CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206162Orig1s000

OTHER REVIEW(S)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Germline Gene Mutation Test
Device Trade Name:	BRACAnalysis CDx™
Device Procode:	PJG
Applicant's Name and Address:	Myriad Genetic Laboratories, Inc. 320 Wakara Way Salt Lake City, UT 84108
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P140020
Date of FDA Notice of Approval:	December 19, 2014

Priority Review: *Granted priority review status on October 15, 2014, because BRACAnalysis CDx™ addresses an unmet medical need, as there is no approved alternative and as demonstrated by significant clinically meaningful advantage.*

II. INDICATIONS FOR USE

BRACAnalysis CDx™ is an *in vitro* diagnostic device intended 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 EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in *BRCA1* and *BRCA2* are detected using multiplex PCR. Results of the test are 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, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108.

III. CONTRAINDICATIONS

Patients who have undergone a previous allogeneic bone marrow transplant should not be tested with the BRACAnalysis CDx™.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the BRACAnalysis CDx™ labeling.

V. DEVICE DESCRIPTION

BRACAnalysis CDx™ is an *in vitro* diagnostic device performed in a single laboratory, Myriad Genetic Laboratories, Inc. (Myriad), in Salt Lake City, UT. The test includes a sample collection kit, which is sent to ordering laboratories and healthcare providers. The collection kit contains the following components:

- Monoject™ Blood Collection Tube (part no. 8881-311743);
- Test Request Form;
- Instructions for Sample Collection and Mailing;
- Technical Information Summary.

BRACAnalysis CDx™ consists of the following two assays to detect sequence variants and large rearrangements in the *BRCA1* and *BRCA2* genes:

- BRACAnalysis CDx™ Sanger Sequencing;
- BRACAnalysis CDx™ Large Rearrangement Test (BART® CDx).

All reportable variants, including deleterious and suspected deleterious mutations, are confirmed by repeat analysis with the BRACAnalysis CDx™ Sanger Sequencing test or the BART® CDx test, or by confirmatory testing. Approximately 98% and 99% of all variants detected by the BRACAnalysis CDx™ Sanger Sequencing test and the BART® CDx tests, respectively, are confirmed by repeat testing; the remaining variants (about 2% and 1%, respectively) require confirmatory analysis by the following tests:

- Alternate Primer Sequencing (APS);
- Confirmatory PCR Analysis (CPA).

BRACAnalysis CDx™ is intended to be performed with serial number-controlled instruments, as indicated in the table below.

Instruments for Use with BRACAnalysis CDx™

Instrument	Serial Number(s)
QIASymphony SP	14957
Tecan Freedom Evo 150	1310005128; 1402003965
Tecan Infinite F200 Pro Platereader	1309001987
MasterCycler EP & MasterCycler Pro 384 & 96 well	5344 003700; 5344 009645; 5344 010536; 5344 010537; 5344 010530; 5344 010552; 5344 010572; 5344 026026; 5344 010613; 5344 010521; 5344 012323; 5344 009646; 6324CH818083; 6324CH718080; 6324CK418379; 6324CH018081; 6324CK118382; 6324CK318376; 6324CH418082; 6324CH618076; 6324CK818381; 6324CK018387; 6324CK518383; 6324CK218385; 6324AR315529; 6324AR715518; 6324AR915513; 6324AR015528; 6324AR415521; 6324AR815510;

	6321CP818805
ABI 3730xl	1408-038; 16112-015; 18127-015; 25193-005; 24189-002; 24180-009; 25193-003; 1412-027
E-Gel iBase	2113127
E-Gel Imaging System InGenius3	IG3/1219
E-Gel Safe Imager Real-time Transilluminator	12093074

Blood Collection and DNA Extraction

Peripheral whole blood (~7 mL) is collected in a blood collection tube containing EDTA, and then the sample is mailed to Myriad at ambient temperature. At Myriad, the blood sample is accessioned, aliquoted, and then processed using an automated DNA extraction process. One aliquot (1 mL) per sample is loaded onto the QIASymphony SP instrument, which is configured for silica-based isolation and purification of genomic DNA using QIAGEN Software v4.0.1. When the extraction run is complete, the DNA is suspended in ~185 µL TE buffer. The DNA is then quantified and normalized using an automated robotic platform (Tecan Freedom EVO® 150 with Tecan EVOWare v2.4.8.7) and fluorometer (Tecan Infinite® F200 PRO with Magellan v7.0 Software). DNA samples are stored at 4°C until tested for variants in the *BRCA* genes.

Detection of Sequence Variants

Sequence analysis of the *BRCA* genes is conducted with the BRACAnalysis CDx™ Sanger Sequencing test. For *BRCA1*, full sequence determination of approximately 5,400 base pairs (bp) comprising 22 coding exons and approximately 750 adjacent bp in the non-coding intervening (intron) sequences is performed. Exons 1 and 4, which are non-coding, are not analyzed. For *BRCA2*, full sequence determination of approximately 10,200 bp comprising 26 coding exons and approximately 900 adjacent bp in the non-coding intervening sequences is performed. Exon 1 is non-coding, and therefore, is not analyzed. The intronic regions of *BRCA1* and *BRCA2* that are analyzed generally do not extend more than 20 bp proximal to the 5' end and 10 bp distal to the 3' end of each exon.

The BRACAnalysis CDx™ Sanger Sequencing test uses primers that define specific base pair sequences to amplify each of the targeted regions by polymerase chain reaction (PCR). Each primer also contains an M13 tail on the 5'end to facilitate the downstream sequencing reactions. An automated robotic platform (Tecan Freedom EVO® 150 with Tecan EVOWare v2.4.8.7) is used to add the appropriate primers and DNA samples to the wells of 384-well PCR plates containing Sanger PCR MasterMix, which consists of pre-mixed reagents for the amplification reactions. Following inoculation, the PCR plates are centrifuged and then placed onto a thermocycler (Eppendorf MasterCycler EP or MasterCycler Pro 384) for PCR amplification. In total, 35 PCR reactions are carried out for *BRCA1*, and 49 PCR reactions for *BRCA2*.

The amplified products are each directly sequenced in the forward and reverse directions using fluorescent dye-labeled sequencing primers. Fluorescently-labeled Sanger

sequencing fragments are generated using the Eppendorf MasterCycler thermocyclers, and then purified prior to sequencing on the Applied Biosystems (ABI) 3730xl. To evaluate the possibility of carryover throughout the procedure, each batch run includes two negative controls for the BRACAnalysis CDx™ Sanger Sequencing test: a No Genomic DNA Control and an M13 F+R Negative Control. In each control, no DNA template is added. The No Genomic DNA Control contains all PCR components and a PCR primer pair for one targeted amplicon. The M13 F+R Negative Control includes all PCR components in addition to the M13 forward and reverse primer pair. The controls must produce the expected results in order to evaluate the data from test samples.

Chromatographic tracings of each amplicon are automatically generated with the ABI Sequence Analysis Software v5.3.1 and Gene Mapper v4.0, and subsequently analyzed using Myriad's proprietary Alignment Software v1.7.4 and Mutation Calling Software v1.9.6 to identify possible sequence variants. The variant calling software numerically compares each base of the sequencing traces to consensus wild-type sequences, and any mismatches are flagged as potential variants. The flagged variants may then be routed for review by trained data analysts. In this case, two independent reviewers visually inspect the traces to confirm the variant calls. If the analysts do not agree, the results are reviewed by a supervisor for final determination. All reportable variants are independently confirmed by repeated PCR amplification of the indicated gene region(s) and subsequent sequencing.

Detection of Large Rearrangements

BRACAnalysis CDx™ Large Rearrangement Test (BART® CDx) is a multiplex PCR assay intended to detect large genomic rearrangements (e.g., deletions and duplications) across all coding regions, limited flanking intron regions, and the proximal promoter regions of the *BRCA1* and *BRCA2* genes. DNA is normalized to 2 ng/µL and then added to the wells of 384-well PCR plates containing pre-mixed reagents using the Tecan Freedom EVO® 15 automated robotic platform. The PCR plates are centrifuged, and then amplified products are generated using Eppendorf MasterCycler thermocyclers. During this process, fluorescently labeled primers are incorporated into the amplified DNA. In total, 11 multiplex PCR reactions are performed, and on average, there are 12 amplicons per multiplex with at least 2 amplicons per exon. The reactions are run in duplicate to obtain at least 4 data points for each region.

The amplified products are purified using the AMPure® magnetic bead system and then loaded onto the Applied Biosystems (ABI) 3730xl for fragment analysis. Chromatographic traces are generated with the ABI Gene Mapper v4.0 software and analyzed for the presence of wild-type and variant fragments. The fragment data from separation of the PCR products are sized using an internal lane standard with fragments of known sizes. Myriad's proprietary large rearrangement analysis software, MiniART Application v0.2, compares the relative peak intensities within a sample, and between samples run in the same batch, to generate statistical values and a gene dosage scatter plot. Briefly, each exon is represented by a minimum of 4 data points, so data from all amplicons of all samples in the same batch are normalized across the batch and then combined to yield one data point per sample per exon on the gene dosage scatter plot. Three housekeeping genes are used as additional copy number controls. The traces and scatter plot are reviewed by two independent trained analysts. Any sample flagged

during data review is reprocessed and reanalyzed. Any sample with a potential large rearrangement is reviewed by a trained supervisor to verify the result.

In order to verify that the BART® CDx test can produce the expected results, two positive controls and one negative control are included in each run. The positive controls are two independent cell lines with defined *BRCA* large rearrangements. The negative control contains all of the components for the BART® CDx PCR reactions, with the exception of DNA template. If the controls produce the expected results, then the data from the test samples are assessed.

Confirmatory Testing

All reportable variants, including deleterious and suspected deleterious mutations, are confirmed by additional testing prior to result reporting. Approximately 98% of reportable sequence variants are confirmed by repeating the BRACAnalysis CDx™ Sanger Sequencing test for the indicated gene region(s), and about 99% of large rearrangements are confirmed by repeat BART® CDx testing. Certain variants that cannot be confirmed with repeat testing are subject to confirmatory analysis using Alternate Primer Sequencing (APS) or Confirmatory PCR Analysis (CPA).

Approximately 2% of atypical variant results are confirmed using the APS test. APS is based on the same PCR and Sanger sequencing methods used in the BRACAnalysis CDx™ Sanger Sequencing test; however, PCR is conducted in 96-well PCR plates. The APS test is performed using alternative primer sequences, or primer combinations that flank the primer binding sites used in the BRACAnalysis CDx™ Sanger Sequencing assay, to allow for the identification of potential heterozygous base changes at primer binding sites that may have resulted in inefficient PCR amplification in the BRACAnalysis CDx™ Sanger Sequencing or BART® CDx tests. For example, a heterozygous base change could yield either unequal PCR amplification in the BRACAnalysis CDx™ Sanger Sequencing test or artifacts - such as apparent single exon deletions - in the BART® CDx test. The APS test is therefore used to confirm these types of rare results from the BRACAnalysis CDx™ Sanger Sequencing or BART® CDx tests.

The CPA test is used for follow up testing for about 1% of atypical results, such as single exon deletions, from the BART® CDx test. Sequence-specific primers that span one or more exons are used to amplify breakpoint-specific genomic regions in a 96-well PCR plate format. The amplified products are evaluated using gel electrophoresis and subsequent imaging (E-Gel Imaging System InGenius3, Invitrogen E-Gel® Safe Imager and E-Gel® iBASE™ Power System with GENESys Gel Documentation System v1.4.0.0 software) and may be verified by sequencing. A size-based analysis of the PCR products is performed by comparing the PCR products from the sample of interest against wild-type PCR products. The confirmatory assays are generally performed as needed to confirm the presence of certain variants.

Variant Classification

Upon completion of testing at Myriad, a test report is sent to the ordering physician. The results of each test component, along with the classification of the germline variant(s) detected by the BRACAnalysis CDx™, are provided. Variant classification is conducted

according to a defined classification process by an in-house committee consisting of Laboratory Directors, the Chief Medical Officer, representatives from Medical Services, Genetic Counselors, and other trained professionals, including PhD-level scientists, board-certified clinical molecular geneticists, or equivalent. Based on the classification criteria, each identified variant is classified into one of five categories. If multiple variants are detected with different classifications, the overall test interpretation is determined by the highest tiered variant classification, as listed below. Variants determined to have a classification of polymorphism are not included on the test report.

1. Deleterious Mutation;
2. Suspected Deleterious Mutation;
3. Variant of Uncertain Significance;
4. Favor Polymorphism;
5. Polymorphism (considered 'No Mutation Detected').

The BRACAnalysis CDx™ is intended as an aid in selecting ovarian cancer patients with deleterious or suspected deleterious germline *BRCA* variants who may be eligible for treatment with Lynparza™ (olaparib). The majority (> 90%) of deleterious or suspected deleterious variants identified by Myriad in *BRCA1* and *BRCA2* are classified using objective criteria based on the type and genomic position of the variants, as described in the table below. Deleterious or suspected deleterious mutations classified by other criteria that are based on available evidence may be subject to change.

Objective Classification Criteria for Deleterious and Suspected Deleterious Variants

Classification	Variant Type	Position*
Deleterious	Nonsense	Truncates the reading frame at or before the most 3' known deleterious mutation
	Frameshift	Truncates the reading frame at or before the most 3' known deleterious mutation
	Large Rearrangement	Deletion of an exon or exons predicted to disrupt the reading frame or a critical functional domain
		Duplication of a non-terminal exon or exons predicted to disrupt the reading frame or a critical functional domain
		Insertion of non-*BRCA* sequence that disrupts the reading frame or a critical functional domain
Suspected Deleterious	Splicing	Intronic variants that disrupt the consensus splice donor sites (+1, +2 intronic position) and splice acceptor sites (-1, -2 intronic position)

* There are exceptions that are classified on a case-by-case basis. For example, a silent variant in exon 9 (C197C) in *BRCA1* has been reported to affect mRNA splicing (Miki et al. 1994; Dosil et al., 2010). Also, alternative splicing of exon 11 in *BRCA1* is partially functional (Thakur et al., 1997; Kim et al., 2006; Huber et al., 2001).

Once the identified variants are classified, the completed dataset for each sample is reviewed and a report is sent to the designated physician. All mutations and genetic variants are named according to the convention of Beaudet and Tsui (1993). Nucleotide numbering starts at the first transcribed base of *BRCA1* and *BRCA2* based on GenBank entries U14680 and U43746, respectively.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no FDA-cleared or -approved alternatives for *BRCA* mutation testing of DNA isolated from whole blood specimens for the selection of ovarian cancer patients who are eligible for treatment with Lynparza™ (olaparib).

VII. MARKETING HISTORY

Myriad Genetic Laboratories, Inc. initially designed and developed BRACAnalysis as a laboratory developed test, and the first commercial sample was tested in 1996. The BRACAnalysis test has been used to detect the presence of mutations within the *BRCA1* or *BRCA2* genes in the hereditary cancer predisposition setting. BRACAnalysis is not FDA-cleared or -approved.

BRACAnalysis CDx™ has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect *BRCA* test results, and subsequently, improper patient management decisions in ovarian cancer treatment. Patients with false positive results may undergo treatment with Lynparza™ (olaparib) without any clinical benefit, and may experience adverse reactions associated with olaparib therapy. Patients with false negative results may not be considered for treatment with Lynparza™ (olaparib), and therefore, may receive other treatment options. There is also a risk of delayed results, which may lead to a delay in treatment with Lynparza™ (olaparib).

For the specific adverse events related to Lynparza™ (olaparib) that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

The specific performance characteristics of the BRACAnalysis CDx™ were determined by studies using samples from ovarian cancer patients, as well as samples from breast cancer patients and unaffected individuals from families with and without a high risk for Hereditary Breast and Ovarian Cancer. Samples were selected to represent a range of variants detected by the BRACAnalysis CDx™, as reflected in the device labeling.

1. **Accuracy**

a. BRACAnalysis CDx™ Sanger Sequencing Test

Accuracy of the BRACAnalysis CDx™ Sanger Sequencing test was verified by comparison against a validated next generation sequencing (NGS)-based

assay. The two methods sequenced overlapping regions of the *BRCA1* and *BRCA2* genes (a total of 17,337 bases), and were used to independently evaluate a panel of 100 patient-derived specimens. All specimens were tested in a blinded manner. The specimens covered a range of variants, including single nucleotide variants, deletions up to 5 bp, and insertions up to 2 bp.

After variant and non-variant calls (relative to wild-type sequences) were made for each test, the results were compared. From the set of samples tested, a total of 796 variant bases (representing 790 variants) and 1,732,907 non-variant bases were identified by the NGS-based test. For each sample tested with the BRACAnalysis CDx™ Sanger Sequencing test, successful calls were made for all amplicons that are part of the assay, and the no call rate was 0%. All variant and non-variant base calls between the two tests were concordant. The agreement analysis between the results from both tests demonstrated a positive percent agreement (PPA), negative percent agreement (NPA), and overall agreement of 100%. The lower bounds of the 95% confidence intervals (CI) for PPA and NPA were 99.62% and 99.99%, respectively, which met the pre-specified acceptance criteria for the study. The results are summarized in the table below.

BRACAnalysis CDx™ Sanger Sequencing Test vs. NGS-Based Assay

Results	NGS Assay	Sanger Assay	Concordant Calls
Variant Bases	796	796	796
Non-Variant Bases	1,732,907	1,732,907	1,732,907
Total Bases*	1,733,703	1,733,703	1,733,703
Positive Percent Agreement (PPA) = 100% (95% CI: 99.62%, 100%)			
Negative Percent Agreement (NPA) = 100% (95% CI: 99.99%, 100%)			
Overall Agreement = 100% (95% CI: 99.99%, 100%)			

*There were 3 one-base insertions in this sample set.

b. BRACAnalysis CDx™ Large Rearrangement Test (BART® CDx)

The performance of the BART® CDx test was evaluated by comparing it to a validated microarray-based test. A set of 100 samples was processed in a blinded manner using the BART® CDx and the microarray tests. The types of large rearrangements evaluated in this study were as follows: single exon and multi-exon deletion and duplication, the Portuguese founder mutation, and multi-exon triplication.

Accuracy of the results from the BART® CDx test was demonstrated by comparison against the positive and negative calls from the validated microarray test. Based on the microarray results, 26 samples were positive for a large rearrangement in *BRCA* genes, and 74 samples were negative. For the BART® CDx test, 95 samples yielded valid results and 5 samples had invalid results, or no calls. Among the 95 samples with callable results, 94 samples had results that matched those from the microarray assay, while one did not. The miscalled, or discordant, variant was identified as a multi-exon duplication by the BART® CDx test while the microarray test detected a multi-exon triplication. Although both tests detected an increase in dosage of

the same region, the BART® CDx test is not designed to differentiate between duplications and triplications, and therefore, this is a limitation of the BART® CDx test. Based on the results, PPA was 84.6% (95% CI: 65.1% - 95.6%) and the NPA was 97.3% (95% CI: 90.6% - 99.7%). The overall agreement was 94% (95% CI: 87.4% - 97.8%). The results are summarized in the table below.

BART® CDx Test vs. Microarray Assay

LR* Status	Variant Type	Array Results	BART® CDx Results		
			Concordant	Miscall	No Call
Positive	Single exon deletion	7	5	0	2
	Single exon duplication	3	2	0	1
	Multi-exon deletion	11	11	0	0
	Multi-exon duplication	3	3	0	0
	Multi-exon triplication	1	0	1	0
	Portuguese founder mutation	1	1	0	0
	TOTAL	26	22	1	3
Negative	NMD**	74	72	0	2
	TOTAL	100	94	1	5

* Large Rearrangement
** No Mutation Detected

2. **Analytical Sensitivity – DNA Input**

a. BRACAnalysis CDx™ Sanger Sequencing Test

PCR Amplification is the critical step in the BRACAnalysis CDx™ Sanger Sequencing test for generating high levels of specific amplicons for the sequencing reactions. To assess the acceptable range of genomic DNA input to achieve the PCR performance requirements of the test, DNA extracted from five clinical specimens were each diluted to evaluate six DNA input concentrations (0.2 ng, 1 ng, 4 ng, 20 ng, 40 ng, and 100 ng) per PCR reaction. The specimens carried variant types, such as single nucleotide variant and small deletion up to 5 bp. Each sample was tested for eight representative amplicons in duplicate. The amplicons were selected to represent the range of amplicon sizes, GC-content, and coverage applicable to the BRACAnalysis CDx™ Sanger Sequencing test, as indicated in the table below. The rate of successful calls at each DNA input level was assessed, in addition to the concordance between the replicates per amplicon.

Amplicon Characteristics

Gene	Amplicon	Amplicon Description		
		Length (bp)	% GC	Coverage
BRCA1	1	496	41	Bi-directional
	2	506[a]	42	Bi-directional
	3	292	42	Bi-directional
	4	279	55[c]	Bi-directional
	5	82[b]	29	Uni-directional[e]
	6	257	36	Bi-directional

BRCA2	7	445	36	Bi-directional
	8	290	27[d]	Bi-directional

[a] Longest amplicon in the assay.
[b] Shortest amplicon in the assay.
[c] Most GC-rich amplicon in the assay.
[d] Least GC-rich amplicon in the assay.
[e] The presence of a homopolymer track renders one sequencing direction unreadable.

The optimal DNA input concentration for PCR amplification is 20 ng, as specified in the protocol for the BRACAnalysis CDx™. At this level, all of the results for each sample met the quality criteria and generated callable results. The duplicate results for each amplicon were fully concordant for all of the variant and non-variant calls. For input levels at 100 ng and 40 ng, the no call rate was 0%, and all results were fully concordant. At 4 ng, the no call rate was 1%, and all callable results were concordant. At 1 ng, the no call rate was 4% and no miscalls were observed. At 0.2 ng, although the callable results were concordant, the no call rate was 44%, and therefore the acceptance criteria were not met for this input level. The DNA input level of 20 ng, which is specified in the standard protocol, is within the tolerated range of tested DNA input concentrations from 1 ng to 100 ng.

b. BRACAnalysis CDx™ Large Rearrangement Test (BART® CDx)

The BART® CDx test is a multiplex PCR assay that amplifies specific regions in the *BRCA1* and *BRCA2* genes. To evaluate the DNA input range for the PCR step, DNA concentrations higher and lower than the optimal DNA input amount of 8 ng, which is specified in the assay protocol, were evaluated. DNA samples from five patient specimens were each diluted and tested at seven different DNA input levels: 2 ng, 4, ng, 6 ng, 8 ng, 10 ng, 12 ng, and 14 ng. Samples with and without large rearrangements (e.g., multi-exon deletions) were included.

The rate of successful calls for each sample per DNA input level was assessed, as well as the concordance across DNA concentrations. DNA input levels ranging from 2 ng to 12 ng produced callable results for all samples tested, and the results were fully concordant. At 14 ng, one sample did not yield callable results and, therefore, failed to meet the acceptance criteria of the study. The results demonstrate that DNA input levels from 2 ng to 12 ng generate similar results to those at 8ng, which is the DNA concentration specified for the BART® CDx test.

3. Analytical Specificity – Cross Reactivity

a. BRACAnalysis CDx™ Sanger Sequencing Test

The ability of the BRACAnalysis CDx™ Sanger Sequencing test to detect sequence variants is highly dependent upon the specificity of the primers for PCR amplification. To assess the potential for amplification of non-specific products from human genomic DNA, *in silico* analysis of the PCR primers

used in the assay was performed. Non-standard primer combinations were not evaluated since the assay consists of only singleplex PCR reactions. No non-specific products were predicted for any of primer pair combinations.

b. BRACAnalysis CDx™ Large Rearrangement Test (BART® CDx)

A specificity analysis was conducted to determine if the PCR primers used in the BART® CDx test have the potential to amplify non-target sequences in the human genome. A bioinformatics program was used to align primer pairs against genomic sequence to predict if there may be any non-specific amplicons. Every possible primer pair combination per multiplex reaction was evaluated. In total, 3,016 combinations were assessed. Non-specific products were not predicted for any of the potentially cross-reactive primer pairs in any of the BART® CDx multiplex PCR reactions.

4. **Interference**

To evaluate how potential interfering substances may impact the performance of the BRACAnalysis CDx™, the effects of three classes of substances were assessed: 1) endogenous substances normally present in human whole blood (i.e., hemoglobin, Albumin, IgG, and bilirubin); 2) an exogenous substance (i.e., K_3EDTA); and 3) substances used in the standard process of the device (i.e., ethanol and bleach). Three whole blood samples from healthy subjects carrying a total of 30 different *BRCA* variants were evaluated. The types of variants included single nucleotide variant and small deletion up to 2 bp. The endogenous and exogenous substances were spiked into each blood sample, and then the samples were processed, along with a corresponding set of unspiked blood samples. The concentrations tested for some of the endogenous substances were based on the CLSI guideline document EP7-A2. In accordance with standard protocol for the assay, the method-specific substances - ethanol and bleach - were added to genomic DNA samples after the DNA quantification step. All of the samples were tested with the BRACAnalysis CDx™ Sanger Sequencing test and the BART® CDx test.

The variant and non-variant calls were compared across the spiked and unspiked samples to determine if the potential interferents may lead to alterations in the test results. All non-spiked blood specimens yielded 100% callable and concordant results that passed the acceptance criteria for both the BRACAnalysis CDx™ Sanger Sequencing test and the BART® CDx test. Treatment with each potentially interfering substance at the maximum concentration tested, with the exception of IgG at 60 g/L, did not affect the performance of either test (i.e., hemoglobin at 20 g/dL, albumin at 50 g/L, conjugated bilirubin at 5 mg/dL, K_3EDTA at 5%, ethanol at 12.75%, and 10% bleach at 0.5%). Samples with IgG at 60 g/L yielded a no call rate of 33%, which failed to meet the acceptance criteria for the BART® CDx test and demonstrated that IgG concentrations at 60 g/L interfere with the assay performance. At an IgG concentration of 9.5 g/L, which is near the average level typically detected in blood, all samples generated callable results that matched those of the corresponding unspiked samples. Thus, at 9.5 g/L of IgG, the acceptance criteria were met.

