CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208447Orig1s000

MULTI-DISCIPLINE REVIEW

Executive Summary
Nonclinical Pharmacology/Toxicology
Clinical Pharmacology
Statistical and Clinical Evaluation

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	New Drug Application
Application Number(s)	208447
Priority or Standard	Priority
Submit Date(s)	10/31/2016
Received Date(s)	10/31/2016
PDUFA Goal Date	6/30/2017
Division/Office	Division of Oncology Products 1/Office of Hematology and Oncology Products
Review Completion Date	3/22/2017
Established Name	Niraparib
(Proposed) Trade Name	Zejula™
Pharmacologic Class	Poly(ADP-ribose) polymerase (PARP) inhibitor
Code name	MK-4827
Applicant	TESARO INC
Formulation(s)	Capsules: 100 mg
Dosing Regimen	300 mg (three 100 mg capsules) taken orally once daily
Applicant Proposed Indication(s)/Population(s)	ZEJULA™ is a poly(ADP-ribose) polymerase (PARP) (b) (4) inhibitor indicated for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	ZEJULA™ is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy

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

DRISK=Division of Risk Management

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Glossary

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

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

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1 Executive Summary

1.1. Product Introduction

Niraparib (Zejula™) is a new molecular entity and inhibitor of *poly(ADP-ribose) polymerase (PARP) 1 and 2*. PARP is a family of proteins involved in DNA repair. Inhibition of PARP enzymatic activity can result in DNA damage, apoptosis and cell death.

The Applicant's proposed indication at the time of NDA submission (October 31, 2016) was:
ZEJULA ™ is a poly(ADP-ribose) polymerase (PARP) (b) (4) *inhibitor indicated for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.*

The Applicant submitted a revised indication on January 26, 2017:
ZEJULA ™ is a poly(ADP-ribose) polymerase (PARP) (b) (4) *inhibitor indicated for the maintenance or treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer following a complete or partial response to platinum-based chemotherapy.*

The recommended indication is:
ZEJULA™ is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

The recommended dose for niraparib is 300 mg administered once a day by mouth without regard to food. Treatment should be continued until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for the approval of niraparib, according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), is primarily based on the efficacy and safety data from a double-blind, placebo-controlled, randomized (2:1), multicenter clinical trial of niraparib versus placebo conducted in 553 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. All patients had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen. Patients were assigned to one of two cohorts based on the results of the BRACAnalysis CDx. Patients with deleterious or suspected deleterious germline BRCA mutations (gBRCAm) were assigned to the germline BRCA mutated (gBRCAmut) cohort (n=203), and those without germline BRCA mutations were assigned to the non-gBRCAmut cohort (n=350). The trial demonstrated statistically significant and clinically meaningful improvement in PFS for patients randomized to niraparib as compared with placebo. In the gBRCAmut cohort median PFS in the niraparib arm was 21 months (95% CI: 12.9, not reached) and median PFS in the placebo arm was 5.5 month (95% CI: 3.8, 7.2), [hazard ratio (HR) 0.26 (95% CI: 0.17, 0.41); p value <0.0001]. In the non-gBRCAmut cohort (HRD+ subgroup) median PFS in the niraparib arm was 12.9 months (95% CI: 8.1, 15.8) and median PFS in the placebo arm was 3.8 months (95% CI: 3.5, 5.7), [HR 0.26 (95% CI: 0.17, 0.41); p value <0.0001]. In the non-gBRCAmut cohort (entire cohort) median PFS in the niraparib arm was 9.3 months (95% CI: 7.2, 11.2) and median PFS in the placebo arm was 3.9 months (95% CI: 3.7, 5.5), [HR 0.45 (95% CI: 0.34, 0.61); p value <0.0001]. Most common adverse reactions (incidence ≥20%) were thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal pain/distention, mucositis/stomatitis, diarrhea, fatigue/asthenia, decreased appetite, headache, insomnia, nasopharyngitis, dyspnea, rash, and hypertension. The safety profile of niraparib is acceptable for the intended population and supportive of a favorable benefit-risk profile of niraparib for this indication. All disciplines were in agreement with approval of niraparib, or did not identify any outstanding issues that precluded approval. In summary, niraparib for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy demonstrates a favorable benefit-risk profile with enough evidence to recommend approval.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

Niraparib (Zejula™) is an orally available poly (ADP-ribose) polymerase (PARP) inhibitor recommended for approval for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers are serious and life-threatening diseases. Ovarian cancer is the fifth cause of cancer death in women and represents 5% of all cancer deaths. In 2017, it is estimated that there will be 22.440 new cases of ovarian cancer and an estimated 14,080 women will die in the U.S. The majority of patients receive primary debulking surgery after diagnosis, followed by adjuvant chemotherapy with platinum plus taxanes with or without bevacizumab. Response rates in this first-line setting are high, but most patients recur within 2 years and die within 3-4 year after diagnosis. Currently, only bevacizumab is FDA approved as a maintenance therapy for the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Bevacizumab is typically administered in conjunction with the chemotherapy regimen (carboplatin and paclitaxel or carboplatin and gemcitabine) used in the relapse setting, and then is continued as a single agent in patients who are in response at the end of the 6-8 cycles of combination chemotherapy.

The effectiveness of niraparib was demonstrated in NOVA study, an international, multicenter, randomized (2:1), double-blind, placebo-controlled, clinical trial evaluating the efficacy and safety of treatment with niraparib 300 mg orally daily versus placebo in patients (n=553) with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen. Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis test. Patients with deleterious or suspected deleterious germline BRCA mutations (gBRCAm) were assigned to the germline BRCA mutated (gBRCAmut) cohort (n=203), and those without germline BRCA mutations were assigned to the non-gBRCAmut cohort (n=350). Tumors of patients randomized to the non-gBRCAmut cohort were tested for the presence of homologous recombination deficiency (HRD) using the myChoice® HRD test. The primary analysis of PFS was performed in the gBRCAmut and non-gBRCAmut cohort independently at a significance level of 1-sided 0.025. Within the non-gBRCAmut cohort, the HRD+ subgroup was tested first and followed by the entire cohort.

