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RESEARCH**

*APPLICATION NUMBER:*

**206162Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206162
Priority or Standard	Priority
Submit Date(s)	2/3/14
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Division / Office	DOP1/OHOP
Reviewer Name(s)	Amy McKee CDTL Geoffrey Kim (efficacy) Gwynn Ison (safety)
Review Completion Date	12/2/14
Established Name	Olaparib/AZD2281
(Proposed) Trade Name	Lynparza™
Therapeutic Class	PARP inhibitor
Applicant	AstraZeneca
Formulation(s)	Oral
Dosing Regimen	400 mg BID
Indication(s)	Monotherapy in patients with deleterious or suspected deleterious germline <i>BRCA</i> mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

Template Version: March 6, 2009

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

Based on the findings described in this clinical review of the new drug application for olaparib (NDA 206162), the reviewers recommend accelerated approval of olaparib for the following indication:

Lynparza is a poly ADP ribose polymerase (PARP) inhibitor indicated 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 indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

### 1.2 Risk Benefit Assessment

The recommendation for approval is based on the single, open-label, non-randomized trial in which olaparib demonstrated a robust overall response rate with a clinically meaningful duration of response in patients with deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*)-associated ovarian cancer who had received three or more prior lines of chemotherapy. This trial enrolled 193 patients with *gBRCAm*-associated ovarian cancer, including 137 patients who received three or more lines of prior chemotherapy and with measurable disease who were treated at a dose of 400 mg PO BID. The overall response rate in the patients with measurable disease was 34% (95% CI: 26, 42) with a median duration of response of 7.9 months. Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML) has been confirmed in six out of 298 (2%) patients with *gBRCAm*-associated cancer enrolled in this study and represents the key safety concern regarding olaparib therapy. There exists the potential for an increased risk for the development of MDS/AML due to numerous insults to the DNA damage repair pathway. Other safety considerations include the risk of non-infectious pneumonitis and the overall tolerability due to prolonged, low-grade gastrointestinal disturbances, fatigue, and anemia.

Heavily pre-treated ovarian cancer, defined here as three or more prior lines of chemotherapy, is a life-threatening condition for which there are numerous available therapies, but an exhaustive review of the literature reveals limited data regarding the activity of these agents in this setting. Given all available data, the estimate of the response rates of these agents in the *gBRCAm* population in this heavily pre-treated setting is approximately 10-20%. This estimate will vary from individual to individual primarily based on the progression-free interval of the last

chemotherapy regimen. It is reasonable to expect that after three prior lines of chemotherapy, patients will have received treatment with a platinum-taxane combination, an anthracycline, and, depending on their platinum-sensitivity status, retreatment with a platinum-based doublet, single agent platinum, or another agent such as topotecan. Recently, bevacizumab was approved in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of patients with platinum-resistant ovarian cancer who have received two or fewer lines of chemotherapy.

The observed response rate of 34% in the patients with gBRCAm-associated ovarian cancer who have received three lines of chemotherapy is better than what would be expected of available therapy and represents an improvement on a surrogate endpoint that is reasonably likely to predict clinical benefit. The most concerning adverse reaction associated with olaparib therapy is the development of MDS/AML, but the incidence of MDS/AML does not appear to be increased over other agents that would be prescribed in this setting, such as alkylating agents or etoposide. In addition, the package insert contains instructions to prescribers regarding the need to monitor patients for the development of these conditions. Further data regarding the incidence of MDS/AML in the gBRCAm ovarian cancer population will be submitted as part of a post marketing requirement. Other toxicities, such as hematological and gastrointestinal toxicities, can be managed through dose interruptions and dose reductions.

This was a complex review due to numerous factors that arose during olaparib development. The following table summarizes key interdisciplinary review issues that arose and how they were resolved.

Table 1: Major Review Issues

<b>Issue</b>	<b>Discipline</b>	<b>Resolution</b>
Loss of randomization due to a post-analysis identification of the gBRCAm population of Study 19.	Clinical, Statistical	Study 19 was not deemed to be an acceptable trial to support the maintenance indication.
Estimation of the treatment effect of olaparib therapy due to flaws in the design of Study 19.	Clinical, Statistical	Overall response rate from Study 42 was used to support approval. Design flaws have been corrected in the SOLO-2 trial.
Magnitude of PFS benefit needed to support a maintenance indication.	Clinical, Statistical	Study 19 was not deemed to be an acceptable trial to support the maintenance indication, and the estimation of treatment effect was not reliable. This issue will be readdressed after the results of SOLO-2 are available.
Toxicity of therapy in the maintenance setting.	Clinical	Olaparib is not being approved for the maintenance setting. The intended patient population is in need of therapy

		and the risks appear comparable, if not favorable, to the risks of therapy associated with standard treatment in this setting.
Risk of MDS/AML	Clinical	Post-marketing requirement of MDS/AML reporting is contingent upon approval. This issue will also be addressed in the randomized trials.
Approval of a different formulation than that being studied in potential confirmatory trials.	CMC, Clinical Pharmacology, Clinical	The capsule formulation that is being approved meets approval standards. Outstanding pharmacology issues will be addressed as post-marketing requirements. If confirmatory trials support conversion to regular approval, the applicant has a transition plan in place to continue supply for patients already taking the capsule formulation and introducing the tablet formulation into the market.
Response rate of 34% reasonably likely to predict clinical benefit	All disciplines	Applicant is conducting 2 potential confirmatory trials: SOLO-2: randomized, placebo controlled trial in the maintenance gBRCAm, platinum sensitive setting. Study 10: Randomized, open-label trial of olaparib against investigators choice of chemotherapy in patients who have received 2 or more lines of platinum-based chemotherapy for gBRCAm associated ovarian cancer.
Accelerated approval will harm accrual to potential confirmatory trials	Clinical	SOLO-2 is fully accrued. Study 10 is enrolling patients in an earlier stage than the indicated population.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

## 1.4 Recommendations for Postmarket Requirements and Commitments

### Clinical Post Marketing Requirements:

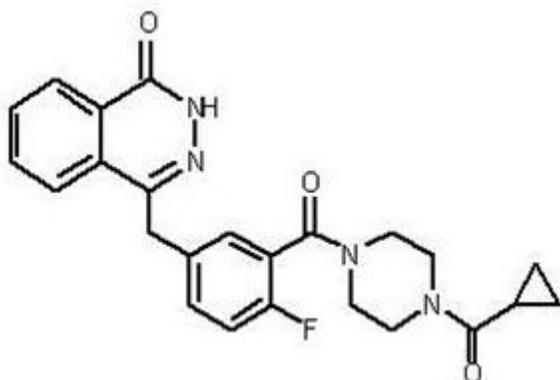
1. Submit the results of progression free survival (PFS) and overall survival (OS) analyses from study D0818C00002, SOLO-2, the ongoing randomized double-blind, placebo-controlled, multi-center trial to assess the efficacy of olaparib maintenance monotherapy in relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and / or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations (documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)) who have responded following platinum based chemotherapy.
2. Submit the results of progression free survival (PFS) and overall survival (OS) analyses from study D0816C00010, a randomized trial establishing the superiority of olaparib over physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline *BRCA1/2* mutations.
3. Provide annual summaries of all cases of Acute Myelogenous Leukemia / Myelodysplastic Syndrome identified in patients treated with Lynparza (olaparib). These reports should summarize all cases identified up until that reporting date (new cases and those reported in previous years), and should include patients treated with Lynparza on clinical trials and outside of clinical trials (including spontaneous safety reports).

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Olaparib is an inhibitor of the mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme.

The chemical name is 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one and has the following chemical structure:



The empirical molecular formula for Lynparza is  $C_{24}H_{23}FN_4O_3$ , and the relative molecular mass is 434.46.

Olaparib is a crystalline solid, is non-chiral and shows pH-independent low solubility of approximately 0.1 mg/mL across the physiological pH range.

Lynparza is available in 50 mg capsules for oral administration.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved agents for the treatment of ovarian cancer with deleterious gBRCA mutations who have received more than three prior chemotherapy regimens. Agents that are approved for the treatment of ovarian cancer are depicted in the table below:

Table 2: FDA-Approved Agents for Ovarian Cancer

Drug	Year Approved	Response Rate <sup>1</sup>	Line of Therapy
Cisplatin	1978	NA	NA
Carboplatin	1991	NA	NA
Paclitaxel	1992	15-20%	2 <sup>nd</sup>
Pegylated Liposomal Doxorubicin <sup>2</sup>	1999	18%	2 <sup>nd</sup> -6 <sup>th</sup>
Topotecan	1996	21%	2 <sup>nd</sup>
Altretamine	1990	18%	NA
Gemcitabine (plus Carboplatin)	2006	47%	2 <sup>nd</sup>
Cyclophosphamide	Pre-1984	NA	NA
Melphalan	Pre-1984	NA	NA
Avastin (plus paclitaxel)	2014	53%	2 <sup>nd</sup> -3 <sup>rd</sup>

1 – Data taken from the Product Package Insert unless otherwise noted

2 – Data taken from Study 12 in patients with gBRCAm associated ovarian cancer treated with PLD

Other treatment options that are not specifically indicated for, but are commonly used for the treatment of patients with heavily pretreated ovarian cancer are depicted in the table below:

Table 3: Other Commonly Used Agents for Ovarian Cancer

<b>Drug</b>	<b>Reference</b>	<b>Response Rate</b>	<b>Line of Therapy</b>
Docetaxel	Rose 2003	22%	2 <sup>nd</sup> and 3 <sup>rd</sup>
Etoposide	Rose 1998	30%	2 <sup>nd</sup>
Ifosfamide	Markman 1992	12%	2 <sup>nd</sup> and 3 <sup>rd</sup>
Oxaliplatin	Piccart 2000	17%	2 <sup>nd</sup> and 3 <sup>rd</sup>
Irinotecan	Bodurka 2003	17%	2 <sup>nd</sup> and 3 <sup>rd</sup>
Vinorelbine	Rothenberg 2004	3%	3 <sup>rd</sup>
Tamoxifen	Williams 2001	10%	NA
Letrozole	Smyth 2007	9%	2 <sup>nd</sup> – 4 <sup>th</sup>

### 2.3 Availability of Proposed Active Ingredient in the United States

Olaparib is not approved for use in the United States.

### 2.4 Important Safety Issues with Consideration to Related Drugs

There are no other approved PARP inhibitors.

A major potential safety signal is the development of MDS/AML in patients with gBRCAm associated ovarian cancer. As noted in the proposed package insert, myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) have been confirmed in 6 out of 298 (2%) patients enrolled in a single-arm trial of Lynparza monotherapy, in patients with deleterious or suspected deleterious germline *BRCA*-mutated (gBRCAm) advanced cancers. In a randomized, placebo-controlled trial, MDS/AML occurred in 3 out of 136 (2%) patients with advanced ovarian cancer treated with Lynparza. Overall, MDS/AML were reported in 22 of 2,618 (<1%) patients treated with Lynparza. The majority of MDS/AML cases (17 of 22 cases) were fatal, and the duration of therapy with Lynparza in patients who developed secondary MDS/cancer-therapy related AML varied from <6 months to >2 years. All patients had previous chemotherapy with platinum agents and/or other DNA damaging agents. Of the 22 cases of MDS/AML reported in the safety database, 17 occurred in patients with germline BRCA mutations.

As described in section 2.6 of this review, BRCA and PARP are key components of the DNA damage repair pathway. Specifically, both BRCA1 and BRCA2 critically interact with Fanconi Anemia proteins in the homologous recombination pathway (D'Andrea 2003). Fanconi Anemia is a rare autosomal recessive disease characterized by bone marrow failure and increased susceptibility for the development of MDS/AML. Limited data exists regarding the increased risk for the development of MDS/AML in patients with germline BRCA mutations; however,

due to the interactions among BRCA1, BRCA2 and Fanconi Anemia proteins, BRCA deficiency may increase the risk for the development of MDS/AML (Friedenson 2007). The addition of further DNA damage induced by chemotherapy or other environmental factors, coupled with further impairment of compensatory repair pathway by means of PARP inhibition, may prime patients with germline DNA repair deficiencies for the development of MDS/AML. As of the current available data, there appears to be a safety signal in terms of developing MDS/AML; however, it is inconclusive as to whether this signal is elevated in patients receiving PARP inhibitors compared to the risk of development associated with the use of agents known to cause tMDS/tAML. This safety signal will be closely monitored in randomized clinical trials and will be an important risk consideration (b) (4)

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The major regulatory milestones for olaparib development in gBRCAm-associated ovarian cancer are depicted in Table 1 below.

Table 4: Key Regulatory Activities Related to Clinical Development

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

Committee		therapy for gBRCAm-associated platinum sensitive ovarian cancer. The panel voted 11 versus 2 that the safety and efficacy results from Study 19 in the gBRCAm population DO NOT support an accelerated approval.
Post-ODAC Meeting	July 21, 2014	FDA agreed that the sponsor could submit data regarding olaparib monotherapy in patients with gBRCAm-associated ovarian cancer who have been treated with 3 or more lines of chemotherapy to the NDA as a major amendment to potentially support a non-maintenance indication.

## 2.6 Other Relevant Background Information

### Ovarian Cancer

Ovarian cancer is the fifth leading cause of cancer mortality in women with an estimated 22,000 new cases diagnosed and 14,270 deaths from the disease in the US in 2014 (Siegel R, 2014). Standard therapy for advanced ovarian cancer consists of surgical debulking and a chemotherapy regimen consisting of a platinum agent and a taxane (Stuart G, 2011, Armstrong D, 2006, Katsumata N, 2009). Therapy for relapsed disease is dependent on the interval between the date of the final dose of initial therapy and date of relapse, with platinum-sensitive ovarian cancer being defined as relapse that occurs greater than six months from the date of the last dose of platinum-based chemotherapy (Thigpen J, 1994). Therapy for platinum-sensitive disease typically consists of platinum-based chemotherapy, and a platinum doublet regimen is associated with an improvement in overall survival when compared to single agent platinum (Collaborators, 2003). The time interval between the date of the last platinum-based treatment and progression is positively correlated with the probability of responding to further platinum therapy, as those patients who have a longer platinum-free interval will have a higher response rate to further platinum treatment (Pujade-Lauraine E, 2002). Non-platinum regimens typically are not used in the platinum-sensitive setting due to the overall survival advantage seen with platinum doublets; however, intolerance to platinum agents is a clinical concern, as the risk of cumulative toxicities, particularly carboplatin allergy or neuropathy, increases over the course of continued treatments.

### BRCA

The BRCA genes, BRCA1 and BRCA2, encode proteins involved in the DNA damage repair pathway. Deleterious mutations of BRCA1 and BRCA2 are associated with an increased risk of the development of breast and ovarian cancers; however, not all mutations are considered to be deleterious (Mik Yi, 1994, Wooster R, 1995). The majority of deleterious mutations are protein-truncating mutations. Missense mutations and large rearrangements of DNA segments within the BRCA genes also result in loss of function. It is estimated that the incidence of deleterious germline BRCA mutation (gBRCAm)-associated ovarian cancer is approximately 10-15% of all

cases of ovarian cancer, corresponding to an annual incidence of approximately 2000 cases per year in the U.S. (Pal, 2005, Zhang, 2011).

Patients with gBRCAm-associated ovarian cancer are treated no differently than patients without a deleterious mutation, but the presence of a mutation appears to be positively correlated with increased survival and responsiveness to chemotherapy (Chetrit, 2008, Alsop, 2012 Bolton, 2012). Due to the increased susceptibility to chemotherapy, it is expected that the patient with gBRCAm-associated ovarian cancer will be exposed to multiple lines of various chemotherapeutic agents.

### **PARP**

Poly (ADP-ribose) polymerase (PARP1) is a nuclear enzyme involved in the repair pathway of single strand breaks. PARP family of proteins consists of 18 proteins, two of which are nuclear and involved in DNA repair, PARP-1 and PARP-2. These proteins recognize and bind to areas of DNA damage and cleave NAD<sup>+</sup> to nicotinamide and highly-negatively charged ADP-ribose polymers that bind to DNA histones (Kraus 2013). While the exact role of ADP-ribosylation is not known, it is hypothesized that the negatively charged polymers alter the chromatin environment in a manner to allow access of other SSB repair proteins to the damaged DNA (El-Khamisy et al., 2003). However, other mechanisms for DNA repair can compensate for dysfunction in the PARP pathway. PARP-1 knockout mice are viable and do not have signs of early onset tumors (de Murcia et al., 1997). PARP also binds to DSB and may be involved in a backup DSB repair pathway involving XRCC1, a key protein in the nucleotide excision repair pathway, and ligase III (Audebert et al., 2004), but are not required for DSB repair by HR (Yang et al., 2004).

### **Treatment of 4<sup>th</sup> Line Ovarian Cancer**

There are very limited data regarding the response rates of either the approved products or commonly used off-label products in the 4<sup>th</sup>-line setting. Several institutions have described their experience with third-line chemotherapy regimens, and the reported response rates ranged from 5% to 40% (Bruchim 2013, Nishio 2008, Tangjitgamol 2004, Villa 2009). As germline BRCA mutations appear to be associated with chemosensitivity, it is assumed that there will be a higher proportion of gBRCAm patients who are still responsive to chemotherapy in the 4<sup>th</sup> line and beyond. However, it is also assumed that by the 4<sup>th</sup> line of chemotherapy, these patients will have been treated with multiple courses of platinum-based therapy and are likely to have cumulative toxicity of prior therapy. Therefore, there exists an unmet medical need for therapeutic products that demonstrate a favorable risk-benefit profile in the heavily pretreated ovarian cancer patient population, regardless of platinum sensitive or platinum resistant status.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear reasonable.

### **3.2 Compliance with Good Clinical Practices**

The clinical study protocols for Studies 2, 9, 12, 19, 20, 24, and 42 were submitted to Independent Ethics Committees (IEC) and/or Institutional Review Boards (IRB) for review. Written approvals were required prior to initiation of the study.

The applicant provided statements that the aforementioned studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements. The PI at each center ensured that the patient was given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients were also notified that they were free to discontinue from the study at any time. Patients were given the opportunity to ask questions and allowed time to consider the information provided. Informed consent was obtained from all subjects prior to the conduct of any study-related procedures.

The Office of Scientific Integrity (OSI) conducted clinical inspections of four clinical sites and the applicant. These sites were that of Dr. Phillip Harter (Germany), Dr. Charlie Gourley (UK), and two sites of Dr. Ursula Matulonis (Boston, USA). These sites were chosen due to relatively high enrollment numbers to Study 19 and were inspected with primary regards toward the conduct of Study 19. The sites of Dr. Matulonis and Dr. Gourley also enrolled patients onto Study 12. Dr. Gourley's site also enrolled patients onto studies 2 and 24. After the major amendment was submitted to the NDA, the decision was made to not pursue additional clinical site inspections as there were no major conduct deficiencies at the inspected clinical sites and it is reasonable to assume that the study site conduct would not be drastically different for the other studies whose data are used to support the revised indication. In addition, a large portion of data in support of the revised indication comes from Israel. At the time of the submission of the major amendment, the State Department issued a travel warning to US citizens recommending the deferral of non-essential travel to Israel. Sending an inspection team to Israel at that time did not appear to be an appropriate use of FDA resources especially considering that no major deficiencies were identified at the clinical sites and the applicant.

### **3.3 Financial Disclosures**

Disclosure of financial interests of the investigators who conducted the clinical trials, including statements of due diligence in cases where the applicant was unable to obtain a signed form from the investigator, supporting this NDA was submitted in the FDA form 3454. These disclosures

were certified by Darci Bertelsen, Director of Regulatory Affairs, AstraZeneca. Disclosures of financial interests were submitted for the following sub-investigators are summarized in the table below.

Table 5: Disclosures of Financial Interests

Name	Study	Role in Study	Number of patients enrolled at site	Potential to affect outcome of study
(b) (4)	Study 12	Sub-investigator	(b) (6)	No
	Study 19	Investigator		No
	Study 20	Sub-investigator		No

**Reviewer's Comments:**

*The financial interests of the sub-investigators identified in the table above have a very low likelihood of affecting the outcomes of the study due to small numbers of patients enrolled at each respective site.*

**4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

**4.1 Chemistry Manufacturing and Controls**

See the CMC review. Due to reports of capsules melting (b) (4) the following statement was added to the label:

Lynparza should not be exposed to temperatures greater than 40°C or 104°F. Do not take Lynparza if it is suspected of having been exposed to temperatures greater than 40°C or 104°F.

**4.2 Clinical Microbiology**

Not applicable to this application.

**4.3 Preclinical Pharmacology/Toxicology**

See the Pharmacology/Toxicology Review.

**4.4 Clinical Pharmacology**

See the Clinical Pharmacology Review.

#### 4.4.1 Mechanism of Action

The proposed language in section 12.1 of the label is as follows:

Lynparza is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines *in vitro* and decrease tumor growth in mouse xenograft models of human cancer both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in BRCA. *In vitro* studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death.

#### 4.4.2 Pharmacodynamics

See the Clinical Pharmacology Review and the Pharmacology/Toxicology Review.

#### 4.4.3 Pharmacokinetics

See the Clinical Pharmacology Review.

### 5 Sources of Clinical Data

#### 5.1 Tables of Studies/Clinical Trials

Table 6: Clinical Studies in Support of NDA 206162

Study Number	Design	Endpoint	gBRCAm (n)	$\geq 3$ lines Chemotherapy
D0810C00002	Phase 1 Expansion Cohort	ORR	5	3
D0810C00024	Bioavailability Study	ORR	20	11
D0810C00012	Randomized	PFS	32	16
D0810C00020	Single Arm Study	ORR	17	12
D0810C00042	Single Arm Study	ORR	193	137
D0810C00009	Single Arm Study	ORR	33	26

D0810C00019	Randomized	PFS	53	NA
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## 5.2 Review Strategy

The clinical review initially was based on the clinical study report for the randomized trial in the maintenance treatment of platinum-sensitive ovarian cancer, Study 19, including the applicant’s presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant, study reports for other olaparib clinical trials and literature review of ovarian cancer. Following the 11-2 ODAC vote that the results from Study 19 do not support accelerated approval of olaparib, the applicant submitted a major amendment and revised the indication for patients with gBRCAm-associated ovarian cancer treated with more than three lines of chemotherapy. The clinical review then shifted and is now based primarily on the clinical study report and all related data pertaining to the indicated population of Study 42. Safety and efficacy are supported by data derived from Studies 2, 9, 12, 20, 24, and 42.

## 5.3 Discussion of Individual Studies/Clinical Trials

This NDA is based on the objective response rate and duration of response from a single, open-label, non-randomized trial, Study 42.

**Study Title:** 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 *BRCA1* And/Or *BRCA2* Mutation

Supportive data on overall response rate were provided from Studies 2, 9, 12, 20, and 24. The table below provides a description of the design of these studies.

Table 7: Clinical Studies with Supportive ORR Data

Study	Design	Objectives of Study	Endpoint	gBRCAm (n)	≥ 3 lines Chemotherapy
2	Phase 1 Expansion Cohort	To determine the safety, tolerability, DLT, PARP inhibitory dose range and MTD of olaparib when administered orally to patients with advanced solid tumors	ORR	5	3
24	Ph I, randomized, 2 period, cross-over, relative BA Followed	Bioavailability of olaparib tablet formulation compared	ORR	20	11

	by tablet dose escalation phase (to establish MTD), and expansion phase (to compare efficacy and tolerability of tablet vs capsule)	to capsule formulation; safety and tolerability of capsule and tablet formulations at various doses			
12	Randomized, open-label, active control, multicenter	To compare the efficacy of 2 different dose levels of olaparib with pegylated liposomal doxorubicin in patients with advanced <i>BRCA1</i> or <i>BRCA2</i> associated ovarian cancer	PFS	32	16
20	Single Arm Study, multi-center, non-comparative	To determine ORR of olaparib in known <i>BRCA</i> or high-grade serous/undifferentiated ovarian cancer and known <i>BRCA</i> or triple negative breast cancer including enrichment for tumors with <i>BRCA</i> mutations	ORR	17	12
9	Single Arm Study, multi-center, non-comparative	To assess the efficacy of olaparib at two dose levels in terms of objective tumor response rate when administered orally to patients with <i>BRCA1</i> - or <i>BRCA2</i> - associated ovarian cancer	ORR	33	26

### 5.3.1 Study Design

Study 42 was a single-arm, open-label, multicenter study assessing the response rate of olaparib in patients with advanced cancers who have a deleterious *gBRCA* mutation. Initially, up to 150 patients with known *gBRCA*m status were to be recruited; however, after protocol amendments, this number was increased to 300 patients, with the intention that 220 patients with either breast

or ovarian cancer would be enrolled with the other patients having prostate, pancreatic, or other tumor types associated with gBRCA deficiencies.

### 5.3.2 Study Drug Administration and Schedule

Patients were to be treated with olaparib capsules 400 mg twice daily until disease progression or intolerance to study medication. Tumor assessments were performed at baseline and at every 8 week intervals until objective disease progression by RECIST v1.1 criteria or until 6 months had elapsed. After 6 months, if the patient had not progressed, the scan intervals were extended to a 12 week interval.

### 5.3.3 Study Endpoints

The primary objective of the study was to assess the efficacy of oral olaparib in patients with advanced cancer who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation by assessment of tumor response.

Other objectives were to assess the efficacy of oral olaparib in patients with advanced cancers who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation, by assessment of objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR) and disease control rate (DCR).

### 5.3.4 Eligibility Criteria

Key inclusion criteria were as follows:

- $\geq 18$  years of age
- Confirmed documented deleterious or suspected deleterious BRCA mutation.
- Histologically or, where appropriate, cytologically confirmed malignant solid tumor refractory to standard therapy and for which no suitable effective standard therapy exists.
- For the ovarian cancer setting patients must have documented progressive or recurrent disease according to either RECIST or GCIG criteria either during or within 6 months of completion of their most recent platinum-based chemotherapy regimen OR greater than 6 months from completion of most recent platinum-based chemotherapy, but not suitable for further platinum therapy. This should be discussed with the AstraZeneca Study Physician prior to obtaining consent.
- Normal organ and bone marrow function
  - Hemoglobin  $\geq 9.0$  g/dl
  - ANC  $\geq 1.5 \times 10^9$  /L
  - WBC  $> 3 \times 10^9$  /L
  - Platelet count  $\geq 100 \times 10^9$  /L
  - Total bilirubin  $\leq 1.5$  x ULN
  - AST/ALT  $\leq 2.5$  x ULN (if liver metastases  $\leq 5$  x ULN)
  - Serum creatinine  $\leq 1.5$  x ULN
  - ECOG PS  $\leq 2$

- At least one lesion (measurable or non-measurable) at baseline that can be accurately assessed by CT/MRI and is suitable for repeated assessment at follow-up visits

Key exclusion criteria were as follows:

- Any previous treatment with a PARP inhibitor, including olaparib.
- Patient with any other malignancy which has been active or treated within the previous 5 years, with the exception of a second suspected BRCA-related malignancy, adequately treated cone-biopsied in situ carcinoma of the cervix uteri, endometrial carcinoma stage 1A or 1, or non-melanoma skin lesions.
- Patients receiving CYP3A4 inhibitors
- Persistent toxicities (>CTCAE grade 2), excluding alopecia, caused by previous cancer therapy.
- Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.

