VUS	50 (36.8)	64 (49.6)	114 (43.0)
Missing	33 (24.3)	22 (17.1)	55 (20.8)

VUS: variant of unknown significance
[Adapted from Trial 19 Appendix 12.1.15 BRCA Diagnostic Testing Table 4]

Table 21 shows correlation between local test results and Myriad test results for *gBRCA* mutation status in Trial 19.

Table 21: Trial 19 – gBRCA mutation status by local and Myriad tests

CRF g*BRCA* Status	Myriad g*BRCA* Status				
	Mutant	**Wild Type**	**VUS**	**Missing**	**Total**
Mutant	29 (10.9)	0	0	31 (11.7)	60 (22.6)
Wild Type	1 (0.4)	18 (6.8)	0	19 (7.2)	38 (14.3)
Missing	35 (13.2)	73 (27.5)	4 (1.5)	55 (20.8)	167 (63.0)
Total	65 (24.5)	91 (34.3)	4 (1.5)	105 (39.6)	265 (100.0)

VUS: variant of unknown significance
[Source: Trial 19 CSR Table 48]

Reviewer's comments:

1. *The gBRCAm subgroup was identified based on blood samples that were available and evaluable. Not all samples were available for retesting. gBRCAm status was not known for 21% of patients enrolled in the trial. Therefore, the randomization as executed in the ITT population does not hold in the subgroup. Randomization ensures balance in both measured and unmeasured baseline characteristics between the two treatment arms and this cannot be assumed in subgroups which are based on convenience samples.*
2. *Of the 48 patients for whom data were available from both the CRF and Myriad, there was agreement in classifying patients as mutant or wild type except for 1 patient (E1102004). Per CSR, this discrepancy was considered to result from the time lag in updating the BIC database.*
3. *A total of 53 patients were identified as having a deleterious gBRCA mutation in the olaparib arm as compared to 43 patients in the placebo arm based on local and/or Myriad tests.*

This review will focus on analyses based on g*BRCA*m subgroup with 96 patients (olaparib: N=53, placebo: N=43).

6.3.2.3.2 Patient Disposition

Table 22 presents patient disposition for the g*BRCA*m population. Disease progression was the most common reason for discontinuation from treatment for both arms, and was more frequent in the placebo arm.

Table 22: Trial 19 – Patient disposition (g*BRCA*m population)

Disposition	**Olaparib N=53 n (%)**	**Placebo N=43 n (%)**
Randomized	53	43
Receiving Treatment	10 (18.9)	2 (4.7)
Never Treated	0	0
Discontinued from Treatment	43 (81.1)	41 (95.3)
Adverse event	4 (7.5)	0
Progressive disease	29 (54.7)	36 (83.7)
Severe non-compliance	0	1 (2.3)
Withdrawal by patient	7 (13.2)	3 (7.0)
Other reasons	3 (5.7)	1 (2.3)
Ongoing Study	20 (37.7)	16 (37.2)
Discontinued from Study	33 (62.3)	27 (62.8)
Death	27 (50.9)	22 (51.2)
Lost to follow-up	1 (1.9)	3 (7.0)
Withdrawal by patient	5 (9.4)	2 (4.7)

Note : Data cut-off date November 26, 2012.

6.3.2.3.3 Demographic and Baseline Characteristics

Table 23 presents the baseline demographics.

Table 23: Trial 19 – Baseline demographics (g*BRCA*m population)

Characteristic	**Olaparib N=53**	**Placebo N=43**
Age (years)		
n	53	43
Mean (SD)	56.9 (9.8)	53.8 (10.8)
Median	56.0	55.0
(range)	38.0 – 89.0	33.0 – 84.0
Age Group, n (%)		
n	53	43
< 50	14 (26.4)	13 (30.2)

≥ 50 to < 65	29 (54.7)	24 (55.8)
≥ 65	10 (18.9)	6 (14.0)
Race		
n	53	43
White	49 (92.5)	42 (97.7)
Black and African American	2 (3.8)	0
Asian	1 (1.9)	1 (2.3)
Other	1 (1.9)	0
Region		
n	53	43
US	10 (18.9)	5 (11.6)
Non-US	43 (81.1)	38 (88.4)

Table 24 summarizes the important baseline disease characteristics in the ITT population and g*BRCA*m population.