The major efficacy outcome measure was progression free survival (PFS), determined by independent review committee (IRC). The trial demonstrated statistically significant and clinically meaningful improvement in PFS per IRC assessment for patients randomized to niraparib as compared with placebo in in all three pre-specified patient groups; the gBRCAmut cohort [HR 0.26 (95% CI: 0.17, 0.41); p value <0.0001], the non-gBRCAmut cohort (HRD+ subgroup) [HR 0.37 (95% CI: 0.24, 0.58); p value <0.0001], and the non-gBRCAmut cohort (entire cohort)[HR 0.45 (95% CI: 0.34, 0.61); p value <0.0001],respectively. In the gBRCAmut cohort median PFS in the niraparib arm was 21 months (95% CI: 12.9, not reached) and median PFS in the placebo arm was 5.5 month (95% CI: 3.8, 7.2). In the non-gBRCAmut cohort (HRD+ subgroup) median PFS in the

niraparib arm was 12.9 months (95% CI: 8.1, 15.8) and median PFS in the placebo arm was 3.8 months (95% CI: 3.5, 5.7). In the non-gBRCAmut cohort (entire cohort) median PFS in the niraparib arm was 9.3 months (95% CI: 7.2, 11.2) and median PFS in the placebo arm was 3.9 months (95% CI: 3.7, 5.5). At the time of the PFS analysis, limited overall survival data were available with 17% deaths across the two cohorts.

The most common adverse reactions (AR) experienced in at least 20% of patients on NOVA study were thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal pain/distention, mucositis/stomatitis, diarrhea, fatigue/asthenia, decreased appetite, headache, insomnia, nasopharyngitis, dyspnea, rash, and hypertension. Dose reductions or interruptions due to ARs occurred in 69% of patients receiving niraparib, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to ARs was 15%.

The most concerning AR identified with niraparib were Acute Myeloid Leukemia (AML)/Myelodysplastic Syndrome (MDS) and the cardiovascular effects. In the NOVA study, AML and MDS occurred in 5 out of 367 (1.4%) of patients who received niraparib and in 2 out of 179 (1.1%) patients who received placebo. Mean pulse rate and blood pressure increased over baseline in the niraparib arm relative to the placebo arm at all on-study assessments, which may be related to pharmacological inhibition of the dopamine, norepinephrine and serotonin transporters. Mean greatest increases from baseline in pulse rate on treatment were 24.1 and 15.8 beats/min in the niraparib and placebo arms, respectively. Grade 3-4 hypertension occurred in 9% of niraparib treated patients compared to 2% of placebo treated patients in NOVA study. Labeling adequately describes and conveys the AML/MDS and cardiovascular concerns in the Warnings and Precautions section, and no further mitigation strategy such as a REMS is recommended.

In conclusion, niraparib demonstrated a statistically significant and clinically meaningful improvement in PFS in a large, randomized, double blind clinical study. Despite immature OS data, in patients with a life-threatening and incurable malignancy, this PFS improvement represents a clinically meaningful benefit due to the substantial delay of progression and postponement of subsequent toxic therapies. The safety profile is acceptable in the intended population, as evidenced by no boxed warnings. Appropriate labeling for dose modification and inclusion of MDS/AML, bone marrow suppression and cardiovascular effects in warnings and precautions identifies these concerns to prescribers and assists with appropriate management.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Ovarian cancer is the fifth cause of cancer death in women and represents 5% of all cancer deaths. • In 2017, it is estimated that there will be 22.440 new cases of ovarian cancer and an estimated 14,080 women will die in the U.S.	• **Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers are serious, life-threatening, and incurable. There is an unmet medical need to develop therapies for these cancers.**
Current Treatment Options	• The majority of patients with ovarian cancer receive primary debulking surgery after diagnosis, followed by adjuvant chemotherapy with platinum plus taxanes with or without bevacizumab. Response rates in this first-line setting are high, but most patients recur within 2 years and die within 3-4 year after diagnosis.	• **Currently, only bevacizumab is FDA approved as a maintenance therapy for the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.**
Benefit	• NOVA is an international, multicenter, randomized (2:1), double-blind, placebo-controlled, clinical trial evaluating the efficacy and safety of treatment with niraparib 300 mg orally daily versus placebo in patients (n=553) with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen. • Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis test. • The trial demonstrated statistically significant and clinically meaningful improvement in PFS per IRC assessment for patients randomized to niraparib as compared with placebo in both the gBRCAmut cohort [HR 0.26 (95% CI: 0.17, 0.41); p value <0.0001] and the non-gBRCAmut cohort [HR 0.45 (95% CI: 0.34, 0.61); p value <0.0001], respectively. In the gBRCAmut cohort median PFS in the niraparib arm was 21 months (95% CI: 12.9, not reached) and median PFS in the placebo arm was 5.5 month (95% CI: 3.8, 7.2). In the non-	• **Evidence of effectiveness was supported by a statistically significant and clinically meaningful PFS improvement in all 3 pre-defined subgroups. The study was large, double-blind, placebo controlled, and randomized which decreases uncertainty. Supportive subgroup analyses further substantiate the evidence of niraparib benefit. Despite immature OS, in this population, the substantial improvement in PFS represents a clinically meaningful benefit due to delay of progression and postponement of subsequent toxic therapies.** • **Since the magnitude of benefit appears to be the largest in the gBRCAmut cohort followed by the HRD+ subgroup, the use of the BRACAnalysis test**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	gBRCAmut cohort median PFS in the niraparib arm was 9.3 months (95% CI: 7.2, 11.2) and median PFS in the placebo arm was 3.9 months (95% CI: 3.7, 5.5). • PFS results were consistent across all patient subgroups	**is recommended as a "complimentary diagnostic test", as it may aid clinicians in assessing which patients benefit most from treatment with niraparib.**
Risk	• The most common adverse reactions (AR) experienced in at least 20% of patients on NOVA were thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal pain/distention, mucositis/stomatitis, diarrhea, fatigue/asthenia, decreased appetite, headache, insomnia, nasopharyngitis, dyspnea, rash, and hypertension. Dose reductions or interruptions due to ARs occurred in 69% of patients receiving niraparib, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to ARs was 15%.	• **The safety profile of niraparib is acceptable for the intended population.** • **AML/MDS, bone marrow suppression and cardiovascular effects are the AR being described in the warnings and precautions section of labeling.**
Risk Management	• Niraparib is intended to be prescribed by oncologists. • Oncologists are well versed in the identification and management of the toxicities associated with niraparib. • Labeling details dose interruption, reduction, or discontinuation • AML/MDS, bone marrow suppression and cardiovascular effects are the AR being described in the warnings and precautions section of labeling. • Laboratory and vital sign monitoring is recommended before and during treatment.	• **The safe use of niraparib can be managed through accurate labeling and routine oncology care.** • **No REMS is indicated.**