5. **Reproducibility and Repeatability**

a. **Combined Reproducibility**

Reproducibility of the BRACAnalysis CDx™ was assessed by testing a set of 20 patient-derived samples over three independent runs using two or three instruments of each type, three reagent lots, and three operators for each manual processing step. The three runs were conducted over non-consecutive days using the BRACAnalysis CDx™ Sanger Sequencing test and the BART® CDx test. The confirmatory assays were also performed, in accordance with the standard protocols.

Across all tested samples, sequencing variants (single nucleotide variants and deletions up to 5 bp) and large rearrangements (single exon deletion, single exon duplication, and multi-exon deletion) were represented. For both tests, the no call rate was 0%, since all runs produced successful calls for all samples. For each sample, all calls were consistent across all runs. The positive percent agreement (PPA), negative percent agreement (NPA), and overall agreement were all 100%, which met the acceptance criteria for the study.

b. Intra-Run Repeatability

i. BRACAnalysis CDx™ Sanger Sequencing Test

To determine if the BRACAnalysis CDx™ Sanger Sequencing test is reproducible across replicates of the same sample within a single batch run, three blood samples were tested in triplicate using ten amplicons of the test. The amplicons were selected to represent the range of genomic regions that are evaluated in the BRACAnalysis CDx™ Sanger Sequencing test. These include the longest amplicon, the shortest amplicon, the most GC-rich amplicon, and the least GC-rich amplicon. Regions for which the presence of a homopolymer track renders only one sequencing direction readable were also included. The amplicons were tested in two batches, such that 9 amplicons were run in one batch and 1 amplicon in another. For the batch with 9 amplicons, all of the replicates for each sample produced 100% callable and concordant results. For the batch with only one amplicon, 8 of 9 reactions were callable and the callable results were concordant within each sample.

ii. BRACAnalysis CDx™ Large Rearrangement Test (BART® CDx)

To demonstrate that the BART® CDx test can generate repeatable results across replicates of the same samples within a single batch run, ten specimens were processed in triplicate within one run. Variants of the following types were represented in the study: single exon duplication and multi-exon deletion. All replicates for each of the samples passed the

quality criteria and therefore produced callable results, all of which were fully concordant.

6. Guardbanding

a. BRACAnalysis CDx™ Sanger Sequencing Test

Guardbanding studies were performed to evaluate if the performance of the BRACAnalysis CDx™ Sanger Sequencing test is robust to withstand process variations around two key parameters: PCR annealing temperature, and sequencing annealing temperature. Five samples were tested in duplicate per tested condition, and variant types included single nucleotide variant and small deletion (up to 5 bp).

i. **PCR Annealing Temperature**

The thermal cycling profile was guardbanded by varying the PCR annealing temperature by ±1°C, ±2°C and ±3°C. The expected call for each sample was defined by the results obtained under the PCR annealing temperature specified in the standard protocol. The results from each test condition were compared to the expected calls. For three test conditions (+1°C, -2°C and -3°C), all replicates for each amplicon tested per sample yielded callable results that matched the expected call. Similar results were observed for the other test conditions (-1°C, +2°C and +3°C), with the exception that only one replicate of one of the tested amplicons for one sample generated no call. Overall, the acceptance criteria were met, and all test conditions were tolerated.

ii. **Sequencing Reaction Annealing Temperature**

The annealing temperature for the sequencing reaction was challenged by varying the temperature by ±1°C, ±2°C and ±3°C. The expected call for each sample was defined by the results obtained under the PCR annealing temperature specified in the standard protocol. The results from each test condition were compared to the expected calls. For three test conditions (-1°C, +2°C and -3°C), all replicates for each amplicon tested per sample yielded callable results that were in agreement with the expected call. For the other test conditions (+1°C, -2°C and +3°C), one replicate for one of the tested amplicons for one sample generated no call, while all other replicates generated results that matched the expected call. Overall, the acceptance criteria were met, and all test conditions were tolerated.

b. BRACAnalysis CDx™ Large Rearrangement Test (BART® CDx)

The robustness of two critical parameters of the BART® CDx test was assessed: PCR annealing temperature and injection time of the PCR product input for capillary electrophoresis. In both cases, the same set of 28 unique samples was assessed and analyzed, of which two were run in duplicate. Two samples were positive for multi-exon deletions.

i. **PCR Annealing Temperature**

The PCR annealing temperature was varied by ±1°C, ±2°C, and ±3°C. The expected call for each sample was defined by the results obtained under the PCR annealing temperature specified in the standard protocol. The results from each test condition were compared to the expected calls. Four test conditions (±1°C, -2°C, and -3°C) yielded reportable and concordant calls for all samples. At the two other conditions (+2°C and +3°C), one sample yielded a miscalled deletion result. Upon confirmatory testing, a variant in one of the BART® CDx PCR primer annealing sites was identified to be the cause for the decreased primer binding efficiency at the two elevated temperatures, leading to the miscall result.

ii. Injection Time

Different levels of PCR product injected onto the ABI 3730xl platform were assessed by altering the injection time of the PCR product. The injection time was set at 2, 4, 5, 6, 7, 10, or 20 seconds, while the voltage was held constant (2 kV), resulting in 4, 8, 10, 12, 14, 20 or 40 kV·s, respectively. Results obtained under optimal conditions (i.e., 12 kV·s) were used to compare results obtained under the test conditions. All conditions, except 40 kV·s, resulted in callable, concordant results for all samples. At 40 kV·s, calls of acceptable quality were not obtained for any sample, indicating that this setting falls outside of the linear detection range of the capillary electrophoresis instrument. Thus, the optimal condition of 12 kV·s is within the acceptable PCR input injection conditions from 4 kV·s to 20 kV·s.

7. Cross Contamination

The potential for crossover contamination within a run and between runs was evaluated for three processes of the BRACAnalysis CDx™: 1) DNA extraction from whole blood specimens, 2) the BRACAnalysis CDx™ Sanger Sequencing test, and 3) the BART® CDx test. Specimens with different *BRCA* genotypes (for sequence variants and large rearrangements) were processed adjacent to each other in microtiter plate formats to maximize the potential for carryover between wells within a plate and between plates in separate batch runs. Two sequential batches were evaluated for inter-run carryover, and each run was evaluated separately for intra-run carryover.

a. DNA Extraction

DNA extraction from whole blood samples is an automated process using the QIASymphony robotic platform. Four blood samples were processed in triplicate from DNA extraction to data review. After isolation of genomic DNA, two samples were processed through the BRACAnalysis CDx™ Sanger Sequencing test and all four samples went through the BART® CDx test. For all samples in all batches, callable results were generated. All replicates were

fully concordant within each run and between runs. Thus, sample crossover events were not detected.

b. BRACAnalysis CDx™ Sanger Sequencing test

Two samples with unique BRCA sequence variants were set up within one PCR plate in a checkerboard pattern at alternating high (20ng for the first sample) and low (4 ng for the second sample) DNA input levels. In the first run, there were 84/90 (93%) reportable calls and 6/90 no calls for the two samples tested. All callable results were concordant. In the second run, there were 89/90 (99%) reportable calls, all of which were concordant. Although the no call rate was higher than observed in some other analytical studies, no miscall results were generated.

c. BRACAnalysis CDx™ Large Rearrangement Test (BART® CDx)

For the BART® CDx test, a total of ten samples were evaluated. In each batch, eight unique samples without *BRCA* large rearrangements were included with two samples with a large rearrangement. The two samples that were positive for a large rearrangement were tested in triplicate per run, while the samples that did not carry a large rearrangement were tested in six replicates per run. In the first run, two pairs of samples were set up in triplicate at high (12 ng for the large rearrangement negative samples) and low (4 ng for the samples with large rearrangements) DNA input levels. For all replicates of all samples in each batch, callable results were generated and were fully concordant with the expected results. Carryover events leading to miscall results were not observed.

8. Stability

a. Specimen Stability

To define the storage conditions and evaluate the stability of whole blood specimens for use with the BRACAnalysis CDx™, blood samples stored at defined temperatures and durations were assessed. Blood samples (25-30 mL) from five individuals were collected in EDTA tubes, aliquoted, and immediately tested (time point T_0) or stored at two temperatures, 4°C (storage temperature specified in the standard protocol) and 30°C, for some specified amounts of time. Blood samples were stored at 4°C for 14 days, 30 days, and 37 days. At 30°C, samples were stored for 3 days, 5 days, and 7 days. At each time point, duplicate aliquots per sample were processed and analyzed with the BRACAnalysis CDx™ Sanger Sequencing test and the BART® CDx test. No large rearrangements were detected in the samples, and sequence variants included single nucleotide variants.

Results from each time point were compared to those from time point T_0 to determine if the same results may be obtained from stored samples. For all indicated time points at 4°C and 30°C, all replicates per sample yielded callable results that matched the results from T_0. These data support that whole blood

specimens are stable for up to 30 days when stored at 4°C and up to 5 days at 30°C.

b. Reagent Stability

The storage and stability conditions for a defined set of reagents used in the BRACAnalysis CDx™ were evaluated. Three lots of each set of reagents were stored under specified temperature conditions and then tested at defined time points. Critical reagents used in three processes were evaluated: the BRACAnalysis CDx™ Sanger Sequencing test, the BART® CDx test, and DNA quantification and normalization. Under all of the test conditions, results from each time point were compared against those from time point T_0. The parameters tested for each reagent are listed in the table below.

Reagent Stability Storage Conditions

Assay / Step	Reagent	Temp	Expiration	Time Points Tested
Sanger sequencing	PCR plate	-20 °C	TBD*	0 mo**
		30 °C	24 hr	0, 12, 24, 36 hr
	Oligo plate	-80 °C	TBD*	0 mo**
		4 °C	< 30 d	0, 30 d**
		30 °C	7 d	0, 4, 7, 11 d
	CAPSeq plate	-20 °C	TBD	0 mo**
BART®	BART® PCR	-80 °C	TBD	0 mo**
Quantification	Standards	30 °C	48 hr	0, 24, 48, 72 hr
		4 °C	30 d	0, 15, 30, 45 d

* To Be Determined,
** Real-time stability studies are underway.

For the BRACAnalysis CDx™ Sanger Sequencing test, three reagent sets were assessed: PCR plates with pre-mixed reagents (excluding DNA template and PCR primers), Oligo plates which contain the PCR primers, and CAPSeq plates which contain the components of the PCR reaction for sequencing. A set of five specimens with single nucleotide variants or deletions up to 2 bp were tested. For all time points and storage conditions tested for each reagent, variant and non-variant calls were successfully generated and concordant with the corresponding results from T_0. Expiration dating for each reagent is shown in the table above. Real-time stability testing for some reagents is ongoing.

For the BART® CDx test, PCR plates with pre-mixed reagents (except for DNA template) were evaluated using a different set of five samples. A multi-exon deletion was detected in one sample, while the others did not contain a large rearrangement. Stability testing for the BART® CDx PCR plate at -80°C is ongoing.

For the DNA quantification and normalization process, the stability of the standards used for quantification was tested. Duplicate calibration curves were generated for the three lots at each time point, and the concentrations of two control DNA samples were then calculated. Across all tested time points,

minimal variation was observed for the calculated concentrations of the control DNA samples, supporting the expiration dating of 30 days at 4°C for the quantification standards.

c. Control Stability

The stability of eight assay controls used in the BRACAnalysis CDx™ was evaluated. Three lots of each control used in the BRACAnalysis CDx™ Sanger Sequencing test and BART® CDx test were produced and assessed. For the CPA assay, two lots of each control were evaluated. If three lots were tested, five replicates of each control lot were tested at each time point, for a total of 15 replicates. If two lots were available, the 15 replicates of each control were also tested, where eight replicates were tested with one lot and seven replicates with the second lot. For the positive controls, testing to the observable positive control endpoint was evaluated. For the negative controls, two testing endpoints were defined; the first test observed the expected negative outcome of each control, and the second test was designed to yield a positive outcome by spiking the samples with amplifiable DNA template to demonstrate that the expected negative outcome in the first test was not due to defective PCR reagents or a processing error. The controls and storage conditions for this study are listed in the table below.

Control Stability Storage Conditions

Assay	Control	Temp	Expiration	Time Points Tested
Sanger	M13 F+R Negative Control	≤ -65 °C	TBD*	0 mo**
BART®	Cell Line Positive Control	Quantified, normalized gDNA at 4 °C	2 mo	0, 1, 2, 3 mo
	Alternate Positive Control	Quantified, normalized gDNA at 4 °C	< 1 mo	0, 1, 2, 3 mo
	Amplicon Negative Control	-20 °C	TBD*	0 mo**
CPA	PCR Amplification Control 1	Quantified, normalized gDNA at 4 °C	2 mo	0, 1, 2, 3 mo
	PCR Amplification Control 2	Quantified, normalized gDNA at 4 °C	2 mo	0, 1, 2, 3 mo
	No Genomic DNA Control 1	-20 °C	TBD*	0 mo**
	No Genomic DNA Control 2	-20 °C	TBD*	0 mo**

* To Be Determined
** Real-time stability studies are underway.

Results from each time point for the stored controls were compared to the corresponding T_0 results. At T_0, all replicates for each control, except one,

yielded callable, concordant results. The one exception was the M13 F+R Negative Control that was spiked with an M13-tailed PCR amplicon. In this case, one replicate resulted in no call for one lot. As a result, there was a total of 14/15 (93%) successful calls for the spiked M13 Negative Control, and all calls were concordant.

Time points for the following controls are complete: the BART® Cell Line Positive and BART® Alternative Positive Controls (1, 2, and 3 mo), and the CPA PCR Amplification Controls 1 and 2 (1 and 2 mo). For the BART® Cell Line Positive Control, all tested time points met the acceptance criteria. For example, all replicates at 1 month and 3 months produced callable results that were fully concordant, and at the 2 month time point, there was one no call for one lot, while all other replicates had reportable and concordant results. Thus, the 2 month expiration for the BART® Cell Line Positive Control was supported.

For the BART® Alternative Positive Control, all replicates at 1 month and 3 months produced callable results that were fully concordant; however, the 2 month time point failed to meet the acceptance criteria, as there were three no call results. For the CPA PCR Amplification Controls 1 and 2, all replicates at the 1 and 2 month time points generated reportable results that completely corresponded to the T_0 results. Taken together, the results support a current expiration of less than 1 month for the BART® Alternative Positive Control, and less than 2 months for the CPA PCR Amplification Controls 1 and 2. Additional real-time testing is ongoing for the CPA PCR Amplification Controls 1 and 2, as well as the M13 Negative Control, the BART® Amplicon Negative Control, and the CPA No Genomic DNA Controls 1 and 2.

d. Intermediate Product Stability

The stability of intermediate products of the BRACAnalysis CDx™ was evaluated under specific storage conditions. Intermediate products generated from each of five samples were tested in duplicate. Three samples contained sequence variants including single nucleotide variants and a deletion up to 19 bp; one sample had a large rearrangement. In all of the stability evaluations, the results of the tested time points were compared to the initial T_0 results for successful calls and concordance. The intermediate products and storage conditions that were tested are listed in the table below.

Intermediate Product Storage Conditions

Assay	Int. Product	Temp	Stability	Time Points Tested
Sanger	Pre-PCRs in 384-well plates	4 °C	6 hr	0, 6, 9 hr
	PCR in 96-well plates	4 °C	4 d	0, 4, 7 d
	Post-DNA inoculated Pre-PCR plates	4 °C	4 hr	0, 4, 8 hr
		18-32 °C*	2 hr	0, 2, 4 hr

BART®	Post-Elution	4 °C	7 d	0, 4, 7 10 d
		18-32 °C*	6 hr	0, 9, 15 hr
CPA	Post-PCR	4 °C	14 d	0, 7, 14, 21 d

* Ambient temperature in the laboratory

For the BRACAnalysis CDx™ Sanger Sequencing test, all results at T_0 produced callable results that were fully concordant. The results for all test conditions, except the PCR intermediate product in 96-well plates stored at 4 °C for 4 days, produced successful sequencing calls. Although the acceptance criteria were also met for the PCR intermediate product in 96-well plates stored at 4 °C for 4 days, one replicate for one amplicon in one sample failed to yield a callable result. All of the variant and non-variant calls for all time points were concordant with the results from T_0.

For the BART® CDx test, all results at T_0 generated calls, which were concordant for each of the 5 samples. For all time points tested for the two intermediate products, all samples produced successful BART® CDx positive and negative calls that matched the T_0 results. No miscalls were detected. For the confirmatory CPA assay, the post-PCR intermediate product from one sample with a large rearrangement (as detected by BART® CDx) was evaluated, in accordance with the standard protocol. All tested conditions generated results that were fully concordant with the T_0 result. The results support the stability results shown in the table above.

B. Animal Studies

None

C. Additional Studies

Variant Classification Study

To evaluate the robustness and reliability of the variant classification process, a set of 262 unique *BRCA* variants was subjected to classification as if they were new variant observations. The variants were classified in a blinded manner according to defined classification criteria. The resulting classifications for each variant were compared to the existing classifications in Myriad's database, and the concordance rate was determined. One variant that was not previously observed at Myriad - and therefore was not previously classified - was excluded from the study. The majority of variants (185/262) were identified from clinical studies for Lynparza™ (olaparib), and the remaining variants (77/262) were selected for inclusion into the study in order to adequately cover the spectrum of variant types for classification. The results are summarized in the tables below.

Classification Results

Classification	Previous Classification	New Classification
Deleterious (DM)	130	126
Suspected Deleterious (SD)	7	11

Uncertain Significance (VUS)	34	32
Favor Polymorphism (FP)	9	17
Polymorphism (PM)	81	75
Excluded from study	1	1
TOTAL	262	262

Discordant Results by Classification

Previous Classification	New Classification	Discordant Results	
		Classification	Treatment
DM	SD	5	0
SD	DM	1	0
SD	VUS	1	1
VUS	SD	1	1
VUS	FP	2	0
PM	FP	6	0
TOTAL		16	2

Comparison of the new classifications to the previous classifications resulted in agreement for 245 variants (93.9%, 95% CI: 90.2% - 96.5%). There were 16 variants that had inconsistent results; treatment eligibility for Lynparza™ (olaparib) would not be affected by 14 of the inconsistent classifications, but the different classifications for two variants would affect patient selection. Of the two, one is a missense variant classified as suspected deleterious (SD), while the previous classification was a variant of uncertain significance (VUS). The change in classification resulted from structural and functional evidence, which recently became available, to support the SD classification. The other inconsistent result was an intronic splicing variant classified as VUS in this study, but previously was SD. Again, the change in classification was due to recently available evidence. Upon comparison of the two separate and independent variant classifications leading to the same eligibility status for treatment with Lynparza™ (olaparib), the concordance rate was 99.2% (259/261, 95% CI: 97.2% - 99.9%).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The clinical benefit of the BRACAnalysis CDx™ was demonstrated in a retrospective analysis of efficacy and safety data obtained from the open-label, non-randomized study to assess the safety and efficacy of olaparib treatment in patients with ovarian cancer who have a deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*) and who have been previously treated with at least three lines of prior chemotherapy. Patients were enrolled from 13 centers in six countries, including the United States. Local test results for *BRCA* status were used to assess patient eligibility for the trial. Samples from a subset of enrolled patients from the intended population were retrospectively evaluated at one laboratory, Myriad (Salt Lake City, UT), using the BRACAnalysis CDx™, in a clinical bridging study. In the bridging study, there were two objectives: 1) agreement between the BRACAnalysis CDx™ and the local test results for *gBRCAm* detection, and 2) the clinical outcomes (i.e., ORR and DoR) for the patients with ovarian cancer who had received three or more prior lines of chemotherapy, who had measurable disease, and who were positive for deleterious or suspected deleterious germline *BRCA* mutations, as identified by

the BRACAnalysis CDx™. Lynparza™ (olaparib) demonstrated a robust overall response rate with a clinically meaningful duration of response in *gBRCAm* patients with ovarian cancer who had received three or more prior lines of chemotherapy. The magnitude of response in the subset tested with the BRACAnalysis CDx™ was comparable to that in the locally tested *gBRCAm* study population. These results were also supported by additional robustness analyses. Data from this bridging study were used to support PMA approval.

A. Study Design

The major effectiveness study was a single-arm, open-label, multi-center study to assess the safety and efficacy of olaparib treatment in patients with advanced cancers who have a deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*). Patients were treated with 400 mg olaparib twice daily until disease progression or intolerance to study treatment. After starting study treatment, patients attended periodic clinic visits for assessment of safety and efficacy until confirmed objective disease progression. The primary objective of the study was 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 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). Safety information was collected throughout the study. To support approval of Lynparza™ (olaparib), the efficacy evaluation was performed in patients with deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*)-associated ovarian cancer who had received three or more prior lines of chemotherapy and who had measurable disease based on ORR and DoR. The results of this clinical study are described in NDA 206162.

To demonstrate clinical utility of the BRACAnalysis CDx™, a bridging study was conducted. Archived samples were available from a subset of patients with ovarian cancer enrolled in the open-label, non-randomized trial for retrospective analysis of g*BRCAm* status with the BRACAnalysis CDx™. The samples were tested in a blinded manner at Myriad (Salt Lake City, UT). The clinical utility of the BRACAnalysis CDx™ was established by comparing the mutation results and the associated clinical outcomes for the locally tested *gBRCAm* population to those for the subset of patients with confirmed *gBRCA* status upon retrospective testing with the BRACAnalysis CDx™. Additional robustness analyses were also performed.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the clinical study was limited to patients who met the following inclusion criteria*:*

   1. Provision of fully informed consent prior to any study-specific procedures.
   2. Patients must be > 18 years of age.
   3. Confirmed documented deleterious or suspected deleterious *BRCA* mutation. (The presence of a loss-of-function germline mutation in the *BRCA1* and/or *BRCA2* gene must be confirmed prior to consent according to local practice).

4. Histologically or, where appropriate, cytologically confirmed malignant solid tumour refractory to standard therapy and for which no suitable effective standard therapy exists. Haematological malignancies will be considered if there is a component of disease that can be assessed and followed for response by RECIST v1.1.
5. For the breast cancer setting, patients must have failed at least three previous lines of chemotherapy (not including tyrosine kinase inhibitors and hormonal treatments) in the metastatic/advanced setting. Patients who are hormone receptor positive must have also failed prior hormonal therapy. Patients who are HER2 receptor-positive must have failed prior trastuzumab.
6. For the ovarian cancer setting patients must have documented progressive or recurrent disease according to either RECIST v1.1 or Gynecologic Cancer Intergroup (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.

   Note that in the ovarian cancer setting, eligibility also includes patients who have developed recurrent ovarian cancer with macroscopic peritoneal metastases outside the pelvis or distant metastases. In addition, patients with primary peritoneal carcinoma or Fallopian tube carcinoma may be considered for the study.
7. For pancreatic cancer setting, patients must have failed systematic chemotherapy in the advanced or metastatic setting.
8. For the prostate cancer setting, patients must have:
   - hormone-refractory disease, defined as a testosterone value in the castration range
   - at least 2 consecutive rising PSA values above their nadir and measured at least two weeks apart
   - at least 6 weeks from discontinuation of anti-androgen therapy.
   - must have failed at least one systemic therapy for metastatic hormone-refractory disease.
9. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:
   - Hemoglobin ≥9.0 g/dL
   - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
   - White blood cells (WBC) >3 x 10^9/L
   - Platelet count ≥100 x 10^9/L
   - Total bilirubin ≤1.5 x institutional upper limit of normal (ULN).

- Aspartate transaminase (AST) (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present in which case it must be ≤ 5x ULN
- Serum creatinine ≤1.5 x institutional upper limit of normal (ULN)

10. ECOG performance status ≤2
11. Patients must have a life expectancy ≥12 weeks
12. Evidence of non-childbearing status for women of childbearing potential, or postmenopausal status: negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on day 1.

    Postmenopausal is defined as:

    - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    - Luteinizing hormone and follicle-stimulating hormone levels in the postmenopausal range for women under 50
    - radiation-induced oophorectomy with last menses >1 year ago
    - chemotherapy-induced menopause with >1 year interval since last menses
    - or surgical sterilization (bilateral oophorectomy or hysterectomy).
13. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.
14. At least one lesion (measurable and/or non-measurable) at baseline that can be accurately assessed by CT/MRI and is suitable for repeated assessment at follow-up visits.

Patients were <u>not</u> permitted to enroll in the study if they met any of the following exclusion criteria:

1. Involvement in the planning and/or conduct of the study (applies to both

   AstraZeneca staff and/or staff at the study site)
2. Any previous treatment with a PARP inhibitor, including olaparib.
3. 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.
4. Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used). The patient can receive a stable dose of bisphosphonates for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment. Prostate cancer patients may also continue to receive Luteinizing Hormone-Releasing Hormone (LHRH).
5. Patients receiving the following classes of inhibitors of CYP3A4

- Azole antifungals
- Macrolide antibiotics
- Protease inhibitors

6. Persistent toxicities (>CTCAE grade 2), excluding alopecia, caused by previous cancer therapy.
7. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment.
8. Patients with spinal cord compression, unless they have received definitive treatment for this and have evidence of clinically stable disease for at least 28 days prior to study entry
9. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
10. 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.
11. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
12. Breast-feeding women.
13. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus.
14. Patients with known active hepatic disease (i.e., Hepatitis B or C).
15. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.
16. Patients with uncontrolled seizures.
17. Previous enrollment in the present study.
18. Treatment with any investigational product during the last 14 days (or a longer period depending on the defined characteristics of the agents used).

2. Follow-up Schedule

Tumor assessments were performed at baseline and at regular intervals thereafter (every 8 weeks $\pm$ 1 week) until objective disease progression or up to 6 months after starting study treatment. If a patient had not progressed after 6 months, the tumor assessments were performed at extended intervals (12 weeks) until disease progression. Following confirmed disease progression, patients discontinued olaparib treatment, and were continued to be contacted to assess survival status

until death or the data cutoff for the primary analysis.

3. Clinical Endpoints

With regard to safety, information about adverse events was collected from time of signed informed consent throughout the treatment period and up to and including 30 days after the patient discontinues olaparib treatment.