#### **Reviewer's Comments:**

*Platinum-resistant ovarian cancer was a key eligibility criterion for this Study; however, patients with platinum-sensitive ovarian cancer could also be enrolled if they were not "suitable" for platinum-based chemotherapy. Investigators did not record whether ovarian cancer patients were platinum-resistant or platinum-unsuitable. and it cannot be determined what proportion of patients were platinum-resistant versus platinum-unsuitable.*

#### **5.3.5 Duration of Treatment**

After starting study treatment, patients attended periodic clinic visits for assessment of safety and efficacy until confirmed objective disease progression according to RECIST 1.1. Following confirmed disease progression patients discontinued olaparib treatment, but could have received any cancer treatment at the investigator's discretion. All patients continued to be contacted to assess survival status until death or the data cut-off for the primary analysis, whichever is the sooner. The analysis of all primary and secondary objectives occurred 6 months after the last patient has commenced study treatment (data cut-off).

#### **5.3.6 Primary Endpoint Evaluation**

RECIST 1.1 criteria was used to assess patient response to treatment by determining tumor response, progression-free survival (PFS) times, objective response rates (ORR), duration of response (DOR) and disease control rate (DCR).

The methods of assessment of tumor burden used at baseline -CT or MRI scans of neck, chest, abdomen, pelvis as appropriate to the tumor type under investigation - were used at each subsequent follow-up assessment.

Following the baseline assessment, efficacy for all patients were assessed by objective tumor assessments every 8 weeks  $\pm$ 1 week up to 6 months after starting study treatment and then every 12 weeks thereafter until objective disease progression as defined by RECIST 1.1.

If a patient discontinued treatment (and does not receive subsequent cancer therapy) prior to progression then the patient should have continued to be followed until objective disease progression as defined by RECIST 1.1.

For patients with measurable disease at baseline, categorization of objective tumor response assessment was based on the RECIST 1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression was calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) was calculated in comparison to the baseline tumor measurements obtained before starting treatment.

For patients with non-measurable disease only at baseline, categorization of objective tumor response assessment was based on the RECIST 1.1 criteria of response: CR, PD and Non-CR/Non-PD.

If the investigator was in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) or the appearance of a new lesion, it was advised to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirmed progression, then the date of the initial scan should have been declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must have been an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions was usually not sufficient to qualify for unequivocal progression status.

Following progression, patients continued to be followed up for survival every 8 weeks as outlined in the study plan.

The analysis for this study was based on the tumor assessments recorded on the CRF.

### 5.3.8 Major Protocol Amendments

There were three amendments made to the Study 42 protocol. Amendment 1 was made on March 31, 2010, and consisted of minor changes to patient eligibility and study conduct. Amendment 2 was made on August 26, 2010, and was performed to increase the amount of patients included in the study and to include an additional blood sample collection to enable confirmation of gBRCAm status by a central laboratory. Amendment 3 was made on August 8, 2011, and was performed to extend the final data cutoff by six months to allow for longer safety follow up and to update recommendations for the management of hematological toxicities, including specific recommendations for the diagnosis of suspected MDS/AML.

## 6 Review of Efficacy

### Efficacy Summary

This application is based on the objective response rate (ORR) and duration of response (DOR) in the cohort of 137 patients with deleterious or suspected deleterious germline *BRCA* mutated (gBRCAm) advanced ovarian cancer, who have been treated with three or more prior lines of chemotherapy in a single, open-label, non-randomized trial, Study 42. The ORR and DOR observed in this patient population is supported by ORR and DOR data derived from an additional 68 patients enrolled in Studies 2, 9, 12, 20, and 24.

- The applicant reports an ORR of 34% (95% CI: 26, 42) with a median DOR of 7.9 months in the 137 patients in Study 42.
- When pooled together with the additional 68 patients in the other studies the ORR of 31% (95% CI: 25, 38) and median DOR of 7.8 months supports the primary efficacy results.
- The ORR of > 30% represents an improvement over existing therapies and is reasonably likely to predict clinical benefit in this rare disease.
- The Oncology Drug Advisory Committee voted 11-2 that the results from the randomized trial in the platinum-sensitive maintenance setting do not support granting accelerated approval.
- The applicant has a potential confirmatory trial underway assessing the safety and effectiveness of olaparib in the platinum-sensitive maintenance setting.
- The applicant will also conduct a randomized trial in assessing the safety and effectiveness of olaparib against physician's choice chemotherapy in patients who have received more than two lines of platinum-based chemotherapy.

### 6.1 Indication

The proposed indication is as follows:

Lynparza is a poly ADP ribose polymerase (PARP) inhibitor indicated 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 indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

#### 6.1.1 Methods

The clinical review is based primarily on the clinical study reports for Study 42 and for Studies 2, 9, 12, 19, 20 and 24, case report forms, primary data sets for efficacy and safety submitted by the applicant and literature review of ovarian cancer.

#### 6.1.2 Demographics

Demographic data for Study 42 is summarized in Table X. Enrollment occurred in six countries, with 29% of the patients enrolled in the United States.

Table 8: Country of Enrollment, Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 42

<b>Country of Enrollment</b>	<b>N = 137 (%)</b>
Australia	21 (15)
Germany	17 (12)
Spain	7 (5)
Israel	50 (36)
Sweden	2 (1)
USA	40 (29)

The majority (94%) of the patients were White/Caucasian. Median age was 58, and the distribution of age ranges are depicted in the table below.

Table 9: Age Distribution, Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 42

<b>Age Range</b>	<b>N = 137 (%)</b>
<50	26 (19)
>=50-<65	83 (61)
>=65	28 (20)

Tumor characteristics are depicted in the table below.

Table 10: Tumor Characteristics, Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 42

Origin of Primary Site of Disease	N = 137 (%)
Fallopian Tube	3 (2)
Ovary	125 (91)
Peritoneum	7 (5)
Primary Peritoneal	2 (1)

The majority of patients (93%) had a baseline ECOG performance status of 0 or 1. The median number of prior chemotherapy regimens was 5 and the maximum number of prior regimens was 14. The various prior chemotherapies that the patients received are depicted in the table below.

Table 11: Prior Chemotherapy, Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 42

Chemotherapy	Number of patients receiving therapy N=137
CARBOPLATIN	136
PACLITAXEL	131
DOXORUBICIN	110
GEMCITABINE	73
CYCLOPHOSPHAMIDE	49
CISPLATIN	46
TOPOTECAN	36
FLUOROURACIL	26
METHOTREXATE	20
ETOPOSIDE	9
VINOURELBINE	6
EPIRUBICIN	4
INVESTIGATIONAL DRUG	3
MELPHALAN	3
TRABECTEDIN	3
MITOMYCIN	2
OXALIPLATIN	2
PEMETREXED	2
CAPECITABINE	1

**Reviewer's Comments:**

*As depicted by the table above, the majority of patients who have received three or more lines of chemotherapy will have received a platinum agent, a taxane, an anthracycline and/or gemcitabine. In addition, there is frequent off-label use of other chemotherapy agents, often with little or no evidence of efficacy in the literature to support use of these agents in these settings.*

### 6.1.3 Subject Disposition

A total of 317 patients were enrolled in the study from 13 centers in six countries. At the time of data-cut-off (31 July 2012), a total of 298 patients had received treatment. Of these, 62 patients were in the breast cancer group, 193 patients in the ovarian cancer group, 23 patients in the pancreatic cancer group, 8 patients in the prostate cancer group, and 12 patients in the other cancer group. Of the 193 patients in the ovarian cancer group, 137 patients had measurable disease at baseline and had received three or more prior lines of chemotherapy.

As of the data cutoff, 15 patients continued to receive olaparib at the data cutoff. The reasons for discontinuation are summarized in the table below.

Table 12: Treatment Discontinuation, Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 42

<b>Reason for Treatment Discontinuation</b>	<b>N = 137 (%)</b>
Ongoing treatment	15 (11)
Adverse event	9 (7)
Development of study specific discontinuation criteria	69 (50)
Other	3 (2)
Severe non-compliance to protocol	2 (1)
Subject decision	8 (6)
Subjective disease progression	31 (23)

As of the data cutoff, 48 patients remained on study at the data cutoff. The reasons for study discontinuation are summarized in the table below.

Table 13: Study Discontinuation, Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 42

<b>Reason for Study Discontinuation</b>	<b>N = 137 (%)</b>
Ongoing Study	15 (11)
Death	81 (59)
Eligibility criteria not fulfilled	1 (1)
Subject decision	7 (5)

Four patients received treatment for over two years and were still on therapy at the time of data cutoff.

### 6.1.4 Analysis of Primary Endpoint(s)

The primary objective of the study was to assess the efficacy of oral olaparib in patients with advanced cancer who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation by assessment

of tumor response. An independent radiologic assessment was not done. Treatment with olaparib resulted in a robust, investigator-assessed ORR (34%) and durable duration of responses (median 7.9 months) in this heavily pre-treated population of 137 patients who have been treated with three or more lines of chemotherapy and who have measurable disease. The ORR and DOR results are depicted in the table below.

Table 14: Overall Response and Duration of Response in Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 42

	<b>N=137</b>
Objective Response Rate (95% CI)	34% (26, 42)
Complete Response	2%
Partial Response	32%
Median DOR in months (95% CI)	7.9 (5.5 <sup>1</sup> , 9.6)

1 - The lower bound of the 95% CI differs from that calculated by the sponsor as the FDA analysis was performed with a newer version of JMP/SAS. The sponsor's calculation of 5.6 was included in the label.

**Reviewer's Comments:**

*As noted in the background section, there are no data from clinical trials assessing the activity of therapy in the 4<sup>th</sup>-line ovarian cancer setting. It is widely recognized that the response rates are as high as 80-90% in the front-line setting; however, the expected response rates decline with each subsequent line of therapy. Considering the available literature, the expected response rate in the 4<sup>th</sup>-line setting, at best, would be roughly 10-15%. The intended patient population would be expected to have a higher response rate to therapy, as gBRCAm status appears to be positively associated with chemosensitivity with prolonged progression-free and overall survival. It is important to recognize that the median number of lines of chemotherapy in these 137 patients is five, and by the 4<sup>th</sup> line of chemotherapy, patients will have already been exposed to agents that are expected to have activity and will either be retreated with chemotherapy they have already been exposed to or be treated with off-label regimens, with limited data available to support their use. The response rate of 34% observed in Study 42, along with pooled corroborative evidence generated in other studies in the same patient population, confirms that this drug has robust anti-tumor activity in this patient population and is reasonably likely to predict clinical benefit.*

6.1.5 Analysis of Secondary Endpoints(s)

Other efficacy endpoints of Study 42 that were not discussed in section 6.1.4 include PFS and OS. The results of these analyses are depicted in the table below but are uninterpretable in the absence of a control arm.

Table 15: PFS and OS, Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 42

	<b>N=137</b>
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Progression Free Survival	Median 7 months (95% CI: 5.5, 8.7)
Overall Survival	Median 14.4 months (95% CI: 12.2, 18.4)

#### 6.1.6 Other Endpoints

See Section 6.1.7 for analyses pertinent to BRCA mutations.

#### 6.1.7 Subpopulations

The primary analysis for this NDA review was performed in the subpopulation of Study 42 consisting of the 137 patients with *gBRCAm*-associated ovarian cancer patients who have been treated with three or more lines of chemotherapy and who have measurable disease. The table below depicts the overall response rate for the entire cohort of 167 ovarian cancer patients with measurable disease enrolled on Study 42 and for the cohort of 30 ovarian cancer patients with measurable disease who have received fewer than three lines of chemotherapy.

Table 16: ORR in Other Cohorts, Study 42

<b>Entire Ovarian Cancer with Measurable Disease</b>	<b>N=167</b>
Objective Response Rate (95% CI)	36% (29, 44)
Complete Response	4%
Partial Response	32%
<b>Ovarian Cancer &lt; 3 Chemotherapy Regimens with Measurable Disease</b>	<b>N=30</b>
Objective Response Rate (95% CI)	47% (28, 66)
Complete Response	13%
Partial Response	33%

#### Reviewer's Comments

*While the point estimate for ORR in the patient population who received less than 3 lines of chemotherapy appears higher than the ORR observed in the  $\geq 3$  lines of therapy population, the sample size is considerably smaller and the confidence interval is much wider. In addition, the 47% response rate is lower than the 53% ORR reported in the paclitaxel-bevacizumab cohort of the AURELIA trial in 3rd line platinum-resistant patients. Accelerated approval of olaparib for earlier lines of therapy would not be appropriate as a meaningful therapeutic benefit over existing treatments has not been demonstrated.*

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See sections 4.4.2 and 4.4.3.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Pooled Analysis

As part of the major amendment to the NDA, FDA requested that the applicant gather pooled data on the overall response rates for 205 patients with measurable disease who have been treated with three or more lines of chemotherapy for gBRCAm-associated ovarian cancer at the dose of 400 mg BID across their clinical trial database. Studies 2, 9, 12, 20 and 24 were identified as having sufficient numbers of patients and are briefly described as follows. A total of 68 patients from these five studies were included in this analysis.

### **Study 2**

**Title:** A Phase I, Pharmacokinetic and Biological Evaluation of a Small Molecule Inhibitor of Poly ADP-Ribose Polymerase-1 (PARP-1), KU-0059436, in Patients with Advanced Tumors

**Design:** This was an open-label, dose-escalating, non-randomised, multi-centre phase I study of olaparib administered orally to patients with advanced solid tumours. The study was initially conducted at 2 centers in the UK and The Netherlands. For the expanded phase of the study (BRCA 1 and 2 breast, prostate and ovarian patients; as amended by protocol amendments 5 and 6), 3 additional centres were added (in the UK, Belgium and Poland).

This study was designed to establish the PID and MTD of olaparib and to explore the safety, tolerability, PK and PD profiles and anti-tumour activity in the patient population. The study involved two distinct phases for evaluation of schedule and dose:

(a) A dose escalation phase.

(b) An expansion phase at a single dose level in a population of up to a maximum of 60 patients with BRCA 1 or 2 mutations, to include 20 evaluable ovarian cancer patients (as amended by protocol amendment 6).

**Number of Patients Contributing to the Pool: 3**

### **Study 9**

**Title:** A Phase II, Open-Label, Non-Comparative, International, Multicenter Study To Assess the Efficacy And Safety Of KU-0059436 Given Orally Twice Daily In Patients With Advanced BRCA1- Or BRCA2-Associated Ovarian Cancer

**Design:** This was an international, multicenter, proof-of-concept, Phase II study. Two sequential patient cohorts received continuous oral olaparib in 28-day cycles. The first cohort received 400 mg bd and the second cohort received 100 mg bd.

**Number of Patients Contributing to the Pool: 26**

### **Study 12**

**Title:** A Phase II, Open-Label, Randomized, Comparative, International Multicenter Study to Compare the Safety and Efficacy of Two Different Doses of AZD2281 Given Orally Twice Daily Versus Intravenous Liposomal Doxorubicin Given Monthly in Patients With Advanced BRCA1- or BRCA2-Associated Ovarian Cancer Who Have Failed Previous Platinum-Based Chemotherapy

**Design:** This was a Phase II, open-label, randomized, comparative, multi-center study to compare the safety and efficacy of 2 different doses of olaparib with intravenous (iv) liposomal doxorubicin in the treatment of patients with advanced BRCA1- or BRCA2-associated ovarian cancer who have failed previous platinum-based chemotherapy.

Patients were randomized (1:1:1) to receive either olaparib 200 mg twice daily (bd) orally,

olaparib 400 mg bd orally, or liposomal doxorubicin 50 mg/m<sup>2</sup> iv. Olaparib was administered continuously. Dose modifications due to toxicity were allowed. Liposomal doxorubicin was administered at an initial dose of 50 mg/m<sup>2</sup> every 4 weeks, but could be modified in subsequent cycles due to toxicity.

**Number of Patients Contributing to the Pool: 16**

### Study 20

**Title:** Phase II, Open Label, Non-Randomized Study of AZD2281 in the Treatment of Patients with Known *BRCA* or Recurrent High Grade Serous/Undifferentiated Tubo-Ovarian Carcinoma and in Known *BRCA* or Triple Negative Breast Cancer to Determine Response Rate and Correlative Markers of Response

**Design:** This was a Phase II, open label, non-randomized correlative study of olaparib as a single agent given twice daily to patients with recurrent breast and ovarian cancer. The study enrolled both *BRCA* inherited mutation carriers and non-carriers. Patients with either triple negative breast cancer (TNBC) or serous ovarian cancer who had previously tested negative for the *BRCA* mutation were enrolled in the ‘unknown *BRCA* mutation status’ arms of the study. Patients were enrolled into 4 arms as follows:

1. TNBC with unknown *BRCA* mutation status.
2. Known *BRCA* mutation positive breast cancer.
3. High grade serous/undifferentiated tubo-ovarian carcinoma with unknown *BRCA* mutation status.
4. Known *BRCA* mutation positive ovarian cancer.

Ten patients were planned to be enrolled into each of the known *BRCA* mutation positive arms. For the unknown *BRCA* mutation status arms an optimal 2-stage Simon design was used. Fifteen patients with unknown *BRCA* mutation status were planned to be enrolled to each of the TNBC and high grade serous/undifferentiated ovarian groups in ‘stage 1’. One or more responses were required in these 15 patients to progress to ‘stage 2’ (in which further patients were to be recruited) otherwise accrual was to be stopped. In the TNBC group, a further 20 patients were to be recruited in stage 2 while in the high grade serous/undifferentiated ovarian group a further 40 patients were to be recruited in stage 2. Note that the number of additional patients to be recruited to the high grade serous/undifferentiated ovarian group in stage 2 was increased from 20 to 40 patients by CSP amendment 4.

Patients with unknown *BRCA* status at entry had to provide a DNA sample for *BRCA* mutation analysis, which was performed at Myriad Genetics.

**Number of Patients Contributing to the Pool: 12**

### Study 24

**Title:** A phase I, randomized, 2 period cross over study to determine the comparative bioavailability of two different oral formulations of AZD2281 in cancer patients with advanced solid tumors

**Design:** This study was a Phase I, randomized, 2 period cross over study originally intended to determine the comparative bioavailability of two different oral formulations of olaparib in cancer patients with advanced solid tumors.

The objectives of this study were to generate single dose PK data for the tablet in man, to generate information on dose linearity for the tablet and to compare, in man, the exposure achieved after dosing with the tablet with that achieved following dosing of the capsule. The objective of the continued supply expansion phase (CSEP) of the study was to explore the safety and tolerability of olaparib following multiple dosing of a tablet formulation. This was then followed by a tablet dose escalation phase to determine the safety and tolerability of higher tablet doses. Finally two randomized expansion phases were conducted to compare the safety and tolerability of chosen tablet doses with that of the capsule formulation and to compare the safety and tolerability of a number of alternative tablet dose schedules with each other.

**Number of Patients Contributing to the Pool: 11**

**Pooled Demographics**

The median age of the pooled patient population was 53. The majority of patients had an ECOG performance status of 0-1 (99%). The age distribution of the patient population is depicted in the table below.

Table 17: Age Distribution in Pooled Patient Population with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy

<b>Age Range</b>	<b>N = 68 (%)</b>
<50	20 (29)
>=50-<65	33 (49)
>=65	15 (22)

**Overall Response Rate**

The overall response rate and median duration of response for the pooled patient population outside of Study 42 is depicted in the table below.

Table 18: Overall Response and Duration of Response in Pooled Patient Population with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy

	<b>N= 68</b>
Objective Response Rate (95% CI)	26% (16, 37)
Median DOR in months (95% CI)	7.0 (5.5, 9.5)

A summary of the overall response rate and duration of response for all patients with gBRCAm associated ovarian cancer, measurable disease and treated with 3 or more lines of chemotherapy are summarized in the table below.

Table 19: Overall Response and Duration of Response in Pooled Patient Population by Trial with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy

Study Number	N	Responders	ORR % (95% CI)	Median DOR mo (95% CI)
42	137	43	34 (26, 42)	7.9 (5.6, 9.6)
9	26	8	31 (14, 52)	8.1 (5.6, NC)
12	16	3	19 (4, 46)	6.4 (5.6, 7.3)
20	12	3	25 (5, 57)	3.7 (3.7, 9.1)
24	11	2	18 (2, 52)	5.5 (NC, NC)
2	3	2	67 (9, 99)	NC (NC, NC)
<b>Overall</b>	<b>205</b>	<b>64</b>	<b>31 (25, 38)</b>	<b>7.8 (5.6, 9.5)</b>

### Reviewer's Comments

*The pooled analysis of overall response rates and duration of response across the clinical trials corroborate the findings of Study 42. As this data adds no additional information other than supportive evidence, [REDACTED] (b) (4) the data from Study 42 will be included in section 14.1 of the package insert.*

### Resistance

As noted in section 6.1.4, the duration of response observed in Study 42 was 7.9 months. There are several proposed mechanisms of resistance to PARP inhibitors including genetic reversion mutations that restores functionality of BRCA 1 or 2 or loss of 53BP1, but to date, no major mechanism has been identified clinically that accounts for resistance to olaparib therapy.

One theoretical concern regarding PARP inhibitors is that the same mechanisms that impart resistance to PARP inhibitors confer platinum and/or chemoresistance as well. Ang et al. published their experience with post-progression chemotherapy following olaparib therapy and noted an overall response rate of 36% in a group of 89 patients enrolled on different trials of olaparib therapy (Ang 2013). For patients in this cohort who received subsequent platinum-based therapy, the ORR was 40%. While these data preclude any conclusion regarding the potential of attenuation of post-progression therapy, the response rates observed suggest that response to subsequent therapy is not abrogated. The attenuation of the effectiveness of subsequent therapy is not a concern in the 4<sup>th</sup>-line setting, as patients already will have received those agents with meaningful clinical benefit; however, [REDACTED] (b) (4), this potential effect will need to be addressed.

### 6.1.10 Additional Efficacy Issues/Analyses

#### BRCA Mutations

The development of olaparib in ovarian cancer has been focused on patients harboring germline, deleterious mutations of BRCA 1 or 2 due to the hypothesis that the inhibition of various components of the DNA damage repair pathway will lead to impaired cell survival and drive the cancer cell toward apoptosis.

To date, the development of olaparib in gBRCAwt-associated ovarian cancer has been limited. Study 19 is a randomized double-blind, multicenter, placebo-controlled study assessing progression-free survival in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer, in partial or complete response to their last platinum-containing regimen. Patients were randomized to olaparib treatment or matching placebo. Study 41 is a randomized, multicenter study comparing the efficacy and tolerability of olaparib in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in patients with platinum sensitive advanced serous ovarian cancer. Study 20 is an open label, non-randomized study of olaparib in the treatment of patients with known BRCA or recurrent high grade serous ovarian cancer in known BRCA or TNBC to determine response rate and correlative markers of response. The table below summarizes the outcome measures and number of confirmed wtBRCA ovarian cancer patients included in the study.

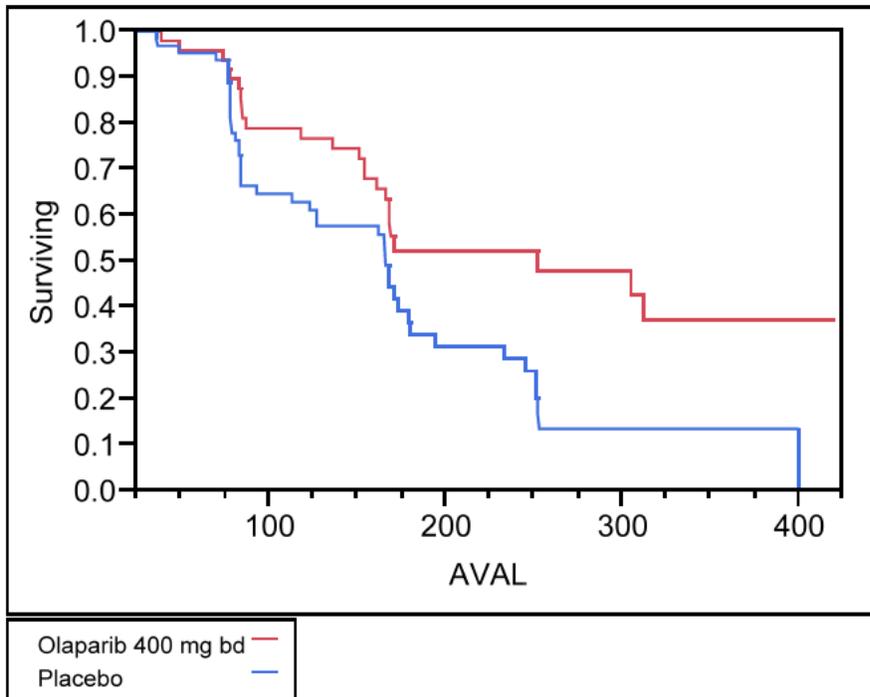
Table 20: Studies with gBRCAwt

<b>Study</b>	<b>Primary Endpoint</b>	<b>gBRCAwt (n) (olaparib arms)</b>	<b>Efficacy Result</b>
19	PFS	50	Uncertain due to Non-proportional Hazards
41	PFS	3	Uncertain due to insufficient numbers
20	ORR	47	ORR = 25% (14-38)

As demonstrated in the table above, there were insufficient numbers of patients with confirmed BRCA status to conduct meaningful analysis of the gBRCAm or gBRCAwt populations in Study 41.

In Study 19, in the patients with confirmed gBRCAwt or gBRCA mutations with variations of unknown significance (n=114), the hazard ratio for PFS using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy is 0.50 (95% CI: 0.29, 0.82); however, the treatment effect of olaparib therapy in terms of PFS cannot be reliably ascertained due to the suggestion of non-proportional hazards. The Kaplan-Meier curve for PFS is depicted in the figure below.

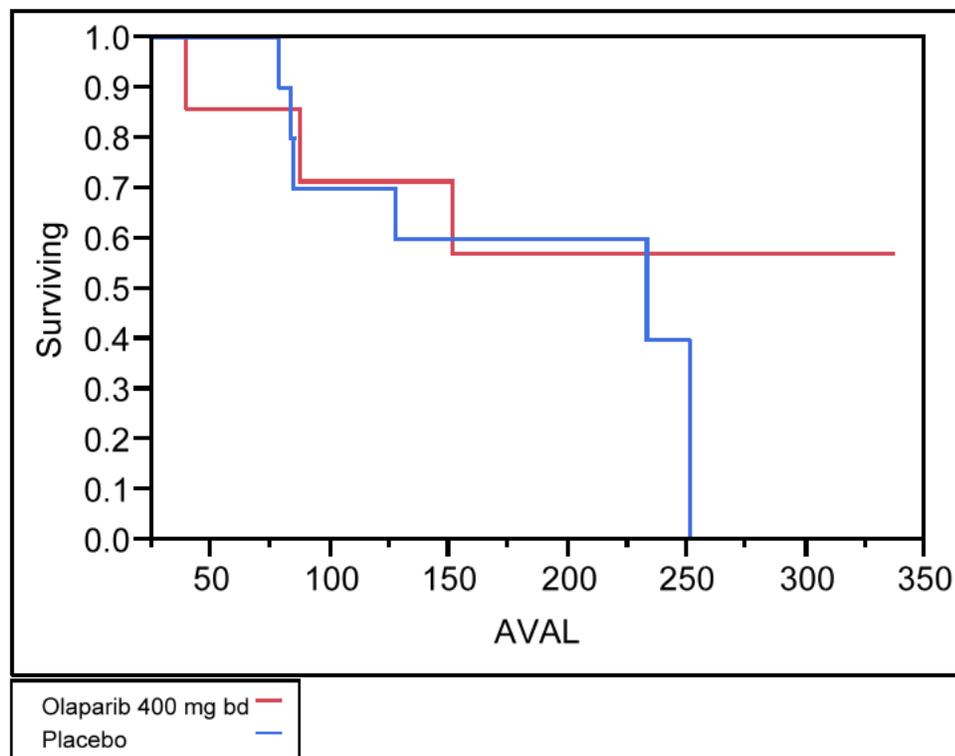
Figure 1: PFS of gBRCAwt Study 19



In Study 20, there were 47 patients with confirmed gBRCAwt status. Of these 47 patients, 48% had received 1 or 2 previous lines of chemotherapy and 11 had a partial response by RECIST criteria (ORR=24% (95% CI: 14, 38)).