2 Therapeutic Context

2.1. Analysis of Condition

Ovarian cancer is the fifth cause of cancer death in women and represents 5% of all cancer deaths. In 2016, it was estimated that there would be 22.280 new cases of ovarian cancer and an estimated 14,240 women will die in the U.S. The 5-year overall survival rate of ovarian cancer patients is 46% across all stages and 29% in patients with metastatic disease. Ovarian cancer is predominantly a disease of postmenopausal women, and most patients have advanced disease (Stage III-IV) at the time of diagnosis, when the prognosis is particularly poor. The majority of patients receive primary debulking surgery after diagnosis, followed by adjuvant chemotherapy with platinum plus taxanes with or without bevacizumab. Response rates in this first-line setting are high, but most patients recur within 2 years and die within 3-4 year after diagnosis. Once patients recur, the choice of subsequent chemotherapy is based upon is based upon the interval since the last platinum regimen, with patients who have recurrence > 6 months from the last platinum regimen typically receiving another platinum-based regimen. Despite high response rates to re-treatment with platinum following recurrence, relapse is inevitable. Patients often experience multiple relapses and receive multiple lines of chemotherapy (including platinum-based therapy) over the course of their disease.

2.2. Analysis of Current Treatment Options

The indication for approval will be niraparib is a PARP inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete response to platinum-based chemotherapy. The FDA approved treatment for the similar indication is shown in Table 1. It is notable that only bevacizumab is approved as a maintenance therapy for the treatment of recurrent, platinum-sensitive ovarian cancer. The administration for bevacizumab differs from that of niraparib in that bevacizumab is typically administered in conjunction with the chemotherapy regimen used in the relapse setting, and then is continued as a single agent in patients who are in response at the end of the 6-8 cycles of combination chemotherapy. Niraparib is not given concurrently with chemotherapy, but instead is administered as a “switch maintenance” therapy to patients who achieve a response (PR or CR) at the end of platinum-based chemotherapy. The main reason for this is due to the overlapping hematologic toxicity associated with niraparib and platinum-based chemotherapy that preclude concurrent administration of the agents without significant dose delays and reductions.

Table 1 Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Bevacizumab (Avastin)	Platinum sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with either carboplatin/ paclitaxel or carboplatin/ gemcitabine, followed by single agent maintenance	2016	15 mg/kg IV every 3 weeks in combination with carboplatin/ paclitaxel or carboplatin/ gemcitabine for 6-10 cycles, followed by 15 mg/kg IV every 3 weeks as a single agent.	2 studies supported approval: -**Study 11** (OCEANS)- Statistically significant 4 month improvement in PFS (HR= 0.45, 95% CI= [0.35, 0.83]) of bevacizumab + chemotherapy over chemotherapy + placebo. ORR was also higher for bevacizumab arm (78% vs. 57%) -**Study 12** (GOG-213)- Main efficacy outcome OS no statistically significant difference between arms (42.6 mos Bev vs. 37.6 mos without Bev).	Bevacizumab is associated with the following safety considerations: GI perforation/ fistula, arterial thromboembolic event, VTE, hypertension, proteinuria, posterior reversible encephalopathy syndrome	This indication is slightly different from the niraparib indication, particularly with regard to the relevance of the gBRCA mutation for response.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Niraparib is not approved for use in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 100996 for niraparib was originally submitted to the FDA by Merck in May 2008. The application received orphan drug designation for the treatment of ovarian cancer in April 2010. In May 2012, niraparib was licensed by Tesaro, and IND transferred to Tesaro in September 2012. An End-of-Phase 2 meeting (EOP2) happened in 2013 where discussion of the clinical development plan and the Phase 3, double-blind, placebo controlled trial occurred. The proposed trial was for use of niraparib as a maintenance therapy in relapsed platinum-sensitive ovarian cancer patients who had either gBRCA mutation or tumor with high grade serous histology. FDA provided advice on issues regarding gBRCA mutation testing, the PFS primary endpoint in an ovarian cancer maintenance setting, as well as on the proposed plan to assess patient reported outcomes. Additional meetings and guidance were provided to the Sponsor in 2015. A pre-NDA meeting occurred on 9/29/16, where format for the NDA submission was discussed.

A waiver for pediatric investigations was requested on 4/1/16, and the determination of this waiver is still pending at this time. The IND was granted fast track designation for the treatment of patients with recurrent, platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer on 9/7/16. A request for breakthrough designation for niraparib for monotherapy maintenance treatment of adult patients with gBRCA or homologous recombination deficiency (HRD)-positive platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum based chemotherapy was granted on 10/14/16.