With regard to effectiveness, the efficacy evaluation was performed in patients with deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*)-associated ovarian cancer who had received three or more prior lines of chemotherapy and who had measurable disease. The efficacy variables used to assess clinical benefit were objective response rate (ORR) and duration of response (DoR). The analyses were based on the assessment of response based on RECIST 1.1.

For the clinical bridging study, there were two objectives: 1) agreement between the BRACAnalysis CDx™ and the local test results for *gBRCAm* detection, and 2) the clinical outcomes (i.e., ORR and DoR) for the patients with ovarian cancer who had received three or more prior lines of chemotherapy, who had measurable disease, and who were positive for deleterious or suspected deleterious germline *BRCA* mutations, as identified by the BRACAnalysis CDx™.

B. Accountability of PMA Cohort

Based on local test results, a total of 317 patients with advanced cancers were enrolled in the study. There were 193 patients with deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*)-associated ovarian cancer, among whom 137 had measurable disease and had received three or more lines of prior chemotherapy. Out of the 137 patients, specimens from 61 patients were available for retrospective testing with the BRACAnalysis CDx™ in the clinical bridging study.

C. Study Population Demographics and Baseline Parameters

Study enrollment occurred at 13 centers in six countries (Australia, Germany, Spain, Israel, Sweden, and United States). Among the 137 *gBRCAm* patients with ovarian cancer who had received three or more lines of chemotherapy, 40 patients (29%) were enrolled in the US.

Baseline demographic characteristics and tumor information for the 137 *gBRCAm* patients with ovarian cancer who had measurable disease and who had received three or more lines of chemotherapy are provided in the table below. Also shown are the characteristics for the subset of 59 patients with confirmed *gBRCAm* results with the BRACAnalysis CDx™ and for 78 patients who were not tested with the BRACAnalysis CDx™ test (due to unavailability of archived specimens). In general, the demographics for patients with and without a BRACAnalysis CDx™ test result are similar, apart from the ECOG Performance status for which there was a higher proportion of patients with a performance status of 0 in the subgroup with a BRACAnalysis CDx™ test result.

Demographic characteristics for patients with ovarian cancer, 3 or more prior lines of chemotherapy and measurable disease at baseline

Characteristic	All patients (n=137)	Patients with BRACAnalysis CDx™ result (n=59)	Patients without BRACAnalysis CDx™ result (n=78)
	n (%)	n (%)	n (%)
Age (years)			
Mean (SD)	57.5 (9.02)	56.4 (7.89)	58.3 (9.75)
Median (range)	58.0 (35-79)	56.0 (36-75)	59 (35-79)
Age group (years)			
<50	26 (19.0)	11 (18.6)	15 (19.2)
≥50 to <65	83 (60.6)	39 (66.1)	44 (56.4)
≥65	28 (20.4)	9 (15.3)	19 (24.4)
Sex			
Female	137 (100)	59 (100)	78 (100)
Race			
White	129 (94.2)	56 (94.9)	73 (93.6)
Black/African-American	1 (0.7)	1 (1.7)	0 (0)
Asian	6 (4.4)	2 (3.4)	4 (5.1)
Other	1 (0.7)	0 (0)	1 (1.3)
ECOG performance status			
0	76 (55.5)	41 (69.5)	35 (44.9)
1	52 (38.0)	17 (28.8)	35 (44.9)
2	8 (5.8)	1 (1.7)	7 (9.0)
Missing	1 (0.7)	0 (0)	1 (1.3)
Site of tumour			
Ovary	125 (91.2)	55 (93.2)	70 (89.7)
Fallopian tube	3 (2.2)	1 (1.7)	2 (2.6)
Peritoneum	7 (5.1)	3 (5.1)	4 (5.1)
Primary peritoneal	2 (1.5)	0 (0)	2 (2.6)

Due to rounding of % values, some groups may sum to greater than 100.0%.

An assessment of the distribution of *BRCA* mutations between the patients with and without a BRACAnalysis CDx™ test result who had measurable disease and who received at least three lines of prior chemotherapy are summarized in the table below. The distributions of the mutations are generally similar between the groups.

***BRCA* mutation characteristics for patients with ovarian cancer, 3 or more prior lines of chemotherapy and measurable disease at baseline**

Characteristic	All patients (n=137)	Patients with BRACAnalysis CDx™ result (n=59)	Patients without BRACAnalysis CDx™ result (n=78)
	n (%)	n (%)	n (%)
BRCA1 variants	106 (77.4)	41 (69.5)	65 (83.3)
BRCA2 variants	30 (21.9)	18 (30.5)	12 (15.4)
BRCA1 & *BRCA2* variants	1 (0.7)	0 (0)	1 (1.3)
Frameshift	102 (74.5)	39 (66.1)	63 (80.8)
Nonsense	18 (13.1)	11 (18.6)	7 (9.0)
Missense	7 (5.1)	4 (6.8)	3 (3.8)
Splice site	4 (2.9)	2 (3.4)	2 (2.6)
Large rearrangement	2 (1.5)	1 (1.7)	1 (1.3)
Synonymous variant	1 (0.7)	1 (1.7)	0 (0.0)
In-frame deletion	2 (1.5)	1 (1.7)	1 (1.3)
Intronic variant	1 (0.7)	0 (0)	1 (1.3)

Due to rounding of % values, some groups may sum to greater than 100.0%.

D. Safety and Effectiveness Results

1. Safety Results

The safety, with respect to treatment with Lynparza™ (olaparib), will not be addressed in detail in the SSED for the BRACAnalysis CDx™. Adverse event information was obtained from multiple clinical studies. Major safety considerations related to the drug include the potential for an increased risk for the development of myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML) and the risk of non-infectious pneumonitis. The most common adverse reactions (≥20%) in clinical trials were anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dyspepsia, headache, decreased appetite, nasopharyngitis/URI, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash and upper abdominal pain. Refer to the drug label for more information.

2. Effectiveness Results

The analysis of efficacy analysis was based on objective response rate (ORR) and duration of response (DoR) observed in 137 patients with deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*)-associated ovarian cancer who had received three or more prior lines of chemotherapy and who had measurable disease. In this cohort, the ORR was 34% (95% CI: 26% - 42%) with a median

DoR of 7.9 months. The observed ORR represents an improvement over existing therapies and is reasonably likely to predict clinical benefit in the indicated population. The results are listed in the table below.

The effectiveness analysis for the BRACAnalysis CDx™ was based on a subset of 61 *gBRCAm* patients with ovarian cancer who had received three or more prior lines of chemotherapy, who had measurable disease, and for whom specimens were available for retesting with the BRACAnalysis CDx™. The level of concordance between the local test results, as reported in the Case Report Form, and the results from the BRACAnalysis CDx™ was determined to be 96.7% (59/61, 95% CI: 88.7% - 99.6%). Among the discordant results, one sample did not yield a callable result with the BRACAnalysis CDx™, and another sample had different classification results between the local test and the BRACAnalysis CDx™ (deleterious vs. variant of unknown significance, respectively), although the specific variant that was detected by both tests matched. The clinical outcome data for the 59 patients with confirmed *gBRCAm* status was as follows: ORR was 41% (95% CI: 28% - 54%), and median DoR was 8.0 months. Taken together, the results in the subset of *gBRCAm* patients tested with the BRACAnalysis CDx™ were comparable to those observed in the cohort of 137 patients, which supports effectiveness of the device. The results are summarized in the table below.

Clinical Study Results

Subset*	Total Subjects n	Subjects with Response n (%)	ORR	95% CI	Progressed n (%)	Median DoR (months)	95% CI
All	137	46 (33.6)	0.34	(0.26, 0.42)	30 (65.2)	7.9	(5.6, 9.6)
With BRACAnalysis CDx™ result	59	24 (40.7)	0.41	(0.28, 0.54)	14 (58.3)	8.0	(3.8, NC)
No BRACAnalysis CDx™ result	78	22 (28.2)	0.28	(0.19, 0.40)	16 (72.7)	7.9	(6.0, 9.6)

*Ovarian cancer patients with measurable disease who received at least three lines of prior chemotherapy

3. Subgroup Analyses

Additional robustness analyses were conducted to consider the potential impact of missing data arising from patients with a positive BRACAnalysis CDx™ test result, but who may have been negative by the local test. Patients with such test results are part of the intended use population of the BRACAnalysis CDx™; however, they were excluded from the clinical trial due to negative results upon local test screening. To account for this missing data, the efficacy of olaparib treatment in patients with positive results from the BRACAnalysis CDx™ was estimated assuming different combinations for the following parameters:

- The objective response rate (ORR) among patients with positive results with both the BRACAnalysis CDx™ and local tests was fixed at 41%, which was observed from the trial.

- The missing ORR among patients with positive BRACAnalysis CDx™ and negative local test results was assumed to be 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% to exhaust all possibilities that do not exceed the ORR estimated from patients with positive results with both the BRACAnalysis CDx™ and local tests.
- The proportion of cases with negative local test results are assumed to be 5%, 10%, 15%, 20%, 25%, or 30%. Based on published literature, the germline *BRCA* mutation rate in unselected ovarian cancers is from 11% to 15% (Hennessy, et al. 2010; Pal, et al. 2005).
- The negative percent agreement (NPA) of the two tests (i.e., negative results by both tests) was fixed at 0.988 (159/161), as was observed from multiple clinical studies as well as literature (Kurian et al. 2014).

Combining all of the above assumed parameter values, the ORR modeled for the BRACAnalysis CDx™ test-positive population, including those who may have tested negative by local tests, was calculated. The confidence intervals are calculated based on the imputed ORR from the subset of 137 patients with deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*)-associated ovarian cancer who had received three or more prior lines of chemotherapy and who had measurable disease in the study. The smallest ORR value estimated for the BRACAnalysis CDx™ test-positive population, including those who may have tested negative by local tests, is 34% (95% CI: 26% - 43%), which is not significantly different from that observed for the overall subpopulation of 137 patients who had measurable disease and who had received 3 or more lines of prior chemotherapy (34%, 95% CI: 26% - 42%). The results are listed in the table below.

Estimated ORR for the BRACAnalysis CDx™-Positive Population

		Assumed ORR for BRACAnalysis CDx™-positive and Local Test-Negative							
		5% % (95%CI)	**10%** % (95%CI)	**15%** % (95%CI)	**20%** % (95%CI)	**25%** % (95%CI)	**30%** % (95%CI)	**35%** % (95%CI)	**40%** % (95%CI)
Assumed Prevalence Local Test-Negative	**5%**	34% (26, 43)	35% (27, 44)	36% (28, 44)	37% (29, 46)	38% (30, 47)	39% (30, 47)	40% (32, 49)	41% (33, 50)
	10%	37% (29, 46)	38% (30, 47)	38% (30, 47)	39% (30, 47)	39% (30, 47)	40% (32, 49)	40% (32, 49)	41% (33, 50)
	15%	38% (30, 47)	39% (30, 47)	39% (30, 47)	39% (30, 47)	40% (32, 49)	40% (32, 49)	40% (32, 49)	41% (33, 50)
	20%	39% (30, 47)	39% (30, 47)	39% (30, 47)	40% (32, 49)	40% (32, 49)	40% (32, 49)	40% (32, 49)	41% (33, 50)
	25%	39% (30, 47)	40% (32, 49)	40% (32, 49)	40% (32, 49)	40% (32, 49)	40% (32, 49)	40% (32, 49)	41% (33, 50)
	30%	40% (32, 49)	40% (32, 49)	40% (32, 49)	40% (32, 49)	40% (32, 49)	40% (32, 49)	41% (33, 50)	41% (33, 50)

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any

clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study was supplemented by retrospective testing at one site. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Molecular and Clinical Genetics Panel, an FDA advisory committee, for review and recommendation.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The clinical benefit of the BRACAnalysis CDx™ was demonstrated in a retrospective analysis of efficacy and safety data obtained from the open-label, non-randomized study in which Lynparza™ (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. Results from local testing for *gBRCAm* were used to determine patient eligibility for the clinical study. The study enrolled 193 *gBRCAm* ovarian cancer patients, among whom 137 had received at least three lines of prior chemotherapy with measurable disease at baseline. Of the 137 patients, specimens from 61 patients were available for retrospective confirmation of g*BRCAm* status using the BRACAnalysis CDx™. After testing, 59 cases (96.7%) were verified to have deleterious or suspected deleterious germline *BRCA* mutations. Analysis of the subset of 59 patients revealed that the response rate was 41% (95% CI: 28% - 54%) and the median duration of response was 8.0 months. The results are similar to those observed in the overall population of 137 patients, for which the response rate was 34% (95% CI: 26% - 42%) and the median duration of response was 7.9 months. Additional robustness and worst case scenario analyses to include missing results supported an improvement in response rate in *gBRCAm* ovarian cancer patients.

The performance of the BRACAnalysis CDx™ was also supported by the analytical validation studies. As demonstrated in the analytical specificity study, the assay is highly specific for all targeted regions in the *BRCA1* and *BRCA2* genes. The device also demonstrated consistent performance to detect specific sequence variants and large rearrangements in the *BRCA* genes. Further, sequencing and large rearrangement results from the BRACAnalysis CDx™ correlated with results obtained from validated comparator methods.

B. Safety Conclusions

The BRACAnalysis CDx™ is an *in vitro* diagnostic device, which involves testing whole blood specimens collected from patients with ovarian cancer. The risks of the device are based on data collected in the clinical study conducted to support PMA

approval as described above. Risks of the BRACAnalysis CDx™ are associated with failure of the device to perform as expected or failure to correctly interpret test results. If incorrect, or false, results are reported, then ovarian cancer patients may not receive the proper treatment. Patients with false positive results may undergo treatment with Lynparza™ (olaparib) without any clinical benefit, and may experience adverse reactions associated with olaparib therapy. Patients with false negative results may not be considered for treatment with Lynparza™ (olaparib), and therefore, may receive other treatment options. There is also a risk of delayed results, which may lead to a delay in treatment with Lynparza™ (olaparib).

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in the clinical study, which were used to support PMA approval as described above. The clinical benefit of the BRACAnalysis CDx™ was demonstrated in a retrospective analysis of efficacy and safety data obtained from the open-label, non-randomized study in which Lynparza™ (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. Patients were enrolled into the clinical study based on local testing results for *gBRCAm*. Samples from a subset of enrolled patients with measurable disease who had received at least three lines of prior chemotherapy were subsequently tested with the BRACAnalysis CDx™ to verify *gBRCAm* status. The overall concordance rate between the local test results and those from BRACAnalysis CDx™ was 96.7% (95% CI: 88.7% - 99.6%). The observed clinical benefit in the subset of confirmed *gBRCAm* patients was comparable to that observed in the overall population. In the overall population of *gBRCAm* patients with previously treated ovarian cancer, the response rate was 34% (95% CI: 26% - 42%) and the median duration of response was 7.9 months. These results were also supported by additional robustness analyses. Overall, the response rate in patients with *gBRCAm*-associated ovarian cancer 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.

Additional factors to be considered in determining probable risks and benefits for the BRACAnalysis CDx™ included: analytical performance of the device, representation of variants in the major effectiveness study, and the availability of alternative tests. First, the primary risks associated with the BRACAnalysis CDx™ are the possibility of inaccurate, or false, results that may lead to mismanagement of patient treatment. The performance of the device is supported by analytical validation studies, and additional analytical testing will be conducted in the post-approval setting. Second, a limited range of variant types were included in the clinical bridging study. Confirmatory clinical studies are being conducted to verify the results of the major effectiveness study, and additional variant types will likely be represented. Third, there is currently no FDA-approved or -cleared device for the selection of *gBRCAm* patients with previously treated ovarian cancer for treatment with Lynparza™ (olaparib).

In conclusion, given the available information above, the data support the use of the BRACAnalysis CDx™ as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline *BRCA* mutations for fourth-line treatment with Lynparza™ (olaparib), and the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the open-label, non-randomized clinical study and the associated bridging study support the utility of the BRACAnalysis CDx™ as an aid in selecting patients with previously treated ovarian cancer who may be eligible for treatment with Lynparza™ (olaparib). Lynparza™ (olaparib) demonstrated improvement in objective response rate and duration of response in ovarian cancer patients who have been previously treated with at least three lines of prior chemotherapy and who have deleterious or suspected deleterious germline *BRCA* mutations, as identified with the BRACAnalysis CDx™.

XIII. CDRH DECISION

CDRH issued an approval order on December 19, 2014. The final conditions of approval cited in the approval order are described below.

1. As reflected in the labeling for BRACAnalysis CDx™, a limited range of variant types was included in some of the analytical validation studies. Additional testing of samples is required to establish the analytical performance characteristics of the BRACAnalysis CDx™ for all variant types that may be detected. Samples that adequately cover the range of small deletions, small insertions, and large rearrangements detected by the device, should be included, with consideration to variant lengths and genomic contexts. The results from these studies should be included in the labeling, and the results should be submitted within 7 months from the date of the approval order.

2. Since a limited range of variant types were included in the clinical validation study, results from the ongoing clinical trials (Study D0816C00002 and Study D0816C00010) using the BRACAnalysis CDx™ should be provided upon completion of the trials. If patients were enrolled based on results from a clinical trial assay (CTA), a bridging study between the CTA and BRACAnalysis CDx™ will be required. The results from these studies should be reflected in the labeling.

3. Defined criteria are used to classify variants detected by BRACAnalysis CDx™. Variant classifications may be subject to change over time based on newly available evidence that is evaluated in your classification process. To monitor the robustness of the variant classification process, continued evaluation of the process will be needed. When samples are received to be tested with BRACAnalysis CDx™, all variants that are detected should be treated as new variants and classified according to the current classification criteria. The current classification results should then be compared to the penultimate classifications (if variants were previously identified), with tabulation of agreement between the two classification results. A summary of the results should

be provided annually. The following should be included: the variants detected, the agreement between the previous and current classifications per category, the numbers of variants that changed per classification category, description(s) of the classification changes, and the criteria used for each classification (e.g., the criteria used for the previous classification, the criteria used for the current classification, and the rationale for any differences or changes to the classification criteria). The results from these studies could lead to labeling changes.

4. There was limited representation of deleterious and suspected deleterious germline *BRCA1* and *BRCA2* variants in the registrational clinical study. As treatment outcome data (e.g., literature) becomes available with broader representation of variants, the sponsor should assess and report on whether or not the variant classification criteria are in line with the drug efficacy results.

5. The BRACAnalysis CDx™ is intended to be used with EDTA blood collection tubes. The sponsor should track and report on the results from samples provided in K_2EDTA and K_3EDTA collection tubes. If the results from these studies lead to labeling changes, then a future PMA supplement would be required.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling. Refer to drug label for Lynparza™ (olaparib) for additional information related to use of the drug.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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/s/

EUNICE Y LEE
12/19/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA#	206162
Product Name:	Lynparza (Olapraib) 50 mg Capsules
PMR 2824-1 Description:	Submit the progression free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial D0818C00002, SOLO-2, the ongoing randomized double-blind, placebo-controlled, multi-center trial to assess the efficacy of olaparib maintenance monotherapy in relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and / or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations (documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)) who have responded following platinum based chemotherapy.

PMR Schedule Milestones:

Interim Report (PFS analysis)	02/2016
Trial Completion Date:	12/2018
Final Report Submission (OS analysis):	03/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Olaparib is being approved under subpart H (accelerated approval); therefore confirmatory trials are needed to confirm safety and efficacy in the proposed population: advanced, relapsed gBRCAm associated ovarian cancer. These patients have a serious and life-threatening condition with an unmet need for better therapies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   N/A

Reference ID: 3670063

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☒ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   Randomized double-blind, placebo-controlled, multi-center study 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 (Study D0818C00002, SOLO-2).

   Required (PMRs)

   ☐ Observational pharmacoepidemiologic study
   ☐ Registry studies
   ☒ Primary safety study or clinical trial
   ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   ☐ Thorough Q-T clinical trial
   ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
   ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Reference ID: 3670063

☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon (PMCs):

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3670063

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA#	206162
Product Name:	Lynparza (Olapraib) 50 mg Capsules
PMR 2824-2 Description:	Submit the progression free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial 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.

PMR Schedule Milestones:

Interim Report (PFS analysis)	06/2018
Trial Completion Date:	03/2020
Final Report Submission (OS analysis):	06/2020

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Olaparib is being approved under subpart H (accelerated approval); therefore confirmatory trials are needed to confirm safety and efficacy in the proposed population: advanced, relapsed gBRCAm associated ovarian cancer. These patients have a serious and life-threatening condition with an unmet need for better therapies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

N/A

Reference ID: 3670063

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☒ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized study 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 (Study D0816C00010)

Required (PMRs)

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Reference ID: 3670063

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon (PMCs):

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3670063

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA#	206162
Product Name:	Lynparza (Olapraib) 50 mg Capsules
PMR 2824-3 Description:	Collect and analyze all cases of Acute Myelogenous Leukemia / Myelodysplastic Syndrome identified in patients treated with Lynparza (olaparib) on an annual basis. These interim 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) to provide an accurate assessment of the long-term incidence and risk of AML/MDS.

PMR Schedule Milestones:		
Final Report Submission:		06/2020
Other:	Interim Report #1	12/2015
	Interim Report #2	12/2016
	Interim Report #3	12/2017
	Interim Report #4	12/2018
	Interim Report #5	12/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

There have been 21 confirmed cases of AML or MDS in the submitted Lynparza (olaparib) database, to date. However, the risk for the development of these events persists for years, even after discontinuation of olaparib therapy. We propose that the Sponsor submits annual updates to the NDA, summarizing new cases of AML or MDS, for 5 years after NDA approval. Each update should include detailed descriptions of each new patient diagnosed with MDS/AML, including the underlying cancer for which they received olaparib, previous chemotherapy and radiation therapy received, dose and regimen of olaparib received, duration of therapy with olaparib, exact timing of the diagnosis with regard to olaparib therapy (eg, if during therapy or after discontinuation). Details on bone marrow cytology, blast percent, cytogenetics, and flow cytometry should also be given. Finally, the Sponsor should describe any therapy administered to each patient for the treatment of MDS/AML, and should report the ultimate outcome for each patient (eg, event ongoing at the time of the report or death, including the exact date and cause of death).

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2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of continued monitoring of all patients receiving olaparib therapy after NDA approval is to better understand the incidence of this adverse event (MDS/AML) in relation to olaparib therapy. It will also help to improve physicians' ability to counsel their patients on the possibility of this event, as well as to effectively monitor patients for this event.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The goal of continued monitoring of all patients receiving olaparib therapy after NDA approval is to better understand the incidence of this adverse event (MDS/AML) in relation to olaparib therapy. It will also help to improve physicians' ability to counsel their patients on the possibility of this event, as well as to effectively monitor patients for this event.

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Required (PMRs)

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

The annual updates should include analyses of patients treated in all new, ongoing, and completed trials with olaparib, as well as patients receiving olaparib outside of clinical trials.

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon (PMCs):

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

Reference ID: 3670063

☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3670063

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA#	206162
Product Name:	LYNPARZA, Olaparib capsules,50 mg
PMR 2824-4 Description:	Submit the final report for trial D0816C00006 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, and Phase I Study of the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Renal Function or Renal Impairment".

PMR Schedule Milestones:	Interim report (planned primary PK analysis):	09/2015
	Trial Completion:	08/2016
	Final Report Submission:	11/2016
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☒ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☒ Small subpopulation affected
   ☒ Theoretical concern
   ☐ Other

   About 44% of olaparib (15% unchanged) is eliminated in urine. Increased olaparib exposures (plasma concentrations) may be seen in patients with renal impairment. A clinical trial evaluating olaparib in patients with varying levels of renal impairment is currently ongoing. The final report is required to allow for informative labeling recommendations including possible dose adjustments in patients with varying levels of renal impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Increased olaparib exposures may be seen in patients with renal impairment. Increased olaparib exposure would likely result in increases in toxicities such as anemia and fatigue. Results of the renal impairment trial will allow for informative labeling recommendations including possible dose adjustments in patients with varying levels of renal impairment.

Reference ID: 3670063

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☒ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   This trial is an open-label, non-randomized, multicenter, comparative, phase 1 trial to determine the pharmacokinetics of olaparib in patients with advanced solid tumors and normal renal function or mild or moderate renal impairment.

   Required

   ☐ Observational pharmacoepidemiologic study
   ☐ Registry studies
   ☐ Primary safety study or clinical trial
   ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   ☐ Thorough Q-T clinical trial
   ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
   ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
   ☒ Pharmacokinetic studies or clinical trials
   ☐ Drug interaction or bioavailability studies or clinical trials
   ☐ Dosing trials

Reference ID: 3670063

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3670063

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA#	206162
Product Name:	LYNPARZA, Olaparib capsules,50 mg
PMR 2824-5 Description:	Submit the final report for trial D0816C00005 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, Phase I Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Hepatic Function or Mild or Moderate Hepatic Impairment."

PMR Schedule Milestones:	Interim report (planned primary PK analysis):	09/2015
	Trial Completion:	08/2016
	Final Report Submission:	11/2016
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☒ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☒ Small subpopulation affected
   ☒ Theoretical concern
   ☐ Other

   Olaparib is extensively metabolized in the liver. Increased olaparib exposures (plasma concentrations) are likely to be seen in patients with hepatic impairment. A clinical trial evaluating olaparib in patients with varying levels of hepatic impairment is currently ongoing. The final report is required to allow for informative labeling recommendations including possible dose adjustments in patients with varying levels of hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Increased olaparib exposures are likely to be seen in patients with hepatic impairment. Increased olaparib exposure would likely result in increases in toxicities such as anemia and fatigue. Results of the hepatic impairment trial will allow for informative labeling recommendations including possible dose adjustments in patients with varying levels of hepatic impairment.

Reference ID: 3670063

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☒ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   This trial is an open-label, non-randomized, multicenter, comparative, phase 1 study to determine the pharmacokinetics of olaparib in patients with advanced solid tumors and normal hepatic function or mild or moderate hepatic impairment.

   Required

   ☐ Observational pharmacoepidemiologic study
   ☐ Registry studies
   ☐ Primary safety study or clinical trial
   ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   ☐ Thorough Q-T clinical trial
   ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
   ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
   ☒ Pharmacokinetic studies or clinical trials
   ☐ Drug interaction or bioavailability studies or clinical trials
   ☐ Dosing trials

Reference ID: 3670063

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3670063

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA#	206162
Product Name:	Lynparza (Olapraib) 50 mg Capsules
PMC 2824-6 Description:	Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to end of expiry.