Table 24: Trial 19 – Baseline disease characteristics (g*BRCA*m population)

Characteristic	**Olaparib N=53**	**Placebo N=43**
ECOG PS, n (%)		
n	53	43
0 (normal activity)	47 (88.7)	32 (74.4)
1 (restricted activity)	5 (9.4)	10 (23.3)
2 (In bed ≤ 50% of the time)	0	1 (2.3)
Unknown	1 (1.9)	0
Primary Tumor Location, n (%)		
n	53	43
Ovary	47 (88.7)	37 (86.1)
Fallopian tube	1 (1.9)	1 (2.3)
Primary peritoneal	5 (9.4)	5 (11.6)
Tumor Grade, n (%)		
n	53	43
G1 (Well differentiated)	0	0
G2 (Mod. differentiated)	12 (22.6)	11 (25.6)
G3 (Poorly differentiated)	39 (73.6)	31 (72.1)
G4 (Undifferentiated)	1 (1.9)	0
Gx (Unassessable)	1 (1.9)	1 (2.3)
Number of Prior Chemotherapy Regimens, n (%)		
n	53	43
≤ 3	42 (79.2)	31 (72.1)
> 3	11 (20.8)	12 (27.9)
gBRCA Mutation Type, n (%)		
n	53	43
BRCA1	40 (75.5)	30 (69.8)
BRCA2	13 (24.5)	13 (30.2)
Median Time From Most Recent	195	189

Disease Progression to Randomization (days)		
Median Time From Completion of Final Platinum Chemotherapy to Randomization (days)	40	43

Reviewer's comments:

1. *Baseline demographics appear to be balanced between the two treatment arms except ECOG performance status in the gBRCAm population. More patients in the olaparib arm have ECOG performance status "0 (normal activity)" compared to those in the placebo arm.*
2. *A sensitivity analyses for PFS adjusting for imbalanced ECOG performance status was performed by this reviewer to evaluate the robustness of the primary PFS analysis. See Section 6.3.2.4.1 for more details.*

6.3.2.3.4 Stratification Discrepancies

Per the CSR, the stratification factors from the source-data-verified CRF data were used in all efficacy analyses.

Table 25 summarizes the IVRS/IWRS stratification factors based on CRF. An imbalance in ethnic was observed between the two treatment arms.

Table 25: Trial 19 – Stratification factors at randomization based on CRF (g*BRCA*m population)

	Olaparib N=53	**Placebo N=43**
Platinum Sensitivity		
n	53	43
>6 - ≤12 months	22 (41.5)	21 (48.8)
>12 months	31 (58.5)	22 (51.2)
Objective Response		
n	53	43
CR	29 (54.7)	22 (51.2)
PR	24 (45.3)	21 (48.8)
Ethnic: Jewish Descent		
n	53	43
Yes	10 (18.9)	12 (27.9)
Ashkenezi Jewish	10 (18.9)	9 (20.9)
Mizrahim Jewish	0	0
Sephardic Jewish	0	1 (2.3)
Other	0	2 (4.7)
Missing	0	0
No	43 (81.1)	31 (72.1)

Stratification assignment was performed using an IVRS. It was noted that there were 34 patients (35.4%) in the g*BRCA*m population with inconsistent stratification factor data from IVRS and stratification factor data from the electronic case report forms (eCRF) (Table 26).

Table 26: Trial 19 – Discrepancies between IVRS randomization stratification factors and eCRF stratification factors (g*BRCA*m population)

	Olaparib N=53	Placebo N=43
Total Number of Subjects with Discrepancies	21 (39.6)	13 (30.2)
For Each Stratification Factor		
Platinum Sensitivity	12 (22.6)	4 (9.3)
Objective Response	8 (15.1)	11 (25.6)
Ethnic: Jewish Descent	2 (3.8)	0

Table 27 presents the distribution of patients by stratification factors from both IVRS and eCRF.

Table 27: Trial 19 – Stratification factors at randomization from CRF and IVRS (g*BRCA*m population)

Stratum	Platinum Sensitivity	Objective Response	Ethnic: Jewish Descent	Olaparib N=53	Placebo N=43
			CRF		
1	>6 - ≤12 m	CR	Yes	2 (3.8)	3 (7.0)
2	>6 - ≤12 m	CR	No	9 (17.0)	9 (20.9)
3	>6 - ≤12 m	PR	Yes	2 (3.8)	1 (2.3)
4	>6 - ≤12 m	PR	No	9 (17.0)	8 (18.6)
5	>12 m	CR	Yes	5 (9.4)	2 (4.7)
6	>12 m	CR	No	13 (24.5)	8 (18.6)
7	>12 m	PR	Yes	1 (1.9)	6 (14.0)
8	>12 m	PR	No	12 (22.6)	6 (14.0)
			IVRS		
1	>6 - ≤12 m	CR	Yes	2 (3.8)	4 (9.3)
2	>6 - ≤12 m	CR	No	9 (17.0)	5 (11.6)
3	>6 - ≤12 m	PR	Yes	1 (1.9)	2 (4.7)
4	>6 - ≤12 m	PR	No	14 (26.4)	10 (23.3)
5	>12 m	CR	Yes	3 (5.7)	3 (7.0)
6	>12 m	CR	No	13 (24.5)	9 (20.9)
7	>12 m	PR	Yes	2 (3.8)	3 (7.0)
8	>12 m	PR	No	9 (17.0)	7 (16.3)

Reviewer's comments:

1. *There were 34 (35.6%) patient with inconsistent stratification data between IVRS and CRFs.*

2. *As shown in Table 12, the distribution of patients was balanced between the two treatment arms by stratification factors from both sources. The only exception is that based on the CRF data, among patients with platinum sensitivity > 12 months and PR responses, more patients in the placebo arm are Jewish compare to those in the olaparib arm. However, the stratification factors from CRF data were used in all efficacy analyses, and the efficacy analyses in the gBRCAm population used adjusted Cox proportional hazards model with Jewish descent as one of the adjusted factors, therefore, this imbalance has been adjusted in the primary efficacy analysis.*
3. *This reviewer performed a sensitivity analysis based on stratification data from IVRS. The improvement seen in primary PFS analysis is maintained when IVRS-based stratification values were used. See Section 6.3.2.4.1 for more details.*

6.3.2.3.5 Protocol Deviations

Table 28 shows the summary of major protocol violations and deviations.