The final component of the rolling submission for this New Drug Application 208447 was received by the FDA on 10/31/16.

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) inspected several clinical sites and the Sponsor, Tesaro, upon request from the clinical review team. The sites that were inspected are shown in Table 2. The conclusion from the OSI review summary is that the data submitted in support of NDA 208447, mainly from Study PR-30-5011-C appear to be reliable. See also the full OSI Inspection Summary dated 2/28/17 by Dr. Lauren Iaconon-Connors.

Table 2 OSI Clinical Inspection Summary

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Jonathan Berek Site 1015 300 Pasteur Drive HG-333 Stanford, CA 94305	Protocol PR-30-5011-C Subjects: 14	February 13-17, 2017	Preliminary Classification NAI
CI#2: Ursula Matulonis (Site 1009) Dana-Farber Cancer Institute 450 Brookline Ave. Boston, MA 02215	Protocol PR-30-5011-C Subjects: 9	January 24-30, 2017	Preliminary Classification NAI
CI#3: Ursula Matulonis (Site 1009B) Beth Israel Deaconess Medical Center 330 Brookline Ave. Boston, MA 02215	Protocol PR-30-5011-C Subjects: 2	February 6-7, 2017	Preliminary Classification NAI
CI #4: Michel Fabbro (Site 33002) 208 av. des Apothicaires Montepellier, Herault 342987 France	Protocol PR-30-5011-C Subjects: 20	February 13-17, 2017	Preliminary Classification NAI
CI#5: Mansoor Mirza (Site 45003) Department of Oncology 5073 Righospitalet	Protocol PR-30-5011-C Subjects: 26	February 13-17, 2017	Preliminary Classification NAI

Copenhagen Ø, Capital 2100 Denmark			
CI#6: Sponsor: Tesaro, Inc. 1000 Winter Street Suite 3300 Waltham, MA 02451	Protocol PR-30-5011-C Site numbers: 001009, 001009B, 001015, 033002, 045003	January 4- 20, 2017	Preliminary Classification NAI

4.2. Product Quality

The product quality review is summarized in the Executive CMC Summary by Xiao Hong Chen, PhD, dated 3/9/17. NDA 208447 was recommended for approval, from the CMC perspective. The overall recommendation for the facility evaluation was "acceptable".

Novel excipients: No.
Any impurity of concern: No.

Three post-marketing commitments (PMCs) related to product quality were recommended by the FDA CMC review team, and agreed upon by the Applicant. They are presented in Section 8 of this review.

4.3. Clinical Microbiology

The FDA review for process and clinical microbiology was conducted by Kumar Janoria. A summary of the conclusions of this review is included in the Executive CMC Summary by Xiao Hong Chen, PhD, dated 3/9/17. The review team concluded that the presented data were acceptable for approval.

4.4. Devices and Companion Diagnostic Issues

The Review Division consulted CDRH during review of the niraparib NDA, as BRACAnalysis and myChoice® HRD tests were used in NOVA study. Enrollment into the cohorts of the NOVA study was determined by the results of Myriad's Integrated BRACAnalysis testing and prior to unblinding the study, the tumors of patients randomized to the non-gBRCAmut cohort were tested for the presence of homologous recombination deficiency (HRD) using Myriad's

myChoice® HRD test. Per NOVA's Statistical Analysis Plan, the primary analysis of PFS was performed in the gBRCAmut and non-gBRCAmut cohort independently and within the non-gBRCAmut cohort, the HRD+ subgroup was tested first and followed by the entire cohort.

Since the evidence of effectiveness was supported by a statistically significant and clinically meaningful PFS improvement in all pre-defined subgroups, BRACAnalysis
are not essential for the safe and effective use of niraparib and would not be designated as companion diagnostic tests. However, they may aid clinicians in assessing which patients benefit most from treatment with niraparib; therefore they are designated as "**complementary diagnostics"**.

PMA Supplement (P140020/S009) for the BRACAnalysis CDx was submitted on 12/20/16. The supplement requested a new indication for the BRACAnalysis CDx test, to expand its intended use statement to include niraparib. The original PMA P140020 was approved in 2014 as a companion diagnostic test for use with Lynparza (olaparib).

The conclusion from the CDRH review team is that the PMA supplement for the BRACAnalysis CDx support the reasonable assurance of safety and effectiveness of the device, when used in accordance with the indications for use. The PMA supplement review for BRACAnalysis test by CDRH has been completed and the supplemental PMS P140020/S009 will be approved on the same day as NDA 208447 for niraparib.

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Reference ID: 4074987

5 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was required.

6 Pediatrics

Niraparib was not studied in pediatric patients. The Applicant has submitted a PREA waiver and it will be reviewed prior to the action date.

7 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended.

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

Not applicable.

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

Not applicable.

7.1. Recommendations on REMS

Not applicable.

8 Postmarketing Requirements and Commitments

PMR 3187-1:

Conduct a dedicated pharmacokinetic trial in patients with moderate hepatic impairment to determine an appropriate starting dose of niraparib in patients with moderate hepatic impairment.

Final protocol submission: 6/2017
Trial completion: 11/2018
Final study report submission: 2/2019

PMC 3187-2:

One Post-Marketing Commitment (3/6/17) was put forth by CDRH, regarding HRD CDX. The final wording is as follows:

Submit to FDA the appropriate analytical and clinical validation study for the in vitro diagnostic assay used to identify patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer with homologous recombination deficiency (HRD) in clinical trial entitled "A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer" to inform product labeling for both the device and for Niraparib.

Final report submission: 12/2017.