PMC Schedule Milestones:		
	Study Completion:	02/2017
	Final Report Submission:	04/2017
	Other: First Interim Report (includes 6 months of data)	11/2015
	Second Interim Report (includes 12 months of data)	05/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The applicant provided insufficient data in the NDA to confirm stability to the end of expiry for the attribute of (b) (4) in the drug product.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Review issue: Insufficient characterization of (b) (4) in the drug product to demonstrate stability to ensure that the efficacy in the commercial product is comparable to that observed in the clinical product.

Goal of study: Provide stability data, through to end of expiry, from a controlled ICH primary stability study conducted on the commercial product to demonstrate stability of (b) (4) in olaparib capsules.

Reference ID: 3670063

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A stability study with the process validation batches (minimum of 3): specifically, ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to end of expiry.

Required (PMRs)

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Reference ID: 3670063

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon (PMCs):

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3670063

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN JENNEY
12/11/2014

KATHERINE M FEDENKO
12/11/2014

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	206162
Brand Name	To be determined
Generic Name	Olaparib
Sponsor	AstraZeneca
Indication	Ovarian cancer
Dosage Form	Capsules (50 mg)
Drug Class	PARP (poly ADP ribose polymerase) inhibitor
Therapeutic Dosing Regimen	400 mg bd (capsule formulation) (eight 50 mg capsules)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	400 mg bd (capsule formulation)
Submission Number and Date	SDN 041 / 2014 01 31
Review Division	Division of Oncology Products 1

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The sponsor submitted pooled QT/CTc data from two studies, namely, D0816C00004 and D0816C00007, which investigated the effect of food and itraconazole on the pharmacokinetics of olaparib. No large change (i.e., > 20 ms) in the QTc interval was detected when olaparib was administered up to 300 mg b.i.d. The study did not include positive control (moxifloxacin) arms.

Both studies consisted of Part A and Part B. Part A of D0816C00004 is a randomized, open-label, two-treatment, two-period crossover study whereas Part A of D0816C00007 is a randomized, open-label study. Part B is an open-label study in the patients who completed in Part A.

In Part A, study D0816C00004 received a single oral dose of olaparib tablets 300 mg in each of the two treatment periods (once in the overnight fasted state and once immediately following a high-fat meal) and study D0816C00007 received a single oral dose of olaparib 100 mg and a single oral dose of olaparib 100 mg administered concomitantly with itraconazole. In Part B, subjects received olaparib 300 mg twice daily (bd) in 2 studies.

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A total of 119 subjects (60 and 59 in studies D0816C00004 and D0816C00007, respectively) completed in part A and a total of 109 subjects (56 and 53 in studies D0816C00004 and D0816C00007, respectively) completed in Part B. Overall summary of findings are presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Olaparib up to 300 mg BID (FDA Analysis)

Study	Treatment	Time (hour)	Mean	Std Dev	90% CI (ms)
D0816C00004	Olaparib 300 mg + (Fasted) (Part A)	2	3.1	10.8	(0.8, 5.5)
	Olaparib 300 mg + (High Fat) (Part A)	8	2.2	11.9	(-0.5, 4.8)
	Olaparib 300 mg BID (Part B)	4	-0.4	13.3	(-3.5, 2.7)
D0816C00007	Olaparib 100 mg + Fasted (Part A)	3	3.1	13.7	(0.1, 6.2)
	Olaparib 100 mg + Itraconazole (Part A)	4	4.1	15.9	(0.6, 7.7)
	Olaparib 300 mg BID (Part B)	1.5	0.8	14.5	(-2.7, 4.3)

The mean drug concentration-time profile is illustrated in Figure 2. The PK results are presented in Table 25.

Observed C_{max} in this study (following administration of 300 bid [tablet]) is expected to be higher than following the intended clinical dose of 400 mg bid (capsule). Sponsor does, however, not disclose how much higher.

Co-administration with itraconazole increased mean Cmax by about 40%. It is not known if the exposure following 300-mg tablets bid will result in lower or higher exposure compared to what is expected following itraconazole and 400 mg bid (capsules) co-administration.

Hepatic impairment may decrease olaparib clearance. However, exposure data in patients with hepatic impairment is not available.

Although it is possible that patients with hepatic impairment and or concomitant CYP3A4 inhibitors will be exposed to higher olaparib concentrations than those studied here, considering the indication; this reviewer agrees with applicant's conclusion that no clinically relevant effect of olaparib on the QT interval after multiple dosing of 300 mg is observed.

2 PROPOSED LABEL

The sponsor did propose any labelling language related to clinical QT assessment.

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QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.6 Cardiac Electrophysiology

The effect of Tradename on the QTc interval was evaluated in a pooled study in 119 patients with solid tumors. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study at the therapeutic drug exposure.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Olaparib is a novel oral PARP inhibitor that exploits deficiencies in DNA repair pathways to preferentially kill cancer cells. An orphan drug designation was granted by the FDA for ovarian cancer on 16 October, 2013.

3.2 MARKET APPROVAL STATUS

Olaparib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

The effect of olaparib on the hERG-encoded potassium channel was investigated in hERG-expressing Chinese Hamster Ovary (CHO) cells. In this assay, olaparib had an IC_{50} of 226 μM (95% confidence interval 193 to 266).
Source: Nonclinical Written Summary – Pharmacology, page 24

Intravenous administration of the test article KU0059436, at doses of 1.5 and 5 mg/kg appeared to have no noticeable effects on the cardiovascular or respiratory parameters of anaesthetized dogs when compared with a vehicle control group. A higher dose of the test article (15 mg/kg) elicited a slight increase in heart rate. However, this increase in heart rate was not statistically significant compared with the vehicle treated group.
Source: Study report for 2229/053, page 29

3.4 PREVIOUS CLINICAL EXPERIENCE

Table 2 summarizes the estimated number of subjects treated with the proposed product and the proposed regiment in sponsor's studies.

Table 2: Number of patients exposed to olaparib 400 mg bd monotherapy

Study/pooled dataset	Number of patients receiving olaparib 400 mg bd (all tumour types)	Number of patients receiving olaparib 400 mg bd with *BRCA* mutated ovarian cancer
Olaparib 400 mg bd monotherapy pooled dataset[a]	735	397
Study 19 *(pivotal Ph II PSR ovarian cancer study)*	136	74
Study 1 *(Ph I dose escalation study in Japanese patients)*	6	NA
Study 2 *(Ph I FTIM study)*	8	5[b]
Study 7 *(Ph I concentration-response study)*	12	NA
Study 8 *(Ph II gBRCA breast proof of concept study)*	27	NA
Study 9 *(Ph II gBRCA ovarian proof of concept study)*	33	33
Study 12 *(Ph II gBRCA ovarian monotherapy dose finding)*	55[c]	54[d]
Study 20 *(Ph II relapsed ovarian and breast cancer study)*	90	17
Study 24 *(Ph II formulation comparison study)*	37	21
Study 42 *(Ph II advanced gBRCA mutated tumours study)*	298	193
Study D9010C00008 *(Ph II monotherapy colorectal cancer study)*	33	NA
Study 41 maintenance phase *(Ph II ovarian combination followed by maintenance)*	66	20
Total	**801**	**417**

Source: Summary of clinical safety, Table 1, page 36

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of olaparib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 75918. The sponsor submitted pooled QT/CTc data from two studies (Studies D0816C00004 and

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D0816C00007) . The sponsor submitted the study report for olaparib, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Final report on the Statistical Analysis of the pooled QT/QTc data from Studies D0816C00004 and D0816C00007

4.2.2 Protocol Number

D0816C00007 and D0816C00004

4.2.3 Study Dates

The last patients in studies D0816C00004 and D0816C00007 completed Part B on 01 April 2014 and 26 April 2014 respectively

4.2.4 Objectives

D0816C00004

Part A
To determine the effect of food on the pharmacokinetics of olaparib and the effect of olaparib on QT interval following a single oral dose of olaparib tablets.

Part B
To determine the effect of olaparib on the QT interval following multiple oral dosing of olaparib tablets.

Part C
To provided additional safety data collection.

D0816C00007

Part A
To assess the effect of itraconazole, a cytochrome P450 3A4 (CYP3A4) inhibitor, on the PK parameters of olaparib and determine the effect of olaparib on the QT interval following single oral dosing

Part B
To determine the effect of olaparib on the QT Interval following multiple oral dosing.

Part C
To provided additional safety data collection.

4.2.5 Study Description

4.2.5.1 Design

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D0816C00004

Part A
This was a randomised, open-label, two-treatment period crossover design. Each patient received a single oral dose of olaparib tablets 300 mg in each of the two treatment periods (once in the overnight fasted state and once immediately following a high-fat meal), with at least 5 and no more than 14 days (washout) between doses.

D0816C00007

Part A
This was a non-randomised, open-label, two-treatment design. Patients received the following 2 study treatments: a single oral dose of olaparib alone (tablet formulation), and a single oral dose of olaparib administered concomitantly with itraconazole. A lower 100 mg single dose of olaparib was chosen for this study to protect the patients against higher exposures of olaparib due to the anticipated inhibitory effect of itraconazole.

D0816C00004 and D0816C00007 Part B
Part B in both studies was an open-label study in the same patients who participated in Part A. Upon completion of Part A, providing the patient continued to meet the study inclusion and exclusion criteria, and following a washout period of at least 7 days (5 days in Study D0816C00004) and no more than 14 days between the last dose in Part A and Day -1 of Part B), each patient received olaparib 300 mg twice daily (bd) for 5 days.

4.2.5.2 Controls
No placebo or positive (moxifloxacin) control arms.

4.2.5.3 Blinding
All arms and were open label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms
D0816C00004

- Olaparib 300 mg + (Fasted) (Part A)
- Olaparib 300 mg + (High Fat) (Part A)
- Olaparib 300 mg bid (Part B)

D0816C00007

- Olaparib 100 mg + fasted (Part A)
- Olaparib 100 mg + itraconazole (Part A)
- Olaparib 300 mg bid (Part B)

4.2.6.2 Sponsor's Justification for Doses
A lower 100mg single dose of olaparib was chosen for this study to protect the patients against higher exposures of olaparib due to the anticipated inhibitory effect of itraconazole.

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The 300mg bd dose was selected to assess the effect of multiple doses on the QT effect because this is the maximum tolerated dose (MTD) for the tablet formulation and is also the Phase III tablet dose.

Reviewer's Comment: The dose and formulation in this trial (300-mg tablets) is not the same as the proposed to be marketed dose and formulation (400-mg capsules). However, the applicant claims in their clinical overview (section 3.3.2 page 49) that the 300-mg bid tablet results in mean steady state exposures higher than those following a 400-mg bid capsule. Considering the indication, this reviewer agrees with applicant's dose justification.

4.2.6.3 Instructions with Regard to Meals

Data was obtained following both fasted and fed administration.

Reviewer's Comment: This is acceptable.

4.2.6.4 ECG and PK Assessments

Pharmacokinetic samples were collected as defined in Table 3 while ECG was collected as defined in Table 4.

Reviewer's Comment: Acceptable. The sampling schedule is able to capture the effect at the peak concentrations and potential delayed effect up to 24 hours.

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Table 3: PK Schedule, Study D0816C00004 (upper) D0816C00007 (lower)

Day	Time (hours)	Part A PK blood	Part B PK blood
Day 1and Day5	Pre-dose	+	+
	Dose		
	0.25	+	
	0.5	+	+
	1	+	+
	1.5	+	+
	2	+	+
	3	+	+
	4[a]	+	+
	6	+	+
	8	+	+
	12	+	+
Day 2	24	+	
Day 3	48	+	
Day 4	72	+	

Day	Time (hours)	PART A OLP PK blood	PART B OLP PK blood	PART A ITR PK blood
Day 1, Day 5, Day 9	Pre-dose	+	+	+
	Dose			
	0.25	+		
	0.5	+	+	+
	1	+	+	+
	1.5	+	+	+
	2	+	+	+
	3	+	+	+
	4[a]	+	+	+
	6	+	+	+
	8	+	+	+
	12	+	+	+
Day 2, Day 10	24	+		+
Day 3, Day 11	48	+		
Day 4, Day 12	72	+		

OLP: olaparib; ITR: Itraconazole

Sourse: C-QT pharmacometric report 5.3.5.3. Tables 1 and 2.

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Table 4: dECG Schedule, Study D0816C00004 (upper) D0816C00007 (lower)

Time (hours)	Part A (Control), Day -1	Part A (Olaparib Fasted), Day 1	Part A (Olaparib Fed), Day 1	Part B (Control), Day -1	Part B (Olaparib), Day 5
Pre-dose (time 0)	X	X	X	X	X
0.5	X	X	X		
1	X	X	X	X	X
1.5	X	X	X	X	X
2	X	X	X	X	X
3	X	X	X	X	X
4	X	X	X	X	X
6	X	X	X	X	X
8	X	X	X	X	X
12	X	X	X	X	X
24		X	X		

Time (hours)	Part A (Control), Day -1	Part A (Olaparib), Day 1	Part A (Olaparib & Itraconazole), Day 9	Part B (Control), Day -1	Part B (Olaparib), Day 5
Pre-dose (time 0)	X	X	X	X	X
0.5	X	X	X		
1	X	X	X	X	X
1.5	X	X	X	X	X
2	X	X	X	X	X
3	X	X	X	X	X
4	X	X	X	X	X
6	X	X	X	X	X
8	X	X	X	X	X
12	X	X	X	X	X
24		X	X		

Sourse: C-QT pharmacometric report 5.3.5.3. Tables 3 and 4.

4.2.6.5 Baseline

Baseline is defined as the pre-dose measurement taken on the same day that the post-dose measurements are taken.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

There were 80 patients enrolled into study D0816C00004 where 60 patients were dosed and completed Part A and 56 patients completed Part B. Study D0816C00007 had enrolled 83 patients with 59 patients dosed and completed Part A and 53 completed Part B. This brings a total of 119 patients in the pooled data for QT/QTc analysis for Part A and 109 patients for Part B.

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4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoints for both studies were changes from baseline in QTcF.

D0816C00004:

For Part A (fed), the highest mean increase from baseline in QTcF (mean [SD]) was 0.8 (10.38) ms which occurred at 30 minutes post-dose . A mean increase was also noted at 2 hours post-dose (0.6 [9.73) ms).

For Part A (fasted), mean increases from baseline in QTcF were observed at 30 minutes, 1 hour, 1 hour 30 minutes, 2 hours, 3 hours, 4 hours, and 12 hours post-dose, with the maximum mean increase for the fasted treatment condition occurring at 1 hour and 30 minutes post-dose (7.3 [9.84] ms).

For Part B, mean increases from baseline in QTcF were observed at 1 hour, 1 hour 30 minutes, 2 hours, 3 hours, and 4 hours post-dose, with the maximum mean increases occurring at 1 hour and 30 minutes post-dose (4.1 [8.83] ms), and 3 hours post-dose (4.1 [10.88] ms).

Table 5: Summary of descriptive statistics for change from baseline for ECG variables: QTcF (D0816C00004)

QTcF- Friderica's Correction Formula (ms)													
		Result						Change (post-baseline)					
Treatment	Time point	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Day-1 (A)	Pre-dose	60	415.0	17.80	344	416.5	451						
	30 mins Post Dose	60	417.1	18.69	351	421.0	447	60	2.1	8.20	-18	3.5	17
	1 Hour Post Dose	59	417.7	18.05	366	420.0	457	59	3.0	9.18	-31	4.0	22
	1 Hour 30 mins Post Dose	60	418.7	18.23	352	421.0	459	60	3.7	8.47	-18	4.5	23
	2 Hour Post Dose	60	417.1	16.78	377	417.0	459	60	2.1	10.16	-34	2.0	33
	3 Hour Post Dose	60	417.0	16.99	356	418.5	453	60	2.0	9.97	-32	2.0	22
	4 Hour Post Dose	60	416.2	17.58	361	418.0	475	60	1.1	10.29	-32	-1.0	26
	6 Hour Post Dose	58	410.9	18.46	361	410.5	464	58	-4.0	10.56	-25	-4.5	17
	8 Hour Post Dose	59	408.5	16.33	366	409.0	457	59	-6.2	10.32	-31	-7.0	22
	12 Hour Post Dose	58	414.6	18.00	369	414.0	465	58	-0.5	12.03	-21	-1.0	31
	24 Hour Post Dose	59	411.2	18.07	352	412.0	461	59	-3.8	10.17	-33	-4.0	25
Fed (A)	Pre-dose	58	413.7	16.67	359	416.0	461						
	30 mins Post Dose	56	413.9	19.24	343	414.5	460	55	0.8	10.38	-18	1.0	40
	1 Hour Post Dose	55	412.6	18.48	350	413.0	464	54	-0.3	7.80	-28	1.0	13
	1 Hour 30 mins Post Dose	57	410.2	18.16	350	411.0	463	56	-2.9	7.86	-23	-4.5	16
	2 Hour Post Dose	56	413.6	18.48	360	414.0	467	55	0.6	9.73	-19	0.0	35
	3 Hour Post Dose	56	411.6	15.55	360	412.5	461	55	-1.2	9.66	-20	-2.0	30

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QTcF- Friderica's Correction Formula (ms)													
		Result						Change (post-baseline)					
Treatment	Time point	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
	4 Hour Post Dose	56	413.5	14.67	386	413.0	465	55	-0.8	9.30	-27	0.0	19
	6 Hour Post Dose	56	411.1	16.70	360	413.0	463	55	-2.0	10.60	-26	0.0	21
	8 Hour Post Dose	56	411.0	18.96	344	413.5	478	55	-2.0	11.14	-29	-3.0	31
	12 Hour Post Dose	56	410.1	18.43	349	409.0	471	55	-3.5	10.09	-34	-3.0	17
	24 Hour Post Dose	43	406.7	19.08	361	406.0	476	42	-4.9	11.97	-44	-3.5	16
Fasted (A)	Pre-dose	59	413.2	19.60	352	413.0	455						
	30 mins Post Dose	59	416.3	18.02	377	414.0	473	59	3.1	11.03	-16	2.0	36
	1 Hour Post Dose	58	418.7	19.29	355	416.5	477	58	5.8	9.70	-14	5.0	32
	1 Hour 30 mins Post Dose	59	420.5	19.35	348	419.0	471	59	7.3	9.84	-14	5.0	27
	2 Hour Post Dose	59	419.8	18.18	363	420.0	474	59	6.7	10.63	-16	6.0	32
	3 Hour Post Dose	57	418.9	17.80	360	419.0	474	57	5.9	9.89	-22	5.0	32
	4 Hour Post Dose	57	418.3	18.13	369	419.0	470	57	5.3	13.37	-41	5.0	41
	6 Hour Post Dose	56	411.9	17.69	376	411.5	486	56	-0.8	14.62	-24	-1.0	34
	8 Hour Post Dose	55	409.7	16.47	371	410.0	462	55	-2.6	12.77	-35	-3.0	27
	12 Hour Post Dose	53	413.6	19.50	363	412.0	478	53	0.7	11.98	-26	2.0	30
	24 Hour Post Dose	47	410.0	18.56	370	412.0	470	47	-3.5	13.67	-42	-3.0	26

N Total; SD standard deviation.
For each treatment, baseline (pre-dose) was defined as the pre-dose measurement taken on the same day that the post-dose measurements were taken.
Only scheduled time points are summarised.

QTcF- Friderica's Correction Formula (ms)													
		Result						Change (post-baseline)					
Treatment	Time point	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Day-1 (B)	Pre-dose	54	414.6	18.50	357	412.5	476						
	1 Hour Post Dose	53	418.1	17.23	378	417.0	480	53	3.8	9.42	-13	3.0	28
	1 Hour 30 mins Post Dose	53	417.9	17.31	385	416.0	486	53	3.6	9.34	-12	3.0	28
	2 Hour Post Dose	53	417.9	17.25	375	416.0	476	53	3.6	9.83	-25	4.0	26
	3 Hour Post Dose	53	416.4	17.95	353	415.0	483	53	2.1	8.73	-15	1.0	20
	4 Hour Post Dose	53	416.0	19.09	363	415.0	483	53	1.7	9.51	-27	2.0	22
	6 Hour Post Dose	54	411.0	18.92	348	408.0	482	54	-3.6	9.93	-33	-4.0	16
	8 Hour Post Dose	54	409.5	18.76	337	409.0	471	54	-5.1	10.09	-26	-5.0	26
	12 Hour Post Dose	49	412.5	19.76	345	413.0	472	49	-2.8	12.48	-23	-4.0	40
Olaparib 300 mg bd (B)	Pre-dose	54	412.7	18.30	349	414.0	451						
	1 Hour Post Dose	54	414.7	20.48	356	414.0	475	54	2.0	8.06	-17	3.0	24
	1 Hour 30 mins Post Dose	54	416.8	21.30	342	415.5	474	54	4.1	8.83	-22	3.5	23
	2 Hour Post Dose	54	416.4	20.71	338	414.0	472	54	3.6	9.89	-23	5.0	23
	3 Hour Post Dose	54	416.9	20.90	344	418.5	475	54	4.1	10.88	-26	3.0	27
	4 Hour Post Dose	54	416.6	20.01	339	414.5	475	54	3.9	10.10	-18	2.0	27
	6 Hour Post Dose	53	408.0	17.31	348	408.0	435	53	-4.0	8.73	-19	-5.0	14

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QTcF- Friderica's Correction Formula (ms)													
		Result						Change (post-baseline)					
Treatment	Time point	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
	8 Hour Post Dose	53	405.4	17.87	330	407.0	439	53	-6.6	11.09	-33	-8.0	14
	12 Hour Post Dose	52	407.0	21.49	332	408.0	482	52	-6.0	13.26	-28	-7.5	32

ECG Electrocardiogram; n Total; SD standard deviation; QT QT interval of ECG.
For each treatment, baseline (pre-dose) was defined as the pre-dose measurement taken on the same day that the post-dose measurements were taken. Only scheduled time points are summarised.

D0816C00007:

For study D0816C00007, all patients who had at least 1 evaluable time-matched QT/QTc interval value at a scheduled time point, time-matched between Day -1 (baseline) and Day 1, and Day -1 (baseline) and Day 9 for Part A, and time matched between Day -1 (baseline) and Day 5 for Part B.

For the olaparib alone dosing period of Part A, a mean increase from baseline in QTcF (mean [SD]) of 2.3 (7.31) ms occurred at 2 hours post-dose (Table 24). Smaller increases were also noted at 1 hour, 1 hour and thirty minutes, 3 hours and 4 hours post-dose.

For the olaparib + itraconazole dosing period of Part A, mean increases from baseline in QTcF were observed at 30 minutes, 1 hour, 1 hour and thirty minutes, 2 hours, 3 hours, and 4 hours post-dose, with the maximum mean increase occurring at 2 hours post-dose (2.8 [7.20] ms).

For Part B, mean increases from baseline in QTcF were observed at 1 hour, 1 hour and 30 minutes, 2 hours, and 3 hours post-dose, with the maximum mean increase occurring at 1 hour and 30 minutes post-dose (3.1 [8.90] ms).