In summary, there is very limited data regarding the efficacy of olaparib in the gBRCAwt ovarian cancer population. The suggestion of non-proportional hazards limits the interpretation of PFS in Study 19, and the 2.8-month median difference in PFS is not considered clinically meaningful, especially in light of the discussion at the Advisory Committee meeting. The response rate of 24% seen in Study 20 suggests some activity in gBRCAwt-associated ovarian cancer, but this is considered exploratory. There is even more limited data in patients with somatic BRCA mutations found in tumors with a gBRCAwt background. This data is limited to 18 patients in Study 19, and the Kaplan-Meier curve for PFS is depicted in the figure below.

Figure 2: PFS of tBRCAm without gBRCAm, Study 19



#### Determination of Deleterious Mutations in BRCA1 or BRCA2

It is important to note that not all mutations in BRCA1 or BRCA2 are considered to have a deleterious effect on BRCA function. Most mutations that are considered deleterious result from premature termination codons due to small frameshift deletions or insertions, nonsense alterations, or large deletions or duplications. Large rearrangements can also result in loss of function. Founder mutations in the Ashkenazi Jewish population have been well described and consist of the BRCA1 – 185delAG, BRCA1 5382insC, and BRCA2 – 6174delT mutations. Of the 193 patients with ovarian cancer enrolled on Study 42, 67 patients harbored the BRCA1 – 185delAG mutation, 12 patients harbored the BRCA1 5382insC mutation, and 20 patients harbored BRCA2 – 6174delT mutations. This comprised 51% of the mutations found in this cohort. For a list of BRCA mutations of patients enrolled onto olaparib studies, please refer to Appendix 9.4. For further details regarding the BRACAnalysis CDx™, please refer to the CDRH review. The following is the proposed Intended Use language for the companion diagnostic device.

#### INTENDED USE

BRACAnalysis CDx™ is an *in vitro* diagnostic (b)(4) for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes using genomic DNA obtained from whole blood specimens collected in (b)(4) EDTA. Single nucleotide variants and small indels are identified by PCR and Sanger

sequencing. Large deletions and duplications in BRCA1 and BRCA2 are detected using multiplex (b) (4) PCR. Results of the test (b) (4) used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza™ (olaparib). This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories.

## 7 Review of Safety

### Safety Summary

#### 7.1 Methods

In the primary review, the datasets, case report forms, and patients' narratives were examined from Study 19 and other select studies included in the submission. Adverse event information, laboratory data, and examinations were also evaluated for Study 19.

After the major amendment, submitted on 7/24/14, a pooled analysis of safety data from six studies (Studies 2, 9, 12, 20, 24, and 42) not including Study 19, was performed. The data in these six studies were submitted to support an amended indication for use of olaparib in the treatment of patients with advanced, relapsed ovarian cancer with a gBRCA deleterious or suspected deleterious mutation, who had received three or more prior lines of chemotherapy. A summary of the studies included in the major amendment is shown below in Table 24.

To summarize the relevance of the data to the safety analysis, the primary safety review for this NDA was based upon the results from Study 19, followed by the supportive results from the pooled analysis submitted after the major amendment. In most sections of this review, findings from Study 19 are discussed first, followed by the results from the pooled safety analysis.

##### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

According to the Sponsor, an estimated 2034 patients with ovarian, breast, pancreatic, gastric, and other solid tumors have received treatment with olaparib across the dose range of 10 mg daily up to 600 mg twice daily, as of May 20, 2013. Olaparib has been given as monotherapy to 1162 patients (15 studies), and in combination regimens to 872 patients (23 studies). The details of the safety database for patients receiving the proposed monotherapy dose of olaparib 400 mg BID are discussed further in Section 7.1.3.

### 7.1.2 Categorization of Adverse Events

Adverse events in study 19 are broken down by category as shown in Table 21.

Table 21: Study 19 Safety Overview

	<b>Olaparib N=136 (%)</b>	<b>Placebo N= 129 (%)</b>
<b>Deaths due to AE</b>	9 (7)	6 (5)
Within 30 days	3 (2)	0
In follow-up*	6 (4)	6 (5)
<b>Discontinuations due to AE</b>	6 (4)	2 (2)
<b>SAEs</b>	25 (18)	13 (10)
<b>G 3-4 AEs</b>	40 (29)	19 (15)
<b>G 1-4 AEs</b>	132 (97)	119 (93)

\*More than 30 days after last dose of study drug

Adverse events from the pooled analysis of patients receiving three or more prior lines of therapy are shown by category in Table 22. It is notable that there were more discontinuations, serious adverse events, and severe (G3-4) adverse events in the post-amendment population (n=223). This is likely related, to some extent, to that fact that these patients were more heavily pretreated prior to enrolling onto studies where they received olaparib.

Table 22: Safety Overview Major Amendment

	<b>Olaparib N= 223 (%)</b>
<b>Deaths due to AE</b>	8 (4)
<b>Discontinuations due to AE</b>	15 (7)
<b>SAEs</b>	77 (35)
<b>G 3-4 AEs</b>	119 (53)
<b>G 1-4 AEs</b>	220 (99)

*Reviewer comment: The breakdown of adverse events seen in the population of patients analyzed after the major amendment likely indicates that olaparib is not as well tolerated in more heavily pretreated patients, and these patients may need more dose delays and reductions than patients who have received fewer prior therapies.*

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Approximately 735 patients with advanced solid tumors on 11 studies (including the pivotal Study 19) have received treatment with the proposed olaparib dose for approval of 400 mg twice daily. Within this database, 397 patients with BRCA-mutated cancers were treated with olaparib on 7 different studies. The details of the monotherapy pooled patients, and of those with gBRCA mutated ovarian cancer, in the safety database are described in Table 23.

Table 23: Table of Monotherapy Pooled Patients

Study No.	Phase	Olaparib doses in mg	Population	Comparator (if any)	Number of patients enrolled (Number receiving olap 400 BID)	# gBRCA mut.
D0810C000019 Study 19	2	400 BID	Plat-sensitive ovarian cancer (subgroup gBRCA mutated)	-	264 (136)	74
D0810C00001 Study 1	1	100, 200, 400 BID	Adv. solid tumors	-	12 (6)	-
D0810C00002 Study 2	1	10 od to 600 BID	Adv. solid tumors; exp cohort gBRCA ovarian, prostate, breast)	-	98 (8)	5
D0810C00007 Study 7	1	10 BID to 400 BID	Breast cancer	-	60 (12)	-
D0810C00008 Study 8	2	100 BID, 400 BID	gBRCA Breast cancer	-	54 (27)	-
D0810C00009 Study 9	2	100 BID, 400 BID	gBRCA Ovarian cancer	-	57 (33)	33
D0810C00012 Study 12	2	200 BID, 400 BID	gBRCA Ovarian cancer	Doxil	96 (55)	54
D0810C00020 Study 20	2	400 BID	gBRCA Ovarian, gBRCA Breast, Triple-negative breast cancers	-	90	17
D0810C00024 Study 24	1	400 BID	Adv. Solid tumors; expansion gBRCA	-	134 (37)	21

			breast and ovarian cancers			
D0810C00042 Study 42	2	400 BID	gBRCA-mutated advanced tumors	-	298	193
D9010C00008 Study 8	2	400 BID	Colorectal cancer	-	33	-
<b>Total</b>					<b>1068 (735)</b>	<b>397</b>

After the major amendment, the overall pooled safety database was amended to include the total of 300 patients with relapsed ovarian cancer with gBRCA mutation across 6 studies. These included studies shown in Table 24, and they were Studies 2, 9, 12, 20, 24, and 42. Study 19 was not included in this population. Also depicted in Table 24 is a breakdown of the 223 patients, by study, who had received 3 or more prior treatment regimens before receiving study therapy with olaparib.

Table 24: Studies in Pooled Safety Analysis

Study	Number of patients	Number of patients treated with $\geq 3$ prior regimens
2	5	4
9	33	26
12	32	16
20	17	12
24	20	11
42	193	154
<b>Total</b>	<b>300</b>	<b>223</b>

## 7.2 Adequacy of Safety Assessments

Trial D0810C000019 (study 19) comprised the primary focus of the original safety review. The remaining studies in Section 7.1.3 were supportive.

After the major amendment, which changed the proposed indication to be for *olaparib in patients with gBRCA mutated ovarian cancer who have received three or more prior lines of chemotherapy*, Study 42 became a major focus of the safety review, with the remaining 5 studies (2, 9, 10, 12, 20, and 24) as supportive.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In study 19, the patients from the gBRCA mutation population who required dose modification, either as interruptions or reductions, are shown in Table 25. As expected, more patients on olaparib required a dose modification of some kind during the study. In all categories, the modifications were most commonly due to an adverse event.

Table 25: Study 19 Dose modifications gBRCA mutation population

	Olaparib N=53 (%)	Placebo N=43 (%)
<b>Dose modification (interruption or reduction)</b>	<b>25 (47)</b>	<b>16 (37)</b>
Dose modification due to AE	17 (32)	4 (9)
<b>Dose interruption</b>	<b>17 (32)</b>	<b>8 (19)</b>
Dose interruption due to AE	13 (25)	3 (7)
<b>Dose reduction (less than 800 mg/ d)</b>	<b>19 (36)</b>	<b>12 (28)</b>
Dose reduction due to AE	8 (15)	2 (5)
<b>Dosing permanently discontinued</b>	<b>43 (81)</b>	<b>41 (95)</b>
Dosing permanently discontinued due to AE	5 (9)	0

The olaparib dose modifications for patients who had received three or more prior lines of chemotherapy (safety population after the major amendment) are shown in Table 26. The overall number of patients who underwent a dose modification of olaparib therapy in the major amendment safety population is similar to the numbers treated with olaparib on Study 19. As noted previously, in the population assessed after the major amendment, more patients permanently discontinued therapy due to adverse events than on Study 19. The dose modifications for patients treated with three or more prior therapies are shown in Table 26.

Table 26: Safety population- Dose modifications due to adverse events for patients treated with 3 or more prior regimens

<b>Safety population</b>	<b>N= 223 (%)</b>
Dose modification (interruption or reduction)	94 (42)
Dose interruption	88 (40)
Dose reduction (less than 800 mg/ d)	9 (4)
Dosing permanently discontinued	15 (7)

### 7.2.2 Explorations for Dose Response

Based upon available pharmacokinetic data, there does not appear to be an exposure-response relationship for the efficacy variables of PFS or overall response rate at the proposed dose. Study 19 did not have PK data available, and this assessment comes from data from studies other than Study 19. However, there did appear to be an exposure-response relationship for anemia, and this analysis is described in Section 7.5.1.

### 7.2.3 Special Animal and/or In Vitro Testing

See the summary of the Pharmacology/Toxicology review in Section 4.3.

### 7.2.4 Routine Clinical Testing

Please reference the laboratory and vital sign analyses in Sections 7.4.2 and 7.4.3.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of the Clinical Pharmacology review in Section 4.4.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This NME is the first in class of the PARP inhibitors for which an NDA has been submitted.

## 7.3 Major Safety Results

### 7.3.1 Deaths

On study 19, there were a total of 77 deaths (56.6%) on olaparib and 77 deaths (60.2%) on placebo. The majority of deaths on both arms were due to disease progression (68 on olaparib and 71 on placebo). There were 3 deaths on olaparib (none on placebo), within 30 days, which were due to adverse events. Those deaths are described further in Table 27. The narratives for the 3 patients who died are presented below the table.

Table 27: Death due to AE within 30 days on Study 19

	<b>Olaparib N=136</b>	<b>Placebo N=128</b>
<b>Deaths due to AE (per Sponsor)</b>	<b>3</b>	<b>0</b>
Hemorrhagic stroke	1	0
Cholestatic jaundice and PD	1	0
PD and MDS	1	0

The following information was provided by the Sponsor in patient narratives on deaths in Study 19.

1. **1808004**- AE only- hemorrhagic stroke. Details as follows: This 48 y/o patient with a history of Stage IIIC poorly differentiated “fibrous” ovarian cancer enrolled on study on (b) (6). She had initiated C8 of therapy with olaparib and was found to have G2 thrombocytopenia (starting 7/27/10), which worsened to G3, then G4. She suffered a hemorrhagic stroke on (b) (6) and died on (b) (6). The adverse event was said to be related to the study drug.

*Reviewer comment: This patient is also discussed further in section 7.3.4, with the summary of MDS/AML. It was noted that this patient had severe cytopenias, including thrombocytopenia, during the time leading up to her death due to hemorrhagic stroke. It was noted in this patient’s narrative that she had 16% blasts present on peripheral smear, raising suspicion that she had AML. However, a bone marrow biopsy and other testing to confirm this diagnosis were not performed before the patient died due to hemorrhagic stroke, which was likely the result of the severe thrombocytopenia.*

2. **0805001**- AEs and PD- cholestatic jaundice, femur fracture, PD, respectively. This was an 80 y/o patient with poorly differentiated Stage IV serous ovarian cancer originally diagnosed on 2/9/05. She enrolled on study on 11/4/09 and had ascites at the time of enrollment; she was otherwise noted to have only non-measurable disease at study baseline. She received 37 cycles of therapy with olaparib. Her course was complicated by a traumatic femur fracture on (b) (6) that required surgery. She developed G2 cholestatic jaundice on 8/13/12 and had therapy with olaparib discontinued at that time (deemed to be due to AE, per the investigator; total bilirubin 8.0). The patient narrative states that the patient had progressive disease as the primary cause of treatment discontinuation, however this is not reflected on the patient’s CRF (the CRF states that

study drug was discontinued on 8/13/12 due to the AE of cholestatic jaundice). She died on (b) (6). The investigator and Sponsor listed progressive disease as the primary cause of death and liver failure as the secondary cause. The Sponsor did not attribute the jaundice to the study drug.

3. **1801002-** AE and PD, MDS and PD, respectively. This 77 y/o was a patient whose primary cause of death is listed as PD, which also was the reason for treatment discontinuation. However, from a time point prior to her treatment discontinuation, she was noted to have pancytopenia, ranging from G3-4, requiring treatment delays and modifications. She finally was diagnosed with MDS about six weeks after discontinuing olaparib. She ultimately died 117 days after stopping olaparib and her cause of death was listed as progressive ovarian cancer and MDS. It does not appear that she received any further therapy for either the ovarian cancer or for MDS.

After the major amendment, there were 8 patients, from three of the six studies included, with deaths due to adverse event, shown in Table 28. The narrative descriptions for each of the patients who died are presented below the table.

Table 28: Deaths due to Adverse Event from Pooled Safety Database

Deaths due to adverse event	<b>Olaparib N=300</b>	<b>Study number</b>
<b>Total</b>	<b>8</b>	
Acute leukemia (AML)	2	42
Pulmonary embolus	1	42
Wound dehiscence	1	42
CVA	1	42
COPD	1	42
Sepsis	1	2
Intestinal perforation	1	9

Patient Narratives for Deaths:

Study 42

1. E302009-acute myeloid leukemia (AML)-63 y/o white female, with history of BRCA mutated breast cancer and ovarian cancer. Previous chemotherapy regimens included: CMF (1995 for breast cancer); Tamoxifen 1996-1999; epirubicin + cyclophosphamide 7/06- 2/07; carboplatin + Taxol 7/07- 1/08; carboplatin + gemcitabine 8/08- 3/09; Caelyx 11/09- 5/10. She had also previously received XRT to the left breast. She started olaparib on study 42 on 7/5/10. The patient discontinued olaparib “due to death” in (b) (6), and the cause of death was acute leukemia. The CRF shows that myelodysplasia may have started 8/3/10; on 8/10/10, it is noted that the AE worsened to acute leukemia.

Her course was complicated by sepsis (b) (6). The patient died due to acute leukemia on (b) (6).

E4007006- AML- 63 y/o female with h/o BRCA mutated ovarian cancer with peritoneal metastases originally diagnosed 10/18/07. She was treated with carboplatin + paclitaxel for 6 cycles ending 3/3/08. She subsequently received carboplatin +paclitaxel again from 3/3/09 until 9/7/09. In June 2010, she received single agent cisplatin for 10 cycles. She began therapy on Study 42 with olaparib on 1/23/11. Therapy was interrupted temporarily on study day 141 (6/12/11) due to myelosuppression. She permanently discontinued therapy with olaparib on 6/26/11 and was diagnosed with AML on 7/20/11. She received one cycle of daunorubicin on 7/24/11 as treatment for AML. She died on (b) (6). The primary cause of death was AML, and ovarian cancer was the secondary cause.

*Reviewer comment: These two patient deaths due to AML are concerning in the context of a small study. Although both patients had received multiple chemotherapy regimens prior to receiving olaparib, the signal for a causative relationship between olaparib therapy and the eventual development of MDS or AML is present. In my opinion, these two events and deaths are probably related to olaparib therapy, and support the inclusion of this potential drug related adverse reaction in the warnings and precaution section of the label. They also support the recommendation of the Post-Marketing Requirement that mandates that the Sponsor provide the Agency with annual updates on new and existing cases of MDS/AML for the first 5 years post-approval. This information will be important to monitor, and the results may require future labeling updates, depending on what the data shows.*

2. E2601027- pulmonary embolus (PE)-56 y/o white female with BRCA mutated breast cancer (right breast) diagnosed originally in 1998. She then developed breast cancer on the left side in 2005. She was diagnosed with primary peritoneal cancer in 3/08. She received chemotherapy with gemcitabine + carboplatin for 6 cycles and achieved a partial response. She was treated again with 4 cycles of gemcitabine + carboplatin in 4/10 and had progressive disease. She initiated therapy with olaparib on Study 42 on 3/8/11 but remained on study (b) (6) when she developed progressive disease. She suffered a PE and died on (b) (6). It is unclear from the CRF whether she had disease progression diagnosed the day prior to the PE, but the cause of the PE was said to be related to her underlying cancer (according to the investigator).

3. E7001005- wound dehiscence- 49 y/o white female h/o BRCA mutated metastatic ovarian cancer and breast cancer. Prior therapy for breast cancer included CMF from 12/94-5/95, followed by tamoxifen ending in 1/96. Ovarian cancer was diagnosed 5/20/03. Prior therapy for ovarian cancer included carboplatin + paclitaxel for six cycles ending 10/03. She received Taxol again from 11/03-7/04. She received six more cycles carboplatin + paclitaxel in 6/05. In 3/07, she received three more cycles of carboplatin. She received single agent doxorubicin from 7/07 to 1/08. She received four additional cycles of carboplatin + paclitaxel from 7/08-9/08. She began therapy on Study 42 with olaparib on 2/9/11. She experienced abdominal pain (colic) starting on 5/4/11. She experienced an SAE of G3 bowel obstruction on (b) (6), which required hospitalization. She subsequently died of suture /wound dehiscence on (b) (6).
4. E7201003- CVA- 58 y/o white female h/o BRCA mutated metastatic ovarian cancer diagnosed 11/19/08. Prior chemotherapy included carboplatin + paclitaxel in 1/09, as well as cisplatin + paclitaxel for six cycles in 4/09. She then received Caelyx for three cycles ending 2/10. Next, she received nine cycles of paclitaxel ending 5/10. She also received therapy with Sendoxan, tamoxifen, and mitoxantrone in 2010. She began therapy with olaparib on Study 42 on 2/11/11. On study day (b) (6), she experienced hemiparesis and confusion and subsequently suffered a CVA, which was fatal.
5. E4001042- chronic obstructive pulmonary disease (COPD)- 70 y/o white female with h/o heavy smoking, COPD and BRCA mutated metastatic ovarian cancer diagnosed 5/24/09. She received six cycles of carboplatin + paclitaxel resulting in a PR, with progression documented 9/23/09. She next received two cycles of carboplatin + docetaxel in 11/09, with CR documented. She subsequently received topotecan for four cycles 7/10-8/10 and had disease progression. She started on study 42 on 9/27/10. She died (b) (6); the cause of death was recorded as COPD. At tumor staging on 2/2/11, there were new lesions noted on CT scan in the lungs consistent with PD, although it was also noted that the Investigator's overall assessment was for SD (due to new lung lesions being likely a pulmonary inflammatory reaction).

#### Study 2

6. D0810C00002/001-0036-sepsis- 65 y/o white female is ovarian cancer diagnosed on 12/10/90. Prior chemotherapy included cisplatin + paclitaxel from 5/95-8/95, cisplatin + gemcitabine 9/98- 1/99, carboplatin alone 3/04- 8/04, then carboplatin + paclitaxel 8/05-9/05. She started on Study 2 on 10/26/06 with olaparib 400 mg BID. Her course was complicated by cytopenias starting on (b) (6). She became septic on (b) (6) and died on (b) (6) due to sepsis G5.

#### Study 9

7. Study 9- E0613005-intestinal perforation- white female with BRCA mutated ovarian cancer originally diagnosed 5/14/04 and found to have metastatic disease 5/18/05. Prior therapy for ovarian cancer included carboplatin + paclitaxel from 6/04 to 10/04, as well as carboplatin+ paclitaxel from 5/05 to 10/05. She then received carboplatin a gemcitabine from 5/06 till 10/06 and liposomal doxorubicin from 11/06 till 1/07. She also received tamoxifen from 2/07 to 3/07. She enrolled on Study 9 and began therapy with olaparib 800 mg per day on 7/9/07. She initially experienced G3 large bowel obstruction on (b) (6). She was hospitalized from (b) (6). She began C10 of olaparib on 5/6/08. She subsequently experienced an intestinal perforation on (b) (6) and died on (b) (6) of intestinal perforation and subsequent septicemia.

*Reviewer comment: Regarding attribution for the remaining deaths due to AE from the pooled safety analysis (besides the deaths due to AML/ MDS), although all of the events may have been related to olaparib therapy, the ability to definitively define attribution in these cases is limited. Although the death due to sepsis was likely related to the myelosuppression caused by olaparib, the remaining deaths, including intestinal perforation, wound dehiscence, PE, and CVA are all events that could occur in patients with advanced cancer, specifically advanced ovarian cancer. In this reviewer's opinion, it is unlikely that olaparib had a substantial contribution to these adverse events leading to the deaths of these patients.*

### 7.3.2 Nonfatal Serious Adverse Events

There were 38 patients with 53 serious adverse events (SAEs) on Study 19. Specifically, 25 patients (18.4%) on olaparib had 34 SAEs and 13 patients (10.2%) on placebo had 19 SAEs. The events are listed in Table 29.

Table 29: Study 19 Serious Adverse Events

<b>Serious Adverse Events</b>	<b>Olaparib n=136 N</b>	<b>Placebo n=128 N</b>
<b>Patient with any SAE</b>	<b>25 (18%)</b>	<b>13 (10%)</b>
<b>Blood and lymphatic system disorders</b>		
Anemia	3	0
Pancytopenia	1	1
Thrombocytopenia	1	0

<b>Cardiac disorders</b>		
Cardiac insufficiency	1	0
<b>Gastrointestinal disorders</b>		
Intestinal obstruction (small or large)	3	4
Constipation	1	0
Diarrhea	1	0
Vomiting	1	0
Melena	1	0
Intra-abdominal hemorrhage	1	0
Gastritis	0	2
Abdominal pain	0	1
Impaired gastric emptying	0	1
Nausea	0	1
<b>General disorders and administration site conditions</b>		
Hernia pain	1	0
Pyrexia	1	0
<b>Immune system disorders</b>		
Iodine allergy	1	0
<b>Infections and infestations</b>		
Pneumonia	1	1
Urinary tract infection	1	1
Upper respiratory tract infection	1	0
Appendicitis	1	0
Liver abscess	1	0
Endophthalmitis	0	1
Influenza	0	1
<b>Injury, poisoning, procedural complications</b>		
Femur fracture	1	0
Post-procedural hematoma	1	0
<b>Metabolism and nutrition disorders</b>		
Dehydration	0	1
<b>Musculoskeletal and connective tissue disorders</b>		
Osteoporosis	1	0
<b>Neoplasms benign, malignant and unspecified</b>		
Breast cancer in situ	1	0
Myelodysplastic syndrome	1	0
Bladder cancer	0	1
<b>Nervous system disorders</b>		
Syncope	1	0
<b>Respiratory, thoracic, and mediastinal disorders</b>		
Dyspnea	2	0
Pulmonary embolism	1	0

Cough	1	0
<b>Vascular disorders</b>		
Deep vein thrombosis	1	0
Vena cava thrombosis	1	0
Essential hypertension	0	1

In the population of patients treated with three or more prior lines of therapy (after the major amendment), there were 77 patients (35%) who experienced at least one serious adverse event. These events are depicted in Table 30. It is notable that certain serious adverse events had higher incidences in the more heavily pretreated population of patients, including anemia, bowel obstruction, nausea /vomiting, and infection. This may indicate that olaparib is not as well tolerated by patients who have received multiple prior lines of therapy.

Table 30: Serious adverse events in patients treated with 3 or more prior therapies

<b>Serious Adverse Events</b>	<b>Olaparib n=223 N</b>
<b>Patient with any SAE</b>	<b>77 (35%)</b>
<b>Blood and lymphatic system disorders</b>	
Anemia	12
Neutropenia/ febrile neutropenia/ leukopenia	5
Thrombocytopenia	3
Bone marrow failure	1
<b>Cardiac disorders</b>	
Pericardial effusion	2
<b>Gastrointestinal disorders</b>	
Abdominal pain	9
Ascites	1
Constipation	1
Enteritis	1
Bowel obstruction	19
Intestinal perforation	2
Hematemesis	1
Ileus	1
Intestinal perforation	1
Nausea and vomiting	8
Pancreatitis	1
Rectal hemorrhage	1
<b>General disorders and administration site conditions</b>	
Pyrexia	2

Device occlusion	1
Non-cardiac chest pain	1
<b>Infections and infestations</b>	
Sepsis/ infection	7
Urinary tract infection	2
Catheter/ device infection	2
Gastroenteritis	2
Pneumonia	2
URI	1
Abdominal abscess	1
<b>Injury, poisoning, procedural complications</b>	
Bone fracture	2
Suture rupture	2
<b>Investigations</b>	
Hemoglobin decreased	3
<b>Metabolism and nutrition disorders</b>	
Hypokalemia	1
Dehydration	1
<b>Musculoskeletal and connective tissue disorders</b>	
Pain in extremity	1
Intervertebral disc degeneration	1
Back pain	1
Hemarthrosis	1
<b>Neoplasms benign, malignant and unspecified</b>	
Acute leukemia*	2
Myelodysplastic syndrome**	1
<b>Nervous system disorders</b>	
Cerebral ischemia/ CVA	2
Convulsion	1
Cognitive disorder	1
<b>Renal and Urinary disorders</b>	
Acute renal failure/ Renal disorder NOS	2
<b>Reproductive System and Breast disorders</b>	
Vaginal hemorrhage	1
<b>Respiratory, thoracic, and mediastinal disorders</b>	
Dyspnea	4
Pleural effusion	4
Pulmonary embolism	2
Chronic obstructive pulmonary disease	1
<b>Vascular disorders</b>	
Deep vein thrombosis	2

### 7.3.3 Dropouts and/or Discontinuations

On Study 19, the majority of patients on both study arms had discontinued therapy prior to the data cutoff. The disposition for patients at the end of study 19 is shown in Table 31. Very few patients on either arm discontinued therapy due to adverse event, 7 on olaparib and 2 on placebo. The specific adverse events (with CTC grading) for all 9 patients are depicted in Table 32. It is also notable that 2 of the patients who discontinued therapy due to an adverse event went on to die as a result of the event; one due to hemorrhagic stroke and one due to cholestatic jaundice and related sequelae.