There are 3 CMC post-marketing commitments (PMC), as follows:

PMC 3187-3:
Revise as necessary in-coming material quality controls and/or formulation and/or unit operation(s) such that the current practice of releasing drug product (b) (4) *while still maintaining product quality and batch to batch consistency.*

Final report submission: 04/15/2018

Study rationale: The applicant's current manufacturing process involves releasing drug

product (b) (4) *The quality and batch to batch consistency of your drug product should be based on sound understanding of the science and well designed and controlled manufacturing process, instead of on testing.*

PMC 3187-4:
Provide method validation data for accuracy and precision using the revised assay method AM-1971 and capsules made by the manufacturing process approved in the application. The validation of the analytical method should be consistent with the ICH Q2 guidelines.

Final report submission: 04/15/2018

Study rationale: The applicant's current method validation study fails to meet the acceptance criteria for accuracy and precision due to interference. Applicant has committed to submit the requested study after the application is approved and after the method description has been updated with information accepted in the NDA.

PMC 3187-5:

Provide method validation data for accuracy and precision using revised dissolution method AM-1974 and capsules made by the manufacturing process approved in the application. Data should be presented in the form of drug release profiles collected at 5, 15, 30, 45 and 60 minutes. The validation of the analytical method should be consistent with the ICH Q2 guidelines.

Final report submission: 04/15/2018

Study rationale: The applicant's current method validation study fails to meet the acceptance criteria for accuracy and precision due to interference from the drug product. The applicant has committed to submit the requested study after the application is approved and after the method description has been updated with method description information accepted in the NDA."

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/s/

GWYNN ISON
03/22/2017

LALEH AMIRI KORDESTANI
03/22/2017

9 Nonclinical Pharmacology/Toxicology

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9.1. Executive Summary

Zejula (niraparib) is an orally available poly (ADP-ribose) polymerase (PARP) inhibitor. In vitro, niraparib (MK-4827) inhibited the enzymatic activity of several PARP family members, but had greater than 500-fold potency against PARP-1 and PARP-2 (IC_{50} values of 2.8 nM and 0.6 nM, respectively). In vitro, increased amounts of unrepaired DNA single-strand breaks correlated with suppression of cellular PAR enzymatic activity levels. Niraparib inhibited proliferation of a range of BRCA-1 and BRCA-2 deficient cell lines, in vitro. Niraparib decreased tumor growth in mouse xenograft models of human cancer cell lines with deficiencies in *BRCA1/2* and in human patient-derived xenograft (PDx) tumor models with homologous recombination deficiency that had either mutated or wild type *BRCA1/2*. Published reports provide evidence that niraparib can form PARP-DNA complexes resulting in DNA damage, apoptosis and cell death, which is hypothesized to contribute to the mechanism of action of PARP inhibitors (Murai, Huang, et al. 2012). This trapping of PARP-DNA complexes may interfere with DNA replication, requiring homologous recombination repair, such as BRCA-dependent repair, to resolve. Based on available pharmacology data with niraparib, the scientifically valid and clinically relevant Established Pharmacological Class (EPC) is "poly(ADP-ribose) polymerase (PARP) inhibitor."

An in vitro secondary pharmacology screen was conducted to assess the potential for off-target (i.e., non-PARP) binding to a variety of receptors, enzymes and channels. Biochemical assays were conducted to determine an IC_{50} value for the targets for which niraparib inhibited ≥ 50% of ligand binding observed in the initial screen. In vitro, niraparib bound to the dopamine transporter (DAT; IC_{50} = 63 nM), norepinephrine transporter (NET; IC_{50} = 192 nM) and serotonin transporter (SERT; IC_{50} = 363 nM) and inhibited the uptake of dopamine (EC_{50} = 24 nM) and norepinephrine (EC_{50} = 130 nM) in cells at concentrations lower than the C_{min} at steady-state in patients receiving the recommended dose. In a cardiovascular safety pharmacology study, intravenous administration of niraparib to vagotomized dogs over 30 minutes at 1, 3 and 10 mg/kg (20, 60, and 200 mg/m^2) resulted in an increased range of arterial pressures of 13-20, 18-27 and 19-25% and an increased range of heart rates of 2-11, 4-17 and 12-21% above pre-dose levels, respectively. The unbound plasma concentrations of niraparib in dogs at these dose levels were approximately 0.7, 2 and 8 times the unbound C_{max} at steady-state in patients receiving the recommended dose. Findings in this dog study may over represent potential effects on heart rate and blood pressure in humans since bilateral vagotomy will prevent reflex bradycardia in this model, although these findings are consistent with adverse reactions reported in clinical trials with niraparib in patients receiving the recommended dose. The findings are also consistent with adverse reactions associated with US FDA approved drugs whose primary pharmacological activity is to modulate catecholamine levels. In repeat-dose toxicity studies in dogs, blood pressure was not assessed, but

heart rate was measured and no effects were reported. The unbound plasma concentration at the highest dose tested in repeat-dose studies in dogs at the time when heart rate was assessed was approximately 101 nM. The unbound C_{max} at steady-state in patients was between 510 and 850 nM, so it is possible that exposures in repeat-dose studies in dogs did not achieve plasma concentrations high enough to inhibit DAT, NET or SERT or cause hypertension or increased heart rate. It is possible that any effects of niraparib on heart rate or blood pressure would not be as great in non-vagotamized dogs compared to the vagotimized dogs used in the single-dose IV study. Based on all available information, it is likely that niraparib has off-target pharmacological activity on DAT, NET and SERT at plasma concentrations achieved in patients receiving the recommended dose, contributing to the hypertension, palpitations and increased pulse rates and blood pressures observed in patients.