Reference ID: 3658957

Table 6: Summary of descriptive statistics for change from baseline for ECG variables: QTcF (D0816C00007)

		QTcF- Friderica's Correction Formula (ms)											
		Result						Change (post-baseline)					
Treatment	Time point	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Day-1 (A)	Pre-dose	58	419.3	18.58	380	420.0	467						
	30 mins Post Dose	58	419.2	17.71	377	418.0	476	58	-0.1	6.67	-17	1.0	14
	1 Hour Post Dose	58	418.3	19.65	380	416.5	479	58	-1.0	9.15	-29	1.0	12
	1 Hour 30 mins Post Dose	58	418.7	18.55	381	418.5	456	58	-0.6	10.67	-46	0.0	19
	2 Hour Post Dose	58	418.1	19.04	373	417.5	466	58	-1.3	9.95	-24	-1.0	21
	3 Hour Post Dose	58	416.5	18.42	379	414.0	471	58	-2.8	10.59	-33	-1.5	24
	4 Hour Post Dose	58	415.4	17.59	383	415.0	471	58	-3.9	13.97	-48	-1.0	19
	6 Hour Post Dose	56	412.9	17.11	378	412.5	457	56	-6.6	11.28	-40	-8.5	15
	8 Hour Post Dose	56	412.1	18.15	376	411.0	461	56	-7.4	10.32	-39	-6.0	20
	12 Hour Post Dose	53	416.8	18.44	378	418.0	464	53	-3.3	10.92	-36	-3.0	22
	24 Hour Post Dose	57	416.5	16.63	377	414.0	462	57	-2.9	10.46	-31	-2.0	23
Olaparib (A)	Pre-dose	58	418.7	17.57	374	418.0	462						
	30 mins Post Dose	58	418.2	18.34	370	417.5	463	58	-0.4	6.86	-20	1.0	11
	1 Hour Post Dose	58	419.3	18.20	373	418.0	469	58	0.7	8.04	-23	2.5	15
	1 Hour 30 mins Post Dose	57	419.9	18.34	368	419.0	471	57	1.0	7.82	-19	2.0	18
	2 Hour Post Dose	57	420.9	18.80	372	420.0	468	57	2.3	7.31	-12	2.0	19
	3 Hour Post Dose	57	419.9	18.93	370	420.0	458	57	1.3	10.04	-29	2.0	31

Reference ID: 3658957

QTcF- Friderica's Correction Formula (ms)													
		Result						Change (post-baseline)					
Treatment	Time point	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
	4 Hour Post Dose	57	418.7	17.63	368	418.0	456	57	0.1	9.94	-29	1.0	17
	6 Hour Post Dose	57	414.3	16.61	372	414.0	458	57	-4.3	11.69	-35	-3.0	18
	8 Hour Post Dose	57	412.5	17.36	370	410.0	451	57	-6.1	10.42	-37	-6.0	14
	12 Hour Post Dose	57	416.7	15.92	366	418.0	451	57	-1.9	10.08	-30	-3.0	17
	24 Hour Post Dose	50	412.1	16.58	371	413.5	447	50	-6.9	11.90	-28	-5.0	19
Olaparib + Itraconazole (A)	Pre-dose	57	419.2	18.46	373	420.0	459						
	30 mins Post Dose	57	420.1	18.20	371	420.0	457	56	0.5	6.07	-19	0.0	14
	1 Hour Post Dose	58	420.9	18.78	367	421.0	463	57	1.7	6.58	-14	2.0	17
	1 Hour 30 mins Post Dose	57	421.9	19.18	375	422.0	465	56	2.1	7.50	-19	2.5	19
	2 Hour Post Dose	57	422.2	18.50	374	422.0	468	56	2.8	7.20	-11	2.5	22
	3 Hour Post Dose	58	421.0	19.79	362	422.0	454	57	1.7	8.97	-17	2.0	21
	4 Hour Post Dose	58	420.0	19.67	375	421.0	463	57	0.7	9.01	-19	3.0	19
	6 Hour Post Dose	57	412.7	18.39	365	414.0	463	56	-6.2	10.29	-30	-5.5	22
	8 Hour Post Dose	57	412.4	19.73	360	414.0	460	56	-6.4	10.06	-30	-5.0	15
	12 Hour Post Dose	56	415.1	19.55	363	415.5	457	55	-4.8	10.34	-29	-5.0	21
	24 Hour Post Dose	51	413.3	17.94	373	411.0	445	50	-7.2	10.28	-31	-8.0	16

Reference ID: 3658957

QTcF- Friderica's Correction Formula (ms)													
		Result						Change (post-baseline)					
Treatment	Time point	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Day-1 (B)	Pre-dose	50	420.3	18.91	370	421.0	463						
	1 Hour Post Dose	50	420.8	20.80	370	419.5	477	50	0.5	9.36	-25	0.0	19
	1 Hour 30 mins Post Dose	51	419.8	19.90	372	421.0	464	50	0.1	8.98	-28	1.0	15
	2 Hour Post Dose	51	419.3	19.08	369	420.0	464	50	-0.4	8.11	-20	0.5	21
	3 Hour Post Dose	51	418.8	19.42	367	419.0	463	50	-1.1	10.05	-34	-1.0	24
	4 Hour Post Dose	51	416.8	19.13	364	419.0	469	50	-3.0	10.64	-30	-2.0	27
	6 Hour Post Dose	51	412.2	17.17	364	414.0	469	50	-7.7	11.42	-31	-8.5	16
	8 Hour Post Dose	50	414.8	18.13	369	416.5	458	49	-5.2	9.81	-27	-5.0	13
	12 Hour Post Dose	42	417.0	18.06	371	416.0	464	41	-5.2	12.60	-35	-5.0	33
Olaparib 300 mg bd (B)	Pre-dose	49	418.4	18.20	371	419.0	455						
	1 Hour Post Dose	50	417.8	23.09	335	421.5	464	49	1.1	11.92	-46	3.0	27
	1 Hour 30 mins Post Dose	49	420.3	21.38	341	421.0	468	48	3.1	8.90	-18	3.0	26
	2 Hour Post Dose	50	419.6	21.85	334	419.5	468	49	3.0	8.44	-18	3.0	26
	3 Hour Post Dose	49	418.2	20.06	349	421.0	466	48	1.9	9.57	-18	2.5	23
	4 Hour Post Dose	50	416.7	22.04	344	418.0	470	49	-0.1	10.69	-24	-1.0	27
	6 Hour Post Dose	50	412.0	18.84	347	414.5	461	49	-5.0	10.72	-30	-3.0	17
	8 Hour Post Dose	50	410.0	19.04	337	411.5	461	49	-6.9	11.81	-43	-8.0	22

QTcF- Friderica's Correction Formula (ms)													
		Result						Change (post-baseline)					
Treatment	Time point	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
	12 Hour Post Dose	46	413.3	19.77	334	415.0	458	45	-4.4	11.38	-24	-6.0	30

ECG Electrocardiogram; n Total; SD standard deviation; QT QT interval of ECG.
For each treatment, baseline (pre-dose) was defined as the pre-dose measurement taken on the same day that the post-dose measurements were taken.
Only scheduled time points are summarised.

Reviewer's Comments: We will provide our independent analysis evaluating different heart rate corrections and provide statistical analysis results in Section 5.2.

4.2.8.2.2 Assay Sensitivity

No assay sensitivity established because no moxifloxacin positive treatment arm provided.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTc > 500 ms and ΔQTc >60 ms.

Reference ID: 3658957

Table 7: Summary of QT and QTcF changes from baseline to last/any observation on treatment (D0816C00004)

	Fed (A) (N = 60)	Fasted (A) (N = 60)	Total (A) (N = 60)	Olaparib 300 mg bd (B) (N = 60)
Number (%) of patients reaching a value in QTcF above xx ms at any time during treatment				
>450[b] (ms)	2 (3.4%)	3 (5.1%)	4 (6.7%)	4 (7.4%)
>480[b] (ms)	0	1 (1.7%)	1 (1.7%)	1 (1.9%)
>500[b] (ms)	0	0	0	0
Number (%) of patients experiencing an increase[a] in QTcF by more than yy ms at any time during treatment				
>30[b] (ms)	2 (3.4%)	5 (8.5%)	7 (11.7%)	2 (3.7%)
>60[b] (ms)	0	0	0	0
>90[b] (ms)	0	0	0	0
Number (%) of patients experiencing a decrease[a] in QTcF by more than yy ms at any time during treatment				
>30[b] (ms)	3 (5.2%)	3 (5.1%)	6 (10.0%)	1 (1.9%)
>60[b] (ms)	0	0	0	0
>90[b] (ms)	0	0	0	0

QTcF QT correction using Friderica's formula.

a Change from baseline to any observation on treatment.

b Cumulative counts.

On treatment is defined as assessments between the start of treatment and 30 days following the date of last dose of study medication. Baseline (pre-dose) is defined as the pre-dose measurement taken on the same day that the post-dose measurements are taken. There are 60 patients in the QT analysis set; however in the treatment period Fed (A), the percentage calculations are based on a total of 58 patients due to patients E0542007 and E5041004 having missing dECG data during this period. In the treatment period Fasted (A) the percentage calculations are based on a total of 59 patients due to patient E2042002 having missing baseline dECG measurements. In the treatment period olaparib 300 mg bd (B), the percentage calculations are based on a total of 54 patients due to either the patients not going into Part B or missing dECG data at Part B.

Reference ID: 3658957

Table 8: Summary of QT and QTcF changes from baseline to last/any observation on treatment (D0816C00007)

	Olaparib (A) (N = 59)	Olaparib + Itraconazole (A) (N = 59)	Total (A) (N = 59)	Olaparib 300 mg bd (B) (N = 59)
Number (%) of patients reaching a value in QTcF above xx ms at any time during treatment				
>450[a] (ms)	7 (12.1%)	6 (10.3%)	9 (15.3%)	3 (6.0%)
>480[a] (ms)	0	0	0	0
>500[a] (ms)	0	0	0	0
Number (%) of patients experiencing an increase[b] in QTcF by more than yy ms at any time during treatment				
>30[a] (ms)	1 (1.7%)	0	1 (1.7%)	0
>60[a] (ms)	0	0	0	0
>90[a] (ms)	0	0	0	0
Number (%) of patients experiencing a decrease[b] in QTcF by more than yy ms at any time during treatment				
>30[a] (ms)	2 (3.4%)	1 (1.7%)	3 (5.1%)	3 (6.0%)
>60[a] (ms)	0	0	0	0
>90[a] (ms)	0	0	0	0

QTcF QT correction using Friderica's formula.

[a] Cumulative counts.

[b] Change from baseline to any observation on treatment.

On treatment is defined as assessments between the start of treatment and 30 days following the date of last dose of study medication. Baseline (pre-dose) is defined as the pre-dose measurement taken on the same day that the post-dose measurements are taken. There are 59 patients in the QT analysis set; however in the treatment period olaparib (A), the percentage calculations are based on a total of 58 patients due to patient E5074005 having missing dECG numeric data during this period. In the treatment period olaparib + itraconazole (A) the percentage calculations are based on a total of 58 patients due to patient E0573007 having missing no dECG data collected during this period. In the treatment period olaparib 300 mg bd (B), the percentage calculations are based on a total of 50 patients due to either the patients not going into Part B or missing dECG data at Part B.

4.2.8.3 Safety Analysis

In study D0816C00004, a total of 52 (86.7%) patients in Part A, and 41 (68.3%) patients in Part B experienced at least 1 AE, the majority of which were gastrointestinal in origin and of CTCAE grade 2 or lower. In Part A, 6 (10.0%) patients reported CTCAE grade 3 AEs, and 1 (1.7%) of these was an SAE. In Part B, 1 (1.7%) patient reported CTCAE grade 3 AEs and no serious adverse events (SAEs) were reported. There were no AEs leading to olaparib discontinuation during Parts A or B of the study.

In study D0816C00007, a total of 42 (71.2%) patients in Part A and 34 (57.6%) of patients in Part B experienced at least 1 AE, again, the majority of which were gastrointestinal in origin and of CTCAE grade 2 or lower. In Part A, 7 (11.9%) patients reported CTCAE grade 3 AEs (2 (3.4%) in the olaparib alone treatment period and 5 (8.5%) in olaparib+itraconazole treatment period). There were 7 (11.9%) patients who reported SAEs (1 [1.7%] patient in olaparib alone and 6 [10.2%] in olaparib+itraconazole treatment periods respectively). In addition, 1 patient experienced an AE leading to discontinuation from the study. In Part B, 2 patients reported CTCAE grade 3 AEs, 2 SAEs were reported and 2 patients experienced an AE leading to discontinuation from the study.

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In study D0816C00004, there was one cardiovascular AE and in study D0816C00007, four cardiovascular AEs were reported:

- Patient E2841005, a 60 year old male, reported an AE of grade 1 tachycardia during the fasted treatment period and not considered related to olaparib.

- Patient E2071003, a 61 year old female, reported an AE of grade 3 atrial fibrillation from Day 3 to Day 4 of Part B of the study. The event was resolved after treatment with digoxin. The dose was not interrupted or changed and the AE was not considered by the investigator to be related to olaparib.

- Patient E2875009, a 68 year old female, reported an AE of grade 1 tachycardia during Part B of the study, 29 days from the first dose of olaparib in Part A. The event was ongoing and not considered by the investigator to be related to olaparib. This patient discontinued the study drug due to an AE of grade 3 INR increase (from 1.1 at baseline to 4.8 on Day 5 of Part B) which was not considered by the investigator to be related to olaparib. At the highest INR level, the patient had received 2 single doses of olaparib and 1 week of itraconazole (completed Part A). The patient was on tinzaparin since the beginning of the trial for past history of pulmonary embolus. The INR increase was considered related to the disease under progression in addition to anticoagulant medication from baseline. The patient did not finish continuous dosing on Part B Day 1 due to anaemia and increased INR. The tachycardia and increased INR happened as part of the same illness (urinary tract infection), and the patient reported AEs of dehydration, pyrexia, hypokalaemia and hyponatreamia during this period as well.

- Patient E2875010, a 57 year old female, reported an AE of grade 1 first degree atrioventricular block as well as grade 1 sinus bradycardia on Day 10 of the olaparib + itraconazole dosing period of Part A. These events were not considered by the investigator to be related to olaparib.

- Patient E5071003, a 71 year old female, reported an AE of grade 3 cardiac failure on Day 29 during Part B which was not recovered/resolved and led to discontinuation of olaparib. The patient also reported an SAE of pneumonia on Day 21 during Part B of the study that resulted in hospitalization, and interruption of olaparib. Dyspnoea persisted in spite of treatment with antibiotics, and a decreased left ventricular ejection fraction (35%) was observed on an echocardiogram. Olaparib causality could not be ruled out, and therefore these events were considered by the investigator to be related to olaparib.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

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The sponsor has not submitted PK results from the two submitted studies. A tabulated summary of selected exposure parameters and a figure of the concentration-time profiles are shown in reviewer's analysis.

4.2.8.4.2 Exposure-Response Analysis

The applicant has submitted a separate exposure response analysis report (C-QT pharmacomtetric report).

The data was analysed as an overall pool and separately for the two individual studies. Analyses of Study 4 or Study 7 individually demonstrated no direct effect of olaparib on ΔQTcF and on ΔQTcI. In the pooled analysis of ΔQTcF, the relationship with olaparib plasma concentration was best described by a linear model with a coefficient of 0.238, indicating only a small change in Fridericia corrected interval for every µg/ml change in olaparib plasma concentration. In the pooled analysis of ΔQTcI, the relationship with olaparib plasma concentration was best described by the baseline value and a log-linear model of the olaparib plasma concentration with a value of 0.86 for the rate of change in QTcI as the natural logarithm of the olaparib concentration increased.

Sponsor concludes that ΔQTcF and ΔQTcI does not increase to a clinically significant level, Table 9.

Table 9: Prediction of ΔQTcF (upper) and ΔQTcI (lower) at the geometric mean C_{max}

	Study 4			Study 7		
	Part A		Part B	Part A		Part B
	Fasted	Fed	MD	Alone	DDI	MD
Cmax (µg/mL)	5.48	7.00	9.17	2.99	4.24	8.44
Predicted ΔΔQTcF (90% CI) (ms)	1.30 (0.35; 2.26)	1.67 (0.45; 2.88)	2.18 (0.59 3.78)	0.71 (0.19; 1.73)	1.01 (0.27; 1.75)	2.01 (0.54; 3.48)
Conclusion	NCI	NCI	NCI	NCI	NCI	NCI

MD: multiple dose; DDI: co-administration with Itraconazole; NCI: No Clinical Impact

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	Study 4			Study 7		
	Part A		Part B	Part A		Part B
	Fasted	Fed	MD	Alone	DDI	MD
Cmax (µg/mL)	5.48	7.00	9.17	2.99	4.24	8.44
Predicted ΔΔQTcI (90% CI) (ms)	1.60 (0.53; 2.67)	1.78 (0.59; 2.98)	1.99 (0.66; 3.32)	1.19 (0.39; 1.98)	1.42 (0.47; 2.37)	1.99 (0.64; 3.21)
Conclusion	NCI	NCI	NCI	NCI	NCI	NCI

MD: multiple dose; DDI: co-administration with Itraconazole; NCI: No Clinical Impact

Sourse C-QT pharmacometric report, page 7 and 8.

Reviewer's comments: Sponsor's analysis is appropriate and the reviewer agrees with the conclusions. An independent analysis is presented below.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 10, it appears that QTcI is better than QTcB and QTcF. To be consistent with the sponsor's analyses, this reviewer used QTcF for the primary statistical analysis.

Table 10: Average of Sum of Squared Slopes for Different QT-RR Correction Methods Study D0816C00004

	QTcB		QTcF		QTcI	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**
Olaparib 300 mg + (Fasted) (Part A)	59	0.00491	59	0.00614	59	0.00416
Olaparib 300 mg + (High Fat) (Part A)	59	0.00861	59	0.00519	59	0.00485
Olaparib 300 mg BID (Part B)	54	0.00521	54	0.00924	54	0.00535
All	60	0.00433	60	0.00547	60	0.00319

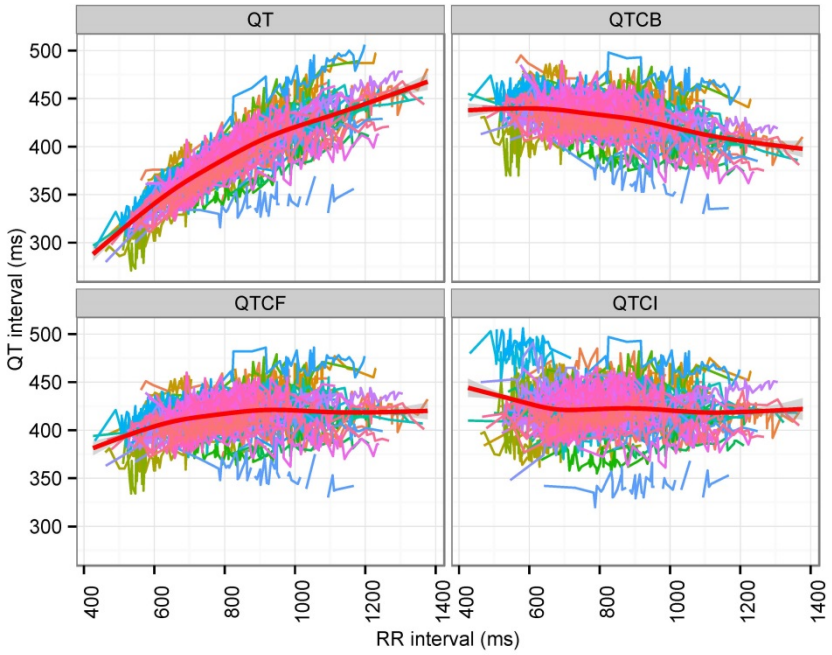
Reference ID: 3658957

Table 11: Average of Sum of Squared Slopes for Different QT-RR Correction Methods Study D0816C00007

	QTcB		QTcF		QTcI	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**
Olaparib 100 mg + Fasted (Part A)	58	0.00536	58	0.00452	58	0.00452
Olaparib 100 mg + Itraconazole (Part A)	58	0.00510	58	0.00670	58	0.00541
Olaparib 300 mg bd (Part B)	50	0.00651	50	0.00812	50	0.00694
All	59	0.00779	59	0.00915	59	0.00660

The relationship between different correction methods and RR is presented in Figure 1.

Figure 1: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The primary endpoint is change from the baseline of QTcF. The descriptive statistics are listed in Table 12 and Table 13. For study D0816C00004, the largest upper bounds of the 2-sided 90% CI for the mean differences for olaparib 300 mg + fasted, olaparib 300 mg + high fat, and olaparib 300 mg b.i.d. are 5.5 ms, 4.8 ms and 2.7 ms, respectively.

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For study D0816C00007, the largest upper bounds of the 2-sided 90% CI for the mean differences for olaparib 100 mg + fasted, olaparib 100 mg + itraconazole and olaparib 300 mg b.i.d. are 6.2 ms, 7.7 ms and 4.3 ms, respectively.

Table 12: Analysis Results of ΔQTcF for Olaparib 300 mg BID Study D0816C00004

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
Olaparib 300 mg + (Fasted) (Part A)	0.5	59	-0.5	11.9	(-3.1, 2.1)
	1	57	1.4	11.2	(-1.1, 3.9)
	1.5	59	2.2	10.9	(-0.2, 4.6)
	2	59	3.1	10.8	(0.8, 5.5)
	3	57	1.7	11.2	(-0.8, 4.2)
	4	57	2.2	11.6	(-0.4, 4.7)
	6	54	1.2	12.0	(-1.5, 3.9)
	8	54	1.4	12.9	(-1.5, 4.3)
	12	52	-1.8	9.9	(-4.1, 0.5)
	24	47	-1.1	12.0	(-4.0, 1.8)
Olaparib 300 mg + (High Fat) (Part A)	0.5	56	-2.8	12.1	(-5.5, -0.1)
	1	54	-5.0	10.7	(-7.5, -2.6)
	1.5	57	-8.4	10.7	(-10.8, -6.0)
	2	56	-3.1	12.4	(-5.9, -0.3)
	3	56	-5.0	11.6	(-7.6, -2.4)
	4	56	-3.5	10.6	(-5.8, -1.1)
	6	55	0.0	10.3	(-2.3, 2.4)
	8	56	2.2	11.9	(-0.5, 4.8)
	12	55	-4.5	10.6	(-6.9, -2.1)
	24	42	-2.2	13.4	(-5.6, 1.3)
Olaparib 300 mg BID (Part B)	1	52	-4.5	11.6	(-7.2, -1.8)
	1.5	52	-2.0	12.3	(-4.8, 0.9)
	2	52	-2.3	11.9	(-5.1, 0.5)
	3	52	-0.6	11.1	(-3.2, 2.0)
	4	52	-0.4	13.3	(-3.5, 2.7)
	6	52	-1.9	11.3	(-4.5, 0.7)
	8	52	-3.1	10.1	(-5.5, -0.8)
	12	48	-6.1	8.6	(-8.2, -4.0)

Table 13: Analysis Results of ΔQTcF of olaparib 300 mg BID Study D0816C00007

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
Olaparib 100 mg + Fasted (Part A)	0.5	57	-1.3	9.6	(-3.5, 0.8)
	1	57	0.6	13.2	(-2.3, 3.6)
	1.5	56	0.8	11.4	(-1.8, 3.3)
	2	56	2.7	10.0	(0.5, 5.0)
	3	56	3.1	13.7	(0.1, 6.2)
	4	56	2.9	12.1	(0.2, 5.6)
	6	54	1.1	10.6	(-1.3, 3.5)
	8	54	0.3	10.3	(-2.1, 2.6)
	12	52	-0.1	11.0	(-2.6, 2.5)
	24	49	-4.5	10.9	(-7.1, -1.9)
Olaparib 100 mg + Itraconazole (Part A)	0.5	56	0.3	10.4	(-2.0, 2.6)
	1	57	1.9	12.3	(-0.8, 4.7)
	1.5	56	2.8	11.7	(0.2, 5.4)
	2	56	3.3	10.7	(1.0, 5.7)
	3	57	3.9	14.5	(0.7, 7.1)
	4	57	4.1	15.9	(0.6, 7.7)
	6	54	0.1	12.3	(-2.7, 2.9)
	8	54	0.5	14.2	(-2.8, 3.7)
	12	50	-2.0	15.0	(-5.5, 1.6)
	24	50	-5.1	12.0	(-8.0, -2.3)
Olaparib 300 mg BID (Part B)	1	48	-1.1	14.6	(-4.6, 2.5)
	1.5	48	0.8	14.5	(-2.7, 4.3)
	2	49	0.6	13.8	(-2.7, 3.9)
	3	48	0.4	13.9	(-3.0, 3.8)
	4	49	0.2	14.7	(-3.3, 3.7)
	6	49	0.5	12.2	(-2.5, 3.4)
	8	48	-4.1	12.7	(-7.2, -1.1)
	12	38	-0.5	9.8	(-3.2, 2.1)

5.2.1.1 Assay Sensitivity Analysis

No assay sensitivity analysis established because no positive control arm included in the study.

Reference ID: 3658957

5.2.1.2 Categorical Analysis

Table 14 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 m, and between 480 ms and 500 ms. No subject's QTcF is above 500 ms.

Table 14: Categorical Analysis for QTcF

Study	Treatment Group	Total N	Value<= 450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms
D0816C00004	Olaparib 300 mg + (Fasted) (Part A)	59	56 (94.9%)	2 (3.4%)	1 (1.7%)
	Olaparib 300 mg + (High Fat) (Part A)	58	56 (96.6%)	2 (3.4%)	0 (0.0%)
	Olaparib 300 mg BID (Part B)	54	50 (92.6%)	3 (5.6%)	1 (1.9%)
D0816C00007	Olaparib 100 mg + Fasted (Part A)	59	50 (84.7%)	9 (15.3%)	0 (0.0%)
	Olaparib 100 mg + Itraconazole (Part A)	58	52 (89.7%)	6 (10.3%)	0 (0.0%)
	Olaparib 300 mg BID (Part B)	52	47 (90.4%)	5 (9.6%)	0 (0.0%)

Table 15 lists the categorical analysis results for ΔQTcF. No subject's change from baseline is above 60 ms.

Table 15: Categorical Analysis for ΔQTcF

Study	Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
D0816C00004	Olaparib 300 mg + (Fasted) (Part A)	59	57 (96.6%)	2 (3.4%)
	Olaparib 300 mg + (High Fat) (Part A)	58	57 (98.3%)	1 (1.7%)
	Olaparib 300 mg BID (Part B)	53	52 (98.1%)	1 (1.9%)
D0816C00007	Olaparib 100 mg + Fasted (Part A)	57	51 (89.5%)	6 (10.5%)
	Olaparib 100 mg + Itraconazole (Part A)	57	51 (89.5%)	6 (10.5%)
	Olaparib 300 mg BID (Part B)	50	50 (100%)	0 (0.0%)

5.2.2 HR Analysis

The primary endpoint is change from the baseline of HR. The descriptive statistics are listed in Table 16 and Table 17. For study D0816C00004, the largest upper bounds of the 2-sided 90% CI for the mean differences for olaparib 300 mg + fasted, olaparib 300 mg + high fat, and olaparib 300 mg b.i.d. are 7.4 bpm, 10.0 bpm and 5.3 bpm, respectively.

For study D0816C00007, the largest upper bounds of the 2-sided 90% CI for the mean differences for olaparib 100 mg + fasted, olaparib 100 mg + itraconazole and olaparib 300 mg b.i.d. are 9.1 bpm, 10.2 bpm and 5.1 bpm, respectively. Table 18 presents the categorical analysis of QRS. Thirty-one subjects and thirty-nine subjects who

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experienced HR interval greater than 100 bpm are in studies D0816C00004 and D0816C00007, respectively.