Table 31: Study 19 Disposition

<b>Reason for discontinuation from active therapy</b>	<b>Olaparib N=136</b>	<b>Placebo N=129</b>
<b>Patients ongoing treatment at data cutoff</b>	23	4
<b>Patients discontinued study treatment</b>	113	125
<b>Adverse event</b>	7	2
<b>Worsening of condition under investigation (PD)</b>	87	110
<b>Voluntary discontinuation</b>	11	8
<b>Severe non-compliance with protocol</b>	2	1
<b>Lost to follow-up</b>	1	0
<b>Other*</b>	6	4

Table 32: Study 19 Discontinuations due to Adverse Event

<b>Adverse Event</b>	<b>Olaparib N=7</b>	<b>Placebo N=2</b>
<b>Hemorrhagic stroke (G4→5)</b>	1	0
<b>Cholestatic jaundice (G4→5)</b>	1	0
<b>Small bowel obstruction (G4)</b>	1	0
<b>Herpes zoster (G2)</b>	1	0
<b>Palpitations/myalgias (G2)</b>	1	0
<b>Thrombocytopenia (G2)</b>	1	0
<b>Rash (G2, 3)</b>	1	1

<b>Nausea (G2)</b>	0	1
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After the major amendment, there were 15 patients from 4 studies who discontinued olaparib therapy due to adverse event, and the specific events are shown in Table 33. In particular, 7 of the 15 patients were treated on Study 42. All 15 patients had received 3 or more prior therapies prior to enrolling on studies to receive olaparib, and the majority of events were gastrointestinal events. Again, this may have been, in part, related to the advanced disease setting of these patients.

Table 33: Discontinuations due to adverse event in patients treated with 3 or more prior therapies

<b>Adverse Event</b>	<b>Olaparib n=15</b>
<b>Anemia/ thrombocytopenia</b>	2
<b>Neutropenia</b>	1
<b>Intestinal obstruction/ ileus</b>	4
<b>Nausea/ vomiting</b>	4
<b>Intestinal perforation</b>	1
<b>Abdominal pain</b>	1
<b>Liver enzyme elevation</b>	1
<b>Cerebrovascular accident</b>	1

*Reviewer comment: In this more heavily pretreated setting, the majority of adverse events leading to discontinuation were related to a gastrointestinal event (mainly intestinal obstruction, but other events as well), in contrast to the AEs leading to discontinuation in Study 19. This is likely related to the more advanced disease setting of these patients, who have had 3 or more prior lines of therapy for ovarian cancer.*

#### 7.3.4 Significant Adverse Events

##### Secondary malignancies

##### 1. Myelodysplastic syndrome/ AML

On Study 19, there were four patients (2.2%) diagnosed with myelodysplastic syndrome/therapy-related acute myeloid leukemia. Three were on the olaparib arm, and one was on placebo. In the entire safety database, including an estimated 2618 patients exposed to olaparib, twenty-one confirmed cases and one unconfirmed case of MDS/AML(1.2%), have been documented on nine studies.

Table 34 depicts the available and most relevant details on each of the twenty-two olaparib-treated patients diagnosed with MDS/ AML in the safety database, including BRCA mutation status, treatment arm, cancer for which olaparib was administered, duration of olaparib therapy, prior chemotherapy regimens, and cytogenetics, if available.

It is notable that most of the patients diagnosed with MDS or AML had received prior chemotherapy regimens including platinum and taxanes, and many received several courses of these agents, plus additional alkylating agents. Most, but not all patients had an underlying BRCA mutation, which likely confers an increased sensitivity to the DNA damaging properties caused by various chemotherapy agents, particularly alkylating agents and platinum therapy. For most patients, information on cytogenetics was not available; however, for the ones that did have information, the chromosomal abnormalities were consistent with the expected aberrations that are seen in therapy-related MDS/ AML (mainly abnormalities in chromosomes 5 and/or 7). The duration of olaparib therapy was variable, but ranged from 91 days to greater than 1700 days. In many cases, patients experienced a variable duration of cytopenias prior to diagnosis with MDS, often requiring delays and modifications of olaparib dosing.

Table 34: MDS/ AML in safety database

#	Study	Patient ID/ Age	Arm	Cancer under treatment	BRCA stat.	Days on study drug	Prior chemo agents received for cancer in question	Dx	Cyto-genetics (if done)	Outcome
1	19	E1801002 77y	Olaparib	Primary peritoneal	Wild gBRC A wild	313	Carboplatin+ paclitaxel; carboplatin+ gemcitabine; anastrozole	MDS-RAE B	5q-, 17p-, abn 7q	Death due to PD of peritoneal cancer
2	19	E0801001 53 y	Olaparib	Ovarian	Mut gBRC A mut	1728	Carboplatin + paclitaxel x 2 courses	AML	-	Ongoing-started daunorubicin + Ara-C
3*	19	E1808004 49 y/o	olaparib	ovarian	Mut gBRC A mut	(b) (6)	Carboplatin + paclitaxel; tamoxifen; bevacizumab + cisplatin + gemcitabine	No dx made, susp. MDS	-	Died of hemorrhagic stroke
4	41	E1405004 78y	Olaparib + carbo/ taxol → olaparib	Ovarian	wild Tumor wild type- retro spectiv ely defined ; Found Med	547	Carboplatin + paclitaxel	MDS	-	Started azacitadine; Death due to cerebral hemorrhage and DIC
5	41	E1503001 61y	Olaparib + carbo/ taxol → olaparib	Primary peritoneal	mut. Tumor mutant Prosp. Found Med	805	Carboplatin + paclitaxel x 3 separate regimens	MDS	-	Ongoing

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6	12	E7001010 71y	olaparib	Ovarian	Mut.	126	Cisplatin + doxorubicin + paclitaxel; tamoxifen; carboplatin + marimistat; carboplatin; topotecan; carboplatin + paclitaxel	MDS/ AML	Abn chromo 5 and 7; IDER	Death
					gBRC A mut					
7	12	E6007014 63 y	olaparib	Fallopian tube	Mut. gBRC A mut	744	Carboplatin + paclitaxel; letrozole; carboplatin + docetaxel	MDS/ AML	5q delet.; monosom y 7	Death s/p cord blood transplant  Note- patient had history of various other benign and malignant tumors (including breast cancer) treated with additional chemotherapy and XRT.
8	42	E0302009 63y	olaparib	Primary peritoneal	Mut.  Myriad BRCA (germli ne)	(b) (6)	Carboplatin + paclitaxel; carboplatin + gemcitabine; Doxil	MDS/ AML	Abn chr. 5 and 7	Death Note- previous breast cancer
9	42	E4007006 63y	olaparib	Ovarian	Mut. Not myriad used (other)	155	Carboplatin + paclitaxel; carboplatin + paclitaxel; cisplatin	AML	-	Death
10	42	E4003003 45y	olaparib	Ovarian	Mut. Not myriad (other)	298	Carboplatin + paclitaxel; cisplatin; carboplatin → cisplatin; doxorubicin; cyclophosphamid e; cisplatin + doxorubicin	MDS	-	Death
11	42	E7802003 55y	olaparib	Ovarian	Mut. Myriad - gBRC A	152	Carboplatin + paclitaxel; cyclophosphamid e + doxorubicin; carboplatin + gemcitabine → maint. Paclitaxel; cyclophosphamid e + bevacizumab	MDS	-	Death
12	42	E7802029 61 y	olaparib	Ovarian/ Peritoneal	Mut.- Myriad - gBRC A	764	Carboplatin + paclitaxel; possibly bevacizumab and topotecan	MDS	-	Ongoing
13	42	E4001012 51 y	olaparib	Breast (also had prior h/o ovarian cancer)	Mut -other- not myriad	1252	Cyclophosphami de, Adriamycin, 5FU; cisplatin + gemcitabine;	MDS vs. erythr oleuk emia	Deletion 5q31	Ongoing (no follow-up provided)
14	9	E0017011 68 y	olaparib	Ovarian	Mut. -	231	Carboplatin + paclitaxel;	AML	-	Death

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					Myriad mutate (gBRC A)		cisplatin + topotecan			
15	9	E0613008 63 y	olaparib	Ovarian	Mut. (other lab, unclear if germlin e)	1759	Cisplatin + paclitaxel; pazopanib	MDS/ AML	-	Death
16	2	001-0078 70 y	olaparib	Ovarian	Mut. (brca2)	981	Carboplatin + paclitaxel; carboplatin x 3 separate regimens	MDS/ AML	Complex karyo; +13, 17p-	Death after transf. to AML Note- also previous h/o breast cancer
17	4	003-2117 64 y	olaparib+ C/P	Breast	Mut.	580	Carboplatin + paclitaxel	MDS/ RAE B1	-	Ongoing
18	98	E8348038 67 y	olaparib + cediranib	Ovarian	Unk.	373	Platinum + taxane; carboplatin + gemcitabine + iniparib;	MDS	-	Ongoing
19	59	0810C005 9/008 60 y	Olaparib+ carboplati n + paclitaxel	Ovarian	Unk.	91	Carboplatin + paclitaxel+ bevacizumab; topotecan + bevacizumab; carboplatin+ paclitaxel + bevacizumab; carboplatin + paclitaxel + bevacizumab (again); carboplatin; Adriamycin;	MDS	2 clones: 5q-; monosom y 6p + monosom y 7q	Ongoing
20	24	E0008004 50 y/o female	Olaparib 400 mg bid	ovarian	Mut.	733	Carboplatin +paclitaxel; doxil; carboplatin + paclitaxel; carboplatin + paclitaxel	MDS	No cytogeneti cs reported	died
21	INV	D0810C00 55/JH001 67 y/o male	Olaparib 100 bid intermit tent (w/ irino/cis/ mito-C)	pancreatic	Mut.	?744	Capecitabine; XRT	MDS	No cytogeneti cs reported	Initiated azacytidine. No further f/u.
22	INV	D0810C00 55/JH004 67 y/o male	Olaparib 100 mg bid intermit tent (w/ irino/cis)	pancreatic	Unk.	350	Gemcitabine; capecitabine; XRT	MDS	No cytogeneti cs reported, 5-6% blasts	Ongoing, no f/u provided.

\*Patient 1808004 was an unconfirmed, but suspected, AML case. This patient was also one of the three olaparib patients who died on Study 19. As discussed previously, this patient suffered a hemorrhagic stroke which occurred within 30 days of stopping study drug, and she died as a result of the stroke. However, the patient had also experienced G4 thrombocytopenia four days prior to the stroke, as well as concurrent neutropenia and anemia. A peripheral smear at that time was reported as having 16% blasts present, and these details raise suspicion that this patient had

an underlying AML. However, this was not confirmed, and she died 3 days after the stroke occurred.

*Reviewer comment: As shown in the table above, the majority of the patients who developed MDS/ AML in this database (17 of 22 patients) have died. It is important to consider the MDS/AML incidence from the olaparib database in the context of the overall annual incidence of MDS/AML in the US. There is an estimated annual incidence of MDS in the US of approximately 3.3 cases per 100,000, or 0.0033%. The incidence in a large case-control study of almost 29,000 ovarian cancer patients who had received prior platinum therapy, was 0.3%. The incidence of MDS and AML in a population of patients carrying a gBRCA mutation is unknown. However, the incidence in Study 19 was markedly higher than these reported figures, at 2.2%. Likewise, the incidence out of the 193 ovarian cancer patients treated in Study 42 was 3.1%. And the incidence in the entire safety database is also notable, in comparison, at 0.8%.*

*Based upon these figures, the risk of treating patients with olaparib needs to be weighed against the potential benefit a given patient may expect to gain from this therapy.*

*It is recommended in the product labeling that patients be monitored with monthly complete blood count assessments while on olaparib therapy. If MDS or AML is confirmed while on therapy, olaparib should be discontinued. This particular adverse reaction has been included in the Warnings and Precautions Section of the product label. Likewise, one of the post-marketing commitments for this NDA approval is for the Sponsor to provide annual comprehensive updates (for 5 years post-approval) to the Agency, summarizing all cases of MDS and AML that have occurred in patients treated with olaparib to that point.*

## 2. Secondary malignancies other than MDS/ AML

In the safety database, there were 21 reports of secondary malignancies other than MDS/AML in 19 patients treated with olaparib and in one patient treated on Study 19 with placebo. A summary of these cases is shown in Table 35. The majority of the solid tumors were skin cancers, and most of patients (17) had a documented BRCA mutation. All patients diagnosed with secondary malignancies had also received other chemotherapy agents at some point. Given the presence of confounding factors in all cases, the definitive contribution of olaparib to the development of secondary malignancies is unclear. However, in the population of patients likely to receive olaparib therapy, the risk of the development of secondary malignancies during or after olaparib therapy is certainly present. Narratives for each of the patients are presented below the table.

Table 35: Secondary malignancies in olaparib-treated patients

No.	Study	Patient ID	Study Treatment	BRCA	Secondary	Time to
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	#			status	cancer diagnosed	onset (days)
1	19	E1701005	olaparib	mutated	Breast	469
2	19	E0106003	olaparib	mutated	Colon cancer	145
3	19	E1203002	Placebo	negative	Bladder cancer	44
4	12	E8001045	olaparib	mutated	Plasma cell myeloma	Post-tx. 784
5	12	E8001062	olaparib	mutated	Lung cancer	1085
					Lung carcinoma cell not specified, "recurrent"	1507
6	20	E0101044	olaparib	negative	Squamous cell skin	836
					Basal cell	787
7	24	E0004006	olaparib	mutated	Breast	204
8	42	E4001075	olaparib	mutated	Breast	504
9	42	E4004011	olaparib	mutated	Gastric cancer	Post-tx D359
10	42	E7801020 Male-pancreatic	olaparib	mutated	Squamous cell skin	361
11	42	E4001012	olaparib	mutated	Basal cell	448
12	42	E4001077	olaparib	mutated	Basal cell	14
13	42	E4001080	olaparib	mutated	Basal cell	176
14	42	E4001005	olaparib	mutated	Basal cell	366
15	42	E4001055	olaparib	mutated	Basal cell	208
16	42	E7801032	olaparib	mutated	Skin cancer	41
17	42	E2601008	olaparib	mutated	Skin (nos)	1
18	63	TN04 Male- CLL primary	olaparib	Not tested	Melanoma	90
19	4	002-01-2109	Olaparib + carbo and taxol—then olaparib mono	mutated	Precursor T-lymphoblastic lymphoma/leukemia	(b) (6) (died D (b) (6))
20	21	E0002986	Olaparib + cisplatin	mutated	Malignant muscle neoplasm	16

On Study 19, the secondary cancers included one patient diagnosed with colon cancer treated on the olaparib arm (gBRCA mutant), one patient with breast cancer *in situ* treated with olaparib (tumor BRCA mutant, gBRCA wild type), and one patient with bladder cancer treated with placebo (tumor BRCA wildtype). The details of these patient narratives are as follows:

1. E0106003- **colon/ appendiceal adenocarcinoma**- 57 y/o female with BRCA mutated ovarian cancer diagnosed originally in 2007. On study 19, she received olaparib and was diagnosed with appendiceal cancer on study D145- date was 4/5/10. Treated with right hemicolectomy and discontinued olaparib on (b) (6) (due to the surgery). Total duration on olaparib 196 days. She died on (b) (6).
2. E1701005- **DCIS**- 65 y/o patient with BRCA mutated ovarian/ peritoneal cancer diagnosed in 2004. She received olaparib on Study 19 starting October 2009 and was diagnosed with DCIS on study D469 (2/7/11). Olaparib was interrupted after the DCIS diagnosis but then restarted. Total time on olaparib was 1127 days, and she was still on therapy at the time of data cutoff 11/26/12.
3. E1203002- **bladder cancer**- 59 y/to female with h/o BRCA-negative ovarian cancer originally diagnosed in 2006. She was randomized to the placebo arm on Study 19 beginning on 10/8/09. She was on placebo for (b) (6) days, when she was diagnosed with bladder cancer on (b) (6). She voluntarily came off Study 19 on 1/20/10. She died on (b) (6) (cause not given). Her total time on placebo was 109 days.

The narratives on the remaining cases of secondary cancers in the safety database are presented below.

## Study 12

4. E8001045- **Plasma cell myeloma**- 50 y/o female with BRCA mutated ovarian cancer diagnosed 2/28/07. Prior chemotherapy included carboplatin + paclitaxel, carboplatin + docetaxel, and tamoxifen. She began olaparib 200 mg bid on Study 12 on 11/17/08. Study closed on 4/30/10 (Day 530), but she continued olaparib because she was benefitting. On 11/3/10 (Day 717), she had progressive ovarian cancer, so discontinued olaparib. One month later, in 12/10, she was noted to have hypercalcemia and was referred for a bone biopsy. She was diagnosed with IgG-kappa multiple myeloma on 1/9/11. She was treated for myeloma with catumaxomab and lenalidomide. The investigator considered the event of plasma cell myeloma to be related to olaparib. She died on (b) (6) of progressive ovarian cancer.
5. E8001062- **Lung cancer**- 65 y/o female with a heavy smoking history was diagnosed with metastatic BRCA mutated ovarian cancer (liver, mediastinum) on 8/28/02. She was treated with paclitaxel+ carboplatin, then tamoxifen (extent of these unclear, though appears she just received each regimen once). Olaparib 400 mg bid started 11/25/08 on

Study 12. Continued beyond study cut off 4/30/10 (day 522) because she was benefitting. On 11/10/11 (day 1085 of olaparib), she was diagnosed with Stage 1 squamous cell carcinoma of lung, by biopsy (tumor was positive for p53 and CK5/6, negative for TTF1). Olaparib was temporarily stopped prior to surgery. On (b) (6) (Day (b) (6)) she underwent definitive R upper lobectomy. She continued olaparib after, but the date of restarting is not given. On 1/6/13 (day 1507), she was found to have recurrent, metastatic lung cancer with multiple new lung nodules (biopsy proven to be consistent with primary lung tumor). As of May 20, 2103, she was still receiving olaparib (Day 1638), and was deemed to still have no sign of recurrent ovarian cancer. She was referred for further treatment for the metastatic lung cancer. Further follow-up is not provided, and it is unclear if olaparib was continued or stopped.

#### Study 20

6. E0101044- **Skin**- 1. Squamous cell 2. Basal cell- 67 y/o female with metastatic BRCA mutation NEGATIVE ovarian cancer diagnosed 9/11/07. She received chemotherapy with cisplatin + paclitaxel. She enrolled on Study 20 and began olaparib 400 mg BID starting on 7/7/09. She continued receiving olaparib after study closure on D252 because she was continuing to benefit. On (b) (6) (Day (b) (6)), she had a basal cell carcinoma removed from her L cheek. On 10/20/11 (D836), she was diagnosed with a squamous cell skin cancer, considered by the investigator to be related to olaparib. On (b) (6) (Day (b) (6)), another basal cell carcinoma, infiltrating type, was resected from her cheek. She was still receiving olaparib on 5/20/13 (Day 1414).

#### Study 24

7. E0004006- **breast cancer**- diagnosed with new left breast cancer- 46 y/o female with h/o BRCA1 mutated ovarian cancer diagnosed originally 4/16/09. The ovarian cancer was “locally advanced” with metastases in the peritoneum, spleen, and lymph nodes. Previous chemotherapy for ovarian cancer included one prior regimen of carboplatin + paclitaxel in 2009. She began therapy with olaparib 400 mg BID on 4/18/11. On Day 204 of olaparib, she was diagnosed with breast cancer. Olaparib was stopped temporarily and she underwent lumpectomy on (b) (6) (Day (b) (6)). Olaparib was restarted on D272, but was then discontinued on Day 282 (1/24/12). The investigator considered the breast cancer to be related to olaparib. Further details on the breast cancer are not provided.

#### Study 42- Phase 2 study in adv. gBRCA mutated tumors

8. E4001075- **breast cancer**- 47 y/o female with BRCA mutated ovarian cancer diagnosed on 9/2/09; metastases to the lymph nodes and liver. Therapeutic history included 4 regimens: carboplatin + paclitaxel; paclitaxel + cisplatin; tamoxifen; carboplatin + paclitaxel. She began therapy with olaparib 400 mg bid (date not given). She continued olaparib beyond the database lock (Day 413) until Day 508. On Day 504 of olaparib

(10/31/12), she was diagnosed with an invasive ductal carcinoma of the right breast. Olaparib was then discontinued 4 days later on 11/4/12. The investigator did not think that the diagnosis of breast cancer was related to olaparib. No further information was provided.

9. E4004011- **gastric cancer**- 57 y/o female with history of BRCA mutated breast cancer diagnosed on 4/28/22 with metastases to the bone. She had previously multiple prior regimens including cyclophosphamide + doxorubicin+ 5-FU; tamoxifen; letrozole; anastrozole; exemestane; fulvestrant; paclitaxel; capecitabine. She had also received XRT to the arm and neck (2 prior regimens). She continued olaparib till D326, although the reason for discontinuation was not given. On day 359 (33 days after olaparib discontinuation), she was diagnosed with G4 gastric cancer. The diagnosis of gastric cancer was considered to be unrelated to olaparib. No further details are provided.
10. E7801020- **squamous cell skin**- 71 y/o male diagnosed with BRCA mutated pancreatic cancer 3/10/10 with metastases to the liver and lymph nodes. He also had a past history of breast cancer. Previous therapy for pancreatic cancer included streptozocin + doxorubicin+ 5-FU; and carboplatin + etoposide. He initiated therapy with olaparib 400 mg bid on 11/19/10. On D361, he was diagnosed with squamous cell skin cancer of L hand, G3. It was removed surgically. This was considered to be unrelated to olaparib. This patient did have 3 prior adverse events related to skin wounds, including puncture wound to the left hand and poor wound healing. The patient continued on olaparib after removal of the squamous cell carcinoma until database lock (D 621, 7/31/12). The squamous cell skin cancer was considered to be unrelated to olaparib.
11. E4001012- **basal cell** – 51 y/o female with BRCA mutated breast cancer diagnosed 11/8/07, with metastases to the skin, soft tissue, bone. She had received 4 courses of prior chemotherapy over 8 years including: paclitaxel + carboplatin; cyclophosphamide + doxorubicin +5FU; cisplatin + gemcitabine; gemcitabine alone. She started on Study 42 on 4/28/10 and initiated olaparib 400 mg bid. On day 448, she was diagnosed with a basal cell carcinoma G2 on the left cheek. The cancer was removed, and no further treatment for the basal cell carcinoma was needed. She continued on olaparib until D826 (7/31/12). The event was considered unrelated to olaparib.
12. E4001077- **basal cell**- 57 y/o female BRCA mutated ovarian cancer diagnosed 2003 with ascites and lymph node involvement. Prior chemotherapy included carboplatin + paclitaxel; carboplatin x 2 separate regimens; 1 course of doxorubicin. She started olaparib on Study 42 on 6/15/11. On D14 of therapy, she was diagnosed with a basal cell carcinoma G3, which was removed. Her course on olaparib was complicated by G3 anemia requiring hospitalization, and G3 abdominal pain, also requiring hospitalization.

She discontinued olaparib on D70 (8/23/11) due to disease progression. She subsequently died on (b) (6) due to progressive ovarian cancer. The basal cell carcinoma was not related to therapy with olaparib.

13. E4001080- basal cell- 49 y/o female with BRCA mutated ovarian cancer first diagnosed 3/8/10. She was treated with carboplatin + paclitaxel over a 5 month period. She began on study 42, and therapy with olaparib 400 mg bid on 7/6/11. On Day 176, she was diagnosed with a G3 basal cell carcinoma on the chest wall, which was removed. The event was considered to be unrelated to olaparib. She continued olaparib therapy until 4/4/12 (D274), when she developed disease progression.
14. E4001005- **basal cell**- 66 y/o male had biliary tract cancer (BRCA mutation positive) with metastases to lymph nodes, diagnosed 4/30/09. Prior chemo included gemcitabine (front line) and cisplatin + 5FU (upon relapse). Patient also had XRT to the abdomen in 2009. Started on Study 42 on olaparib 400 mg bid on 3/31/10. On Day 366 of therapy with olaparib, he was diagnosed with a basal cell carcinoma (G2) on the nose. Olaparib was continued. The basal cell was not considered to be related to olaparib. Patient continued on olaparib until D854 of therapy (data cutoff date).
15. E4001055- **basal cell**- 74 y/o female with a h/o BRCA mutated colorectal cancer with lung metastases first diagnosed 4/29/04. She received carboplatin + taxol; 5FU; FOLFIRI + Bev; 5FU again. She began on olaparib 400 mg bid on 12/22/10. On D208 of therapy, she was diagnosed with a G3 basal cell carcinoma, which was treated surgically. The investigator considered this not to be related to olaparib. She continued olaparib until 2/14/12 (D420).
16. E780132- **skin cancer**- 63 y/o female with history of BRCA mutated ovarian cancer diagnosed on 8/12/01 with metastases to the peritoneum and GI tract. She had received 7 prior regimens for ovarian cancer, including methotrexate + 5FU; doxorubicin + cyclophosphamide+ gemcitabine; carboplatin + paclitaxel; carboplatin + paclitaxel.
17. E2601008- **skin cancer**- 58 y/o ovarian cancer patient previously received carboplatin+ taxol, gemcitabine + carboplatin, doxorubicin, and trabectedin. She began olaparib 400 mg BID on 11/9/10. On DAY 1 of olaparib, she was diagnosed with a G1 skin cancer (histology not given). Olaparib was continued until 7/27/11 (Day 261) due to disease progression. She died of progressive ovarian cancer (b) (6) months later, (b) (6).  
Investigator: Rita Schmutzler in Germany (Site 2601).

**Study 63- Phase I/II investigator-sponsored study to assess olaparib in patients with relapsed/refractory CLL with an 11q deletion or ATM mutation.**

18. D0810C00063/TN04- **melanoma**- 59 y/o male patient with CLL. Prior chemotherapy for CLL included FCR (flud, Cytosan, rituximab) from 12/09- 5/10. He also received chlorambucil in May 2011 and fludarabine + Cytosan from 6/1/11- July 2011. He began olaparib 8/10/11. On 11/8/11 (D90), he was diagnosed with G3 malignant melanoma on the L wrist, requiring surgery (SAE). He underwent wide excision and skin graft. Event considered to not be related to olaparib. Information was not provided as to whether the patient continued on olaparib after the diagnosis of melanoma.

**Study 4- Phase I open-label study to assess safety of olaparib + carboplatin or olaparib + carbo/taxol or olaparib + taxol in patients with advanced solid tumors.**

19. 002-01-2109- **Precursor T- lymphoblastic leukemia/lymphoma**- 70 y/o female with h/o ovarian cancer. Previous therapies for ovarian cancer included surgery (including a prophylactic mastectomy), paclitaxel/ cisplatin/ carboplatin from 8/07- 11/07 and therapy with tamoxifen from 4/09 to 12/09. She began on Study 4 and started treatment with olaparib 100 mg BID in combination with carboplatin+ paclitaxel. She started on this combination regimen from 2/18/10- stopped the paclitaxel 7/27/10, stopped the carboplatin 2/22/11, then continued single agent olaparib (400 mg bid) from 4/5/11 till 1/10/12. Reason for stopping olaparib at that time is unclear. On (b) (6), that patient was hospitalized with dyspnea and febrile neutropenia. She was subsequently diagnosed with Precursor T-cell lymphoblastic lymphoma/leukemia (secondary TLL). She died from this malignancy on (b) (6) days after stopping olaparib. The investigator considered this event to be related to olaparib, but not to carboplatin or paclitaxel.