Table 28: Trial 19 – Summary of major protocol violations and deviations (g*BRCA*m population)

Number of Subjects	**Olaparib N=53 n (%)**	**Placebo N=43 n (%)**
With At Least 1 Important Protocol Deviation	30 (57)	23 (53)
IVRS mis-stratification	21 (40)	13 (30)
With At Least 1 Important Protocol Deviation Other than IVRS	14 (26)	17 (40)
Unable to confirm adequate organ and bone marrow function	0	2 (5)
Not treated on study within 8 weeks of completion of their final dose of platinum-containing regimen	1 (2)	2 (5)
Baseline scan >28 days before first dose	1 (2)	4 (9)
Scans performed outside of the scheduled window on more than two occasions	6 (11)	6 (14)
Disease progression outside of RECIST criteria	1 (2)	2 (5)
Failed to comply with study treatment	2 (4)	1 (2)
Mis-stratification	1 (2)	0
Disallowed concomitant medication	2 (4)	0
Failed to demonstrate sensitivity to penultimate platinum	1 (2)	1 (2)
Issue with version or timing of consent or biomarker consent	2 (4)	3 (7)

Reviewer's comment:

1. *For patients with at least 1 important protocol deviation other than IVRS, the most common major protocol deviations were for patients with RECIST scans performed outside of the scheduled window on more than two occasions.*
2. *The major protocol violations were comparable between the two treatment arms.*

6.3.2.3.6 Post-Study Treatment Anti-Cancer Therapy

As of the data cut-off date for OS (November 26, 2012), subsequent anti-cancer therapy was received by 30 (57%) patients in the olaparib arm and 37 (86%) in the placebo arm in the g*BRCA*m population (Table 29). Cross-over during the study was not permitted.

Table 29: Trial 19 – Summary of subsequent anti-cancer therapy (g*BRCA*m population)

	Olaparib N=53 n (%)	**Placebo N=43 n (%)**
Any subsequent therapy	30 (57)	37 (86)
Type of therapy		
Chemotherapy	28 (53)	35 (81)
Immuno/Hormonal therapy	2 (4)	3 (7)
Other	3(6)	14 (33)
Missing	0	1 (2)

6.3.2.4 Results and Conclusions

6.3.2.4.1 Primary Efficacy Endpoint – Progression Free Survival

Table 30 presents the applicant's efficacy analysis for PFS for the g*BRCA*m population. There were a total of 50 PFS events. The olaparib demonstrated a difference in PFS compared with the placebo based on the adjusted Cox proportional hazards model with a nominal p-value <0.0001. The median PFS was 11.2 months (95% CI: 8.3, NE) for the olaparib arm and 4.1 months (95% CI: 2.8, 5.1) for the placebo arm. The stratified Cox HR was 0.17 with 95% CI (0.09, 0.32).

Table 30: Trial 19 – Progression free survival results (g*BRCA*m population)

	Olaparib (N=53)	**Placebo (N=43)**
Subjects randomized	53	43
Events	17 (32%)	33 (77%)
Censored	36 (68%)	10 (23%)
PFS (months)	11.2	4.1
Median (95% CI)	(8.3, NE)	(2.8, 5.1)
p-value [a]	<0.0001[b]	
Hazard ratio (95% CI) [a]	0.17 (0.09, 0.32)	