Table 16: Analysis Results of ΔHR (bpm) of Olaparib 300 mg BID Study D0816C00004

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
Olaparib 300 mg + (Fasted) (Part A)	0.5	59	-2.0	11.3	(-4.4, 0.5)
	1	57	-0.9	7.7	(-2.6, 0.8)
	1.5	59	-1.4	8.6	(-3.2, 0.5)
	2	59	-1.9	9.3	(-3.9, 0.2)
	3	57	-2.4	8.2	(-4.3, -0.6)
	4	57	-2.2	10.2	(-4.5, 0.0)
	6	55	-0.6	9.7	(-2.8, 1.6)
	8	54	-1.0	8.7	(-3.0, 1.0)
	12	52	1.5	6.0	(0.1, 2.9)
	24	47	4.3	12.7	(1.2, 7.4)
Olaparib 300 mg + (High Fat) (Part A)	0.5	56	7.9	9.3	(5.8, 10.0)
	1	55	6.8	6.4	(5.4, 8.3)
	1.5	57	5.2	7.9	(3.5, 7.0)
	2	56	3.1	6.6	(1.6, 4.5)
	3	56	2.5	7.5	(0.8, 4.2)
	4	57	1.4	9.2	(-0.6, 3.5)
	6	56	-0.0	7.5	(-1.7, 1.7)
	8	56	-0.3	9.5	(-2.4, 1.9)
	12	55	1.3	6.5	(-0.2, 2.8)
	24	42	1.5	12.3	(-1.7, 4.7)
Olaparib 300 mg BID (Part B)	1	52	1.9	9.8	(-0.3, 4.2)
	1.5	52	2.8	10.7	(0.3, 5.3)
	2	52	1.4	9.5	(-0.8, 3.6)
	3	52	0.3	8.8	(-1.8, 2.3)
	4	52	-0.8	11.1	(-3.4, 1.8)
	6	52	1.8	9.2	(-0.3, 4.0)
	8	52	1.3	7.9	(-0.6, 3.1)
	12	48	0.6	7.9	(-1.3, 2.5)

Table 17: Analysis Results of ΔHR of Olaparib 300 mg BID Study D0816C00007

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
Olaparib 100 mg + Fasted (Part A)	0.5	57	-2.6	8.1	(-4.4, -0.8)
	1	57	-2.0	10.6	(-4.3, 0.3)
	1.5	57	-3.8	10.9	(-6.2, -1.4)
	2	56	-4.3	7.9	(-6.1, -2.6)
	3	56	-1.9	11.9	(-4.5, 0.8)
	4	56	-4.3	13.0	(-7.2, -1.4)
	6	54	0.7	8.1	(-1.1, 2.6)
	8	54	-0.9	9.4	(-3.0, 1.3)
	12	52	1.6	8.1	(-0.3, 3.5)
	24	49	6.6	10.2	(4.2, 9.1)
Olaparib 100 mg + Itraconazole (Part A)	0.5	57	-3.9	7.6	(-5.6, -2.2)
	1	57	-3.9	9.9	(-6.1, -1.7)
	1.5	57	-5.2	10.5	(-7.5, -2.9)
	2	57	-4.3	9.5	(-6.4, -2.2)
	3	57	-5.0	11.0	(-7.4, -2.6)
	4	57	-5.5	13.6	(-8.5, -2.5)
	6	54	0.1	9.6	(-2.1, 2.3)
	8	54	-0.3	9.4	(-2.4, 1.9)
	12	50	0.6	9.3	(-1.6, 2.8)
	24	50	7.3	12.4	(4.3, 10.2)
Olaparib 300 mg BID (Part B)	1	48	0.9	10.8	(-1.7, 3.6)
	1.5	49	0.9	12.4	(-2.1, 3.8)
	2	49	-0.4	9.0	(-2.5, 1.8)
	3	48	1.6	7.6	(-0.3, 3.4)
	4	49	2.7	10.0	(0.3, 5.1)
	6	49	0.5	8.9	(-1.6, 2.7)
	8	48	-0.4	9.8	(-2.8, 1.9)
	12	38	1.5	7.6	(-0.6, 3.6)

Table 18: Categorical Analysis for HR

Study	Treatment Group	Total N	HR <= 100 bpm	HR >100 bpm
D0816C00004	Olaparib 300 mg + (Fasted) (Part A)	59	51 (86.4%)	8 (13.6%)
	Olaparib 300 mg + (High Fat) (Part A)	58	47 (81.0%)	11 (19.0%)
	Olaparib 300 mg BID (Part B)	54	42 (77.8%)	12 (22.2%)
D0816C00007	Olaparib 100 mg + Fasted (Part A)	59	42 (71.2%)	17 (28.8%)
	Olaparib 100 mg + Itraconazole (Part A)	58	49 (84.5%)	9 (15.5%)
	Olaparib 300 mg BID (Part B)	52	39 (75.0%)	13 (25.0%)

5.2.3 PR Analysis

The primary endpoint is change from the baseline of PR. The descriptive statistics are listed in Table 19 and Table 20. For study D0816C00004, the largest upper bounds of the 2-sided 90% CI for the mean differences for olaparib 300 mg + fasted, olaparib 300 mg + high fat, and olaparib 300 mg b.i.d. are 5.1 ms, 4.9 ms and 5.4 ms, respectively.

For study D0816C00007, the largest upper bounds of the 2-sided 90% CI for the mean differences for olaparib 100 mg + fasted, olaparib 100 mg + itraconazole and olaparib 300 mg b.i.d. are 5.7 ms, 6.8 ms and 4.7 ms, respectively. Table 21 presents the categorical analysis of PR. Eighteen subjects and thirty subjects who experienced PR interval greater than 200 ms are in studies D0816C00004 and D0816C00007, respectively.

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Table 19: Analysis Results of ΔPR of Olaparib 300 mg BID Study D0816C00004

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
Olaparib 300 mg + (Fasted) (Part A)	0.5	58	-0.1	12.3	(-2.8, 2.6)
	1	56	0.9	9.9	(-1.3, 3.1)
	1.5	58	2.5	11.9	(-0.1, 5.1)
	2	58	1.7	10.7	(-0.6, 4.1)
	3	56	2.5	11.6	(-0.1, 5.1)
	4	56	0.7	9.5	(-1.4, 2.8)
	6	54	0.0	12.2	(-2.8, 2.8)
	8	53	1.2	10.4	(-1.1, 3.6)
	12	51	-0.1	10.8	(-2.6, 2.5)
	24	46	-3.1	16.3	(-7.1, 0.9)
Olaparib 300 mg + (High Fat) (Part A)	0.5	55	-5.6	10.9	(-8.1, -3.1)
	1	54	-2.7	9.7	(-4.9, -0.5)
	1.5	56	-2.6	9.2	(-4.7, -0.5)
	2	55	-0.7	9.8	(-2.9, 1.5)
	3	55	-1.3	9.3	(-3.4, 0.8)
	4	56	-2.7	10.6	(-5.0, -0.3)
	6	55	-0.4	11.4	(-2.9, 2.2)
	8	55	2.2	12.0	(-0.5, 4.9)
	12	54	0.7	10.1	(-1.6, 3.0)
	24	41	-0.4	10.8	(-3.2, 2.4)
Olaparib 300 mg BID (Part B)	1	50	1.4	8.2	(-0.6, 3.3)
	1.5	50	1.0	10.0	(-1.4, 3.3)
	2	50	-0.3	13.0	(-3.4, 2.8)
	3	51	0.9	10.2	(-1.5, 3.3)
	4	51	2.8	11.0	(0.3, 5.4)
	6	51	-1.1	10.7	(-3.6, 1.4)
	8	51	-1.6	11.6	(-4.3, 1.1)
	12	47	-0.8	8.8	(-2.9, 1.4)

Table 20: Analysis Results of ΔPR of Olaparib 300 mg BID Study D0816C00007

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
Olaparib 100 mg + Fasted (Part A)	0.5	57	0.2	9.8	(-2.0, 2.3)
	1	57	-0.6	10.6	(-3.0, 1.7)
	1.5	57	1.7	9.3	(-0.3, 3.8)
	2	56	3.0	12.0	(0.4, 5.7)
	3	56	-0.3	13.5	(-3.4, 2.7)
	4	56	2.2	11.3	(-0.4, 4.7)
	6	54	-1.2	8.7	(-3.2, 0.7)
	8	54	-0.1	10.6	(-2.5, 2.4)
	12	52	-0.6	9.7	(-2.9, 1.7)
	24	49	-4.8	8.8	(-6.9, -2.7)
Olaparib 100 mg + Itraconazole (Part A)	0.5	57	2.1	9.6	(-0.0, 4.3)
	1	57	-0.2	11.1	(-2.6, 2.3)
	1.5	57	4.1	10.2	(1.9, 6.4)
	2	57	3.8	13.7	(0.8, 6.8)
	3	57	2.6	11.8	(-0.0, 5.2)
	4	57	2.9	10.2	(0.6, 5.2)
	6	54	-1.6	11.3	(-4.1, 1.0)
	8	54	-1.6	10.5	(-4.0, 0.8)
	12	50	-1.3	14.5	(-4.7, 2.1)
	24	50	-4.1	12.1	(-7.0, -1.2)
Olaparib 300 mg BID (Part B)	1	48	1.2	13.0	(-2.0, 4.3)
	1.5	48	-0.1	13.0	(-3.3, 3.0)
	2	49	1.1	11.5	(-1.7, 3.9)
	3	48	-0.2	11.9	(-3.1, 2.6)
	4	49	-0.5	10.4	(-3.0, 2.0)
	6	49	-0.0	11.3	(-2.7, 2.7)
	8	48	-0.2	9.8	(-2.5, 2.2)
	12	38	1.4	12.1	(-1.9, 4.7)

Table 21: Categorical Analysis for PR

Study	Treatment Group	Total N	PR <= 200 ms	PR >200 ms
D0816C00004	Olaparib 300 mg + (Fasted) (Part A)	58	53 (91.4%)	5 (8.6%)
	Olaparib 300 mg + (High Fat) (Part A)	57	52 (91.2%)	5 (8.8%)
	Olaparib 300 mg BID (Part B)	53	45 (84.9%)	8 (15.1%)
D0816C00007	Olaparib 100 mg + Fasted (Part A)	59	49 (83.1%)	10 (16.9%)
	Olaparib 100 mg + Itraconazole (Part A)	58	48 (82.8%)	10 (17.2%)
	Olaparib 300 mg BID (Part B)	52	42 (80.8%)	10 (19.2%)

5.2.4 QRS Analysis

The primary endpoint is change from the baseline of QRS. The descriptive statistics are listed in Table 22 and Table 23. For study D0816C00004, the largest upper bounds of the 2-sided 90% CI for the mean differences for olaparib 300 mg + fasted, olaparib 300 mg + high fat, and olaparib 300 mg b.i.d. are 2.6 ms, 1.6 ms and 1.4 ms, respectively.

For study D0816C00007, the largest upper bounds of the 2-sided 90% CI for the mean differences for olaparib 100 mg + fasted, olaparib 100 mg + itraconazole and olaparib 300 mg b.i.d. are 1.8 ms, 1.8 ms and 1.6 ms, respectively. Table 24 presents the categorical analysis of QRS. Six subjects and three subjects who experienced QRS interval greater than 110 ms are in studies D0816C00004 and D0816C00007, respectively.

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Table 22: Analysis Results of ΔQRS of Olaparib 300 mg BID Study D0816C00004

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
Olaparib 300 mg + (Fasted) (Part A)	0.5	59	0.3	4.2	(-0.7, 1.2)
	1	57	-0.2	3.7	(-1.0, 0.7)
	1.5	59	0.5	3.4	(-0.2, 1.3)
	2	59	-0.5	3.5	(-1.2, 0.3)
	3	57	0.0	4.3	(-0.9, 1.0)
	4	57	0.8	3.9	(-0.1, 1.7)
	6	54	1.5	4.7	(0.4, 2.6)
	8	54	0.6	3.3	(-0.2, 1.4)
	12	52	-0.3	3.2	(-1.0, 0.5)
	24	47	0.5	4.6	(-0.6, 1.6)
Olaparib 300 mg + (High Fat) (Part A)	0.5	56	0.6	3.9	(-0.3, 1.5)
	1	55	0.7	3.5	(-0.1, 1.4)
	1.5	57	0.6	4.2	(-0.3, 1.5)
	2	56	0.3	2.4	(-0.2, 0.9)
	3	56	-0.4	3.4	(-1.2, 0.3)
	4	56	0.8	3.8	(-0.1, 1.6)
	6	55	0.0	3.4	(-0.7, 0.8)
	8	56	0.2	3.8	(-0.7, 1.1)
	12	55	0.5	3.5	(-0.3, 1.3)
	24	42	0.4	4.4	(-0.7, 1.5)
Olaparib 300 mg BID (Part B)	1	52	0.2	3.8	(-0.7, 1.1)
	1.5	52	0.6	3.8	(-0.3, 1.4)
	2	52	-0.6	3.8	(-1.4, 0.3)
	3	52	0.0	4.1	(-0.9, 0.9)
	4	52	0.0	4.0	(-0.9, 1.0)
	6	52	-0.3	3.9	(-1.3, 0.6)
	8	52	-0.4	2.9	(-1.1, 0.3)
	12	48	-0.8	3.4	(-1.6, 0.0)

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Table 23: Analysis Results of ΔQRS of Olaparib 300 mg BID
Study D0816C00007

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
Olaparib 100 mg + Fasted (Part A)	0.5	57	1.0	3.7	(0.1, 1.8)
	1	57	-0.4	3.7	(-1.2, 0.4)
	1.5	56	-0.2	3.4	(-1.0, 0.5)
	2	56	-0.2	3.6	(-1.0, 0.6)
	3	56	-0.7	3.2	(-1.4, -0.0)
	4	56	0.2	3.2	(-0.5, 0.9)
	6	54	0.2	3.1	(-0.5, 0.9)
	8	54	0.2	3.5	(-0.6, 1.0)
	12	52	-0.5	5.0	(-1.7, 0.6)
	24	49	0.2	3.7	(-0.7, 1.1)
Olaparib 100 mg + Itraconazole (Part A)	0.5	56	0.8	4.7	(-0.3, 1.8)
	1	57	0.2	4.0	(-0.7, 1.1)
	1.5	56	0.7	3.6	(-0.1, 1.5)
	2	57	0.4	3.7	(-0.4, 1.3)
	3	57	0.2	4.1	(-0.7, 1.2)
	4	57	0.1	4.3	(-0.8, 1.1)
	6	54	0.2	4.6	(-0.8, 1.3)
	8	54	0.9	3.2	(0.1, 1.6)
	12	50	-0.9	4.2	(-1.9, 0.1)
	24	50	0.4	3.3	(-0.3, 1.2)
Olaparib 300 mg BID (Part B)	1	48	-1.2	4.5	(-2.3, -0.1)
	1.5	48	0.4	4.6	(-0.7, 1.5)
	2	49	0.2	3.3	(-0.6, 1.0)
	3	48	-0.3	4.4	(-1.3, 0.8)
	4	49	0.0	4.0	(-1.0, 1.0)
	6	49	-0.1	3.3	(-0.9, 0.7)
	8	48	0.2	3.6	(-0.7, 1.1)
	12	38	0.8	2.9	(0.0, 1.6)

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Table 24: Categorical Analysis for QRS

Study	Treatment Group	Total N	QRS <= 110 ms	QRS >110 ms
D0816C00004	Olaparib 300 mg + (Fasted) (Part A)	59	57 (96.6%)	2 (3.4%)
	Olaparib 300 mg + (High Fat) (Part A)	58	56 (96.6%)	2 (3.4%)
	Olaparib 300 mg BID (Part B)	54	52 (96.3%)	2 (3.7%)
D0816C00007	Olaparib 100 mg + Fasted (Part A)	59	58 (98.3%)	1 (1.7%)
	Olaparib 100 mg + Itraconazole (Part A)	58	57 (98.3%)	1 (1.7%)
	Olaparib 300 mg BID (Part B)	52	51 (98.1%)	1 (1.9%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 2. The PK results are presented in Table 25. C_{max} is expected to be higher following administration of 300 bid (tablet) compared with the intended clinical dose of 400 mg bid (capsule).

Figure 2: Mean olaparib (+SD) concentration-time profiles

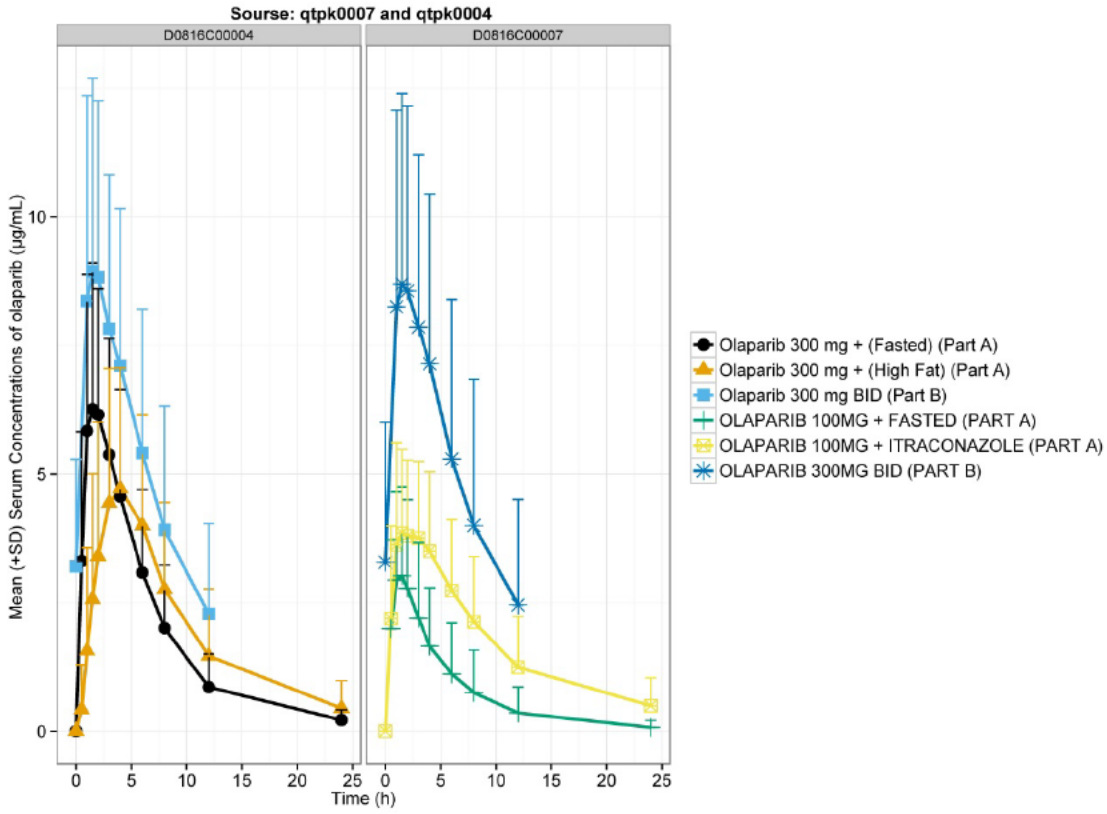

Table 25: Estimated exposure parameter

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TREAT	STUDYID	Geometric mean Cmax	Cmax SD	Median Tmax	Min Tmax	Max Tmax
OLAPARIB 100MG + FASTED (PART A)	D0816C00007	3.11	0.45	1.0	0.5	8
OLAPARIB 100MG + ITRACONAZOLE (PART A)	D0816C00007	4.33	0.37	1.5	0.5	12
OLAPARIB 300MG BID (PART B)	D0816C00007	8.91	0.37	1.5	1.0	6
Olaparib 300 mg + (Fasted) (Part A)	D0816C00004	6.70	0.38	1.5	0.5	6
Olaparib 300 mg + (High Fat) (Part A)	D0816C00004	5.42	0.40	4.0	1.0	12
Olaparib 300 mg BID (Part B)	D0816C00004	9.19	0.35	1.5	1.0	6

Subjects D0816C00004/E2041002, D0816C00007/E5074005, and D0816C00004/E0542001 were excluded from the analysis. All concentrations are in unit: µg/mL

Source: reviewer generated from qtpk0007 and qtpk0004

The relationship between ΔQTcI and pooled olaparib concentrations is visualized in Figure 3 with no evident exposure-response relationship. A linear mixed effect model with subject ID as random effect on intercept and slope was chosen as the final model based on -2LL and AIC. Slope was estimated to 0.21 (95%CI: [-0.03:0.43]). Confidence interval included 0 and was based on a non-parametric bootstrap with 1000 samples with replacement.

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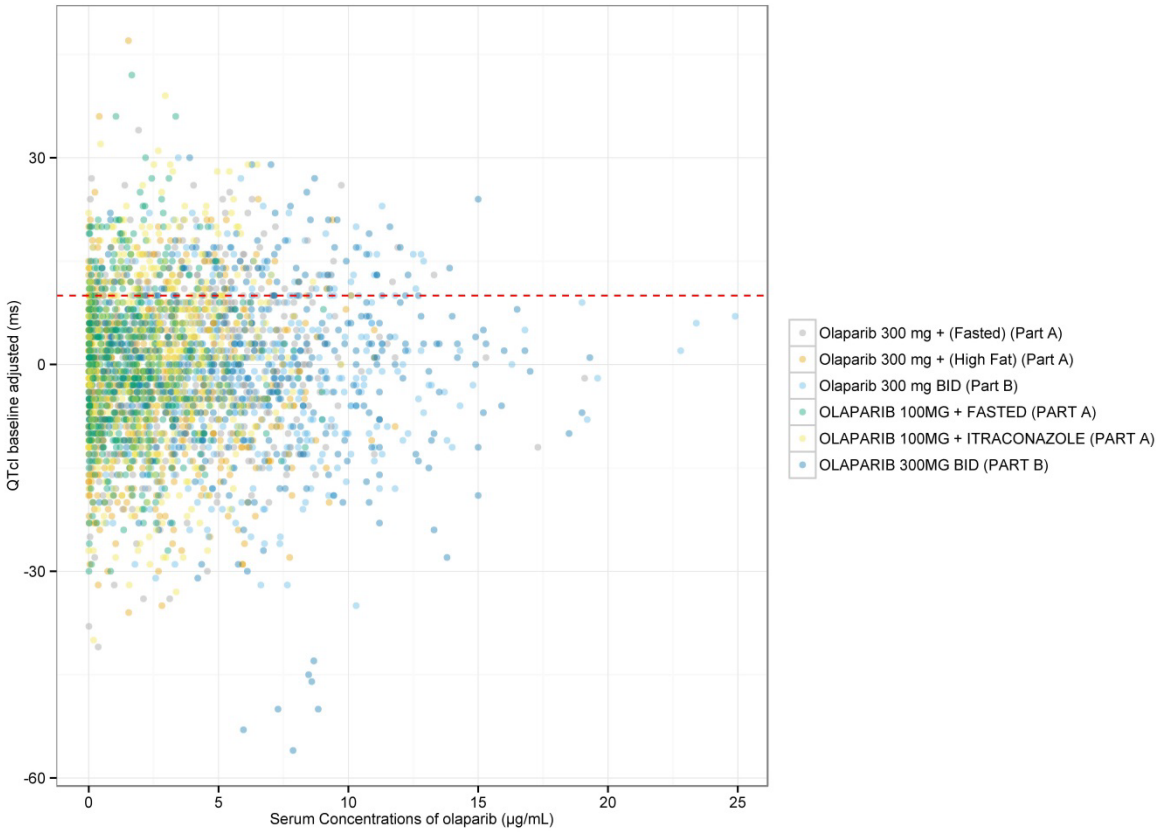
Figure 3: ΔQTcI vs. olaparib concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There was no clinically relevant effect seen on PR or QRS.

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	As monotherapy: 400 mg bd (capsule formulation) 300 mg bd (tablet formulation)	
Maximum tolerated dose	As monotherapy: 400 mg bd (capsule formulation) 400 mg bd (tablet formulation)	
Principal adverse events	As of 02 October 2013, approximately 2103 patients have received treatment with olaparib across the dose range 10 mg od to 600 mg bd (approximately 1214 patients as monotherapy). The majority of patients to date have received the capsule formulation of olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to date. The recommended monotherapy capsule dose is 400 mg bd. The recommended olaparib monotherapy tablet dose is 300 mg bd. Based on data from Phase I Study D0810C00024, the tolerability profile of the 300 mg bd tablet dose is considered similar to the 400 mg bd capsule dose. Administration of olaparib monotherapy has been associated with reports of the following laboratory findings and/or clinical diagnoses, generally of mild or moderate severity (CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation: haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia, mean corpuscular volume [MCV] elevation), decreased appetite, nausea and vomiting, diarrhoea, dyspepsia, stomatitis, (b) (4) abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache and dizziness. In addition in a small number of patients, myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) events in patients with extensive previous exposure to chemotherapy and pneumonitis events with no consistent clinical pattern have also been reported	
Maximum dose tested	Single Dose	600 mg (capsule formulation); 450 mg (tablet formulation)
	Multiple Dose	600 mg bd (capsule formulation) continuous dosing; 450 mg bd (tablet formulation) continuous dosing
Exposures Achieved at Maximum Tested Dose	Single Dose	Capsule*: Mean (%CV) C_{max} = 10.5 µg/mL (38%); Mean (%CV) AUC_{0-12} = 68.7 µg.h/mL (53%) Tablet**: Mean (%CV) C_{max} = 10.8 µg/mL (10%); Mean (%CV) AUC_{0-12} = 51.2 µg.h/mL (15%)

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	Multiple Dose	Capsule*: Mean (%CV) C_{max} = 11.5 µg/mL (42%); Mean (%CV) AUC_{0-12} = 86.8 µg.h/mL (42%) Tablet**: Mean (%CV) C_{max} = 10.4 µg/mL (36%); Mean (%CV) AUC_{0-12} = 64.7 µg.h/mL (22%)
Range of linear PK	Capsule formulation:	Oral doses up to ~ 100 mg*
	Tablet formulation:	Oral doses up to at least 450 mg**
Accumulation at steady state	1.53 (35%) on twice daily dosing of the capsule at 400 mg bd* Not reported for tablet dosing**	
Metabolites	Circulating metabolites: 3*** Each representing ~10% of circulating radioactivity and due to a) hydroxylation and opening of cyclopropyl ring; b) hydroxylation of fluorine containing ring; c) dehydrogenation of piperazine ring Pharmacological activity: Currently untested	
Absorption	Absolute/Relative Bioavailability	Not determined
	t_{max}	For parent (post 400 mg capsule dosing) median (range) = 1.72 h (1 to 4)† For parent (post 300 mg tablet dosing) median (range) = 1.5 h (0.5 to 6)†† Metabolites: undetermined (^{14}C t_{max} was simultaneous with parent drug)
Distribution	Vd/F	Mean (%CV) = 210 L (69%) (400 mg capsule dose) † Mean (%CV) = 146 L (97%) (300 mg tablet dose) ††
	% bound	91% across a concentration range of 0.1 to 1 µg/mL; 81.9% at a concentration of 10 µg/mL
Elimination	Route	35-50% dose eliminated via renal route (10-20% as unchanged drug)***; 12-60% dose eliminated via faecal route (6-14% as unchanged drug)***
	Terminal $t_{½}$	Mean (%CV) = 18.4 h (38%) (400 mg capsule dose)† Mean (%CV) = 12.2 h (44%) for parent (300 mg tablet dose) †† Not determined for metabolites

Reference ID: 3658957

	CL/F	Mean (%CV) = 7.92 L/h (56%) (400 mg capsule dose)† Mean (%CV) = 7.95 L/h (53%) (300 mg tablet dose)††
Intrinsic Factors	Age	No evidence from population analysis that clearance changes with age
	Sex	Predominantly female population studied
	Race	Predominantly Caucasian population studied
	Hepatic & Renal Impairment	Not yet studied
Extrinsic Factors	Drug interactions	Co-administration with itraconazole increased mean C_{max} 1.42-fold (90%CI: 1.33 – 1.52) and increased mean AUC 2.70-fold (90%CI: 2.44 – 2.97) Co-administration with rifampicin decreased mean C_{max} by 71% (90%CI: 0.24 -0.33) and decreased mean AUC by 87% (90%CI: 0.11 – 0.16)
	Food Effects	For the capsule formulation co-administration with a high fat meal delayed t_{max} by approx 2 h, did not affect C_{max} (TR = 1.00; 90%CI: 0.92 – 1.09) and increased mean AUC by 19% (90%CI: 1.08 – 1.31) † For the tablet formulation co-administration with a high fat meal delayed t_{max} by approx 2.5 h, reduced C_{max} by 21% (90%CI: 0.72 – 0.86) and had little impact of mean AUC (TR= 1.08; 90%CI: 1.01 – 1.16) ††
Expected High Clinical Exposure Scenario	Co-administration with potent CYP3A4 inhibitors and/or in patients with hepatic dysfunction	

* data taken from D0810C00002; ** data taken from D0810C00024; *** data taken from D0810C00010
† data taken from D081AC0001; ††data taken from D0816C0004

Reference ID: 3658957

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/s/

DINKO REKIC
11/18/2014

JIANG LIU
11/18/2014

MOH JEE NG
11/18/2014

QIANYU DANG
11/18/2014

MICHAEL Y LI
11/18/2014

NORMAN L STOCKBRIDGE
11/18/2014

MEMORANDUM
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

****Pre-decisional Agency Information****

Memorandum

Date: October 30, 2014

To: Rajesh Venugopal, RPM
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft product labeling for Lynparza (olaparib)
NDA 206162

In response to your consult request dated March 11, 2014, OPDP has reviewed the proposed product labeling (PI) for Lynparza. OPDP's comments are based on the proposed, substantially complete version of the PI, sent to OPDP on October 24, 2014, available at the following link:

\\cdsnas\transfer\DDOP RPM\Rajesh Venugopal\NDA 206162_Olaparib\Labels\Sponsors Post ODAC Updated Labels_08.15.14\Package Insert

OPDP provided verbal comments at the October 20, 2014, labeling meeting, and additionally, has the following comments:

Section	Statement from draft	Comment
14 CLINICAL STUDIES	Deleterious or suspected deleterious, germline BRCA mutation status was verified retrospectively by the companion diagnostic BRACAnalysis CDx™, which is FDA approved for selection of patients for LYNPARZA treatment, (b) (4).	• Does the device name specifically need to be mentioned in the PI (not including a specific name may potentially help with future logistical issues, i.e., not needing to update the PI every time a new diagnostic device is approved/cleared)? • Inclusion of the device name may raise some issues with respect to potential "co-promotion," especially since devices do not have the pre-submission requirement for

		promotional materials as do drugs. • Perhaps consider removing the word “companion”? (This qualifier seems unnecessary and makes it more “promotional”)

If you have any questions, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov.