**Study 21- Phase 1 Open-label study of olaparib with cisplatin**

20. E0002986- **malignant muscle neoplasm**- 43 y/o female with a history of breast cancer with metastases to the liver, bone, and locomotor first diagnosed in 2006. She had received multiple prior chemotherapy regimens, including FEC + taxol/ trastuzumab (5FU, epirubicin, cyclophosphamide), tamoxifen + trastuzumab, paclitaxel + vinorelbine; capecitabine + lapatinib; and letrozole + lapatinib. She also received XRT to the breast, hemipelvis, and sacrum. She began on Study 21 with olaparib 100 mg bid in combination with cisplatin on 1/12/10. On Day 16 of the study, she was diagnosed with a G2 malignant muscle neoplasm. It appears that olaparib was continued, and no further details are given about whether the neoplasm was biopsied, or if histology was ever reported. This patient also had a history of a muscle injury (wound on R triceps), but it is not stated what the location of the muscle neoplasm was. The patient continued on olaparib until 5/11/10 (D120) when disease progression was diagnosed. No other details are provided.

### 3. Pneumonitis

An uncommon but serious adverse event seen in patients receiving olaparib therapy is pneumonitis. In the safety database, there were ten olaparib-treated patients who experienced pneumonitis and two placebo-treated patients, including one on each arm in Study 19. Specific details on each patient are shown in Table 36, including the underlying diagnosis, duration of therapy with olaparib, prior therapies, and outcome. It is notable that five out of the ten patients had an outcome of death. However, several of these cases had confounding factors including underlying infection and lung involvement with tumor, so the attribution of these events is difficult to determine.

Table 36: Cases of Pneumonitis in Safety Database

Study	Age	Study arm	Total days on tx	Dx relative to end of tx	Underlying cancer and year of dx	Prior chemotherapy	XRT (y/n)	Worst Grade and Outcome
19	59	olaparib	336	83	Ovarian (2006)	3 regimens	n	<b>Recovered.</b> G1-olaparib was held. Treated with antibiotics for event. Event recovered D117.
20	45	olaparib	21	10	Breast (2008)	1 regimen	n	<b>Death.</b> G3- led to permanent olaparib discontinuation. This AE did not resolve, was present at time of her death ~3 mos. after study discontinuation.
2	51	olaparib	133	126	Lung (2003)	5 regimens	y	<b>Death.</b> G4 pneumonitis/organizing pneumonia. Progressed to G5 pneumonitis, but could not rule out concomitant PD and “lung

								infection” as primary cause of death.
5	61	Olaparib + gemcitabine	154	Post-tx, D165 (12 d post-olap)	Pancreas (2011)	none	n	<b>Recovered.</b> G3 pneumonitis-diagnosed by bronchoscopy 12 days after discontinuation of olaparib and gemcitabine. Treated with antibiotics and steroids. Could not distinguish whether pneumonitis was due to olaparib, gemcitabine, or both.
6	41	Olaparib + topotecan	~759	748	Thymic carcinoma (2006)	2 regimens	y	<b>Death.</b> G2 pneumonitis, SAE. Resulted in permanent study drug discontinuation and the event were ongoing at time of death.
39	57	Olaparib /paclitaxel	617	612	Gastric (2010)	1 regimen	n	<b>Unknown.</b> G2 pneumonitis, SAE. Study drug discontinued 5 days after onset. No details on therapy or outcome provided.
48	68	Olaparib + gemcitabine + cisplatin	7	7	Lung (unknown date)	unk	unk	<b>Recovered.</b> G3 pneumonitis.

1	74	Olaparib 100 bid	79	89 (10 days post-stopping)	Lung (2008)	1 regimen	y	<b>Death.</b> Likely related to pneumonitis
1	63	Olaparib 200 bid	26	36 (10 d post-stopping)	breast	none	y	<b>Death.</b>
1	37	Olaparib 400 bid	120	132 (12 d post-stopping)	ovarian	2 prior regimens over 6 mos	n	<b>Recovered.</b>
19	63	Placebo	141	99	Ovarian (2006); prior Breast cancer	5 regimens	n	<b>Recovered.</b>
39	51	Placebo / paclitaxel	113	108	Gastric (2006)	2 regimens	n	<b>Recovered.</b>

*Reviewer comment: The adverse event of pneumonitis in the context of olaparib therapy is rare; however, five of the ten cases (50%) reported had a fatal outcome. Therefore, this event has serious potential consequences for patients. As a result, this adverse event has been included in the Warnings and Precautions section of the label. Clinicians are instructed to interrupt treatment with olaparib if pneumonitis is suspected and to discontinue olaparib if pneumonitis is confirmed.*

### 7.3.5 Submission Specific Primary Safety Concerns

Not applicable.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Common adverse events occurring in  $\geq 20\%$  of patients on either arm of Study 19 (patients with gBRCA mutation) are shown in Table 37. The most frequent adverse events occurring more commonly in olaparib-treated patients were nausea, fatigue, and nasopharyngitis/ URI.

Abdominal pain/discomfort was also a common adverse event in both arms, with a slightly higher incidence in placebo-treated patients. It was notable that most adverse events in patients treated on either study arm were grade 1-2 in severity, with few grade 3-4 events overall.

Table 37: Study 19 Adverse Reactions in  $\geq 20\%$  Patients with gBRCA mutated ovarian cancer

Adverse Reactions	Lynparza N=53		Placebo N=43	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
<b>Blood and Lymphatic disorders</b>				
Anemia	25	4	7	2
<b>Gastrointestinal disorders</b>				
Abdominal pain/discomfort	47	0	58	2
Decreased appetite	25	0	14	0
Nausea	75	2	37	0
Vomiting	32	4	9	0
Diarrhea	28	4	21	2
Dyspepsia	25	0	14	0
Dysgeusia	21	0	9	0
<b>General disorders</b>				
Fatigue (includes asthenia, lethargy)	68	6	53	2
<b>Infections and infestations</b>				
Nasopharyngitis/Pharyngitis/URI	43	0	16	0
<b>Musculoskeletal and Connective tissue disorders</b>				
Arthralgia/Musculoskeletal pain	32	4	21	0
Myalgia	25	2	12	0
Back pain	25	6	21	0
<b>Nervous system disorders</b>				
Headache	25	0	19	2
<b>Respiratory, Thoracic, Mediastinal disorders</b>				
Cough	21	0	14	0
<b>Skin and Subcutaneous Tissue disorders</b>				
Dermatitis/ Rash	25	0	14	0

The common adverse events in  $\geq 20\%$  of olaparib treated patients in the database of those who had received three or more prior lines of therapy are shown in Table 38. Many of the events occurred with approximately the same frequency as in the patients treated in Study 19, with a few exceptions. Severe anemia (Grade 3-4) occurred in 18% of patients who had received 3 or

more therapies prior to olaparib. This is more than four times higher than the incidence of Grade 3-4 anemia seen in the olaparib-treated patients on Study 19 (4%). This is likely related most to the fact that the patients treated with olaparib in the pooled safety database were more heavily pre-treated in general, including having received more prior platinum regimens, than those treated on Study 19. Interestingly, other events, including nausea, abdominal pain, and fatigue of all grades had a slightly higher incidence in olaparib-treated patients on Study 19, although severe abdominal pain occurred in 8% of the 223 patients receiving three or more prior lines, compared with 0 patients on Study 19. The reason for this difference is not clear, although all of these events are often reported in patients with ovarian cancer receiving a variety of therapies, and the relatedness to a specific therapy and even the disease itself, is difficult to determine.

Table 38: Adverse events in  $\geq 20\%$  of olaparib treated patients with gBRCA mutated advanced ovarian cancer receiving 3 or more prior lines of chemotherapy

Adverse Reaction	3 or more lines of prior chemotherapy	
	Grades 1-4 N=223 %	Grades 3-4 N=223 %
<b>Blood and Lymphatic disorders</b>		
Anemia	34	18
<b>Gastrointestinal disorders</b>		
Abdominal pain/ discomfort	43	8
Decreased appetite	22	1
Nausea	64	3
Vomiting	43	4
Diarrhea	31	1
Dyspepsia	25	0
<b>General disorders</b>		
Fatigue/ asthenia	66	8
<b>Infections and infestations</b>		
Nasopharyngitis/ URI	26	0
<b>Musculoskeletal and Connective Tissue disorders</b>		
Arthralgia/ musculoskeletal pain	21	0
Myalgia	22	0

#### 7.4.2 Laboratory Findings

The common laboratory findings in Study 19 are shown in Table 39. The most notable laboratory abnormality, similar to the adverse events, was anemia. Grades 1-4 anemia, as a laboratory abnormality, occurred in 85% of patients treated with olaparib. Likewise, 85% of

olaparib-treated patients on Study 19 experienced in increased MCV (macrocytosis). The significance of these findings, particularly the finding of macrocytosis, relates to the link between olaparib and the incidence of MDS and AML. It is known that the presence of an elevated MCV at the time of a bone marrow biopsy for suspected MDS is an independent prognostic factor, increasing the likelihood of diagnosing MDS in a patient with unexplained cytopenias. Given the data, it seems that most of the patients who developed anemia in Study 19 had macrocytosis, as well. However, approximately half of the placebo patients on Study 19 also had anemia and macrocytosis. So, it is clear that although there appears to be some relationship between the anemia, the macrocytic nature of the anemia, and olaparib therapy, there also appear to be other factors involved (such as prior therapy) in this phenomenon. At this point, it still is not clear which patients who develop prolonged anemia (+/- macrocytosis) will ultimately go on to be diagnosed with MDS and/or AML, since the majority of patients with anemia during therapy did not develop the more serious sequelae of MDS or AML. Further follow-up on this issue will be needed to assess the long-term implications and link between prolonged anemia and the later development of MDS/AML after olaparib therapy.

Table 39: Laboratory abnormalities in patients with gBRCA mutated ovarian cancer treated on Study 19

Laboratory parameter*	Lynparza N=53		Placebo N=43	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Decrease in hemoglobin	85	8	58	2
Decrease in absolute neutrophil count	32	8	23	0
Decrease in platelet count	26	6	19	0
Mean corpuscular volume elevation	85	-	44	-
Increase in creatinine	26	0	5	0

The common laboratory abnormalities in ovarian cancer patients with gBRCA mutation who had received 3 or more previous lines of therapy are shown in Table 40. The overall incidence and grade of laboratory abnormalities in these patients was similar to that seen on Study 19, with the exception of a higher rate of grade 3-4 anemia in the more heavily pretreated population (8% on Study 19 vs. 15% in patients treated with 3 or more prior therapies). This may simply be related to the fact that the latter group had been subject to more courses of chemotherapy (mainly platinum therapy) prior to receiving olaparib. As noted previously, longer follow-up will be needed to answer these questions.

Table 40: Laboratory abnormalities reported in patients with gBRCA mutated advanced ovarian cancer receiving 3 or more prior lines of chemotherapy

Laboratory Parameter*	3 or more lines of prior chemotherapy	
	Grades 1-4 N=223 %	Grades 3-4 N=223 %
Decrease in hemoglobin (anemia)	90	15
Decrease in absolute neutrophil count (neutropenia)	25	7
Decrease in platelets (thrombocytopenia)	30	3
Decrease in lymphocytes (lymphopenia)	56	17
Mean corpuscular volume elevation	57	-
Increase in creatinine	30	2

\*Patients were allowed to enter clinical studies with laboratory values of CTCAE grade 1.

*Reviewer comment: The incidence of anemia, particularly severe anemia in the more heavily pretreated population, brings up the question as to whether the higher rate of severe anemia in more heavily pretreated patients will correlate with a higher risk of eventually developing MDS or AML. The macrocytic nature of the anemia lends support to a possible relationship between anemia and MDS/AML. Published literature (Rauw, et al. 2011) assessing the risk of diagnosing MDS or AML, based upon certain pre-bone marrow factors, includes the presence of cytopenias and macrocytosis. Both of these characteristics were independently associated with an increased likelihood of diagnosing MDA or AML.*

#### 7.4.3 Vital Signs

Vital sign abnormalities occurring during therapy with olaparib or placebo on Study 19 are shown in Table 41. The majority of patients on both study arms developed an elevation in systolic blood pressure (mostly grade 1-2), but almost twice as many developed a grade 3-4 elevation in SBP. Likewise, 11% of patients treated with olaparib experienced a grade 3-4 elevation in diastolic blood pressure, compared with only 2% of patients on placebo. The significance of this is not clear, given that olaparib has no known effect on blood pressure or blood vessel formation/ angiogenesis. There were no patients who discontinued olaparib therapy or needed dose reduction of olaparib due to hypertension or symptoms thought to be related to hypertension.

Table 41: Study 19 On-study vital sign abnormalities

Vital Signs Abnormalities	Olaparib N=53		Placebo N=43	
	G1-4 %	G3-4 %	G1-4 %	G3-4 %
<b>High systolic BP</b>	94	17	91	9
<b>Low systolic BP</b>	6	-	2	-
<b>High diastolic BP</b>	85	11	86	2
<b>Low diastolic BP</b>	9	-	0	0
<b>High pulse rate (&gt;100 bpm)</b>	21	-	12	-
<b>Low pulse rate (&lt; 60 bpm)</b>	26	-	19	-

#### 7.4.4 Electrocardiograms (ECGs)

Olaparib was active in the hERG assay at high concentrations but did not show evidence of effects on ECG intervals in anesthetized dogs. The hERG assay IC<sub>50</sub> (226 μM) was > 110-fold higher than the average steady state maximum free plasma concentration following the 400 mg BID dose used in humans. Based upon this, it was concluded by the Sponsor that an effect of olaparib on cardiac repolarization is unlikely. Several clinical studies (Studies 2, 12, and 19) performed thus far have provided standard 12-lead ECG data at baseline and at intervals throughout the study.

In addition, two studies were conducted to assess the effect of olaparib on QT interval. These include Study D0816C00007 which assessed the effect of itraconazole (CYP3A4 inhibitor) on the PK of olaparib (tablet formulation) and Study 4 (D0816C00004), which was a food effect study and also investigated the effect of single and multiple doses of olaparib on QT interval. Analyses of Study 4 or 7 individually demonstrated no direct effect of olaparib on ΔQTcF or on ΔQTcI. For both QT corrections and for all type of analysis (pooled, study 4 and study 7 analyses alone), it was demonstrated that olaparib does not cause a prolongation in QT interval of a magnitude which raises clinical concern.

Finally, according to the clinical data available, there were two events of prolonged ECG QT interval in the pooled safety dataset. The narratives on these two patients are as follows:

- Patient E6003135 (Study 12) was a 55 year-old female with *BRCA*-mutated ovarian cancer who received olaparib 400 mg bd for 79 days. On Day 26, a CTCAE grade 3 QT prolongation was reported, and olaparib treatment was temporarily stopped. Olaparib

was restarted, and the patient continued on treatment with no further events of QT prolongation reported.

- Patient E0103001 (Study 20) was a 52 year-old female with breast cancer (*BRCA* wildtype) who received olaparib 400 mg bd for 71 days. On Day 55, a CTCAE grade 1 event of prolonged QT was reported. Olaparib treatment continued until Day 71, when the patient discontinued due to disease progression. The event resolved on Day 78.

There was also one case of QT prolongation reported in a patient receiving a dose lower than 400 mg BID of olaparib:

- Patient E6007014 (Study 12) was a 63 year-old female with *BRCA*-mutated fallopian tube cancer who received olaparib 200 mg bd for 585 days. On Day 29, an event of CTCAE grade 1 QT prolongation was reported, which resolved on Day 30. Olaparib was continued, and no further events were reported.

There were no events of sudden death, ventricular tachycardia or torsade de pointes reported in the monotherapy pooled dataset.

#### 7.4.5 Special Safety Studies/Clinical Trials

No organ dysfunction studies have been completed, to date. There are currently two ongoing studies; one to assess the effect of renal impairment on the safety, tolerability, and PK of olaparib (Study D0816C00006), and one to assess the effect of mild or moderate hepatic impairment on the safety, tolerability, and PK of olaparib (Study D081600005). The final reports for both of these studies have been requested as post-marketing requirements as part of the approval of the olaparib NDA. These reports are expected to be submitted to the Agency in July 2015.

#### Hepatic Impairment

In the gBRCA population on Study 19 (n=96), the eligibility criteria for transaminases allowed for enrollment of patients with AST/ALT  $\leq 2.5 \times$  ULN (CTC Grade 1), unless liver metastases were present, in which case enrollment was allowed if AST/ALT  $\leq 5 \times$  ULN. At study enrollment (baseline), there were 8 patients on olaparib and 9 patients on placebo with a G1-2 AST elevation; there were 6 patients on olaparib and 4 patients on placebo with a G1-2 ALT elevation. During the course of study 19, G1-4 AST elevation occurred in 30 (57%) of patients treated with olaparib and 25 (58%) of the patients treated with placebo. There were two patients on olaparib and one on placebo who developed a G3-4 abnormality in AST/ALT during the study. The first olaparib patient, **E0805001**, died due disease progression and cholestatic jaundice, and is described in detail in Section 7.3.1 of this review.

The other two patients from Study 19 are as follows:

**E1102005 (olaparib)**- a 70 y/o white female with BRCA mutation and normal AST, ALT, and serum bilirubin levels at baseline. She first developed G1 ALT elevation on treatment Day 141

(AST and bilirubin remained normal). The G1 ALT persisted throughout the study, and then worsened to G3 on Day 420 (at that same time point, AST was G1, GGT was G3, alkaline phosphatase was G2, bilirubin was normal). On Day 431, AST and ALT were both at G3, GGT worsened to G4, alkaline phosphatase was G3, and bilirubin remained normal. Olaparib therapy was discontinued on this date with the reason of “disease under investigation worsened”. No laboratory values are reported after Day 431, and no hepatic related adverse events were reported. The patient continued to be followed until death on Day 869.

**E0709001 (placebo)**- 45 y/o white female with ovarian cancer with liver, GI, and lymph node metastases at the time of study enrollment on the placebo arm of Study 19. Baseline AST 36, ALT 27, Alkaline phosphatase 116, GGT 26, and bilirubin 0.7. On C1D15, AST 42 (G1), ALT 27, alkaline phosphatase 121, GGT 25. These parameters remained stable throughout C2, however on C3D1 (12/2/09), AST was noted to be 54 (G1), ALT 33, alkaline phosphatase 178, and GGT 54 (G1). She discontinued placebo therapy on 12/17/09 due to disease progression and began therapy with carboplatin and gemcitabine. Her liver abnormalities at the time of treatment discontinuation had worsened to AST G2 and ALT G3. She died of progressive ovarian cancer on (b) (6).

The laboratory datasets included for the studies after the major amendment did not contain liver function tests, so a thorough examination of liver abnormalities, based laboratory data, was not possible.

With regard to patient labeling, the current olaparib label indicates that the effect of hepatic impairment on exposure to olaparib has not been studied, (b) (4)

*Reviewer comment: Based upon the data assessed, including laboratory and adverse event data primarily from Study 19, hepatic toxicity is not a major side effect of olaparib therapy. (b) (4)*

*Once the data from the ongoing hepatic impairment study (Study D081600005) is submitted and reviewed, the label will be updated if a different conclusion is reached at that time.*

### Renal impairment

In the gBRCA patient population on study 19 (n=96), there were 6 patients (11%) on olaparib and 2 patients (5%) on placebo who had a Grade 1-2 creatinine elevation reported at baseline. While on study, the number rose to 14 (26%) patients on olaparib with grade 1-2 creatinine elevation. On the placebo arm of Study 19, the number of patients remained stable while on study, at and 2 (5%) with Grade 1-2 creatinine elevation. No patients on either arm were reported to have Grade 3 or 4 creatinine elevations throughout study 19.

After the major amendment, out of the 223 patients in the safety database, 67 (30%) of patients developed a Grade 1-4 creatinine elevation while on olaparib, and 4 patients (2%) developed a Grade 3-4 creatinine elevation.

The Sponsor did not provide narratives for any of these patients. Based upon analysis of the laboratory dataset, the Patient ID numbers for those who developed Grade 3-4 elevations while on olaparib therapy were as follows:

- Study 9- E0017008 (G3- Cr 380)- It appears that this patient had a low grade creatinine elevation (G1-2) throughout most of her time on study. However, she developed on isolated G3 elevation of study day 58. Then next value recorded for this patient was on study day 101, at which time the creatinine value had improved to G2. She appears to have remained therapy until Study day 505 (serum Cr was G1 at that time).
- Study 42- E0302004- G3 (Cr 422)- This patient also had low grade creatinine elevation (G1-2) throughout most of the study. She had one episode of elevation to G3 (Cr 422) on study day 164. Repeat Cr thereafter returned to G2.
- Study 42- E4007001- G3 (Cr 277)- This patient had only 3 on-study levels for creatinine recorded. On studies day 15 and 29, the levels were at Grade 1, but on Study day 48, the value had increased to 277 (Grade 3). This same patient had no adverse events reported to reflect the creatinine elevation (renal failure, etc), but did have one report of grade 2 dehydration, which was noted to recover. The exact timing of this report, with respect to the creatinine elevation could not be determined due to missing dates in the Adverse Event dataset.
- Study 42- E7802023- G4 (Cr 1149)- This patient had isolated creatinine elevations to 353 (G3) on study day 91 and to 1149 (G4) on study day 99. Upon assessing other values on days immediately before and after these dates, she had normal creatinine levels (“grade 0”) at all other time points, therefore, it is likely that these reported elevations to G3 and G4 were most likely due to laboratory errors.

*Reviewer comment: There does not appear to be a significant signal to suggest that olaparib directly causes renal failure/ impairment.*

In the current product labeling, it is noted that for patients with a creatinine clearance > <sup>(b)</sup><sub>(4)</sub> ml/min, there is no change in olaparib exposure, based upon renal function, and therefore no need to alter the olaparib dose in this situation. Currently, information on exposure to olaparib in patients with creatinine clearance <sup>(b)</sup><sub>(4)</sub> is not available, <sup>(b)</sup><sub>(4)</sub>. As noted previously, the results of the formal renal impairment study, Study D0816C00006, are still pending. Any necessary changes to the product labeling will be made after review of these study results, if applicable.

#### 7.4.6 Immunogenicity

An assessment of reactions that may indicate increased immunogenicity or an allergy to olaparib was done. The safety dataset including the patients treated with 3 or more prior lines of therapy (n=223) was assessed for adverse events including the terms:

Dermatitis allergic, drug hypersensitivity, flushing, generalized edema, edema, pruritus, pruritus generalized, rash, rash erythema/ macular/maculo-papular/ papular/ pruritic, swelling face, urticarial, wheezing.

In this analysis, 36 patients (16%) were identified as having had one or more of these adverse events. All events were grade 1-2 in severity. None of the events was considered serious. Two patients had dosing with olaparib temporarily disrupted due to the event, and no patients discontinued therapy due to these events.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

##### Anemia

On study 19, 40% (54/136) of the olaparib treated patients had anemia that was G2 or higher compared with only 10% (13/128) of placebo patients. Likewise, 7% (9/136) of patients on olaparib had G3 or higher anemia compared with <1% (1/128) on placebo.

The ramifications of anemia were evaluated, given that olaparib was to be used in a maintenance setting when patients would otherwise not be receiving any therapy. In the study 19 adverse event dataset, 11 olaparib-treated patients (8%) had a dose modification due anemia or low hemoglobin (regardless of CTC grade). Six of these were dose reductions, and 5 were dose interruptions. This is compared with only 1 patient on placebo who had a dose reduction for anemia.

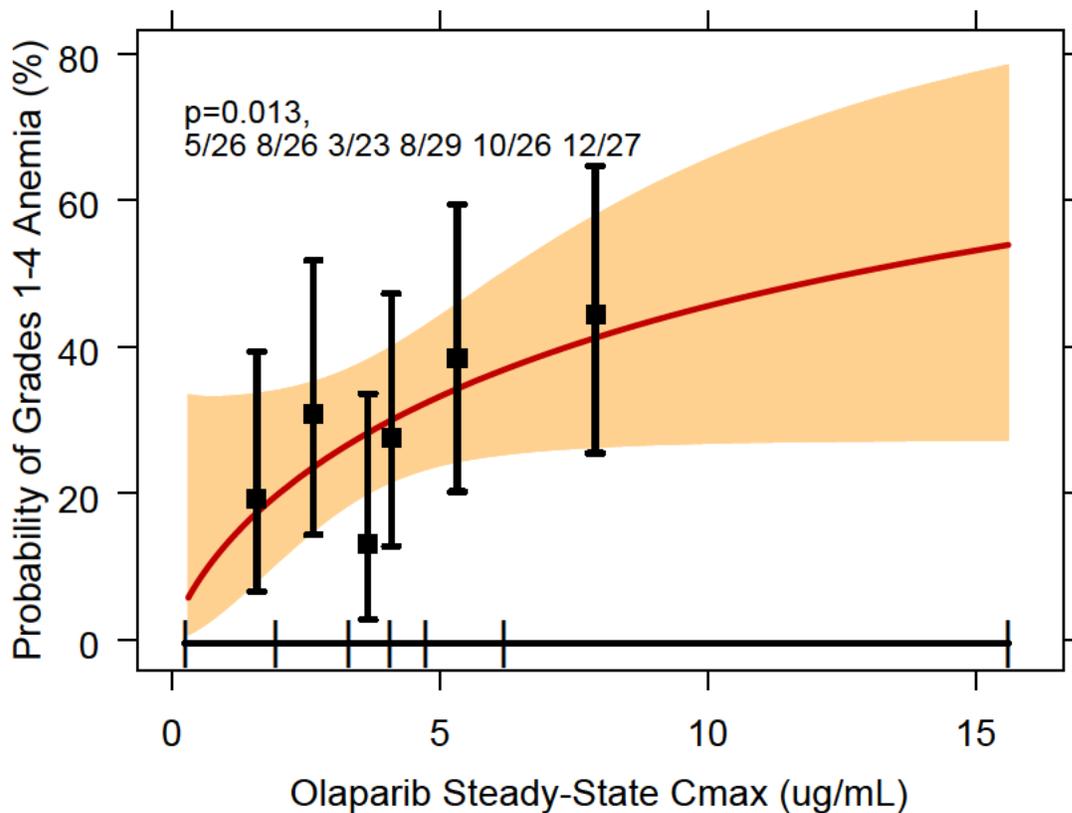
Of the patients who had anemia of G2 or higher on olaparib, 26% required transfusions, compared with only 7% on placebo. And of those who experienced G3 or higher anemia on olaparib, 88% required treatment, which could include transfusion or medications including erythropoietin-stimulating agents or iron supplementation.

When considering the entire safety database of olaparib monotherapy, 43% of olaparib treated patients experienced G2 or higher anemia and 12% experienced G3 or higher anemia. Therefore, the numbers in the entire safety database are comparable to those seen on Study 19.

Finally, an analysis was performed by Drs. Hongshan Li and Liang Zhao in the Office of Clinical Pharmacology to assess whether an exposure-response correlation exists for the adverse event of

anemia. The analysis was performed using data from other studies in the safety database (not including Study 19), and is depicted below in Figure 3. The conclusion from the analysis is that an increased exposure to olaparib does lead to an increased probability of developing anemia.

Figure 3: Exposure-response plot for anemia



### 7.5.2 Time Dependency for Adverse Events

The median duration (and range) of several adverse events on Study 19 was examined and the findings from this analysis are shown in Table 42. The analysis was performed for adverse events where there was a difference in median duration of greater than 20 days, for adverse events that occurred in  $\geq 10\%$  of patients on either arm. As is shown in the table, patients treated with olaparib had numerous AEs that were longer in duration than patients treated with placebo. The relevance of this analysis in the Study 19 patient population was to point to the issue of long term tolerability of olaparib in a maintenance setting. Although the majority of the adverse

events shown in the table were of Grade 1-2 severity, it led to concern whether the tolerability of olaparib for long periods of time would outweigh the benefit patients could expect from this therapy, compared to a treatment-free interval, with the introduction of therapy at the time of relapse instead.