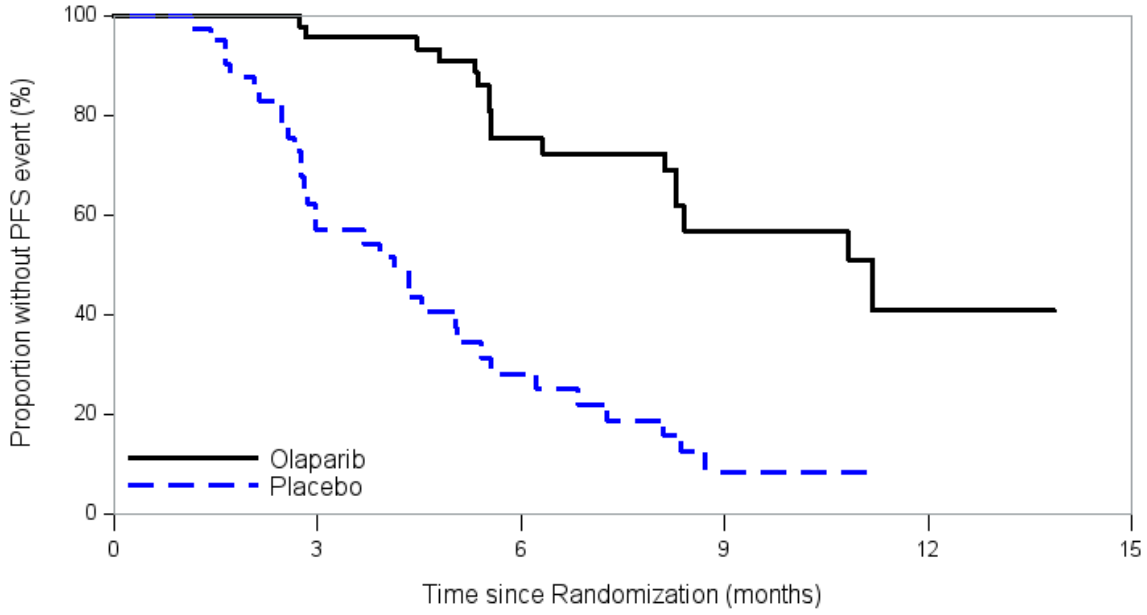
[a] p-value and HR are from a Cox proportional hazards model with factors for treatment (olaparib vs. placebo), time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no). Hazard ratio < 1 favors olaparib.

[b] This is a nominal p-value.

Note: data cut-off date June 30, 2010.

Figure 4 present the Kaplan-Meier (K-M) curves for PFS for g*BRCA*m population.

Figure 4: Trial 19 – Kaplan-Meier survival curves for progression free survival (g*BRCA*m population)



Reviewer's comment:

At the time of the final PFS analysis, using the inverse Kaplan-Meier method, the median follow-up time of the gBRCAm population was 8.3 months, based on investigator assessment.

Applicant's Sensitivity Analyses of Progression Free Survival

Applicant's Sensitivity Analysis 1: Evaluation-time bias

The analysis used an interval-censored approach according to the methodology of Sun and Zhao (Sun et al 2005). The methodology used generalized log-rank tests for interval-censored failure time data. The p-value for treatment group comparisons was calculated using the above methodology. The associated hazard ratio was estimated from a Cox model that analyses the midpoint of the assessment interval.

Applicant's Sensitivity Analysis 2: Attrition bias

Attrition bias was assessed by repeating the primary PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumor assessments were included. In addition, patients who take subsequent therapy prior to progression or death were censored at their last evaluable assessment prior to taking the subsequent therapy.

Applicant's Sensitivity Analysis 3: Independent Central Review (IRC)

A retrospective blinded independent central review of scans was performed as a sensitivity analysis to confirm the robustness of the original primary PFS analysis.

The discordance rate between IRC and INV on the type of PFS event was 23% in both the olaparib arm and the placebo arm, as presented in Table 32.

If considering both the event type and the timing of censoring/event, the discordance rate was 42% in the olaparib arm and 37% in the placebo arm (Table 32). The median timing difference between IRC and INV was 48 days among patients with discordant PFS times.

Table 31: Trial 19 – Comparison of progression based on INV and IRC assessments (g*BRCA*m population)

	Olaparib (N=53)	**Placebo (N=43)**
Overall Agreement, n (%)	41 (77)	33 (77)
Progression by INV, n (%)	17 (32)	33 (77)
PD by IRC, n (%)	10 (19)	25 (58)
Censored by IRC, n (%)	7 (13)	8 (19)
Censored by INV, n (%)	36 (68)	10 (23)
Censored by IRC, n (%)	31 (58)	8 (19)
PD by IRC, n (%)	5 (9)	1 (2)
Missing by IRC, n(%)	0	1 (2)

Table 32: Trial 19 – Discordance between INV and IRC assessments, including event type and timing (g*BRCA*m population)

Olaparib (N=53)			**Placebo (N=43)**		
Type	**Timing**	**Total**	**Type**	**Timing**	**Total**
23%	34%	42%	23%	28%	37%

Table 33 presents the sensitivity analysis of PFS performed by the Applicant.

Table 33: Trial 19 – Sensitivity analysis of progression free survival (g*BRCA*m popultion)

Sensitivity Analysis	**HR**	**95% CI**
1. Evaluation-time bias	0.20	(0.11, 0.36)
2. Attrition bias	0.17	(0.09, 0.31)
3. Independent Central Review (IRC)	0.25	(0.13, 0.49)

Note: data cut-off date June 30, 2010.

Reviewer's comments:

1. *Olaparib demonstrated superior PFS over placebo in the gBRCAm population.*
2. *The results from the sensitivity analyses conducted by the Applicant are consistent with the results from the primary analysis of PFS in the gBRCAm population.*
3. *These sensitivity analyses are exploratory.*

FDA's Sensitivity Analyses

Multiple sensitivity analyses were conducted by this reviewer to evaluate the robustness of the primary PFS analysis in the g*BRCA*m population. The results are summarized in Table 34.