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/s/

MARYBETH TOSCANO
10/30/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 28, 2014
To:	Amna Ibrahim, MD Acting Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Marybeth Toscano, Pharm D, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name)	LYNPARZA (olaparib)
Dosage Form and Route:	Capsules, Oral
Application Type/Number:	NDA 206162
Applicant:	AstraZeneca

1 INTRODUCTION

On January 31, 2014, AstraZeneca submitted for the Agency's review a New Drug Application (NDA) 206162 for LYNPARZA (olaparib) capsules with the proposed indication as monotherapy for the 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on March 11, 2014, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for LYNPARZA (olaparib) capsules.

2 MATERIAL REVIEWED

- Draft LYNPARZA (olaparib) MG received on January 31, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 15, 2014.
- Draft LYNPARZA (olaparib) Prescribing Information (PI) received on January 31, 2014, further revised by the Applicant, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 24, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MORGAN A WALKER
10/28/2014

MARYBETH TOSCANO
10/28/2014

BARBARA A FULLER
10/28/2014

LASHAWN M GRIFFITHS
10/29/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 21, 2014
Requesting Office or Division:	Division of Oncology Products I (DOP1)
Application Type and Number:	NDA 206162
Product Name and Strength:	Lynparza (Olaparib) Capsules, 50 mg
Product Type:	Single Strength Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	AstraZenaca
Submission Date:	May 9, 2014 and August 28, 2014
OSE RCM #:	2014-343
DMEPA Primary Reviewer:	Davis Mathew, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

Reference ID: 3646174

1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling and Prescribing Information (PI) for Lynparza capsules (NDA 206162) for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified the following areas of vulnerability to errors with the proposed container label, carton labeling, and full prescribing information:

A. Prescribing Information

1. Section 16 of the proposed PI is missing storage and temperature excursion data in how supplied/storage and handling.
2. We note that Olaparib is primarily metabolized via CYP3A4 but the proposed PI does not include any information on food drug interaction (e.g. Grapefruit). Per Clinical Pharmacology, the inhibition of CYP3A4 from grapefruit and Seville oranges could result in an increase in plasma concentrations of Olaparib. Therefore, we note that section 17 should include a statement informing patients not to take Olaparib with grapefruit or Seville oranges. However, we defer to clinical pharmacology or the clinical team on this matter.

3. Section 2.2 of the proposed PI lacks important specific dose adjustment criteria information (e.g. grades of nausea) for dose adjustment. However, at the October 6, 2014 internal meeting, the Review Team conveyed that for this proposed product, the specific grades of toxicity are not necessarily warranted in section 2.2 for dose adjustment. Therefore, we'll align to not requesting specific dose adjustment criteria for this proposed PI.

B. Container Label and Carton Labeling

1. The dosage form does not immediately follow the active ingredient. The established name for drug products should include the finished dosage form.[1]
2. Currently the established name appears as "olaparib" rather than in parenthesis and immediately followed by the dosage form "(Olaparib) Capsules." Per Chemistry, Manufacture and Control (CMC) at the October 8, 2014 internal meeting, the established name should appear as "(Olaparib) Capsules".
3. Prominence of the net quantity statement outweighs the prominence of the strength statement on the principal display panel.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 COMMENTS TO THE DIVISION

Prescribing Information

1. Due to the large quantity of capsules a patient must take for the recommended dose (eight capsules), there is the potential for a patient or caregiver to manipulate the capsules (e.g. open or break the capsules) if the patient has difficulty swallowing. We recommend including the statement "Swallow capsule whole. Do not chew, dissolve, or open capsule" in Section 2 Dosage and Administration and Section 17 Patient Counseling Information of the PI.
2. In Section 16, we note there is no excursion data relative to temperatures in the event the capsules are stored or transported in temperatures that deviates from the specified value of 30˚C as stated on the principle display panel. We defer to the Office of New Drug Quality Assessment in determining the appropriate storage and handling conditions.

[1] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft). April 2013. Accessed October 20, 2014 online at http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Reference ID: 3646174

3. We note that per Clinical Pharmacology, the inhibition of CYP3A4 from consuming grapefruit or Seville oranges could result in an increase in plasma concentrations of Olaparib. Therefore, we note that section 17 should include a statement informing patients not to take Olaparib with grapefruit or Seville oranges. However, we defer to clinical pharmacology or the clinical team on whether this increase in plasma concentration of Olaparib is clinically significant enough such that labeling statements should be added.

4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

Carton and Container labeling

1. The established name for drug products should include the finished dosage form.[2] Relocate the dosage form statement so that it immediately follows the established name on the principal display panel (PDP) as such:

   Lynparza

   (Olaparib) Capsules

2. Increase the prominence of the strength statement on the principal display panel by removing the (b) (4) background highlighting the net quantity statement. As currently presented, the prominence of the net quantity statement outweighs the prominence of the strength statement on the PDP. Please note by removing the (b) (4) background highlighting the net quantity statement, the (b) (4) font color on the proposed light (b) (4) background may not provide adequate contrast for legibility. Consider revising the font color of the net quantity statement.
3. Due to the large quantity of capsules a patient must take for the recommended dose (eight capsules), there is the potential for a patient or caregiver to manipulate the capsules (e.g. open or break the capsules) if the patient has difficulty swallowing. We recommend, if space allows, adding the statement "Swallow capsule whole. Do not chew, dissolve or open capsule" on the side panel of the container labels, and on the PDP of the carton labeling.

[2] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft). April 2013. Accessed October 20, 2014 online at http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lynparza that AstraZeneca submitted on August 28, 2014.

Table 2. Relevant Product Information for	
Active Ingredient	Olaparib
Indication	Treatment as monotherapy in adult patients with (b) (4) deleterious or suspected deleterious germline *BRCA (gBRCA)*- mutation (as detected by an FDA-approved test) and who have had three or more prior lines of chemotherapy.
Route of Administration	Oral
Dosage Form	Capsule
Strength	50 mg
Dose and Frequency	400 mg (8 capsules) twice a day (b) (4).
How Supplied	Carton consists of four bottles. Each bottle consists of 112 capsules.
Storage	Not to be stored above 30°C (86 °F)
Container Closure	High density polyethylene (HDPE) bottle

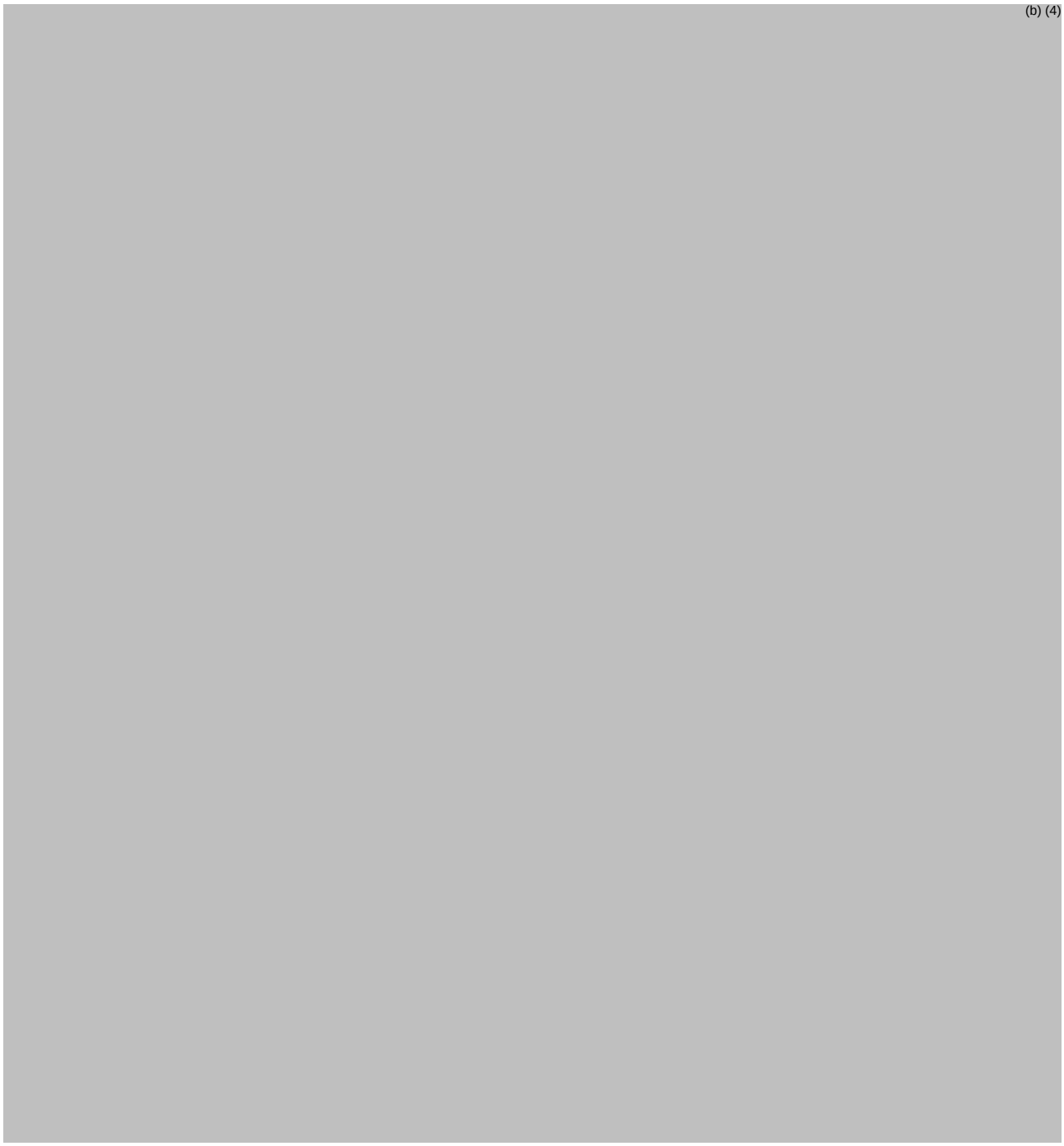
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

We reviewed the following Lynparza labels and labeling submitted by AstraZeneca on May 9, 2014 and August 28, 2014.

- Container label submitted on May 9, 2014
- Carton labeling submitted on May 9, 2014
- Full Prescribing Information submitted on August 28, 2014

G.2 Label and Labeling Images


(b) (4)

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/s/

DAVIS MATHEW
10/21/2014

CHI-MING TU
10/21/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: September 3, 2014

TO: Rajesh Venugopal, Regulatory Health Project Manager
Geoffrey Kim, M.D., Medical Officer
Gwynn Ison, M.D., Medical Officer
Division of Oncology Products 1

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH**:** Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206162

APPLICANT: AstraZeneca Pharmaceuticals LP

DRUG: Olaparib (Lynparza)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): monotherapy for the 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 therapy.

CONSULTATION REQUEST DATE:	February 12, 2014
INSPECTION SUMMARY GOAL DATE:	Original: August 7, 2014; Major Amendment: November 15, 2014
DIVISION ACTION GOAL DATE:	Original: October 3, 2014 Major Amendment: January 2, 2015
PDUFA DATE:	Original: October 3, 2014 Major Amendment: January 2, 2015

I. BACKGROUND:

Ovarian cancer is the fourth most common cancer in women. The disease often presents at a late stage (usually stage II-IV) and therefore has a poor prognosis. Treatment includes surgery and platinum based chemotherapy, but most women develop recurrent disease and die within five years of diagnosis. Carboplatin plus paclitaxel is the current standard regimen for advanced cancer in the first line setting. Despite therapy, the disease often recurs. Patients who continue to have platinum sensitive disease may be retreated with the same drugs, but again recurrence is common.

Olaparib (AZD2281, KU-0059436) is an inhibitor of polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerization (PARP) 1. PARP is a unique post-translational modification of histones and other nuclear proteins that contributes to the survival of proliferating and non-proliferating cells following DNA damage. PARP 1 activation leads to DNA repair through the base excision repair (BER) pathway. While the ability to repair DNA is desirable in normal cells, following cancer therapy it may enable tumor cells to recover from chemotherapy thus preventing effective treatment. For both PARP 1 and PARP 2, inactivation and cleavage promotes apoptosis and is part of the apoptotic cascade. Olaparib is supplied as a white 50 mg capsule. The dose for this study is 200 mg (four 50 mg capsules) taken orally twice a day (BID).

The key study supporting this application is study D0810C00019. The study is a randomized, double blind, multi-center study in patients with platinum sensitive serous ovarian cancer who have received two or more previous platinum containing regimens. Platinum sensitivity is defined as disease progression greater than 6 months after completion of their second last platinum regimen prior to enrolling in this study. The primary purpose of the study is to determine the efficacy of AZD2281 compared to placebo in serous ovarian cancer platinum sensitive patients and in a defined homologous recombination deficiency (HRD) subset. The study will compare progression free survival (PFS) between the two treatment groups and further characterize the safety and tolerability profile of AZD2281 compared to placebo. Secondary endpoints include overall survival (OS) and safety endpoints.

Patients were randomized in a 1:1 ratio (olaparib:matching placebo) to receive either olaparib 400 mg twice daily capsules or olaparib matching placebo capsules. It was planned that 250 patients would be randomized (125 in each group). Subjects had advanced platinum-sensitive serous ovarian cancer, had received 3 or more previous platinum-containing regimens and demonstrated an objective stable maintained response in the last platinum regimen prior to enrolment on the study. Subjects also had an estimated life expectancy of at least 16 weeks and an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0 to 2.

Of the 326 patients enrolled into the study, 61 patients were not randomized due to screening failures. Of the 265 patients randomized into the study, all olaparib patients (136) and 128/129 placebo patients received study treatment.

This was an international multicenter study conducted at 82 clinical centers in 16 countries: Australia (7), Belgium (2), Czech Republic (1), Estonia (1), Germany (8), Israel (7), Canada (3), France (5), Netherlands (1), Poland (7), Romania (3), Russia (6), Spain (5), Ukraine (7), U.K. (8), and U.S.A. (11). This study was conducted under IND 75918.

Four clinical sites were chosen for inspection: Site 1801 and 1802 (Dr. Ursula Matulonis, Massachusetts General Hospital and Dana Farber Cancer Inst, respectively, Boston, Massachusetts), Site 1703 (Dr. Charlie Gourley, Edinburgh, UK), and Site 701 (Dr. Phillip Harter, Wiesbaden, Germany) based on enrollment of large numbers of study subjects and insufficient domestic site data.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	**Protocol #, Site #, and # of Subjects**	**Inspection Date**	**Final Classification**
CI#1: Dr. Ursula Matulonis Massachusetts General Hospital 55 Fruit St. Boston, MA 02114	Protocol: D0810C00019 Site Number: 1801 Number of Subjects: 9	May 20-13, 2014	NAI
CI#2: Dr. Ursula Matulonis Dana Farber Cancer Institute 44 Binney St. Boston, MA 02115	Protocol: D0810C00019 Site Number: 1802 Number of Subjects: 11	April 10-24, 2014	VAI

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#3: Dr. Charlie Gourley Western General Hospital (Lothian NHS board University hospitals division) Cancer Research Centre Western General Hospital Crewe Road South Edinburgh, NA EH4 2UX Great Britain	Protocol: D0810C00019 Site Number: 1703 Number of Subjects: 13	April 28, 2014 – May 2, 2014	Pending Interim classification: NAI
CI#4: Dr.Tanya Neunhoffer (Current PI) Dr.Phillip Harter (Former PI) HSK, Dr. Horst Schmidt Klinik Department of Gynecology and Gynecologic Oncology Ludwig-Erhard-Strasse 100 Wiesbaden, NA 65199 Germany	Protocol: D0810C00019 Site Number: 701 Number of Subjects: 14	May 5-9, 2014	Pending Interim classification: NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **CI#1: – Dr. Ursula Matulonis (Site 1801)**
   Massachusetts General Hospital
   Boston, MA

   a. **What was inspected:** The site screened 12 subjects, and 9 subjects were enrolled. Of the nine enrolled subjects, all received study medication for one or more treatment cycle. At the time of this inspection all subjects were out of active treatment, one had withdrawn consent, and one remains in survival follow up. The study records of all 12 subjects were audited. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206162. All subject records were

reviewed to verify the following: 1) the protocol was followed, 2) subject eligibility, 3) randomization, 4) protocol adherence for assessments performed and the timing of assessments, 5) administration of the investigational product or placebo, 6) concomitant medications, 7) the identification of key personnel involved in collecting and analyzing data at the site, 8) the condition of the subject at time of entry and throughout participation in the investigation, 9) adverse event detection and reporting, and 10) accuracy of data listings provided with the assignment compared to supporting source documentation.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. Records were well maintained and available for review. Records included source documents of protocol required examinations, evaluations and processes and signed informed consent documents. All records were reviewed for signed informed consent documents and source documents of protocol required screening examinations. It was observed that informed consent was documented for all subjects who were screened to participate in the study.

The inspection revealed no significant deficiencies. There was no evidence of underreporting of adverse events. The primary efficacy endpoints in the data listings provided with the assignment were compared to progression free survival results in the source documents, and no discrepancies were observed. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. No Form FDA 483 was issued.

c. Assessment of data integrity: The data for Dr. Matulonis' site (1801), associated with Study D0810C00019 submitted to the Agency in support of NDA 206162, appear reliable based on available information.

2. CI#2: – Dr. Ursula Matulonis (Site 1802)
Dana Farber Cancer Institute
Boston, MA

a. What was inspected: The site screened 11 subjects, and 11 subjects were enrolled. Study records of all subjects were audited. Two subjects are still in active
treatment, 6 were discontinued per protocol defined progressive disease, two were discontinued from treatment secondary to disease progression outside of protocol defined progressive disease (RECIST criteria), and one withdrew consent (though Dr. Matulonis reported this subject also had disease progression outside of protocol defined progressive disease at the time of her consent withdrawal). The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206162. All subject records were reviewed to verify the

following: 1) the protocol was followed, 2) subject eligibility, 3) randomization, 4) protocol adherence for assessments performed and the timing of assessments, 5) administration of the investigational product or placebo, 6) concomitant medications, 7) the identification of key personnel involved in collecting and analyzing data at the site, 8) the condition of the subject at time of entry and throughout participation in the investigation, 9) adverse event detection and reporting, and 10) accuracy of data listings provided with the assignment compared to supporting source documentation.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. The primary efficacy endpoints in the data listings provided with the assignment were compared to progression free survival results in the source documents, and no discrepancies were observed. No evidence was observed of underreporting of adverse events or serious adverse events on the part of the investigator. Test article accountability records were reviewed and appeared adequate.

The FDA field investigator contacted the CDER OSI Reviewer, Lauren Iacono-Connors, on April 14, 2014 while the inspection was ongoing, to report an unusual discrepancy between AEs source documentation for Subject 1802003 and that reported in data listings submitted to the application.

Briefly, when source documents were compared to the background information provided with the assignment non-serious AE reporting discrepancies were noted for subject 1802003. Site staff explained that when they started training on the study in fall 2013, they were instructed by the clinical research coordinator, who was leaving the site that the CRO, (b) (4), told the site that the site should follow non-serious AEs as usual, but no longer needed to report them on the AE CRF. Because the new site staff found no documentation to verify that the site was told to stop collecting non-serious AE CRFs, the new site staff sent an e-mail to the Clinical Operations Leader at (b) (4), looking for clarification on October 10, 2013. The site had not transcribed non-serious AEs to study CRFs since late 2010. This apparently only affected Subject 1802003.

(b) (4) staff responded on October 24, 2013, confirming that the site did not need to complete non-serious AE CRFs. In December 2013 a new Clinical Operations Leader took over the study at (b) (4). It was not until the new Clinical Operations Leader asked for this site to provide some AE information in a February 11, 2014 e-mail that it was found that (b) (4) staff had misinformed the site staff on AE reporting requirements. The site then implemented a corrective action plan that included going through the past few years of clinical notes to document the AEs on CRFs and submit them to the sponsor.

OSI Reviewer Note: The general observation of underreporting non-serious AEs on study Subject 1802003 CRF was discussed with Medical Officer Geoffrey Kim in mid-April 2014. Shortly thereafter, an IR was sent to the sponsor requesting clarification on AE reporting practices and updates to the application as needed. The sponsor provided a response on April 18, 2014. See below.

IR Question #4: "Please provide any information you may have on any safety data that was reported to the sponsor but is not included in the CSR."

Sponsor Response: "As directed in the Clinical Study Protocol (CSP), adverse events (AEs) were collected from time of signed informed consent throughout the treatment period and up to and including the 30-day follow-up period. In February 2014 however, it came to our attention through ongoing data monitoring that AEs relevant to NDA 206162 were apparently not recorded on case report forms (CRFs) for two ongoing patients at site 1802, patients 1802001 and 1802003. On 24 February 2014, the AEs were collected, processed and reviewed to confirm the AEs had no effect on the overall safety conclusions for NDA 206162. The AEs will be included in the analysis for the next safety data submission, the Four Month Safety Update."

SUBJECT	AETEXT	AE Start Date	AE Serious?	CTC Grade	AE End Date
E1802001	SINUS INFECTION	2011-12-07	No	1	2011-12-29
E1802001	ELEVATED CREATININE	2012-10-04	No	1	2012-11-05
E1802003	LEFT WRIST PAIN	2011-02-15	No	1	2011-02-23
E1802003	BACK PAIN	2012-03-21	No	1	2012-05-16
E1802003	SHOULDER PAIN	2011-02-23	No	1	2011-06-17
E1802003	ELEVATED TSH	2012-05-16	No	1	2012-07-11
E1802003	SEIZURES	(b) (6)	No	1	Ongoing

"Any events with a start date after 26 November 2012 will be reported at the 4 Month Safety Update."

"In addition, on (b) (6), Patient 1802003 was admitted to the hospital after experiencing a seizure (grade 2) and an episode of speech impairment (grade 3). These two events were reported to in a single SAE package (SAE due to hospitalization) to (b) (4) in on April 9, 2014 (and to Astra Zeneca on April 11, 2014). However, upon further review, the SAE of seizures and speech impairment were considered to be due to disease progression, brain metastasis. Therefore, with the agreement of the investigator the SAE will be

downgraded. As of April 18, 2014, we are waiting for the investigator signature to confirm this was disease progression and therefore not an SAE."

A Form FDA 483, Inspectional Observations, was issued citing one inspection observation. Briefly, one subject was enrolled who did not meet the inclusion/exclusion criteria and not all subjects were re-consented as required by the IRB in a timely manner.

Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

a. Subject 1802001 was enrolled who did not meet inclusion/exclusion criteria #3, "Female patients with histologically or cytologically diagnosed serous ovarian cancer or recurrent serous ovarian cancer". Subject 1802001 had a diagnosis of clear cell ovarian cancer, not serous ovarian cancer, yet was enrolled in the study on March 18, 2009.