Table 42: Median duration of adverse events on Study 19

AE	N	Olaparib N=53	Placebo N=43	Δ median
		Median (Min-Max) Days	Median (Min-Max) Days	
Abdominal distention	12	147 (30-613)	34 (7-71)	113
Dysgeusia	15	114.5 (16-706)	11 (2-89)	103.5
Abdominal pain upper	16	99 (4-484)	8 (1-15)	91
Nausea	57	96 (1-1174)	26 (1-85)	70
Arthralgia	16	89 (14-850)	22 (7-51)	67
Abdominal pain	28	75 (8-1061)	18 (2-109)	57
Back pain	21	57 (5-191)	8 (3-101)	49
Decreased appetite	19	66.5 (8-271)	18.5 (8-74)	48
Musculoskeletal pain	7	57 (3-194)	9.5 (4-15)	47.5
Constipation	13	44 (16-675)	4 (2-6)	40
Anemia	9	45 (8-254)	14 (14-14)	31
Asthenia	15	128 (26-165)	104 (45-130)	24
Cough	17	42 (3-835)	20 (1-92)	22

### 7.5.3 Drug-Demographic Interactions

In the population of patients treated with olaparib, after receiving three or more prior lines of therapy, the incidence of adverse events by age was assessed, and the results are shown in Table 43. There appeared to be considerable variability, by event, regarding which age group appeared to experience more or fewer adverse reactions. For example, the incidence of anemia was twice as high in patients  $\geq$  age 65 compared with patients  $<$  age 50. On the other hand, nausea was reported in 81% of patients age  $<$ 50 years, compared with only 45% of the patients  $\geq$  age 65. Likewise, fatigue and asthenia were reported in 92% of patients in the 50-65 years age group, compared with 70% of patients  $\geq$  age 65, and 64% of patients  $<$  age 50. In general, one might expect that older patients might tolerate olaparib less well than younger patients, particularly in the setting of having received multiple prior lines of therapy. However, this was not necessarily the case, and it seems that no definitive conclusions can be made on the issue of adverse events and drug tolerability, with respect to age.

Table 43: Adverse event incidence by age for patients receiving  $\geq 3$  prior lines of therapy

Adverse event by PT	N=219		
	Age <50 N=47 (%)	Age 50- <65 N=128 (%)	Age $\geq 65$ N=44 (%)
Anemia	10 (21)	47 (37)	18 (41)
Abdominal pain	24 (51)	56 (44)	16 (36)
Decreased appetite	8 (17)	28 (22)	14 (32)
Nausea	38 (81)	83 (65)	20 (45)
Vomiting	22 (47)	57 (45)	15 (34)
Diarrhea	18 (38)	30 (23)	11 (25)
Dyspepsia	10 (21)	34 (27)	4 (9)
Fatigue/ Asthenia	30 (64)	118 (92)	31 (70)
Nasopharyngitis	10 (21)	34 (27)	12 (27)
Arthralgia/ Musculoskeletal Pain	14 (30)	40 (31)	10 (23)
Myalgia	10 (21)	34 (27)	10 (23)

Given that the studies discussed in this review included only patients with ovarian cancer, an assessment of adverse events by gender could not be performed. Likewise, given that the populations of interest harbored the gBRCA mutation, which is seen almost exclusively in Caucasians (typically of Jewish descent), it was not surprising that approximately 97% of the entire study population on Study 19 was Caucasian. Likewise, on Study 42, when considering the 137 patients with measurable disease who had received 3 or more prior lines of therapy, 94% of the patients enrolled were Caucasian. For this reason, an analysis of adverse event incidence by race could not be performed.

#### 7.5.4 Drug-Disease Interactions

Not applicable.

#### 7.5.5 Drug-Drug Interactions

Please see the Clinical Pharmacology review by Dr. Elimika Pfuma for further details.

### 7.6 Additional Safety Evaluations

None.

#### 7.6.1 Human Carcinogenicity

Specific carcinogenicity studies have not been conducted with olaparib (in animals), however all patients in the clinical trials discussed in this review had cancer prior to study entry. However,

as discussed in Section 7.3.4 of this review, there have been cases of myelodysplastic syndrome and acute leukemia (MDS/AML) diagnosed in patients treated with olaparib (22 cases out of 2,618 treated patients, to date). The duration of therapy with olaparib in patients who developed these secondary malignancies ranged from < 6 months to > 2 years. A monitoring plan for complete blood counts has been recommended in the patient label, both during and after therapy with olaparib. Likewise, the Sponsor has been given a post-marketing requirement (PMR) which will mandate that they submit annual summaries of new and existing cases of MDS/ AML diagnosed in the previous year to the NDA for review. This will continue for 5 years after approval.

#### 7.6.2 Human Reproduction and Pregnancy Data

Olaparib was teratogenic and caused embryo-fetal toxicity in rats at exposures below those in patients receiving the recommended dose of 400 mg BID. Although data in humans is not available, it is assumed that olaparib can cause fetal harm if administered to pregnant women, based upon its mechanism of action and findings in animals. The labeling recommends that patients should be advised of the potential hazard of olaparib to a fetus and should be instructed to avoid becoming pregnant while taking olaparib.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

The original NDA submission contained a request for waiver of pediatric studies (referencing IND 75918 also), including participants up to age 16 years, as the proposed indication is for use as a therapy to treat non-germ cell ovarian cancer. The PeRC committee met on 7/2/14 and agreed with the Division to grant a full waiver for pediatric studies, since epithelial ovarian cancer does not occur in pediatric patients.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

This drug does not have drug abuse potential.

#### 7.7 Additional Submissions / Safety Issues

None.

### 8 Postmarket Experience

Not applicable.

## 9 Appendices

### 9.1 Literature Review/References

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## 9.2 Labeling Recommendations

See the final, approved product labeling.

## 9.3 Advisory Committee Meeting

On June 25<sup>th</sup>, 2014, an Oncologic Drugs Advisory Committee (ODAC) was held to discuss NDA 206162. The ODAC discussion focused on the indication in the platinum-sensitive maintenance setting, which was based primarily on data generated in Study 19. Key issues raised by the FDA review team included:

- Loss of Randomization for gBRCAm Subgroup
- Estimation of the Treatment Effect of Olaparib Therapy
- Risks of Olaparib therapy in the Platinum-Sensitive Maintenance Setting
- Reproducibility of Results in a Larger Trial

The first question posed to the Committee was the following:

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

There were 11 No votes as compared to 2 Yes votes. Primary reasons for the No vote included:

- Lack of OS benefit for maintenance therapy
- Unreliable results due to loss of randomization and small sample size

- Toxicity of therapy and risk of MDS/AML for patients not otherwise undergoing treatment.
- Potential to hinder accrual to confirmatory study.

Following the 11-2 vote, the second question was altered to include a discussion of whether an OS endpoint was necessary for a maintenance indication in ovarian cancer. The ODAC was divided as to whether an OS endpoint should explicitly be required; however, those members who advocated a PFS endpoint did not comment on the magnitude of benefit they felt was sufficient to support an approval. Most members agreed that Patient Reported Outcomes and Health Related Quality of Life Outcomes are important and should be measured.

The FDA briefing document is appended below.

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## Executive Summary

Olaparib is an oral inhibitor of polyadenosine 5'-diphosphoribose polymerases (PARP). The applicant is seeking initial approval of this drug for the indication of maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline *BRCA* (*gBRCA*) mutation as detected by an FDA-approved test 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 study D0810C00019 (Study 19) in 96 patients with deleterious germline *BRCA* mutation (*gBRCAm*)-associated, platinum-sensitive ovarian cancer. Study 19 was a multinational, randomized, double-blind, placebo-controlled trial of 265 patients with platinum-sensitive ovarian cancer who were in response to platinum-based chemotherapy. Patients were randomized 1:1 to receive either olaparib or placebo. Randomization was stratified by the time to disease progression from the completion of the penultimate platinum therapy (6-12 months vs. > 12 months), objective response to the last platinum containing regimen prior to enrollment on study (CR vs. PR), and the ethnic descent of the patient (Jewish vs. Non Jewish). The primary efficacy analysis of Study 19 was investigator-determined progression-free survival (PFS).

In a pre-specified analysis of a retrospectively identified subgroup of 96 patients with *gBRCAm* associated-ovarian cancer, there was an improvement (hazard ratio (HR) 0.17) in PFS for patients randomized to olaparib treatment, with median PFS of 11.2 months in the olaparib arm and 4.1 months in the placebo arm. No alpha adjustments were made for multiplicity introduced by analyzing multiple endpoints (excluding overall survival), or analyses within the *BRCA* subgroups. At the time of the latest interim analysis of overall survival (OS), there was no significant difference between the two arms (HR 0.85).

The safety profile of olaparib revealed that while Grade 1-2 adverse events were frequent, Grade 3-4 adverse events were rare, and deaths from treatment-emergent adverse events (TEAEs) also were rare. Common adverse events include nausea, fatigue, abdominal pain, vomiting, diarrhea and anemia. Patients treated with olaparib had higher rates of gastrointestinal events, anemia, neutropenia, fatigue, asthenia, infections and respiratory disorders than patients treated with placebo.

The Division of Oncology Products 1 seeks the advice of the Oncologic Drugs Advisory Committee regarding the pending NDA for olaparib on the following points:

1. Do the efficacy results from Study 19, namely a seven-month improvement in median progression-free survival and a hazard ratio of 0.17, along with the safety data in the *gBRCAm* population, demonstrate a favorable risk-benefit profile of olaparib maintenance monotherapy in *gBRCAm*-associated, platinum-sensitive, relapsed high-grade serous ovarian cancer that is in response to platinum-based chemotherapy?

2. The potential confirmatory trial is designed to detect a statistically significant but potentially clinically insignificant improvement in PFS. What is the appropriate magnitude of treatment effect for median improvement and hazard ratio to be demonstrated in the SOLO-2 trial to consider olaparib to be of direct clinical benefit to this patient population?

## Background

### Ovarian Cancer

Ovarian cancer is the fifth leading cause of cancer mortality in women with an estimated 22,000 new cases diagnosed and 14,270 deaths from the disease in the US in 2014 (Siegel R, 2014). Standard therapy for advanced ovarian cancer consists of surgical debulking and a chemotherapy regimen consisting of a platinum agent and a taxane (Stuart G, 2011, Armstrong D, 2006, Katsumata N, 2009). Therapy for relapsed disease is dependent on the interval between the date of the final dose of initial therapy and date of relapse, with platinum-sensitive ovarian cancer being defined as relapse that occurs greater than six months from the date of the last dose of platinum-based chemotherapy (Thigpen J, 1994). Therapy for platinum-sensitive disease typically consists of platinum-based chemotherapy, and a platinum doublet regimen is associated with an improvement in overall survival when compared to single agent platinum (Collaborators, 2003). The time interval between the date of the last platinum-based treatment and progression is positively correlated with the probability of responding to further platinum therapy, as those patients who have a longer platinum-free interval will have a higher response rate to further platinum treatment (Pujade-Lauraine E, 2002). Non-platinum regimens typically are not used in the platinum-sensitive setting due to the overall survival advantage seen with platinum doublets; however, intolerance to platinum agents is a clinical concern, as the risk of cumulative toxicities, particularly carboplatin allergy or neuropathy, increases over the course of continued treatments.

Several chemotherapeutic and biologic agents have been studied as maintenance therapy; however, there are currently no approved agents for the maintenance treatment in platinum-sensitive, relapsed ovarian cancer. Chemotherapeutic agents such as doxorubicin, topotecan and platinum agents are associated with increased toxicity without definitive efficacy (Pfisterer, 2006, De Placido, 2004, Bolis, 2006). A GOG study of 12 cycles of paclitaxel vs. 3 cycles of paclitaxel was associated with a seven-month improvement in PFS in the front-line maintenance setting; however, an additional study of a lower dose of paclitaxel did not replicate these findings, and paclitaxel as maintenance therapy was not widely adopted (Markman, 2003, Pecorelli, 2009). Maintenance treatment with agents targeted against VEGF and VEGFR are associated with improvements in PFS without demonstration of a survival benefit (Burger, 2011, Perren, 2011, Aghajanian, 2012, Du Bois, 2013).

## **BRCA**

The BRCA genes, BRCA1 and BRCA2, encode proteins involved in the DNA damage repair pathway. Deleterious mutations of BRCA1 and BRCA2 are associated with an increased risk of the development of breast and ovarian cancers; however, not all mutations are considered to be deleterious (Mik Yi, 1994, Wooster R, 1995). The majority of deleterious mutations are protein-truncating mutations. Missense mutations and large rearrangements of DNA segments within the BRCA genes also result in loss of function. It is estimated that the incidence of deleterious germline BRCA mutation (gBRCAm)-associated ovarian cancer is approximately 10-15% of all cases of ovarian cancer, corresponding to an annual incidence of approximately 2000 cases per year in the U.S. (Pal, 2005, Zhang, 2011).

Patients with gBRCAm-associated ovarian cancer are treated no differently than patients without a deleterious mutation, but the presence of a mutation appears to be positively correlated with increased survival and responsiveness to chemotherapy (Chetrit, 2008, Alsop, 2012 Bolton, 2012). Due to the increased susceptibility to chemotherapy, it is expected that the patient with gBRCAm-associated ovarian cancer will be exposed to multiple lines of various chemotherapeutic agents. Therefore, treatment-free intervals are of utmost importance to this patient population, as they allow adequate recovery from cumulative adverse reactions in preparation for the inevitable additional treatment regimen. Maintenance of a high quality of life is critical.

## **Approved Therapies**

There are no FDA-approved therapies for the maintenance treatment of gBRCAm-associated, platinum-sensitive ovarian cancer. FDA-approved therapies for the treatment of advanced ovarian cancer include, but are not limited, to:

- Carboplatin
- Paclitaxel
- Gemcitabine
- Pegylated Liposomal Doxorubicin
- Topotecan

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. There is also the concern whether the maintenance therapy will attenuate the anti-tumor activity of subsequent treatments.

Recently, a SGO/OCNA “Endpoints in clinical trials: What do our patients consider important?” survey was conducted in which patients with ovarian cancer were asked about the “minimally acceptable” difference of the median variables of PFS and OS they would accept for a new treatment. Patients were given the option of 1, 2, 3, 4 or 5+ months. The majority (>70%) desired a 5 or more month increase of either median PFS or OS, which was the largest increase that the patient could input. The true desired effect may be much larger (Herzog, 2014). The survey results were somewhat surprising, as it was previously assumed that patients would desire an improvement in these metrics of 3-4 months. It is important to note that the survey questions did not specifically address maintenance treatment, but the results shed light on the type of magnitude of effect the surveyed patients with ovarian cancer deem acceptable for new treatments.

### Major Regulatory Milestones for Olaparib Development

The major regulatory milestones for olaparib development in gBRCAm-associated ovarian cancer are depicted in Table 1 below.

Table 44: Key Regulatory Activities Related to Clinical Development

Milestone	Time	Details
IND 75,918 activated	September 2006	
Guidance Meeting	October 2012	Discussed olaparib development program for patients with gBRCAm associated ovarian cancer. FDA considered the gBRCAm subgroup results of Study 19 to be provocative but insufficient to support an approval.
Pre-submission Meeting	March 18, 2013	Joint meeting with FDA/CDER/CDRH and AstraZeneca and Myriad Genetics Inc. to discuss regulatory pathway for the companion diagnostic assay.
Breakthrough Therapy Designation Request	March 19, 2013	Request submitted on the basis of Study 19.
Breakthrough Designation Denial	May 16, 2013	
Pre-NDA Meeting	October 2, 2013	FDA stated its expectation for a potential concurrent NDA and PMA approval and the likelihood that the application would be discussed at an advisory committee
NDA Submission	February 3, 2014	

## Design of the Major Efficacy Trial (Study 19)

Study 19 is a randomized (1:1), double-blind, multicenter, placebo-controlled study assessing progression-free survival in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer, in partial or complete response to their last platinum-containing regimen. Patients were randomized to olaparib treatment or matching placebo.

### Key Inclusion Criteria

- 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  $\geq 1.5 \times 10^9/L$
  - Platelet count  $\geq 100 \times 10^9/L$
  - 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  $\leq 2$

### Key Exclusion Criteria

- Patients with low grade ovarian cancer (Grade 1)
- Patients who have had drainage of their ascites during the final 2 cycles of their last chemotherapy regimen prior to enrolment on the study.
- Persistent Grade 2 or greater toxicities caused by previous cancer therapy.
- Patients requiring treatment with potent inhibitors or inducers of CYP3A4.

### Randomization

Patients were randomized 1:1 to receive olaparib treatment or matching placebo. Randomization was stratified by the time to disease progression from the completion of the penultimate platinum therapy (6-12 months vs. > 12 months), objective response to the last platinum containing

regimen prior to enrollment on study (CR vs. PR), and the ethnic descent of the patient (Jewish vs. Non Jewish).

## **Treatment**

Arm 1           olaparib 400 mg BID  
Arm 2           matching placebo BID

Patients were treated until objective disease progression according to RECIST 1.0 criteria or until the patient withdrew consent. If a patient demonstrated CA-125 progression determined by a two-fold increase from the baseline CA-125 on two occasions, 7 or more days apart, a patient may have an unscheduled tumor assessment to determine progression by RECIST criteria. If progression was not demonstrated, patients would continue treatment until the next radiological assessment. If scans were performed outside of scheduled visit  $\pm$  1 week window interval and the patient had not progressed, subsequent scans were to have been performed at their scheduled time points.

## **Assessments**

All baseline tumor assessments using CT or MRI of the abdomen and pelvis were to be performed no more than 28 days before the start of study treatment and ideally should have been performed as close as possible to the start of study of treatment. Follow-up assessments were to be performed every 12 weeks  $\pm$  1 week after start of treatment until week 60 and every 24 weeks  $\pm$  1 week thereafter.

## **Safety Evaluation**

The Phase 2 trial D0810C00019 (Study 19) included safety assessments at baseline, every week in the first two cycles, on day 1  $\pm$  three days of every subsequent 28-day cycle, at the end of treatment and at a follow-up visit (30 days after the last dose). All adverse events that had not recovered completely by the end of treatment were to be followed until resolution.

At baseline, safety assessments included medical, oncologic, and surgical history, vital signs, physical examination, laboratories (hematology, chemistries, liver enzymes and function, urinalysis, pregnancy test), assessment of ECOG PS and ECG. Safety assessments performed at the start of each cycle were the same as at baseline, except pregnancy tests were not required after baseline. Post-treatment follow-up for survival was to occur every 8 weeks until at least the time of the final PFS analysis.

AEs were coded by body system using a medical dictionary for regulatory authorities (MedDRA®) and were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 3.0.

## Study Efficacy Endpoints

The primary efficacy endpoint was PFS per RECIST criteria as assessed by the investigator. Secondary endpoints included best overall response, CA-125 response (GCIG criteria), overall survival, disease related symptoms as measured by FOSI and health-related quality of life measured by the FACT-O scale.

## Statistical Methods

The primary analysis for PFS was a Cox proportional hazards model with factors for time to progression (6-12 months and >12 months) after the penultimate platinum therapy before study enrolment), objective response (CR or PR, after the last platinum therapy before enrolment on the study) and Jewish decent (yes or no) in accordance with the stratification factors used at randomization. The effect of treatment was to be estimated by the adjusted HR together with its corresponding 80% and 95% confidence intervals (CIs). Kaplan-Meier plots of PFS were presented by treatment group.

The existence of any treatment-by-covariate interactions was to be investigated and the assumption of proportionality was to be assessed. The primary analysis used data programmatically derived from the objective RECIST assessments. An exploratory analysis using the FAS that includes BRCA status in the COX model was to be performed.

No adjustments were made for multiplicity introduced by analyzing multiple endpoints (excluding OS), or analyses within the *BRCA* subgroups.

## Amendments to the Statistical Analysis Plan

The primary efficacy analyses of this study were based on the ITT population. A subgroup analysis of efficacy by *gBRCA* status was performed in order to investigate the efficacy and safety of olaparib in this subgroup. This analysis was not defined in the Clinical Study Protocol (CSP) but was prospectively defined in the SAP (May 28, 2011) that was finalized prior to unblinding of the data for analysis. A summary of key changes are summarized in Table 2 below.

Table 45: Key Changes to the Analysis Plan

Analysis Change	Summary of Changes
Original Clinical Study Protocol (CSP) June 2, 2008	Co-primary population of Homologous Recombination Deficient (HRD) subset was referred to in the statistical methodology portion.
CSP Amendment 3 June 2, 2009	Analysis of PFS in the HRD population was removed as a co-primary objective
Pre-specification	SAP amended to include a subgroup analysis by BRCA status. SAP signed

of BRCA subpopulation June 3, 2010	off prior to unblinding of the data for the primary analysis.
Data cut off for primary PFS analysis June 30, 2010	Data were unblinded following data cut off, but investigators were not unblinded. Preliminary suggestion of differential improvement of PFS in the BRCA subpopulation (known BRCA mutation status was 37% at this time)
Analyses of blood and tumor samples for BRCA mutation status. All of 2012	All available blood samples were tested for <i>BRCA</i> status ( <i>gBRCA</i> ) by the Myriad laboratory developed test and PFS and OS were reanalyzed on the basis of the resulting larger data sets. After testing, the retrospective identification of <i>gBRCA</i> mutation status resulted in 210/265 (79%) of the study population having a known <i>gBRCA</i> status as defined by either the Myriad test or other local testing.

## Study 19 gBRCAm Patient Demographics

A total of 265 patients at 82 sites in 16 countries were enrolled in Study 19. BRCA mutation status was known at the time of randomization in 37% of the ITT population. In 2012, the applicant tested all available blood samples for *gBRCA* mutations, resulting in 79% of the ITT population having a known BRCA mutation status by either the Myriad Integrated BRCAAnalysis test or local testing. Table 3 depicts the summary of BRCA mutation status. 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.

Table 46: BRCA Status

	<b>Olaparib (N=136)</b>	<b>Placebo (N=129)</b>
<i>gBRCA</i> (Rand) <sup>1</sup>	24%	22%
wtBRCA (Rand)	13%	16%
<i>gBRCA</i> (retro) <sup>2</sup>	15%	12%
wtBRCA (retro)	24%	34%
<b><i>gBRCA</i> (CRF+retro)<sup>3</sup></b>	<b>N=53 39%</b>	<b>N=43 33%</b>
wtBRCA (CRF+retro)	37%	50%
tBRCA <sup>4</sup>	6%	8%

1 BRCA mutation status known at the time of randomization

2 Retrospectively identified BRCA mutation status

3 Total number of patients with identified *gBRCA* deleterious mutation

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

Demographic information for the gBRCAm population is depicted in Table 4 below. There were more patients on the olaparib arm who received less than or equal to 3 prior chemotherapy regimens and who had a time to progression on their penultimate platinum regimen interval of greater than 12 months as compared to the placebo arm.

Table 47: Key Demographic Parameters of the gBRCA mutation Population

	<b>Olaparib (N=53)</b>	<b>Placebo (N=43)</b>
Median Age	56	55
Number of Prior Chemotherapy Regimens		
≤ 3	42	31
> 3	11	12
Time to Progression Penultimate Platinum Regimen		
> 6 months; < 12 months	22	21
> 12 months	31	22
Median Time From Most Recent Disease Progression to Randomization (days)	195	189
Median Time From Completion of Final Platinum Chemotherapy to Randomization (days)	40	43
gBRCA Mutation Type		
BRCA1	40	30
BRCA2	13	13

The final platinum chemotherapy regimen prior to randomization of the gBRCAm population is depicted in Table 5 below. There were more patients on the olaparib arm who received single agent platinum prior to receiving olaparib as compared to those receiving placebo.

Table 48: Platinum-containing Regimen Immediately Prior to Randomization (gBRCAm)

<b>Platinum Regimen Immediately Prior to Olaparib Treatment</b>	<b>Olaparib (N=53)</b>	<b>Placebo (N=43)</b>
Platinum and Taxane	30	33
Platinum and Gemcitabine	25	33
Platinum and Anthracycline	11	14
Other Platinum Doublet	11	7
Single Agent Platinum	23	14

## Study 19 Efficacy Analyses

### Efficacy Outcomes

The primary efficacy outcome measure of Study 19 was investigator-assessed PFS using the data cut-off of June 30, 2010. At the time of the PFS analysis, there were 153 total events with one death in the absence of RECIST progression occurring in the olaparib arm. The remainder were progression events by RECIST criteria. Table 6 summarizes the primary efficacy outcome measure in the ITT population.

Table 49: Progression-free Survival Analysis in the ITT Population

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

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

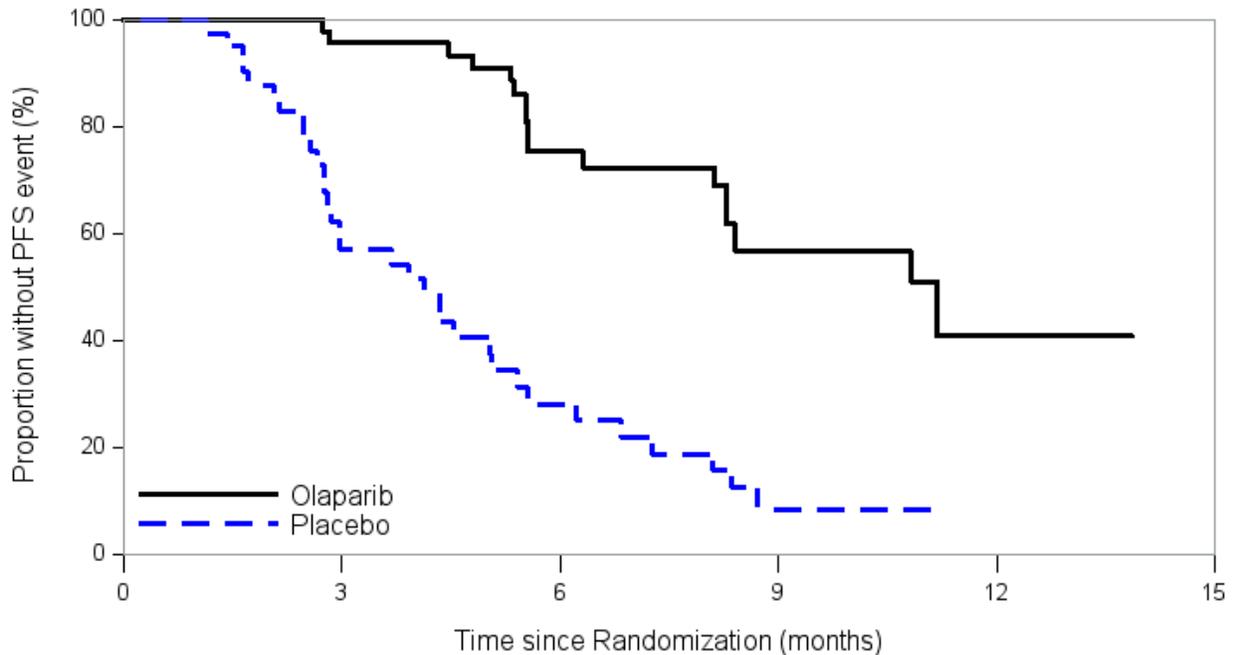
As described above, a pre-planned analysis of PFS in the known gBRCAm subpopulation suggested a differential improvement in this subset. Retrospective identification of BRCA status using patient's archived blood samples increased the gBRCAm population. Table 7 below summarizes the PFS analysis in the gBRCAm population, and Figure 1 depicts the Kaplan-Meier plot of PFS in the gBRCAm population.