Table 34: Trial 19 – FDA's Sensitivity analyses of progression free survival (g*BRCA*m Population)

Sensitivity Analysis	HR	95% CI
PFS (INV)		
Adjusted Cox hazards model	0.17	(0.09, 0.32)
Stratified log-rank test [a]	0.11	(0.05, 0.26)
Unstratified log-rank test	0.20	(0.11, 0.37)
Adjusted for imbalanced ECOG PS [b]	0.16	(0.08, 0.31)
Adjusted Cox model using IVRS stratification factors	0.18	(0.10, 0.34)
Stratified log-rank test using IVRS stratification factor	0.13	(0.05, 0.29)
PFS (IRC)		
Adjusted Cox hazards model	0.25	(0.13, 0.49)
Stratified log-rank test [a]	0.30	(0.15, 0.61)
Unstratified log-rank test	0.28	(0.15, 0.54)

[a] HR is from a stratified Cox proportional hazards model with stratification factors of time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no). Hazard ratio < 1 favors olaparib.

[b] HR is from 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 enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), Jewish descent (yes or no), and ECOG PS group (0 vs. ≥1). Hazard ratio < 1 favors olaparib.

Note: data cut-off date June 30, 2010.

Reviewer's comments:

1. *Results based on stratified Cox hazards model should be interpreted with caution due to sparse data in some of the strata.*
2. *The results of these sensitivity analyses are consistent with the primary efficacy findings in the gBRCAm population.*

FDA's Sensitivity Analyses to Assess the Reliability of Estimate of Treatment Effect based on a Small Sample Size

The primary PFS analysis in the g*BRCA*m population was based on 50 PFS events from 96 patients. The treatment effect size is uncertain due to this small sample size. This reviewer conducted a sensitivity analysis to assess the reliability of the estimate of treatment effect. In this sensitivity analysis, the outcome of patients was artificially altered for four patients only using the following approach: 1) two patients in the olaparib arm who were censored were randomly selected and were now imputed with progression events; 2) two patients in the placebo arm who had progression events were randomly selected and were now censored. The median PFS for the two treatment arms were compared using the imputed data. Several imputed data were assessed based on different sets of randomly selected four patients. One of these imputed data shows that the median PFS improvement drops from 7 months to 4 months (Table 35).

Table 35: Trial 19 – FDA's sensitivity analyses of progression free survival to assess the reliability of estimate of treatment effect (g*BRCA*m population)

	Median PFS (months) Olaparib (N=53)	Median PFS (months) Placebo (N=43)
Primary analysis	11.2 (95% CI: 8.3 – NE)	4.1 (95% CI: 2.8 – 5.1)
Sensitivity analysis	8.4 (95% CI: 8.3 – NE)	4.3 (95% CI: 2.8 – 5.6)

Reviewer's comments:

This sensitivity analysis raises the concerns regarding the reproducibility of the magnitude of treatment effect in a larger randomized trial.

6.3.2.4.2 Secondary Efficacy Endpoint – Overall Survival

Table 36 presents the applicant's efficacy analysis for OS.

Table 36: Trial 19 – Second interim analysis of overall survival (g*BRCA*m population)

	Olaparib (N=53)	Placebo (N=43)
Subjects randomized	53	43
Deaths	27 (50.9)	22 (51.2)
Censored	26 (49.1)	21 (48.8)
OS (months)	32.9	30.2
Median (95% CI)	(28.4, NE)	(18.3, NE)
p-value [a]	0.58 [b]	
Hazard ratio (95% CI) [a]	0.85 (0.48, 1.51)	

[a] p-value and HR are from 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 enrolment),

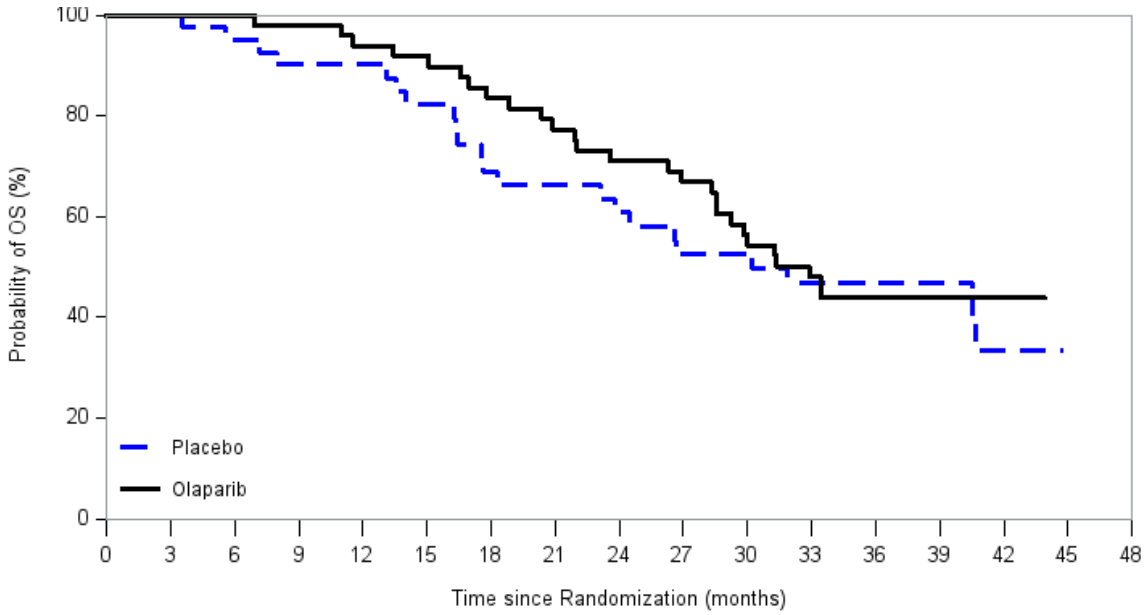
objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no). Hazard ratio < 1 favors olaparib.