OSI Reviewer Note: According to inspection report, and the clinical investigators written response, dated May 9, 2014, to the Form FDA 483, the PI recognized the subject should not have been enrolled in the study on May 22, 2009. This deviation was brought to the attention of the sponsor and the IRB on May 22, 2009, and a Major Deviation/Violation, Exception request was filed with the IRB on May 29, 2009. It was determined by the IRB that no further action was required and the sponsor allowed the subject to remain in the study at the discretion of the PI, Dr. Matulonis. Dr. Matulonis agreed this was a major deviation, and stated it was the first subject in the study and she was focused on the ovarian cancer diagnosis and missed the cytology aspect. She admitted she should have caught the error, but did not until after enrollment.

This was an isolated major deviation for this site, and should not importantly impact study outcomes. However, the review division may consider whether the subjects' data may be included in the study analyses or censored as appropriate.

b. Not all subjects were re-consented as required by the IRB in a timely manner.

c. Assessment of data integrity: The data for Dr. Matulonis' site (1802), associated with Study D0810C00019 submitted to the Agency in support of NDA 206162, appear reliable based on available information.

3. CI#3: – Dr. Charlie Gourley (Site 1703)
Edinburgh, Great Britain

a. What was inspected: The site screened 16 subjects, and 13 subjects were enrolled. Out of the 13 subjects enrolled, 1 subject withdrew before RECIST

progression, and at the time of this inspection there was one subject continuing to receive study drug and four subjects attending ongoing follow-up visits. The study records of all enrolled subjects were audited. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206162, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator assessed all informed consent documents, patient histories, laboratory results, drug accountability, concomitant medications, sponsor correspondence, and progress notes.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. Records were well maintained and available for review. Records included source documents of protocol required examinations, evaluations and processes and signed informed consent documents. All records were reviewed for signed informed consent documents and source documents of protocol required screening examinations. It was observed that informed consent was documented for all subjects who were screened to participate in the study.

The inspection revealed no significant deficiencies. There was no evidence of underreporting of adverse events. The primary efficacy endpoints in the data listings provided with the assignment were compared to progression free survival results in the source documents, and no discrepancies were observed. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. No Form FDA 483 was issued.

c. Assessment of data integrity: The data for Dr. Gourley's site (1703), associated with Study D0810C00019 submitted to the Agency in support of NDA 206162, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

4. CI#4: – Dr. Tanya Neunhoffer (Current PI [Site 701])
Dr. Phillip Harter (Former PI)
Wiesbaden, Germany

a. What was inspected: The site screened 19 subjects, and 14 subjects were enrolled. Out of the 14 subjects enrolled, 1 subject moved to another study site (Subject #16), and at the time of this inspection there were 3 subjects attending ongoing follow-up visits. The study records of all enrolled subjects were audited. The record audit was conducted in accordance with the clinical

investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206162, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator assessed all informed consent documents, patient histories, laboratory results, drug accountability, concomitant medications, sponsor correspondence, and progress notes.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. Records were well maintained and available for review. Records included source documents of protocol required examinations, evaluations and processes and signed informed consent documents. All records were reviewed for signed informed consent documents and source documents of protocol required screening examinations. It was observed that informed consent was documented for all subjects who were screened to participate in the study.

The inspection revealed no significant deficiencies. There was no evidence of underreporting of adverse events. The primary efficacy endpoints in the data listings provided with the assignment were compared to progression free survival results in the source documents, and no discrepancies were observed. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. No Form FDA 483 was issued.

c. Assessment of data integrity: The data for Dr. Neunhoffer's site (1703), associated with Study D0810C00019 submitted to the Agency in support of NDA 206162, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of inspectional findings for clinical investigators Dr. Ursula Matulonis (Sites 1801 and 1802), Dr. Charlie Gourley (Site 1703), and Dr. Tanya Neunhoffer (Site 701), the Study D0810C00019 data appear reliable based on available information.

The preliminary classification for clinical investigator Dr. Ursula Matulonis (Site 1801), Dr. Charlie Gourley (Site 1703) and Dr. Tanya Neunhoffer (Site 701) is No Action Indicated (NAI). One clinical site inspected, Dr. Ursula Matulonis (Site 1802), was issued a Form FDA 483 citing inspectional observations and the classification for this inspection is Voluntary Action Indicated (VAI).

Generally, the investigators execution of the protocol was found to be adequate. Records were well maintained and available for review. Audits of three clinical sites (Sites 1801, 1703 and 701) revealed nothing to indicate under-reporting of AEs/SAEs. In addition, the primary efficacy endpoint data were verifiable for all 4 inspected clinical sites.

The inspection of Dr. Ursula Matulonis (Site 1802) found that there was an unusual discrepancy between non-serious AEs in source documentation for Subject 1802003 and that reported in data listings submitted to the application. Site staff explained that when they started training on the study in the Fall of 2013, they were instructed by the clinical research coordinator, who was leaving the site, that the CRO, (b) (4), told the site that the site should follow non-serious AEs as usual, but no longer needed to report them on the AE CRF. Because the new site staff found no documentation to verify that the site was told to stop collecting non-serious AE CRFs, the new site staff sent an e-mail to the Clinical Operations Leader at (b) (4) looking for clarification on October 10, 2013. The site had not transcribed non-serious AEs to study CRFs since late 2010.

(b) (4) staff responded on October 24, 2013, confirming that the site did not need to complete non-serious AE CRFs. In December 2013 a new Clinical Operations Leader took over the study at (b) (4). It was not until the new Clinical Operations Leader asked for this site to provide some AE information in a February 11, 2014 e-mail, that it was found that (b) (4) staff had misinformed the site staff on AE reporting requirements. The site then implemented a corrective action plan that included going through the past few years of clinical notes to document the AEs on CRFs and submit them to the sponsor.

An IR was sent to the sponsor from DOP1 requesting clarification on AE reporting practices and updates to the application as needed. The sponsor provided a response on April 18, 2014. The validity and impact of this observation on overall safety data was assessed by the sponsor. The sponsor concurred with the inspection observation, and informed that they became aware of the flawed AE reporting practices for the site in February 2014. They subsequently collected all missing AEs from the site and planned to include the missing AEs in the analysis for the next safety data submission, the "Four Month Safety Update" for the application. The extent of missing AEs were limited to 2 subjects; E1802001 and E1802003, all 7 AEs were non-serious and CTC grade 1.

The inspection of Dr. Ursula Matulonis (Site 1802) also found that there was one subject enrolled who did not meet the inclusion/exclusion criteria and not all subjects were re-consented as required by the IRB in a timely manner. Briefly, Subject 1802001 was enrolled who did not meet inclusion/exclusion criteria #3, "Female patients with histologically or cytologically diagnosed serous ovarian cancer or recurrent serous ovarian cancer". Subject 1802001 had a diagnosis of clear cell ovarian cancer, not serous ovarian cancer, yet was enrolled in the study on March 18, 2009. This deviation was brought to the attention of the sponsor and the IRB on May 22, 2009, and a Major Deviation/Violation, Exception request was filed with the IRB on May 29, 2009. The sponsor allowed the subject to remain in the study at the discretion of the PI, Dr. Matulonis. This was an isolated major deviation for this site, and should not importantly impact study outcomes.

However, the review division may consider whether the subjects' data may be included in the study analyses or censored as appropriate.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. These observations were not systemic and do not represent a trend in compliance violations for the overall study. The overall data for Study D0810C00019 in support of this application may be considered reliable based on available information.

Note: The general observations and actions on inspection for two of the clinical sites are based on preliminary review of the EIRs. An inspection summary addendum will be generated if conclusions change upon final review of the EIRs.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAUREN C IACONO-CONNORS
09/03/2014

SUSAN D THOMPSON
09/03/2014

KASSA AYALEW
09/03/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 206162 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proposed Proprietary Name: (b) (4) Established/Proper Name: Olaparib Dosage Form: Capsules Strengths: 50 mg		
Applicant: AstraZeneca Agent for Applicant (if applicable):		
Date of Application: February 3, 2014 Date of Receipt: February 3, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: October 3, 2014	Action Goal Date (if different):	
Filing Date: April 4, 2014	Date of Filing Meeting: March 10, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NME - 1		
Proposed indication(s)/Proposed change(s): Ovarian cancer		

Type of Original NDA: NME AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of Original BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***No but need CDRH consult to review the in vitro diagnostic used from myriad.*** ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

Reference ID: 3484524

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 075918	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

Reference ID: 3484524

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Reference ID: 3484524

Designations and Approvals list at: ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***(Original 351(a)BLAs/BLA supplements only)*** ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement if exclusivity has not yet been granted. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

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Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff :*	☐	☐	☒	

Reference ID: 3484524

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☒	☐	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☒	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

Reference ID: 3484524

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐	X	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☒	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☒	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	CDRH – 2.6.14 OSI Clinical Inspection - 2.12.14 OSE – 3.11.14 OPDP – 3.11.14 Patient Labeling – 3.11.14 ***QT/IRT – TBD once datasets from final study reports arrive in May/June***
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** November 18, 2009 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** October 2, 2013 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

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ATTACHMENT

MEMO OF FILING MEETING

DATE: March 10, 2014

NDA #: 206162

PROPRIETARY NAME (Proposed): (b)

ESTABLISHED/PROPER NAME: Olaparib

DOSAGE FORM/STRENGTH: Capsule/50 mg

APPLICANT: AstraZeneca

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Ovarian cancer

BACKGROUND: Olaparib (AZD2281, KU-0059436) is a potent oral inhibitor of polyadenosine 5'-diphosphoribose polymerase (PARP). These PARP enzymes are required for the efficient repair of DNA single strand breaks. During the repair process PARP auto-modifies itself and dissociates from the DNA to facilitate access for other repair enzymes. Olaparib inhibits the action of PARP by preventing this dissociation, trapping PARP on the DNA and blocking repair of the single strand break.

The proposed indication is for use as monotherapy for the 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. This NDA was received on February 3, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Rajesh Venugopal	Y
	CPMS/TL:	Christy Cottrell	Y
Cross-Discipline Team Leader (CDTL)	Amy McKee		Y
Clinical	Reviewer:	Geoffrey Kim/Gwynn Ison	Y
	TL:	Amy McKee	Y
Social Scientist Review (*for OTC products*)	Reviewer:		N/A

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	TL:		N/A
OTC Labeling Review (*for OTC products*)	Reviewer:		N/A
	TL:		N/A
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		N/A
	TL:		N/A

Clinical Pharmacology	Reviewer:	Elimika Pfuma	Y
	TL:	Qi Liu	N
Biostatistics	Reviewer:	Hui Zhang	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brian Chiu/Tiffany Ricks	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:		N/A
	TL:		N/A
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		N/A
	TL:		N/A
Product Quality (CMC)	Reviewer:	Gaetan Ladouceur/ Anne Marie Russell	Y
	TL:	Ali Al Hakim/Hari Sarker	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Erika Pfeiler	N
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		N/A
	TL:		N/A
Facility Review/Inspection (Office of Compliance_)	Reviewer:		N/A
	TL:		N/A
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	Y
	TL:	Alice Tu	N

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OSE/DRISK (REMS)	Reviewer:	Naomi Redd	N
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Robert Wittorf	Y
	TL:		N/A

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		N/A
	TL:		N/A
Other reviewers	Abraham Tzou – CDRH Eunice Lee – CDRH Okpo Eradiri – Biopharm Hongshan Li – Pharmacometrics Liang Zhao - Pharmacometrics		Y
Other attendees	Richard Pazdur – OHOP Amana Ibrahim – DOP1 Susan Jenney – DOP1 Jenna Lyndley – OSE, DPV Tracy Salaam – OSE, DPV		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

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• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: June 25/26, 2014 ☐ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
PHARMACOMETRICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
BIOPHARMACEUTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment	 ☒ YES

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(EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> **Comments**: No comments for the 74-day letter	☐ Review issues for 74-day letter

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APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☐ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☒ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO ☒N/A
• What late submission components, if any, arrived after 30 days?	The clinical pharmacology data will be submitted as an amendment within 120 days of February 3 submission of the original NDA.
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☒ NO The application was not complete however, a Refuse to File letter will not be sent to the Sponsor as the Agency agreed to this at the Pre-NDA meeting due to the life-threatening nature of the disease. The office director has stated that the Agency would accept late items for a life threatening disease.
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, MD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): May 6, 2014 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	

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REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
	How many labeling meetings - 8 meetings July-Aug? - Done Team meetings- 1 in April? - done Will this have a REMS - No #of REMS Meeting – None # of practices for AC (3 + 1 OHOP,2nd or 3rd meeting at Monday ohop, Pazdur to 2nd and 4th meeting) meeting in June)? - done Wrap-up meeting –yes - done
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and

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	the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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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.

/s/

RAJESH VENUGOPAL
04/07/2014

CHRISTY L COTTRELL
04/08/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206162

Application Type: New NME NDA

Name of Drug/Dosage Form: Olaparib 50 mg Capsules

Applicant: AstraZeneca

Receipt Date: February 3, 2014

Goal Date: October 3, 2014

1. Regulatory History and Applicant's Main Proposals

Olaparib is a PARP (poly ADP ribose polymerase) inhibitor indicated as monotherapy for the 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.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

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Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

NO 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: *Contraindications not listed in HL.*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES

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9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

N/A 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

NO 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

Selected Requirements of Prescribing Information

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or "[*see Warnings and Precautions (5.2)*]".

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Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

NO 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment: (b) (4)

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Reference ID: 3483643

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
1.1 [text]
1.2 [text]
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

Reference ID: 3483643

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJESH VENUGOPAL
04/04/2014

CHRISTY L COTTRELL
04/04/2014

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: 2/12/2014

To: Ni Khin, Acting Division Director, DGCPC
Kassa Ayalew, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
CDEROCDSIPMOs@fda.hhs.gov
Lauren Iacono-Connor, Ph.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: *Geoffrey Kim/Gwynn Ison, DOP1*
Amy McKee 9TL)/Amna Ibrahim (Dep. Dir.), DOP1

From: *Rajesh Venugopal, DOP1*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: 206162
IND#:75918
Applicant: AstraZeneca
Phone:
Email:
Regulatory Point of Contact: Darci Bertelsen, Regulatory Affairs Director
Regulatory Point of Contact Phone: (302) 886-7355
Regulatory Point of Contact Email: darci.bertelsen@astrazeneca.com

Drug Proprietary Name: pending
Generic Drug Name: olaparib (AZD2281, KU-0059436)
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Indicated as monotherapy for the 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 therapy

Reference ID: 3453140

PDUFA: October 3, 2014
Action Goal Date: October 3, 2014
Inspection Summary Goal Date: August 7, 2014

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table ***(Note: All items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).***

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Gourley, Charlie Western General Hospital, Edinburgh (Lothian NHS board University hospitals division) Cancer Research Centre, Western General Hospital, Crewe Road South Edinburgh, NA EH4 2UX GBR Western Europe phone: (b) (4) fax: (b) (4) email: (b) (4)	1703	D0810C00019	13	Randomised, double blind, study on the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with 2 or more platinum containing regimens
Harter, Phillip HSK, Dr. Horst Schmidt Klinik ,Department of Gynecology & Gynecologic Oncology, Ludwig-Erhard-Straße 100 Wiesbaden, NA 65199 DEU Western Europe phone: (b) (4) fax: (b) (4) email (b) (4)	701	D0810C00019	14	Randomised, double blind, study on the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with 2 or more platinum containing regimens
Matulonis, Ursula Dana Faber Cancer Institute, 44 Binney St, LG1B15 Boston, MA 2115 USA United States phone: (b) (4) fax: (b) (4) email: (b) (4)	1802	D0810C00019	11	Randomised, double blind, study on the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with 2 or more platinum containing regimens

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Matulonis, Ursula Massachusetts General Hospital,55 Fruit St. Boston, MA 2114 USA United States phone: (b) (4) fax: (b) (4) email: (b) (4)	1801	D0810C00019	9	Randomised, double blind, study on the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with 2 or more platinum containing regimens

III. Site Selection/Rationale

Site Information

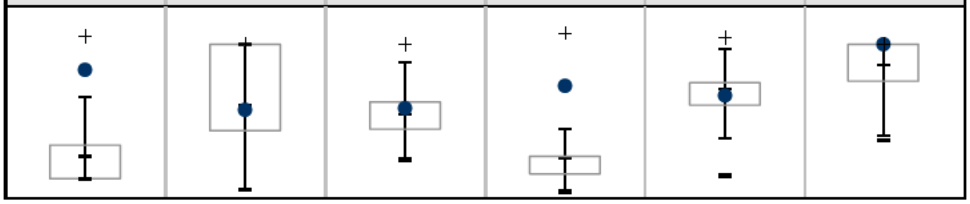
STUDY:	D0810C00019	**SITEID:**	1802

NAME	Matulonis, Ursula
LOCATION	Dana Faber Cancer Institute, 44 Binney St, LG1B15 Boston, MA, USA 2115
PHONE/FAX	(b) (4)
EMAIL	(b) (4)

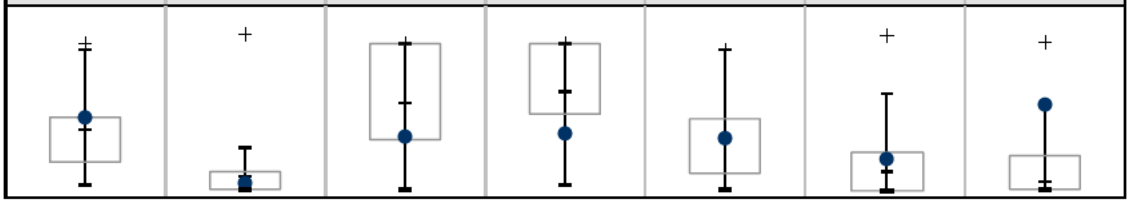
RANK	7	**FINLDISC**	0	**COMPLAINT**	0
SITE RISK	14.8	**OAI**	0	**TSLI**	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	14	1.00	1.00	9.00	2.00	100%
Study Rate	3	0.58	-0.22	1.88	-0.32	86%
Min	1	0.00	-1.00	0.00	-4.14	33%
Site	11	0.55	-0.10	6.00	-0.60	100%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	25.0	2.7	100%	100%	2.0	4.0	21
Study Rate	9.6	0.2	59%	66%	0.7	0.5	1
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	12.0	0.1	36%	36%	0.7	0.8	12



Site Memo

Site Information

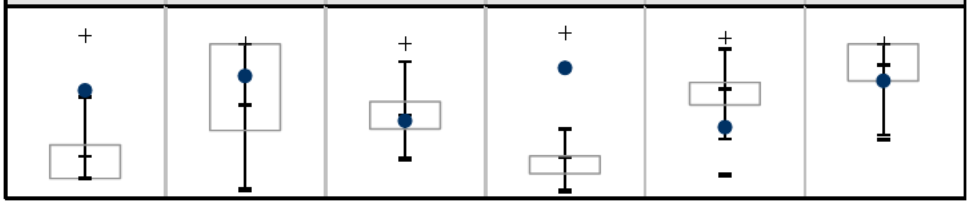
STUDY:	D0810C00019	SITEID:	1801

NAME	Matulonis, Ursula
LOCATION	Massachusetts General Hospital,55 Fruit St. Boston, MA, USA 2114
PHONE/FAX	(b) (4)
EMAIL	(b) (4)

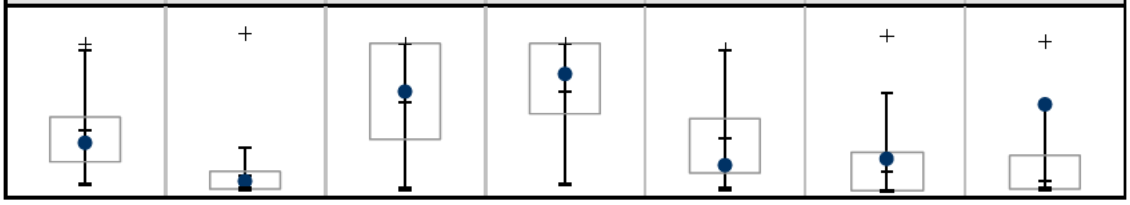
RANK	5	FINLDISC	0	COMPLAINT	0
SITE RISK	15.7	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	14	1.00	1.00	9.00	2.00	100%
Study Rate	3	0.58	-0.22	1.88	-0.32	86%
Min	1	0.00	-1.00	0.00	-4.14	33%
Site	9	0.78	-0.33	7.00	-2.00	75%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	25.0	2.7	100%	100%	2.0	4.0	21
Study Rate	9.6	0.2	59%	66%	0.7	0.5	1
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	7.3	0.1	67%	78%	0.3	0.8	12



Site Memo

Site Information

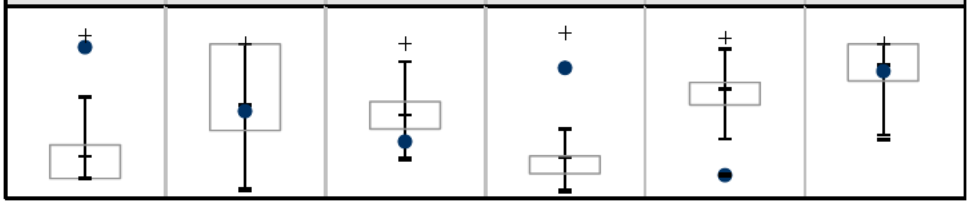
STUDY:	D0810C00019	SITEID:	1703

NAME	Gourley, Charlie
LOCATION	Western General Hospital, Edinburgh (Lothian NHS board University hospitals division) Cancer Research Centre, Western General Hospital, Crewe Road South Edinburgh, NA, GBR EH4 2UX
PHONE/FAX	(b) (4)
EMAIL	(b) (4)

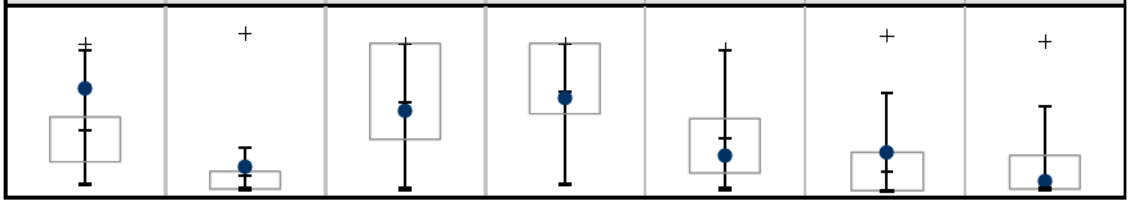
RANK	2	FINLDISC	0	COMPLAINT	0
SITE RISK	21.4	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	14	1.00	1.00	9.00	2.00	100%
Study Rate	3	0.58	-0.22	1.88	-0.32	86%
Min	1	0.00	-1.00	0.00	-4.14	33%
Site	13	0.54	-0.69	7.00	-4.14	81%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	25.0	2.7	100%	100%	2.0	4.0	21
Study Rate	9.6	0.2	59%	66%	0.7	0.5	1
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	16.9	0.4	54%	62%	0.5	1.0	1



Site Memo

Site Information

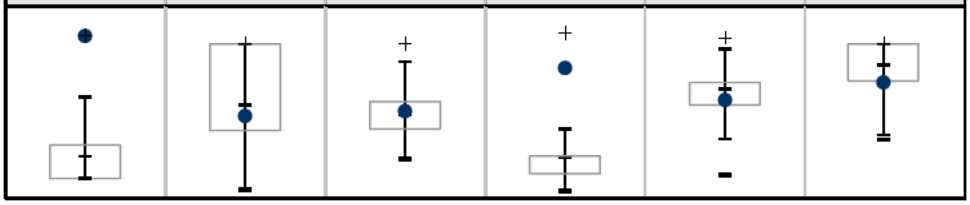
STUDY:	D0810C00019	SITEID:	701

NAME	Harter, Phillip
LOCATION	HSK, Dr. Horst Schmidt Klin k ,Department of Gynecology & Gynecologic Oncology, Ludwig-Erhard-Straße 100 Wiesbaden, NA, DEU 65199
PHONE/FAX	(b) (4)
EMAIL	(b) (4)

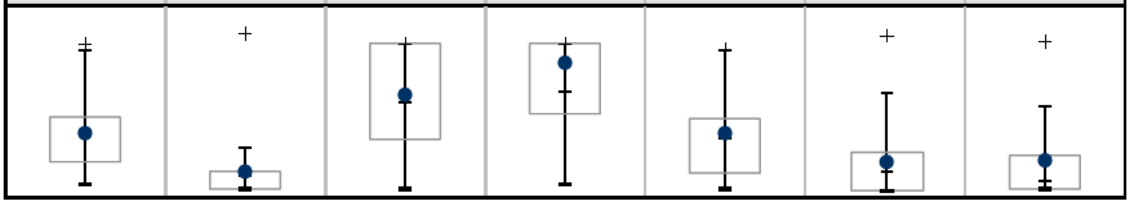
RANK	1	FINLDISC	625	COMPLAINT	0
SITE RISK	23.7	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	14	1.00	1.00	9.00	2.00	100%
Study Rate	3	0.58	-0.22	1.88	-0.32	86%
Min	1	0.00	-1.00	0.00	-4.14	33%
Site	14	0.50	-0.16	7.00	-0.78	74%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	25.0	2.7	100%	100%	2.0	4.0	21
Study Rate	9.6	0.2	59%	66%	0.7	0.5	1
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	9.2	0.3	64%	86%	0.8	0.8	4



Site Memo

Summarize the reason for requesting OSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for OSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

See at end of consult template for OSI's thoughts on things to consider in your decision making process

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ✓ Enrollment of large numbers of study subjects
- ____ High treatment responders (specify):
- ____ Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- ✓ There are insufficient domestic data
- ____ Only foreign data are submitted to support an application
- ____ Domestic and foreign data show conflicting results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites*.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact at 301-796- or at 301-796- .

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer

_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

Things to consider in decision to submit request for OSI Audit

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJESH VENUGOPAL
02/12/2014

AMY E MCKEE
02/12/2014

AMNA IBRAHIM
02/12/2014