Table 50: Progression-free Survival Analysis in the gBRCAm Population

	<b>Olaparib (N=136)</b>	<b>Placebo (N=129)</b>
Median PFS in months (95% CI)	11.2 (8.4, NR)	4.1 (2.8, 5.1)
Hazard Ratio (95% CI) <sup>1</sup>	0.17 (0.09, 0.32)	

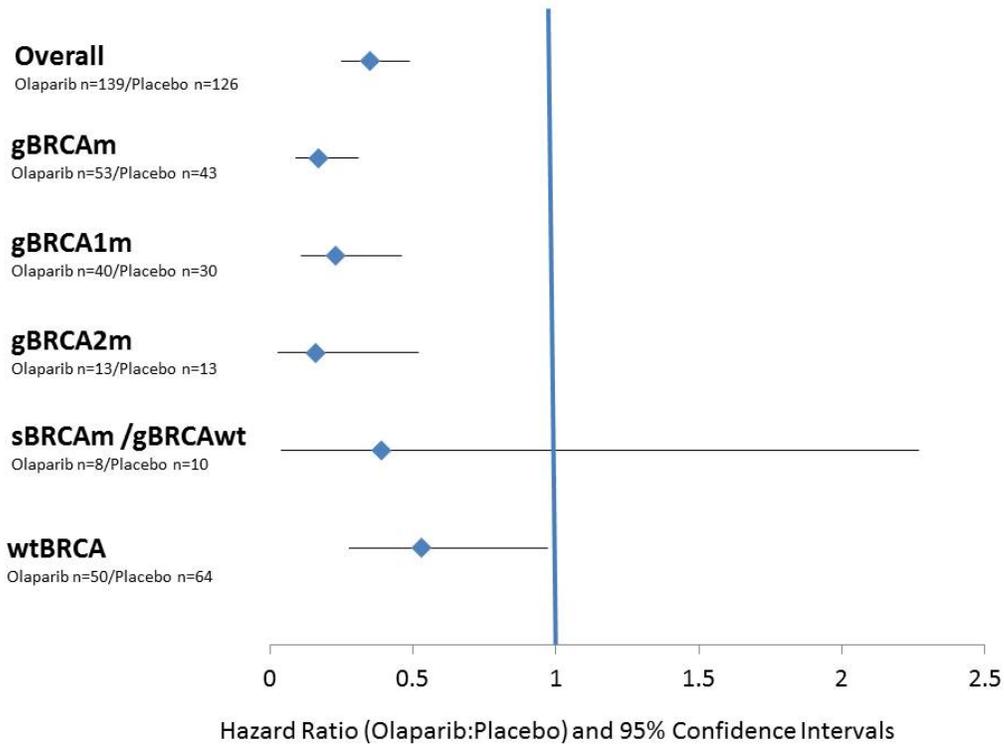
1 - The analysis was performed using a Cox proportional hazards model with factors for treatment (olaparib vs. placebo), time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment), objective response (CR or PR, in the last platinum therapy prior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

Figure 4: Kaplan-Meier Plot of Progression-free Survival in the gBRCAm Population



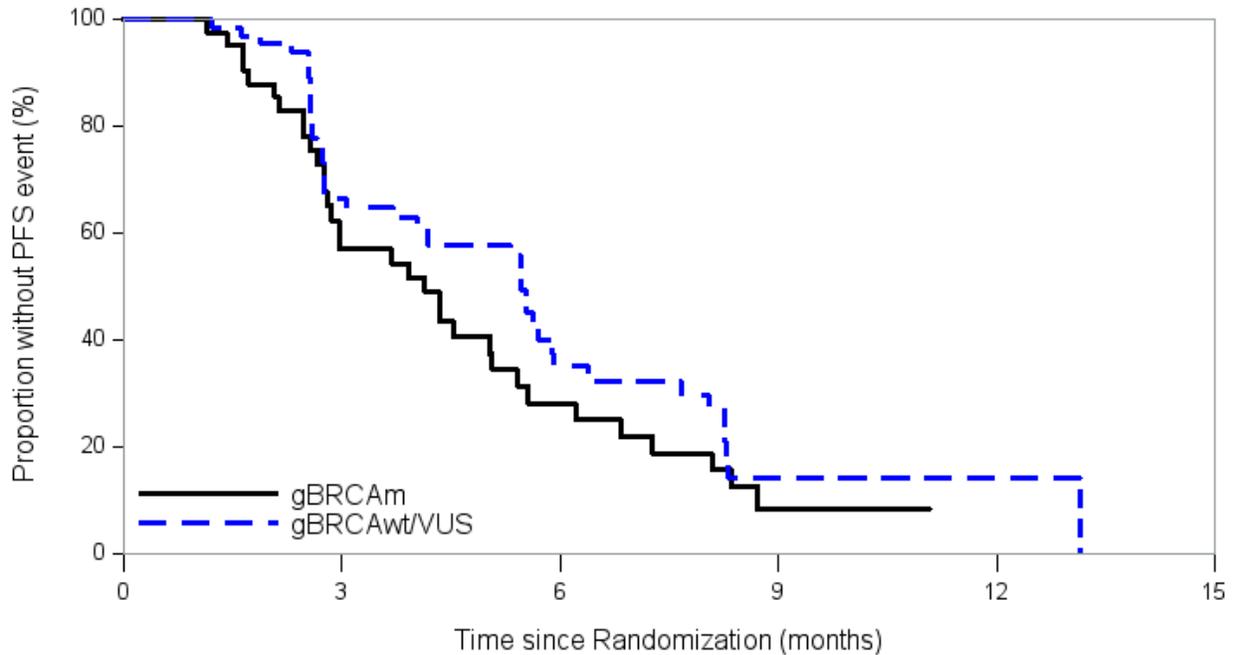
Further subgroup analyses of PFS were conducted by the FDA. These subgroups included patients with gBRCA1m, patients with gBRCA2m, and patients with tissue (somatic) BRCA mutations in the absence of germline mutations and patients with confirmed wtBRCA. As depicted in the forest plot below (Figure 2), the treatment effect was consistent in the gBRCA1m and gBRCA2m populations. There were too few patients with somatic BRCA mutations without gBRCAm to draw any conclusions regarding the efficacy of olaparib in this population. In the patients with confirmed gBRCAwt or gBRCA mutations with variations of unknown significance (n=114), the hazard ratio for PFS using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy is 0.50 (95% CI: 0.29, 0.82); however, the treatment effect of olaparib therapy in terms of PFS cannot be reliably ascertained due to the suggestion of non-proportional hazards.

Figure 5: Forest Plot of PFS Hazard Ratios by Subgroup



An additional exploratory analysis was conducted to ascertain the PFS of patients on the placebo arm as it pertains to BRCA status. In total, there were 64 patients with confirmed gBRCAwt or gBRCAvus status as opposed to 43 patients with gBRCAm status. The Kaplan-Meier curve of PFS in the placebo arm by mutation status is depicted in Figure 3 below and surprisingly suggests that the gBRCAwt/vus population may have had a slightly longer PFS. It would be expected that the gBRCAm population would have a longer PFS when compared to gBRCAwt/vus. If the time from start of platinum-based chemotherapy to progression is calculated for the placebo-treated population, this time interval (9.9 months) is consistent with the median PFS interval seen in other trials (ICON4, OCEANS, CALYPSO) in the platinum sensitive setting, suggesting that the gBRCAm placebo group “underperformed” versus an “overperforming” gBRCAwt/vus group.

Figure 6: Kaplan-Meier Plot of PFS of Placebo Treated gBRCAwt/vus vs. gBRCAm



**Key Secondary Endpoints**

**Overall Survival**

An interim analysis of OS was performed at 58% maturity. The Kaplan-Meier curve for OS in the gBRCAm population is depicted in Figure 4 and Table 8 below.

Figure 7: Kaplan-Meier Plot of Overall Survival in the gBRCAm Population

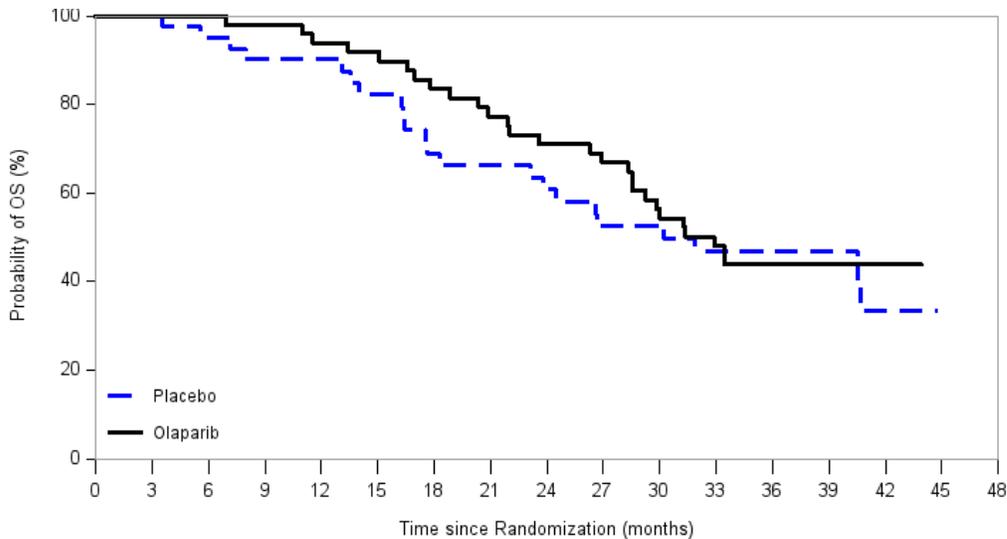


Table 51: Overall Survival Analysis in the gBRCAm Population

	<b>Olaparib (N=136)</b>	<b>Placebo (N=129)</b>
--	-------------------------	------------------------

Median OS in months (95% CI)	32.9	30.2
Hazard Ratio (95% CI)	0.85 (0.48, 1.51)	

#### Patient-Reported Outcomes (PROs)

Patient-reported outcomes were assessed using the Functional Assessment of Cancer Therapy Ovarian (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. 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.

There were no statistically significant differences between treatment groups with respect to the TOI, FOSI, and total FACT-O score. 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 a statistically significant 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.

#### Overall Response Rate (ORR)

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 this analysis.

### Supportive Efficacy Outcomes Derived From Other Trials

The anti-tumor activity of olaparib monotherapy has been assessed in multiple single-arm and randomized trials. Table 8 below depicts a summary of the overall response rates demonstrated across olaparib studies where the number of gBRCAm patients exceeded 30 and the 400 mg dose of olaparib was administered.

Table 52: Overall Response Rates of Olaparib Studies in the gBRCAm Patient Population from trials other than Study 19

Study Number and	N (Olaparib 400mg;	ORR (%)	mDOR
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<b>Description</b>	<b>gBRCAm patients)</b>		<b>(months)</b>
Study 12: Phase 2 monotherapy Dose Finding Study	32	31	6.8
Study 20: Phase 2 Relapsed Ovarian Cancer Study	64	41	9.1
Study 42: Phase 2 Advanced gBRCA Mutated Tumors Study	167	36	7.4
Study 9: Phase 2 gBRCA Ovarian Proof-of-Concept Study	33	33	9.5
<b>Total N</b>	<b>294</b>	<b>33</b>	

## Safety

### Safety population

Table 9 lists all studies submitted in this application from which safety data are comprised. Patients from study D0810C00019 (Study 19) form the core population for the safety analysis of olaparib.

Table 53: Summary of Olaparib Trials in Safety Analysis

<b>Study #</b>	<b>Population</b>	<b>Design</b>	<b>Dose (mg B.I.D.)</b>	<b># Any Olaparib</b>	<b># Olaparib 400 mg B.I.D.</b>
D0810C00001	Advanced Solid Tumors	Dose Escalation	100-400	12	6
D0810C00002	Advanced Solid Tumors	Dose Escalation	10 Q.D. to 600 B.I.D.	98	8
D0810C00004	Advanced Solid Tumors	Dose Escalation	50-400	189	12
D0810C00005	Advanced Solid Tumors	Dose Escalation	50-200	66	0
D0810C00006	Advanced Solid Tumors	Dose Escalation	50-200	19	0
D0810C00007	High-risk Breast Cancer	PD	10-400	60	12
D0810C00008	Advanced BRCAm Breast Cancer	Activity	100 and 400	54	27
D0810C00009	BRCAm Ovarian Cancer	Activity	100 and 400	58	33
D0810C00010	Advanced Solid Tumors	PK, ADME	100	6	0
D0810C00012	BRCAm Ovarian Cancer	Efficacy vs Doxil	200 and 400	64	32
D0810C00019	Platinum-sensitive Ovarian Cancer after $\geq 2$ platinum regimens	Efficacy vs placebo	400	136	136
D0810C00020	BRCAm Ovarian and Breast Cancers	Activity	400	90	90
D0810C00021	Advanced Solid Tumors	Dose Escalation	50-200	54	0
D0810C00024	Advanced Solid Tumors	PK, BA	200-450	134	9

D0810C00039	Advanced Gastric Cancer	Efficacy in combo with chemo vs placebo	100	61	0
D0810C00041	Platinum-sensitive Ovarian Cancer	Efficacy in combo/maintenance with chemo vs chemo alone	200-400	81	81
D0810C00042	gBRCAm Advanced Solid Tumors	Activity	400	298	298
D0810L00001	Advanced Solid Tumors	Dose Escalation	50-400	44	24
D9010C00008	Advanced CRC	Activity	400	33	33
<b>Total Exposed in AZ-sponsored trials</b>				<b>1557</b>	<b>801</b>
<b>ISS Total</b>				<b>2618</b>	

### Drug Modifications/Discontinuations

In study 19, dose modifications occurred in 71 (52.2%) patients on the olaparib arm versus 40 (31.3%) patients on the placebo arm. Nausea, vomiting, abdominal pain, anemia and fatigue accounted for the majority of dose modifications on the olaparib arm, while placebo patients had dose modifications mostly for abdominal pain, fatigue, small intestinal obstruction, anemia and vomiting.

More patients in the overall study population from study 19 discontinued treatment on the placebo arm (97.7%) than on the olaparib arm (83.1%). The primary reasons for treatment discontinuations were disease progression (64% on olaparib versus 85.9% on placebo); adverse events (4.4% on olaparib versus 1.6% on placebo); and patient refusing further treatment (8.1% on olaparib versus 6.3% on placebo).

Table 54: Dose Modifications and Discontinuations in Study 19

	Olaparib N=136	Placebo N=128
<b>Dose modification (interruption or reduction)</b>	<b>71</b>	<b>40</b>
Dose modification due to AE	53	14
<b>Dose interruption</b>	<b>49</b>	<b>21</b>
Dose interruption due to AE	41	11
<b>Dose reduction (less than 800 mg/ d)</b>	<b>57</b>	<b>28</b>
Dose reduction due to AE	31	5
<b>Dosing permanently discontinued</b>	<b>113</b>	<b>125</b>
Dosing permanently discontinued due to AE	6	2
<b>Dose reductions</b>		
Reduction to 200 mg BID	55	27
Reduction to 100 mg BID	14	2
Reduction to 50 mg BID (not allowed)	4	0

## Adverse Events

The most common adverse events ( $\geq 10\%$  on either arm) in Study 19 in all patients are shown in Table 11. Among these, the most common were nausea, fatigue, abdominal pain, vomiting, diarrhea and anemia. Patients treated with olaparib had higher rates of gastrointestinal events, anemia, fatigue, asthenia, infections and respiratory disorders than patients treated with placebo. Grade 3 and 4 adverse events were uncommon on both arms.

Table 55: Common Adverse Events on Study 19 in Overall Population

	<b>Olaparib N=136</b>		<b>Placebo N=129</b>	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
Blood and lymphatic system disorders Anemia	32 (22.8)	3 (2.2)	7 (5.4)	1 (0.8)

	<b>Olaparib N=136</b>		<b>Placebo N=129</b>	
<b>Gastrointestinal disorders</b>				
Abdominal distention	17 (12.5)	0	11 (8.5)	0
Abdominal pain <sup>1</sup>	66 (48.5)	2 (1.5)	55 (42.6)	4 (2.9)
Constipation	28 (20.6)	0	16 (12.4)	0
Diarrhea	37 (27.2)	3 (2.2)	31 (24)	2 (1.6)
Dyspepsia	24 (17.6)	0	11 (8.5)	0
Nausea	98 (72.1)	1 (0.7)	47 (36.4)	0
Vomiting	46 (33.8)	3 (2.2)	18 (14)	1 (0.8)
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
<b>General disorders and administration site conditions</b>				
Asthenia	19 (14)	0	12 (9.3)	0
Fatigue	71 (52.2)	2 (1.5)	51 (39.5)	1 (0.8)
<b>Infections</b>				
Nasopharyngitis	22 (16.2)	0	15 (11.6)	0
Respiratory Tract Infection <sup>2</sup>	30 (22.1)	2 (1.5)	12 (10.9)	0
Urinary Tract Infection	14 (10.3)	0	7 (5.4)	1 (0.8)
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	28 (20.6)	0	17(13.2)	0
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	23 (16.9)	0	18 (14)	0
Back pain	22 (16.2)	2 (1.5)	16 (12.4)	0
Musculoskeletal pain <sup>3</sup>	16 (11.8)	2 (1.5)	18 (14)	0
<b>Nervous system disorders</b>				
Dysgeusia	22 (16.2)	0	8 (6.2)	0
Headache	28 (20.6)	0	16 (12.4)	0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	26 (19.1)	0	13 (10.1)	0
Dyspnea	17 (12.5)	2 (1.5)	8 (6.2)	0

<sup>1</sup>Includes preferred terms abdominal pain, upper abdominal pain and lower abdominal pain.

<sup>2</sup>Includes preferred terms upper respiratory tract infection, respiratory tract infection, respiratory tract infection viral, lower respiratory tract infection, bronchitis, bronchopneumonia and pneumonia.

<sup>3</sup>Includes preferred terms musculoskeletal pain and myalgia.

The most common adverse events ( $\geq 10\%$  on either arm) in Study 19 in patients with gBRCA mutations are shown in Table 12. As with the overall population, the most frequent adverse events were nausea, fatigue, abdominal pain, vomiting, diarrhea and anemia. In the gBRCAm population, patients treated with olaparib had higher rates of gastrointestinal events, anemia, neutropenia, fatigue, asthenia, infections and cough than patients treated with placebo.

Table 56 Common Adverse Events on Study 19 in gBRCA-mutated Population

	<b>Olaparib N=53</b>		<b>Placebo N=43</b>	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
<b>Blood and lymphatic system disorders</b>				
Anemia	14 (26.4)	1 (1.9)	2 (4.7)	1 (2.3)
Neutropenia	7 (13.2)	2 (3.8)	1 (2.3)	0
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
<b>Gastrointestinal disorders</b>				
Abdominal distention	6 (11.3)	0	6 (14)	0
Abdominal pain	12 (22.6)	0	16 (37.2)	1 (2.3)
Abdominal pain upper	13 (24.5)	0	3 (7)	0
Abdominal pain lower	3 (5.7)	0	6 (14)	0
Constipation	9 (17)	0	4 (9.3)	0
Diarrhea	15 (28.3)	2 (3.8)	9 (20.9)	1 (2.3)
Dyspepsia	12 (22.6)	0	4 (9.3)	0
Nausea	41 (77.4)	1 (1.9)	16 (37.2)	0
Stomatitis	6 (11.3)	0	3 (7)	0
Vomiting	17 (32.1)	2 (3.8)	4 (9.3)	0
<b>General disorders and administration site conditions</b>				
Asthenia	9 (17)	0	6 (14)	0
Fatigue	28 (52.8)	0	19 (44.2)	0
Peripheral edema	8 (15.1)	0	4 (9.3)	0
Pyrexia	7 (13.2)	1 (1.9)	0	0
<b>Infections</b>				
Nasopharyngitis	10 (18.9)	0	2 (4.7)	0
Respiratory Tract Infection <sup>1</sup>	17 (32.1)	1 (1.9)	6 (14)	0
Urinary Tract Infection	9 (17)	0	2 (4.7)	1 (0.8)
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	13 (24.5)	0	6 (14)	0
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	9 (17)	0	7 (16.3)	0
Back pain	12 (22.6)	1 (1.9)	9 (20.9)	0
Musculoskeletal pain <sup>2</sup>	8 (15.1)	1 (1.9)	3 (7)	0
<b>Nervous system disorders</b>				
Dizziness	10 (18.9)	0	3 (7)	0
Dysgeusia	11 (20.8)	0	4 (9.3)	0
Headache	12 (22.6)	0	7 (16.3)	0

	<b>Olaparib N=53</b>		<b>Placebo N=43</b>	
Psychiatric disorders Depression	6 (11.3)	0	6 (14)	0
Respiratory, thoracic and mediastinal disorders Cough	11 (20.8)	0	6 (14)	0

<sup>1</sup>Includes preferred terms upper respiratory tract infection, respiratory tract infection, respiratory tract infection viral, lower respiratory tract infection, sinusitis and pneumonia.

<sup>2</sup>Includes preferred terms musculoskeletal pain and myalgia.

### Serious Adverse Events (SAEs)

Nonfatal serious adverse events occurred in 18.4% of patients on the olaparib arm and 10.2% on the placebo arm. The most frequent treatment-related SAE was anemia, with three patients on the olaparib arm and no patients on the placebo arm. SAEs are summarized in the table below.

Table 57: Nonfatal Serious Adverse Events on Study 19 in Overall Population

<b>Serious Adverse Events</b>	<b>Olaparib n=136</b>	<b>Placebo N=128</b>
<b>Any SAE</b>	<b>25 (18.4%)</b>	<b>13 (10.2%)</b>
Anemia	3	0
Thrombocytopenia	1	0
Cardiac insufficiency	1	0
Intestinal obstruction (small or large)	3	4
Constipation	1	0
Diarrhea	1	0
Vomiting	1	0
Melena	1	0
Intra-abdominal hemorrhage	1	0
Gastritis	0	2
Abdominal pain	0	1
Impaired gastric emptying	0	1
Nausea	0	1
Hernia pain	1	0
Pyrexia	1	0
Iodine allergy	1	0
Pneumonia	1	1
Urinary tract infection	1	1

Upper respiratory tract infection	1	0
Appendicitis	1	0
Liver abscess	1	0
Endophthalmitis	0	1
Influenza	0	1
Femur fracture	1	0
Post-procedural hematoma	1	0
Dehydration	0	1
Osteoporosis	1	0
Breast cancer in situ	1	0
Myelodysplastic syndrome	1	1
Bladder cancer	0	1
Syncope	1	0
Dyspnea	2	0
Pulmonary embolism	1	0
Cough	1	0
Deep vein thrombosis	1	0
Vena cava thrombosis	1	0
Essential hypertension	0	1

### Duration of Adverse Events

While the frequency of adverse events in Study 19 was comparable to many therapeutic oncology agents, there were relatively few Grade 3, 4 and 5 events. As olaparib is posed to be used in a setting where a patient typically would not be receiving treatment, the duration of adverse events was examined in Study 19. An analysis was performed for AEs where there was a difference in median duration of greater than 20 days (and no missing data for duration) in AEs that occurred in  $\geq 10\%$  of patients on either arm. As seen in Table 14 below, olaparib-treated patients had numerous AEs that were longer in duration than placebo-treated patients.

Table 58: Median Duration of AEs

AE	N	Olaparib N=53	Placebo N=43	$\Delta$ median
		Median (Min-Max) Days	Median (Min-Max) Days	
Abdominal distention	12	147 (30-613)	34 (7-71)	113
Dysgeusia	15	114.5 (16-706)	11 (2-89)	103.5

Abdominal pain upper	16	99 (4-484)	8 (1-15)	91
Nausea	57	96 (1-1174)	26 (1-85)	70
Arthralgia	16	89 (14-850)	22 (7-51)	67
Abdominal pain	28	75 (8-1061)	18 (2-109)	57
Back pain	21	57 (5-191)	8 (3-101)	49
Decreased appetite	19	66.5 (8-271)	18.5 (8-74)	48
Musculoskeletal pain	7	57 (3-194)	9.5 (4-15)	47.5
Constipation	13	44 (16-675)	4 (2-6)	40
Anemia	9	45 (8-254)	14 (14-14)	31
Asthenia	15	128 (26-165)	104 (45-130)	24
Cough	17	42 (3-835)	20 (1-92)	22

## Deaths

Three olaparib-treated patients and no placebo-treated patients died due to causes other than disease progression within 30 days of the last dose of study drug. The causes of death for these patients were hemorrhagic stroke, cholestatic jaundice and myelodysplastic syndrome. While the patient who experienced cholestatic jaundice likely had progressive disease as a contributing factor to this TEAE that was unlikely to be related to olaparib, a causal relation to olaparib therapy cannot be ruled out for the other two deaths. Table 15 summarizes the deaths on Study 19.

Table 59: All Safety Population Deaths on Study 19

	<b>Olaparib N = 136</b>	<b>Placebo N = 129</b>
<b>Total Deaths</b>	77 (56.6)	77 (60.2)
Progression <sup>#</sup>	68 (50.0)	71 (55.5)
Deaths within 30 Days of Last Dose	3 (2.2%)	0
TEAEs	3 (2.2%)	0
Other	0	0
Deaths in follow-up*	6 (4.4%)	6 (4.7%)
TEAEs	0	0
Other	6 (3.6%)	6 (3.9%)
Unknown	2	0
Other Events <sup>†</sup>	4	6

<sup>#</sup>Includes deaths from progression both during study and in follow-up.

\*More than 30 days after last dose of study drug to clinical data cutoff of November 26, 2012.

† Other events on the olaparib arm included euthanasia, septic shock, cerebrovascular disorder, cerebral hemorrhage.

#### *Myelodysplastic Syndrome/Acute Myeloid Leukemia*

In Study 19, three patients on olaparib treatment (2.2%) have been diagnosed with or had laboratory abnormalities suggestive of MDS or AML. One patient with wild-type gBRCA status and primary peritoneal cancer was diagnosed with MDS while on olaparib treatment at day 313. This patient died, with causes of death listed primarily as ovarian cancer and secondarily as MDS. The second patient, with gBRCAm-associated ovarian cancer, discontinued treatment after 1728 days with olaparib secondary to pancytopenia and was diagnosed 21 days later with AML. The AML was ongoing at last report. There is a third possible case of AML from the olaparib arm; this patient with gBRCAm status experienced Grade 5 hemorrhagic stroke during the course of olaparib therapy. On study day 205, olaparib was discontinued due to Grade 4 thrombocytopenia, neutropenia and leukopenia, Grade 2 anemia and 3% blasts present in the peripheral blood. At a visit two days later, a repeat peripheral blood count revealed a blast count of 16%, and a head CT revealed an intracranial hemorrhage. The patient died two days later without further workup of the pancytopenia or peripheral blasts. However, the narrative provided is suspicious for acute leukemia.

The sponsor estimates that 2,618 patients have been treated with olaparib to date. There have been 21 total cases of MDS and/or AML reported among these patients (0.8%), not including the additional suspected case from Study 19. Of these 21 patients, 16 have died, with 12 deaths due to MDS/AML as the primary or secondary cause. Patients were receiving olaparib for ovarian/primary peritoneal/fallopian tube cancer (n=17), pancreatic cancer (n=2), or breast cancer (n=2). BRCA mutation status was wild type in two patients (ovarian cancer, primary peritoneal), unknown in three patients (ovarian cancer, ovarian cancer, pancreatic cancer) and mutated in the remaining 16 patients. Among these 21 cases, nine either presented with or progressed to AML.