[b] This is a nominal p-value.

Note: data cut-off date November 26, 2012.

Figure 5 presents the Kaplan-Meier (K-M) curves for OS in the g*BRCA*m population.

Figure 5: Trial 19 – Kaplan-Meier survival curves for overall survival (g*BRCA*m population)



Reviewer's comments:

1. *The second interim analysis of OS shows that there is no improvement of OS with treatment of olaparib compared to placebo.*
2. *At the time of the primary PFS analysis, there were insufficient events to support OS analysis.*
3. *The first interim analysis of OS with data cut-off date of December 2011 was performed in December 2011 with 101 deaths occurred at the time analysis. HR was 0.94 (95% CI: 0.63, 1.39). Median OS was 29.7 months for olaparib arm and 29.9 months for placebo arm.*

6.3.2.4.3 Other Secondary Endpoints

The PRO analysis results indicate that there were no differences between treatment groups with respect to the TOI, FOSI, and total FACT-O score.

Per the ODAC Briefing Document, the PRO analyses must be interpreted with caution, as an "improved" score in any of the PRO variables may be due to recovery from the recently completed chemotherapy regimen and may not be a function of treatment with placebo or olaparib. In addition, the lack of an improvement in these PRO measures does not sufficiently rule out a possible decrement in patient's health-related quality of life, as the adverse reaction profile of olaparib therapy may not be sufficiently captured through these instruments.

6.3.2.4.4 Key Results in the ITT population

Table 37 presents the applicant's efficacy analysis for PFS for the ITT population. There were a total of 154 PFS events. The olaparib demonstrated a statistically significant difference in PFS compared with the placebo based on the adjusted Cox proportional hazards model with p-value <0.0001. The median PFS was 8.4 months (95% CI: 7.4, 11.5) for the olaparib arm and 4.8 months (95% CI: 4.0, 5.5) for the placebo arm. The stratified Cox HR was 0.35 with 95% CI (0.25, 0.49).

Table 37: Trial 19 – Progression free survival results (ITT population)

	Olaparib (N=136)	**Placebo (N=129)**
Subjects randomized	136	129
Events	60 (44%)	94 (73%)
Censored	76 (56%)	35 (27%)
PFS (months)	8.4	4.8
Median (95% CI)	(7.4, 11.5)	(4.0, 5.5)
p-value [a]	<0.0001	
Hazard ratio (95% CI) [a]	0.35 (0.25, 0.49)	

[a] p-value and HR are from 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 enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no). Hazard ratio < 1 favors olaparib.

Note: data cut-off date June 30, 2010.

[*Adapted from Trial 19 Clinical Study Report Addendum 1 Tables 4 and 5*]

Figure 6 present the Kaplan-Meier (K-M) curves for PFS in the ITT population.

Figure 6: Trial 19 – Kaplan-Meier survival curves for progression free survival (ITT population)