Niraparib was a low-potency hERG blocker and there were no adverse effects on ECG parameters in repeat-dose studies in dogs receiving oral niraparib at doses up to 15 mg/kg (300 mg/m^2). In the initial screen for potential off-target binding, niraparib bound to the rat L-type calcium channel with a maximum IC_{50} of 3220 nM. The only ECG changes observed in dogs following niraparib administration was an increase in QRS interval (6% compared to predose) at the highest dose level (10 mg/kg or 200 mg/m^2) in the single-dose IV cardiovascular safety study in anesthetized, vagotomized dogs. The exposure of unbound drug at that dose was about 8 times higher than the unbound C_{max} at steady-state in patients. Evaluation of available nonclinical data suggests the potential for niraparib to cause cardiac arrhythmias is low.

Niraparib crossed the blood-brain barrier in rats and monkeys following oral administration. The cerebrospinal fluid (CSF): plasma C_{max} ratios of niraparib administered at 10 mg/kg (120 mg/m^2) orally to two Rhesus monkeys were 0.10 and 0.52. In vivo studies in mice following IP injection of niraparib at up to 25 mg/kg (75 mg/m^2) did not result in binding of niraparib to DAT or a change in total dopamine levels, but did result in increased intracellular dopamine levels in the striatum, suggesting niraparib is active in brain. In a separate study, locomotor activity was not affected in mice following IP injection of niraparib at up to 40 mg/kg (120 mg/m^2) compared to d-amphetamine (10 mg/kg or 30 mg/m^2). Toxicokinetics were not assessed in these studies, thus it is not known whether the plasma concentrations were high enough to inhibit the DAT, NET or SERT transporters in the brain. No clinical signs indicating effects on the CNS were reported in rats or dogs in repeat-dose toxicology studies following oral niraparib administration, although plasma concentrations in dogs were not likely high enough to inhibit DAT, NET or SERT based on their IC_{50} values. In the repeat-dose rat studies, plasma concentrations may have been high enough to inhibit DAT, NET or SERT, but it is not clear that these studies included assessments to adequately detect any resulting effects on the CNS specific to catecholamine modulation. Therefore, available nonclinical data do not rule out the potential for CNS effects of niraparib in patients.

General toxicology studies were conducted to evaluate the effects of daily oral niraparib in rats and dogs for up to 90 days. In rats, daily administration of niraparib at 30/20 mg/kg (180/120 mg/m^2) for 77-85 days resulted in early deaths due to bone marrow toxicity. Decreases in red blood cell mass

(hemoglobin, % hematocrit), red blood cell counts, reticulocyte levels, white blood cells, lymphocytes, monocytes, and neutrophils and increased platelet counts were mainly identified in rats at 30/20 mg/kg (180/120 mg/m^2). In dogs, decreases in reticulocytes were also observed at the dose levels of ≥ 4.5 mg/kg (90 mg/m^2). Associated toxicological findings were observed in bone marrow (femoral and sternal depletion), thymus (hypocellularity lymphocytes), lymph node (erythrocytosis, erythrophagocytosis), spleen (lymphoid tissue depletion, red pulp depletion, and extramedullary hemopoiesis), and liver (reticuloendothelial pigment hepatocellular, extramedullary hemopoiesis). Generally, the hematopoietic system fully or partially recovered by the end of the non-dosing period 28-day recovery period. In humans, niraparib caused hematological toxicities, including anemia, neutropenia, thrombocytopenia and lymphopenia at the recommended clinical dose of 300 mg once daily. Thus, toxicological findings in the hematopoietic system in nonclinical studies were consistent with the frequent adverse events observed in clinical trials.

Minimal to moderate reduction in sperm in epididymis and germ cell depletion and tubular degeneration/atrophy in testis were observed at terminal necropsies at doses ≥ 10 mg/kg (60 mg/m^2) in rats and ≥ 1.5 mg/kg (30 mg/m^2) in dogs. These dose levels resulted in system exposures of approximately 0.3 and 0.012 times the human exposure ($AUC_{0\text{-}24hr}$), respectively, achieved at the recommended clinical dose. Histopathology findings in epididymides and testes were still observed in rats, but not in dogs, at the end of a 28-day non-dosing period, although there was a trend toward reversibility. These effects indicate that niraparib may impair fertility in males of reproductive potential. The effects on the hematopoietic system and the testes by niraparib are consistent with its primary pharmacology.

Additional toxicological findings were observed primarily in rats and included the kidney (minimal to moderate tubular dilation, hyaline case, and chronic nephropathy) and adrenal gland (minimal necrosis) without correlates that would suggest there were effects on organ function. Moreover, histopathology findings in the heart also included minimal chronic cardiomyopathy in rats and hemorrhage in dogs.

The major metabolic pathways observed across species (rat, dog, and human) involved oxidative and conjugated metabolites (i.e., M1, M2, M4-M6, M8, and M10-M22). No unique metabolites were identified in human hepatocytes. In humans, M1 accounted for 9.3% of the total administered dose, and the majority of the circulating metabolites were the isomer glucuronide conjugates of M1 (e.g. M10), which accounted for 56% of the total plasma radioactive exposure. M1 did not inhibit PARP-1 and PARP-2 enzyme activity (IC_{50} >10000 nM) in vitro.

Niraparib was not mutagenic in the Ames bacterial mutagenicity assay, but was clastogenic. Niraparib was positive for the induction of structural chromosome aberrations and negative for the induction of numerical chromosome aberrations in mammalian CHO cells, in vitro. Niraparib was positive in the in vivo rat bone marrow micronucleus assay at all dose levels tested. The genetic toxicity results with niraparib are consistent with its mechanism of action and primary pharmacological activity. The

Applicant did not conduct carcinogenicity studies with niraparib due to its intended use in patients with advanced cancer, consistent with recommendations in ICH S9.