There is concern that the incidence of MDS/AML may be underreported. Currently, the sponsor relies on treating physicians to report the incidence of MDS/AML in those patients who have been treated with olaparib. It is conceivable that patients who were treated with olaparib at a clinical trial site can have a late development of MDS/AML while under the care of their local physician, who would not think of reporting the event back to the sponsor. Therefore, the incidence of MDS/AML associated with olaparib therapy cannot be precisely estimated. The rate of MDS in the general population according to data captured in the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) program is approximately 3.3 per 100,000; however, these data are thought to underestimate the true incidence of MDS due to underreporting to such databases (Cogle CR, 2011). The risk of MDS/AML after platinum-based chemotherapy for ovarian cancer was assessed in a case-control study in 28,971 women in North America and Europe. This study found 96 cases of MDS/leukemia (0.03%) and further noted that there was a cumulative dose-response relationship between platinum-based treatment and risk of MDS/leukemia (Travis LB, 1999). The reported incidence in the olaparib database is higher than

the expected incidence in a general population or in an ovarian cancer population treated with platinum-based therapy, and this safety signal warrants further investigation. The capturing and reporting of patients experiencing MDS/AML while on or following olaparib treatment would likely be a post-marketing requirement should olaparib gain marketing approval.

#### *Exposure Response Relationships*

The pharmacokinetics of olaparib have been characterized in studies that enrolled patients with gBRCAm-associated breast and ovarian cancer. There is high inter-patient variability of olaparib exposure at all dose levels, and there is no clear exposure-response relationship between olaparib exposure and tumor response or progression-free survival. There does appear to be an exposure-response relationship between olaparib exposure and the incidence of anemia. Figures 5 and 6 below depict the relationship between olaparib steady-state C<sub>max</sub> and olaparib AUC and the incidence of anemia of all grades. These data, which have been derived from studies 2, 8, 9, and 12, suggest that an increased exposure to olaparib is positively correlated with the incidence of anemia.

Figure 8: Exposure-Response Relationship Olaparib Steady State C<sub>max</sub> vs. Incidence of Anemia

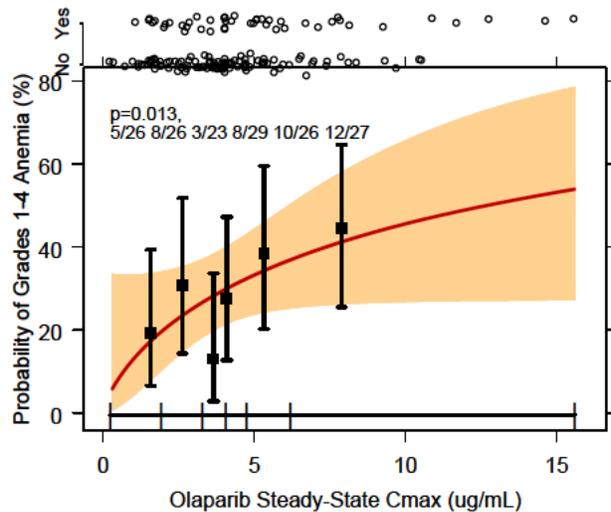
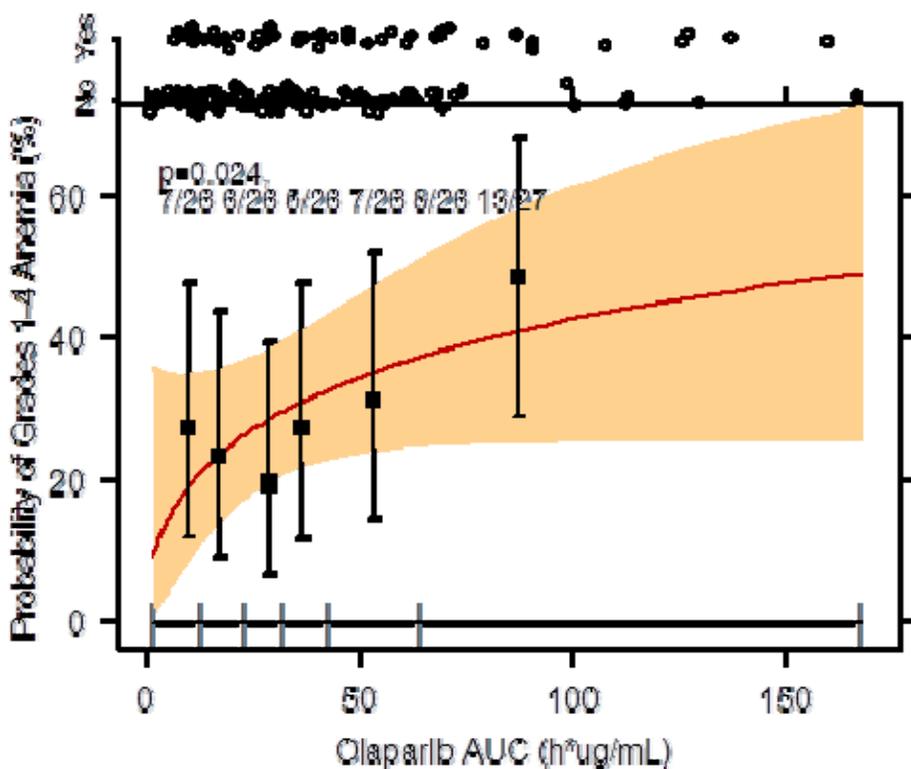


Figure 9: Exposure-Response Relationship Olaparib AUC vs. Incidence of Anemia



## Confirmatory Trial

This New Drug Application is under consideration for accelerated approval under Subpart H, which stipulates that FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trial(s) establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (CFR 314.510)). Approval under this section will be subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome (CFR 314.510).

The applicant is currently conducting a randomized, double-blind, placebo-controlled study (SOLO-2) to assess the efficacy of olaparib maintenance monotherapy in relapsed gBRCAm high-grade serous ovarian cancer (HGSOc) patients (including patients with primary peritoneal and / or fallopian tube cancer) or high-grade endometrioid cancer who have responded following platinum-based chemotherapy. The trial design largely mimics the design of Study 19, and approximately 264 patients will be recruited (2:1 olaparib:placebo ratio). The study is sized to

give sufficient precision of the hazard ratio. This may result in a study that is powered to detect a statistically significant, but relatively small, difference in PFS between study arms. For example, with a median PFS of the control arm of 4 months and a sample size of 158 PFS events, the confirmatory study could detect a minimum statistically significant improvement in PFS of only 1.5 months, with a corresponding HR of 0.73. The results of this trial are expected to be available at the end of 2015.

A key difference between SOLO-2 and Study 19 is the formulation of olaparib administered to the patient. The dose of olaparib used in Study 19 was 400 mg PO BID of the capsule formulation. Each capsule is 50 mg, translating to a total pill count of 16 pills consumed each day. In order to facilitate olaparib dosing, a new tablet formulation was made; however, a bioequivalent dose of the tablet formulation was not established. In order to assess bioequivalence and to determine the safety and preliminary activity of the new formulation, the applicant conducted Study 24, a randomized, two-period cross-over study to determine the comparative bioavailability of two different oral formulations of olaparib in cancer patients with advanced solid tumors. Based on the totality of the efficacy and safety data generated from this study, the 300 mg tablet formulation was chosen as the most suitable dose for SOLO-2 and other randomized trials. The 300 mg tablet dose is estimated to have approximately 1.5 times the relative bioavailability of the 400 mg capsule dose. There is insufficient evidence at this point to determine if there is an exposure-response relationship for efficacy; however, there appears to be an exposure-response relationship for the incidence of anemia. This raises concerns that the overall tolerability of the new tablet formulation may be compromised in SOLO-2 as compared to Study 19. To what degree the new formulation impacts the safety and efficacy of olaparib in the gBRCAm population remains to be seen.

## Summary

### Risk-Benefit Considerations

Olaparib is an active treatment in gBRCAm ovarian cancer as demonstrated by a seven-month median improvement in PFS and a hazard ratio of 0.17 in the gBRCAm subgroup of Study 19. This activity is supported by an observed overall response rate of approximately 33% as monotherapy in the gBRCAm relapsed ovarian cancer setting. Safety concerns pertain to the risks of myelosuppression, fatigue and gastrointestinal disturbances such as nausea and abdominal pain. In addition, there is a small but concerning risk for the development of MDS/AML.

Given that this indication is for maintenance treatment of patients who have just completed a course of cytotoxic chemotherapy and are expected to receive multiple treatment regimens throughout their lives, tolerability and cumulative toxicities are paramount issues in determining the risk-benefit profile of olaparib therapy. The PRO assessments were uninformative in terms of characterizing whether olaparib therapy was effective in delaying disease-related symptoms, and although the toxicities resulting from olaparib therapy were generally self-limiting and

reversible, the patient could have been treatment free and without therapy-related adverse reactions during this time.

The small sample size of gBRCAm patients and the retrospective identification of this patient population call into question the reliability of the estimation of treatment effect. The retrospective identification of the gBRCAm population did not appear to result in gross imbalances of known prognostic factors that could account for the treatment effect seen in Study 19, but it is important to note that the loss of randomization and the selection of a convenient sample of patients who had available whole blood sample for retrospective testing may have led inadvertently to an unequal distribution of unknown factors that may have affected the study results. The hazard ratio of 0.17 certainly suggests that most patients will have some degree of prolongation of PFS from treatment, but the data demonstrating that the placebo-treated gBRCAm performed more poorly in terms of PFS when compared to the placebo-treated gBRCAwt/vus raise the concern that the median improvement of seven months may be due in part to an “underperforming” control arm. The analysis of overall survival suggests no detriment as a result of therapy, but no survival difference was seen between treatment arms.

Study 19 demonstrated positive results in terms of an 83% reduction in the risk of progression or death and a seven-month median improvement in maintenance PFS for patients with platinum-sensitive gBRCAm associated ovarian cancer. However, there are uncertainties related to the validity and the reproducibility of the magnitude of effect seen in Study 19, and there are risks associated with olaparib therapy. Therefore, the options are to consider an accelerated approval now or wait until the results of SOLO-2 are available. The Agency asks the Oncology Drug Advisory Committee to consider the following:

### **Considerations for the Advisory Committee:**

1. Do the efficacy results from study 19, namely a seven-month improvement in median PFS and a hazard ratio of 0.17, along with the safety data in the gBRCAm population, demonstrate a favorable risk-benefit profile of olaparib maintenance monotherapy in gBRCAm-associated, platinum-sensitive, relapsed high-grade serous ovarian cancer that is in response to the last platinum-based chemotherapy regimen?
2. The potential confirmatory trial is designed to detect a statistically significant but potentially clinically insignificant improvement in PFS. What is the appropriate magnitude of treatment effect for median improvement and hazard ratio to be demonstrated in the SOLO-2 trial to consider olaparib to be of direct clinical benefit to this patient population?

## 9. References

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## 9.4 BRCA mutations

The following is excerpted from the sponsor’s “BRCA Diagnostic Testing in Clinical Studies of Olaparib”:

Classification of *BRCA* variants is necessary in order to inform a patient of their inherited risk for breast and ovarian cancer and to help guide appropriate clinical management (prophylactic surgery etc). The analysis and interpretation of germline and tumour *BRCA1* or *BRCA2* mutation status is complex due to the size of the *BRCA1* and *BRCA2* genes and the fact that both are characterised by highly heterogeneous patterns of mutations scattered throughout the entire coding regions and intronic sequences flanking each exon. Whilst the majority of mutations observed are point mutations, large rearrangements of DNA segments within the *BRCA1* and *BRCA2* genes have also been identified in 6%–10% of hereditary breast and ovarian cancers (Judkins et al 2012) and reported to disrupt gene function. The importance of these variants is reflected in the 2012 NCCN guidelines, which recommend that all patients who undergo *BRCA* testing should also be tested for large rearrangements (NCCN 2012).

The majority of *BRCA* mutations are predicted to produce a truncated protein product and result in loss of protein function. Sequence mutations at splice junctions disrupt proper mRNA processing and gene expression. Some specific missense mutations that result in deleterious amino acid substitutions within the key functional domains can cause loss of *BRCA* function in the absence of a truncated protein (Easton et al 2007; Goldgar et al 2004). In addition, deletions and duplications of entire exon(s) within *BRCA*, which include single and multi-exonic deletions/duplications are also predicted to result in loss of protein function and therefore are largely classified as “deleterious” mutations.

The scientific community uses a robust, evidence-based methodology to classify *BRCA1* or *BRCA2* variants and clearly define those that lead to “deleterious” or “suspected deleterious” loss of function mutations. The methods used are based upon the American College of Medical Genetics (ACMG) recommendations for standards for interpretation and reporting of sequence variants. This classification process draws upon comprehensive literature combined with substantial genetics expertise that delivers accurate variant classification and subsequent interpretation of *BRCA* test results.

There are a variety of classification systems in use currently. Details of some of the more commonly used classifications are outlined in Table 2.

**Table 2** Commonly used classification systems

<b>Biological Classification</b>	<b>Myriad Classification</b>	<b>BIC Classification</b>	<b>BReast Cancer IARC database</b>	<b>ACMG</b>
Disrupts normal gene function	Deleterious	Clinically important = Yes	Definitely Pathogenic	Class 1
	Suspected Deleterious		Likely pathogenic	Class 2
Uncertain Does not disrupt normal gene function	Variants of unknown significance	Clinically Important = Unknown	Uncertain	Class 3
	Variant, favour polymorphism	Clinically Important = No	Likely not pathogenic or of clinical significance	Class 4
			Not pathogenic or of no clinical significance	Class 5

One of the most commonly used classification databases is the publicly available Breast Cancer Information Core (BIC) database which was established in 1995 to capture information about naturally occurring variation in the human *BRCA1* and *BRCA2* genes. Mutation data was originally entered primarily by Myriad Genetic Laboratories Inc. (being the commercial laboratory performing the majority of *BRCA1/BRCA2* tests in North America), but is now only updated by individual investigators and hospital-based laboratories. Data from the Breast Cancer Information Core (BIC 2012; Szabo et al 2000) website has reported 1785 distinct mutations, polymorphisms and other genetic variants in *BRCA1* and 2011 distinct mutations, polymorphisms and other genetic variants in *BRCA2*. Other databases which are used include CIMBA (The Consortium of Investigators of Modifiers of *BRCA1/2*), ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles), UMD (The Universal Mutation Database), HGMD (Human Gene Mutation Database), LOVD-IARC database (Leiden Open Variant Database – International Agency For Research On Cancer) and DMuDB (Diagnostic Mutation Database).

The *BRCA* mutation classification used in order to inform patients of their inherited cancer risk is the same as AstraZeneca have used to retrospectively categorize patients' *BRCA* mutation status for efficacy and safety analyses of data from clinical studies of olaparib.

**Reviewer's Comments:**

*The sponsor has summarized current scientific principles in regards to variant BRCA classification. The distribution of various BRCA mutations as detected by local testing found in Studies 12, 19, and 41 as well as Study 42 are depicted in the tables below.*

Table 60: Distribution of Locally Determined Deleterious or Suspected Deleterious BRCA mutations in Study 42

<b>BRCA 1 or 2</b>	<b>Standardized DNA Change</b>	<b>N N=212<sup>1</sup></b>
BRCA1	187delAG	46
BRCA1	5385insC	30
BRCA2	6174delT	14
BRCA1	300T>G	7
BRCA1	3726C>T	4
BRCA1	3819del5	3
BRCA1	3875del4	3
BRCA1	1294del40	2
BRCA1	2316del5	2
BRCA1	2841G>T	2
BRCA1	3960C>T	2
BRCA1	4154delA	2
BRCA1	4446C>T	2
BRCA1	5214C>T	2
BRCA1	IVS13-31A>G	2
BRCA2	4075delGT	2
BRCA2	4859insA	2
BRCA2	5163delA	2
BRCA1	1100delAT	1
BRCA1	1137delG	1
BRCA1	1246delA	1
BRCA1	1371G>T	1
BRCA1	1490delA	1
BRCA1	1623del4	1
BRCA1	1959A>T	1
BRCA1	2080delA	1
BRCA1	2080insA	1
BRCA1	2281delTT	1
BRCA1	2315insA	1
BRCA1	2318delG	1
BRCA1	2457C>T	1
BRCA1	2478insG	1
BRCA1	2537delA	1
BRCA1	2594delC	1
BRCA1	2800delAA	1
BRCA1	2846del4	1
BRCA1	2985del5	1
BRCA1	3053T>G	1

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BRCA1	3171ins5	1
BRCA1	3312insG	1
BRCA1	3366del5	1
BRCA1	339C>T	1
BRCA1	3476delTG	1
BRCA1	3663C>T	1
BRCA1	3832C>T	1
BRCA1	3867G>T	1
BRCA1	3889delAG	1
BRCA1	390delT	1
BRCA1	4050del4	1
BRCA1	4401delA	1
BRCA1	4808C>G	1
BRCA1	5083del19	1
BRCA1	5215G>A	1
BRCA1	526delG	1
BRCA1	5272G>T	1
BRCA1	5273G>A	1
BRCA1	5296del4	1
BRCA1	5443T>G	1
BRCA1	5536delC	1
BRCA1	5622del62	1
BRCA1	962del4	1
BRCA1	del exon 24	1
BRCA1	del exons 1-3	1
BRCA1	Exon 12 ins 6kb	1
BRCA1	exon 13 ins 6kb	1
BRCA1	exon 22 del 510bp	1
BRCA1	IVS16+4A>C	1
BRCA1	IVS19+2delT	1
BRCA1	IVS5+1G>A	1
BRCA1	IVS8+2T>A	1
BRCA1	Large deletion	1
BRCA2	2041insA	1
BRCA2	2157delG	1
BRCA2	3036del4	1
BRCA2	3581del3	1
BRCA2	3773delTT	1
BRCA2	4265delCT	1
BRCA2	4706del4	1
BRCA2	5301insA	1
BRCA2	5638delGT	1

BRCA2	5873C>A	1
BRCA2	617delT	1
BRCA2	6252insG	1
BRCA2	6405delT	1
BRCA2	6503delTT	1
BRCA2	6627del3	1
BRCA2	7708C>T	1
BRCA2	8356del3	1
BRCA2	8395G>C	1
BRCA2	9132delC	1
BRCA2	9325insA	1
BRCA2	9503del4	1
BRCA2	9599A>T	1
BRCA2	9610C>T	1
BRCA2	9663delGT	1
BRCA2	983del4	1
BRCA2	Del exons 21-24	1
BRCA2	exon 25	1
BRCA2	IVS5+1G>T	1

1 – one patient had mutations in both BRCA1 and BRCA2

Table 61: Distribution of Locally Determined Deleterious or Suspected Deleterious BRCA mutations in Study 42

<b>BRCA 1 or 2</b>	<b>DNA Change as Reported on CRF</b>	<b>N (N=193)</b>
BRCA1	185delAG	47
BRCA2	6174delT	12
BRCA1	5382insC	8
BRCA1	187delAG	7
BRCA2	6174 del T	5
BRCA1	187 del AG	2
BRCA1	2594delC	2
BRCA1	c.68 69delAG	2
BRCA1	C61G	2
Both	5382insC - 6174delT	1
BRCA1	1294 del 40	1
BRCA1	1675delA	1
BRCA1	1687C>T p.Gln563X	1
BRCA1	1790delA	1
BRCA1	184delAG	1
BRCA1	185 del AG	1

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BRCA1	185 del-AG	1
BRCA1	185delAG	1
BRCA1	185del AG	1
BRCA1	185del AG BRCA1	1
BRCA1	185delAG & 69delAG	1
BRCA1	185delG	1
BRCA1	2080delA exon 11	1
BRCA1	2804delAA	1
BRCA1	3109 ins AA	1
BRCA1	3124 del A	1
BRCA1	3348delAG	1
BRCA1	3604delA	1
BRCA1	3950 ins T	1
BRCA1	4154delA	1
BRCA1	5083 del 19	1
BRCA1	5083 DEL 19	1
BRCA1	5382 ins C	1
BRCA1	5385insC	1
BRCA1	917-918delTT, exon 11	1
BRCA2:	NM 000059.3	1
BRCA1	BRCA1 185delAG	1
BRCA1	BRCA1, 185delAG	1
BRCA1	BRCA1c.300T>G[C61G]	1
BRCA1	c.[2475delC]+[=]: p.Asp825Glu fsX21 in exon 11	1
BRCA1	C.[3817C>T]+[=]:p.Gln1273 X exon 11	1
BRCA1	c.[5072C>A]+[=]:p.Thr1691Lys in exon 17(NM 007294.2)	1
BRCA1	c.1340_1341 ins G p.His448 fs	1
BRCA1	c.2411_12del AG p.Gln804 fs	1
BRCA1	c.2761C>T(Het):p.Gln921X	1
BRCA1	c.2933delA	1
BRCA1	c.3018_21del TTCA p.His1006Ds	1
BRCA1	c.3018_3021 del TTCA p.His1006 fs	1
BRCA1	c.330 A>G (p.R71G) exon 5	1
BRCA1	c.3485delA p.Asp1162fs	1
BRCA1	c.3607C>T	1
BRCA1	c.3671_3672insTTCC	1
BRCA1	c.3746-3747insA	1
BRCA1	c.3875delGTCT	1

BRCA1	c.4120_4121delAG(Het) p.Ser1374X in exon 12	1
BRCA1	c.5106_5193del88,p.Met166	1
BRCA1	c.5123C>A;p.Ala1708Glu	1
BRCA1	c.5266-5267dupC (p.Gln1756ProfsX1829)	1
BRCA1	c.5266dupC p.Gln1756fs	1
BRCA1	c.5266dupC p.Gln1756ProfsX74	1
BRCA1	c.5503 C>T p.Arg 1835X	1
BRCA1	c.5503C>T, p.Arg1835X	1
BRCA1	c.68_69del(p.Glu23ValfsX17)	1
BRCA1	c.952_1015delp. His318Arg fs	1
BRCA1	c.981_982delAT	1
BRCA1	c5095C>T p.Arg1699Trp	1
BRCA1	c5527G/C,G1803A	1
BRCA1	C61G (300T>G)	1
BRCA1	del185AG	1
BRCA1	deletion of exon 3	1
BRCA1	Deletion of exon 3	1
BRCA1	E1357X(4188G>T)	1
BRCA1	E908X	1
BRCA1	exon 14-20del26kb	1
BRCA1	ins C 5382	1
BRCA1	IVS 18+3 a>c	1
BRCA1	IVS14+1delG (heterozygous)	1
BRCA1	IVS15+1G>A	1
BRCA1	IVS23+2T>C	1
BRCA1	IVS5-11T>G	1
BRCA1	K679X BRCA 1	1
BRCA1	k8020E mutation and CCAG delterion of exon 11	1
BRCA1	p.Gln1111 AsnfsX5	1
BRCA1	P1812A	1
BRCA1	Q491X	1
BRCA1	R1203X	1
BRCA1	R1443X	1
BRCA1	Tyr978X	1
BRCA1	Y978X (3053T>G)	1
BRCA2	3773delTT	1
BRCA2	4391delCTinsA	1
BRCA2	4626delACATT (U43746)	1
BRCA2	5301insA	1

BRCA2	5466insT	1
BRCA2	5638delGT	1
BRCA2	6174 delT	1
BRCA2	617delT	1
BRCA2	6293C>G, S2022X	1
BRCA2	8475delGA	1
BRCA2	BRCA2 61754delT	1
BRCA2	c.[5073dupA]+[=]: p.Trp1692MetfsX3 in exon11	1
BRCA2	c.1670T>G	1
BRCA2	c.2042_43insA,p.615X	1
BRCA2	c.2471_2476delTAAATG	1
BRCA2	c.4554 delA p.Glu 1518 fs	1
BRCA2	c.5303_5304delTT p.Leu1768ArgfsX5) in exon 11	1
BRCA2	c.5645 C>Ap. Ser1882X	1
BRCA2	c.5857 G>T p.Glu1953X	1
BRCA2	c.5864C>Ap.S1955X	1
BRCA2	c.5946delT (p.Ser1982ArgfsX22)	1
BRCA2	c.7845+1G>A	1
BRCA2	c.9117G>A	1
BRCA2	c.9558insA[E3111X]	1
BRCA2	familial BRCA2 gene c.2471_2476TAAATG	1
BRCA2	Heterozygous duplication of 1 nucleotide c.6024dupG in exon 11 of BRCA2. This results in a premature stop codon in BRCA2, causing truncation of the BRCA2 gene or diminished BRCA2 mRNA.	1
BRCA2	S1630X	1

Table 62: Distribution of Locally Determined Deleterious or Suspected Deleterious BRCA mutations in Study 20

<b>BRCA 1 or 2</b>	<b>DNA Change as Reported on CRF</b>	<b>N (N=17)</b>
BRCA1	4154DELA	1
BRCA1	C.1440 DUP A	1
BRCA2	Q1037X (3337 C > T)	1
BRCA1	C4808G	1
BRCA2	4109T-G	1

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BRCA1	3875DELGTCT	1
BRCA2	3523DEL T	1
BRCA1	185DEL AG	1
BRCA1	3790INSTTCC	1
BRCA1	185DELAG	1
BRCA2	P3039P (9345G>A)	1
BRCA1	W321X (1081 G > A)	1
BOTH	187DELAG	1
BRCA1	NUCLEOTIDE 181 IN EXON 5 OF BRCA 1 GENE (P. CYS 61 GLY)	1
BRCA1	3600 DEL 11	1
BRCA1	5385INSC	1
BRCA2	S1630 X (5117C7G)	1

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GEOFFREY S KIM  
12/03/2014

GWYNN ISON  
12/04/2014

AMY E MCKEE  
12/04/2014

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 206162**

**Applicant: AstraZeneca**

**Stamp Date: 2/3/14**

**Drug Name: Olaparib**

**NDA/BLA Type: 1 (NME)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?				
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				
<b>DOSE</b>					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: D0810C00012 Study Title: A Phase II, Open-Label, Randomised, Comparative, International Multicentre Study to Compare the Safety and Efficacy of Two Different Doses of AZD2281 Given Orally Twice Daily Versus Intravenous Liposomal Doxorubicin Given Monthly in Patients With Advanced BRCA1- or BRCA2-Associated Ovarian Cancer Who Have Failed Previous Platinum-Based Chemotherapy	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 97 subjects Arms: Olaparib 200 mg BID (n=32); Olaparib 400 mg BID (n=32); liposomal doxorubicin (n=32) 50mg/m2 Location in submission: Module 5.3.5.1				
<b>EFFICACY</b>					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1: Study 19 Indication: Maintenance monotherapy in patients with germline deleterious BRCA mutation associated platinum sensitive relapsed ovarian cancer following a complete or partial response to platinum based chemotherapy	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		The applicant has certified that the pivotal and supporting studies have been conducted in accordance to GCP and ICH guidelines and adhere to the standards set by each investigational site's IRB/IEC and local regulatory authority
<b>SAFETY</b>					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			Data to date do not suggest effect on QT interval, but "high quality digital ECG data are limited". 2 studies ongoing and will be provided subsequently.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			Study 19 n=136; Study 41 maintenance n= 66; pooled safety database n=735
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			MEDRA
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

If the Application is not fileable from the clinical 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.

Geoffrey Kim  
Gwynn Ison

3/10/14  
3/10/14

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Reviewing Medical Officer

Date

Amy McKee

3/10/14

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Clinical Team Leader

Date

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GEOFFREY S KIM  
04/03/2014

AMY E MCKEE  
04/03/2014