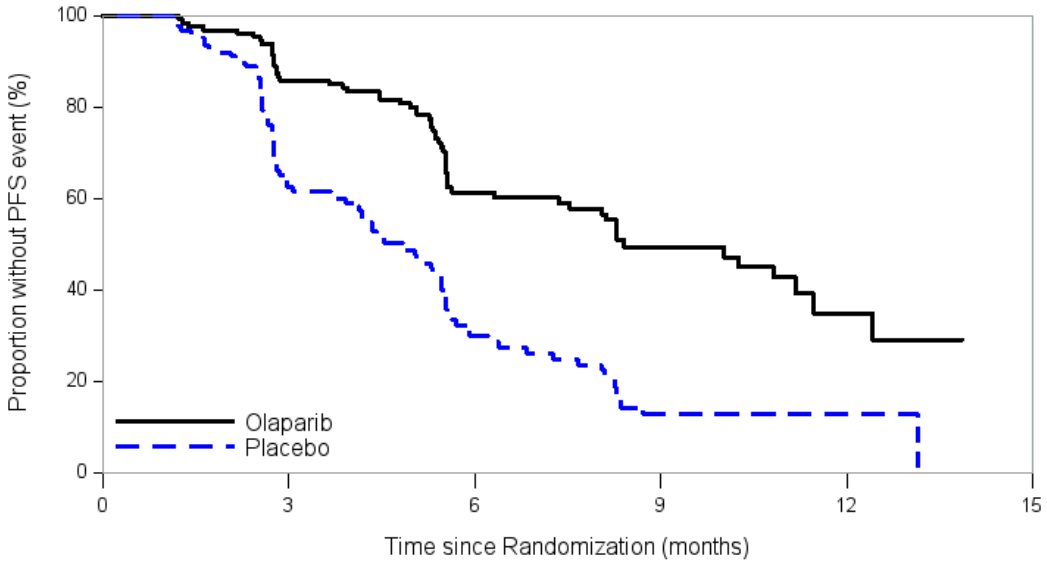


Table 38 presents the applicant's efficacy analysis for OS in the ITT population.

Table 38: Trial 19 – Second interim analyses of overall survival (ITT population)

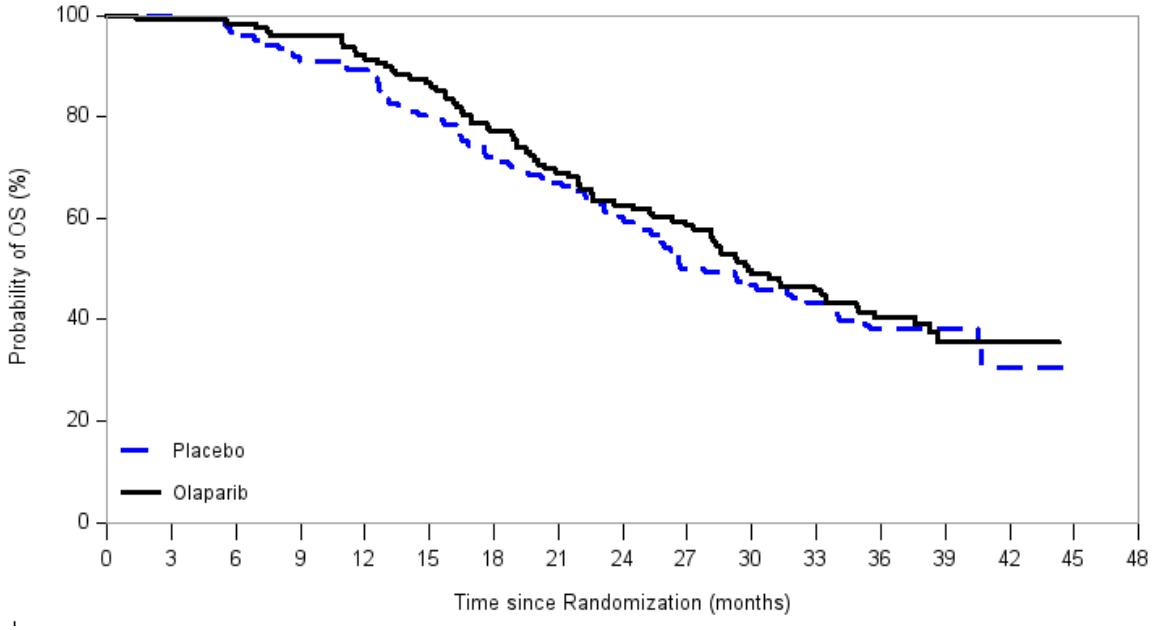
	Olaparib (N=136)	**Placebo (N=129)**
Subjects randomized	136	129
Deaths	77 (57%)	77 (60%)
Censored	59 (43%)	52 (40%)
OS (months)	29.8	27.8
Median (95% CI)	(26.9, 35.7)	(24.4, 34.0)
p-value [a]	0.44	
Hazard ratio (95% CI) [a]	0.88 (0.64, 1.21)	

[a] p-value and HR are from 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 enrolment), objective response (CR or PR, in the last platinum therapy prior to enrolment), and Jewish descent (yes or no). Hazard ratio < 1 favors olaparib.

Note: data cut-off date November 26, 2012.

Figure 7 presents the Kaplan-Meier (K-M) curves for OS in the ITT population.

Figure 7: Trial 19 – Kaplan-Meier survival curves for overall survival (ITT population)



6.3.2.4.5 Conclusions for Efficacy

The data and analyses from Trial 19 demonstrated that olaparib had a statistically significant improvement in the primary endpoint PFS when compared with placebo in the ITT population. The p-value for PFS comparison was <0.0001 based on both log-rank test and adjusted Cox proportional hazards model. The median PFS was 8.4 (95% CI: 7.4, 11.5) months for olaparib and 4.8 (95% CI: 4.0, 5.5) months for placebo. The adjusted Cox proportional hazard ratio was 0.35 (95% CI: 0.25, 0.49).

The data and analyses from Trial 19 also demonstrated that olaparib had an improvement in the primary endpoint PFS when compared with placebo in the g*BRCA*m population. The median PFS was 11.2 (95% CI: 8.3, NE) months for olaparib and 4.1 (95% CI: 2.8, 5.1) months for placebo. The adjusted Cox proportional hazard ratio was 0.17 (95% CI: 0.09, 0.32).