No developmental and reproductive toxicology studies were conducted to support this NDA based on recommendations in the International Council for Harmonization (ICH) Guidance for Industry, "S9 Nonclinical Evaluation for Anticancer Pharmaceuticals." Since niraparib targets rapidly dividing cells (e.g., adverse effects on the hematopoietic system in nonclinical studies and clinical trials) and is genotoxic, it is expected to cause teratogenicity and/or embryo-fetal death if administered to a pregnant woman. Effective contraception use is recommended for females of reproductive potential during treatment with niraparib and for 6 months following the last dose. Since niraparib is genotoxic, 6 months is recommended to minimize the risk for DNA damage in oocytes. For the same reasons, lactating women are advised not to breastfeed during treatment and for 1 month after the last dose. Based on the plasma half-life of niraparib in patients of 36 hours, the majority of niraparib should be cleared after 2 weeks. The Applicant's proposal of 1 month is acceptable.

The submitted nonclinical pharmacology and toxicology data with niraparib are adequate to support approval of this NDA for the proposed indication.

9.2. Referenced NDAs, BLAs, DMFs

None

9.3. Pharmacology

Primary pharmacology

Study Title/Number: Poly (ADP-ribose) Polymerase (PARP) inhibitor assays: enzymatic study of the compounds from Tesaro/1001

Methods: The effect of niraparib on the enzymatic activities of recombinant human PARP enzymes was determined using BPS PARP assay kit. The enzymatic reactions for PARP were conducted in duplicate at room temperature for 1 hour in a 96-well plate coated with histone substrate by adding 50 µL of reaction buffer (Tris HCl, pH 8.0) containing NAD^+, biotinylated NAD^+, activated DNA, a PARP enzyme and the test article (niraparib 0.3 nM-10 µM in 10% DMSO). After the enzymatic reactions, 50 µL of streptavidin-horseradish peroxide was added to each well, and the plate was incubated at room temperature for an additional 30 minutes followed by 100 µL of developer reagent. Luminescence was measured using a BioTek Synergy 2 microplate reader.

Results: Niraparib inhibited recombinant human PARP1/2 enzymes with IC_{50} values of 2.8 and 0.6 nM, respectively. The closest IC_{50} values for inhibition of other PARP family enzymes, TNKS1/2 (IC_{50} values of 1400 nM), were approximately 500-fold higher than for PARP1. The IC_{50} values for PARP family enzymes

other than PARP1/2 were above the maximum niraparib unbound plasma C_{max} at steady-state of approximately 850 nM observed in patients at the recommended dose.

Table 9-1 PARP Enzyme Inhibition by Niraparib

Enzyme	IC_{50} (nM)
PARP1	2.8
PARP2	0.6
PARP3	5200
TNKS1	1400
TNKS2	1400
PARP6	>10000
PARP7	>10000
PARP8	>10000
PARP10	2100
PARP11	>10000
PARP12	>10000
PARP14	>10000
PARP15	>10000

Study Title/Number: Poly (ADP-ribose) Polymerase (PARP) inhibitor assays/PARP-05232016

Methods: The effect of niraparib and M1 (metabolite of niraparib) on the enzymatic activities of recombinant human PARP enzymes was determined using BPS PARP assay kit. The enzymatic reactions for PARP were conducted in duplicate at room temperature for 1 hour in a 96-well plate coated with histone substrate by adding 50 µL of reaction buffer (Tris HCl, pH 8.0) containing NAD^+, biotinylated NAD^+, activated DNA, a PARP enzyme and the test article (niraparib or M1 at 0.3 nM-10 µM in 10% DMSO). After the enzymatic reactions, 50 µL of streptavidin-horseradish peroxide was added to each well, and the plate was incubated at room temperature for an additional 30 minutes followed by 100 µL of developer reagent. Luminescence was measured using a BioTek Synergy 2 microplate reader.

Results: M1 did not inhibit PARP-1 and PARP-2 enzymatic activity. Niraparib inhibited PARP-1 and PARP-2 enzymatic activity with IC_{50} values of 1.1 and 0.4 nM, respectively.

Table 9-2 Inhibitory effects of the compounds on PARP activities

Compounds	IC_{50} (nM)	
	PARP-1	PARP-2
M1	>10000	>10000
Niraparib	1.1	0.4

Study Title/Number: Correlation between PAR suppression and single-strand break repair/ TSR2016082

Methods: The study was designed to evaluate the functional suppression of DNA damage repair by PARP inhibitors and correlate the outcome with reduced poly-ADP-ribose (PAR) levels. Niraparib and olaparib were evaluated for their ability to reduce PAR levels and suppress DNA damage repair in Jurkat cells. Briefly, 1.5 $x10^6$ Jurkat cells/mL were pre-treated with either 0.3 nM to 3000 nM niraparib or olaparib for 1 hour and stimulated with H_2O_2 for 15 minutes to induce DNA damage. After one hour incubation, PAR levels were measured by ELISA, and DNA single strand breaks were quantified by single cell electrophoresis. In the ELISA assay, immobilized PAR monoclonal antibody in a 96-well plate captures cellular PAR and PAR attached to proteins. A polyclonal PAR-detecting antibody was added and followed by a goat anti-rabbit IgG-HRP secondary antibody. A chemiluminescent HRP substrate yields relative light unit (RLU) that directly correlates with the amount of cellular PAR.

Results: Both niraparib and olaparib caused dose-dependent suppression of cellular PAR levels, which correlated with an increase in the amount of unrepaired DNA single strand breaks. The EC_{50} for suppression of DNA damage repair was 376 nM and 1892 nM for niraparib and olaparib, respectively. In both cases, blockage of DNA repair (≥ 5%) was achieved when PAR levels were suppressed by about 90%. DNA repair was normalized to DMSO samples at times of minimum (15 min) and maximum (75 min) repair following H_2O_2 treatment.