6.3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

6.3.4 Benefit-Risk Assessment

The olaparib arm demonstrated an improvement in PFS compared with the placebo arm in the gBRCAm population. However, the gBRCAm subgroup analysis is a pre-specified subgroup analysis with retrospectively identified subpopulation. No adjustment of multiplicity was made

for the gBRCAm subgroup analysis; therefore, the p-value in this subgroup analysis is not interpretable.

Please refer to clinical review of this application for a benefit-risk evaluation.

6.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The proposed indication was based on the g*BRCA*m subgroup with a small sample size (50 PFS events). Further sub-subgroup analyses based on the g*BRCA*m subgroup was not conducted due to the small sample size.

6.5 SUMMARY AND CONCLUSIONS

The applicant is seeking an accelerated approval of olaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer with g*BRCA*m who are in response to platinum-based chemotherapy based on the pivotal randomized, double-blinded, placebo-controlled phase 2 Trial 19.

6.5.1 Statistical Issues

The following statistical issues were identified:

1. The gBRCAm subgroup was identified based on blood samples that were available and evaluable. Not all samples were available for retesting. gBRCAm status was not known for 21% of patients enrolled in the trial. Therefore, the randomization as executed in the ITT population does not hold in the gBRCAm subgroup. Randomization ensures balance in both measured and unmeasured baseline characteristics between the two treatment arms and this cannot be assumed in subgroups which are based on convenience samples.
2. While a positive result in ITT allows for further subgroup analysis, the gBRCAm subgroup was one of 12 subgroups that were pre-specified in the SAP. No adjustments for multiplicity were planned for these multiple subgroup comparisons as well as multiple analyses for the secondary endpoints. Therefore, the p-values from these analyses are not interpretable.
3. The primary PFS analysis was based on 50 PFS events from 96 gBRCAm patients. The sample size is small; therefore, the estimate of magnitude of treatment effect may be unstable.
4. The confirmatory trial of SOLO2 largely replicates Trial 19 except that only gBRCAm patients will be recruited. Study SOLO2 was designed to have sufficient precision of the estimated hazard ratio; therefore, it may be overpowered to show a statistically significant but not clinically meaningful difference in PFS between olaparib and placebo.

6.5.2 Collective Evidence

The data and analyses from Trial 19 demonstrated that olaparib had a statistically significant improvement in the primary endpoint PFS when compared with placebo in the ITT population. The p-value for PFS comparison was <0.0001 based on both log-rank test and adjusted Cox proportional hazards model. The median PFS was 8.4 (95% CI: 7.4, 11.5) months for olaparib and 4.8 (95% CI: 4.0, 5.5) months for placebo. The adjusted Cox proportional hazard ratio was 0.35 (95% CI: 0.25, 0.49).

The data and analyses from Trial 19 demonstrated that the olaparib arm had an improvement in the primary endpoint PFS when compared with placebo in the g*BRCA*m population. The median PFS was 11.2 (95% CI: 8.3, NE) months for olaparib and 4.1 (95% CI: 2.8, 5.1) months for placebo. The adjusted Cox proportional hazard ratio was 0.17 (95% CI: 0.09, 0.32).

The potential confirmatory study, SOLO2, is currently ongoing. Study SOLO2 is a randomized, double-blind, placebo-controlled two-arm phase 3 study of olaparib maintenance monotherapy in platinum sensitive relapsed *BRCA* mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy. The primary endpoint of the trial SOLO2 was progression free survival (PFS) determined by central review of RECIST data. Positive results from the SOLO2 trial in the maintenance setting would confirm the benefit of olaparib in the maintenance disease setting.

6.5.3 Conclusions

Trial 19 shows that olaparib demonstrated an improvement in the primary endpoint PFS in both ITT population and g*BRCA*m population. However, based on the Oncology Drug Advisory Committee votes, the results from Trial 19 in the platinum-sensitive maintenance setting do not support granting accelerated approval due to concerns with the statistical issues, the occurrence and duration of adverse effects, including rare occurrence of secondary cancers, and the impact of accelerated approval of the drug on the accrual of the ongoing SOLO-2 trial.

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/s/

HUI ZHANG
11/21/2014

SHENGHUI TANG
11/21/2014

THOMAS E GWISE
11/21/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206162 **Applicant: AstraZeneca** **Stamp Date: 2/3/2014**

Drug Name: Olaparib **NDA/BLA Type: Original NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			1. All patients were female. 2. Racial and geriatric subgroups were investigated in pivotal study 19, but not in supportive study 41.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.		X		Proposed indication is a subgroup determined retrospectively.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			In pivotoal study 19: 1. No interim

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

				efficacy analysis for primary endpoint PFS 2. Pre-specified interim efficacy analyses for secondary endpoint OS
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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/s/

HUI ZHANG
03/07/2014

SHENGHUI TANG
03/07/2014