Table 9-3 Calculated IC_{50} and IC_{90} value of PAR inhibition and EC_{50} and EC_{90} value of DNA damage repair inhibition

	Olaparib [nM]	Niraparib [nM]
PAR IC50	12	22
PAR IC90	107	56
Comet EC5	78	64
Comet EC50	1892	376
Comet EC90	>10μM	1414

(Copied from Applicant's submission)

Study Title/Number: Antiproliferative activity of MK-4827 on cancer and normal cells/PD003

Methods: Antiproliferative activity of niraparib was evaluated in normal human epithelial cells (renal, prostate, and mammary epithelial cells) and a panel of cancer cells either defective for BRCA-1 or BRCA-2 expression or expressing mutant forms of the two genes (i.e. HeLa and A549 matched pairs silenced for BRCA-1 and BRCA-2; cancer cells transfected with lentivirus expressing shRNA induced BRCA-1/-2 mutation). Briefly, cells were placed in a 96-well plate and incubated for 4 hours at 37°C and 5% CO_2 prior to adding serial dilutions of niraparib. Cells were then incubated for 5-7 days at 37°C and 5% CO_2. Cell viability was assessed by CellTiter-Blue assay. The number of living cells was determined by reading the plate on a fluorimeter (ex: 500 nm, and em: 590 nm). Cell growth was expressed as percentage growth with respect to vehicle treated cells. The concentration required to inhibit cell growth by 50% (CC_{50}) was determined using SigmaPlot 10.0 and the four parameter logistic function.

Results: Niraparib inhibited HeLa BRCA-1-deficient cells at CC_{50} = 34 nM (n =52) with a 25-fold selectivity window over the BRCA-1wt matched pair HeLa Cells (CC_{50} = 850 nM; n =52). Niraparib inhibited the proliferation of BRCA-2 silenced A549 human lung cancer cells lines with a CC_{50} = 11 nM (n =3) with more than 100-fold selectivity over the BRCA2wt matched pair A549 cells (CC_{50} = 1760 nM; n =3). In contrast, normal human cells, including renal, prostate, and mammary epithelial cells, are resistant to niraparib with a CC_{50} ranging from 2900 to >5000 nM (n=1-2). In cancer cell lines carrying BRCA-1 or BRCA-2 mutations (mammary gland adenocarcinoma [MDA-MB436], breast [SUM149PT, SUM1315MO2], and pancreas adenocarcinoma [CAPAN-1]), niraparib demonstrates a CC_{50} ranging from 18 to 73 nM (n=3-9).

Study Title/Number: In vivo anti-tumor activity of the PARP inhibitor niraparib in 27 ovarian carcinoma PDX models/3009-09-0002

Methods: Twenty-seven treatment-naïve ovarian carcinoma patient-derived xenograft (PDX) models were used to evaluate niraparib activity in vivo. Following tumor engraftment and growth to a visible range (0.5-1 cm) by transabdominal ultrasound, mice were randomized to treatment arms. Mice were

orally administered either vehicle (0.5% methyl cellulose) or 60 mg/kg niraparib. Largest tumor diameter and cross-sectional area were measured twice weekly through Day 28. The primary endpoint was tumor area measured by ultrasound area of each tumor divided by the Day 1 area of the same tumor and plotted as a ratio versus time. Tumor homologous recombination (HR) status was scored by the MyChoice HRD test developed by Myriad Genetics. For this study, "resistant" is defined as tumors which remained at or above baseline while "sensitive" is defined as tumors which regressed on therapy. All tumors with a score <42 were resistant; only a subset of tumors >42 were sensitive to niraparib. It has been hypothesized that HGS ovarian carcinomas harboring mutations in homologous recombination (HR) genes are most likely to respond to PARP inhibition.

Results: Tumor regressions were induced by niraparib in 7/27 models (all HR deficient). Regressions were observed in 3/4 BRCA mutant models and in 4/12 wild-type BRCA, HR deficient models. A subset of MyChoice HRD positive PDX models was sensitive to niraparib when dosed daily at 60 mg/kg. MyChoice HRD negative models were not sensitive to niraparib. In conclusion, mutations in HR genes did not always predict niraparib-induced tumor regression.

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Table 9-4 Niraparib response in orthotopic ovarian PDX models

Model#	HRD status[a]	BRCA-1/-2 mutation status[a]	Fold-change from baseline[b]	Tumor response[c]
PH054	positive	BRCA-1mut	0.08	PR
PH039	positive	wt	0.14	PR
PH088	positive	BRCA-1mut	0.17	PR
PH242	positive	wt	0.24	PR
PH013	positive	wt	0.54	PR
PH077	positive	BRCA-2mut	0.54	PR
PH056	positive	wt	0.62	PR
PH038	positive	wt	1.11	SD
PH331	negative	wt	1.35	PD
PH235	negative	wt	1.42	PD
PH048	negative	wt	1.42	PD
PH044	negative	wt	1.43	PD
PH087	negative	wt	1.45	PD
PH080	negative	wt	1.51	PD
PH095	positive	BRCA-2mut	2.05	PD
PH063	positive	wt	2.14	PD
PH098	negative	wt	2.33	PD
PH026	negative	wt	2.76	PD
PH233	positive	wt	2.91	PD
PH061	positive	wt	3.43	PD
PH045	negative	wt	3.48	PD
PH134	positive	wt	3.99	PD
PH249	positive	wt	4.58	PD
PH247	negative	wt	5.31	PD
PH231	positive	wt	5.66	PD
PH081	negative	wt	7.38	PD
PH291	positive	wt	10.60	PD

[a] from Myriad myChoice HRD test, positive tumors have BRCA-1/-2mut or HRD scores ≥42 [1]
[b] tumor area at day 0/ tumor area at day 28
[c] progressive disease (PD, FC >1.20), stable disease (SD, FC=1.20-0.70), or partial response (PR, FC < 0.70)

(Copied from Applicant's submission)

(b) (4)

Secondary Pharmacology

Type of Study	Major Findings
Selectivity	
Study Title/Number: To evaluate, in Merck Screen, the activity of test compound MKW-863/PD011 In vitro: niraparib (0.01 to 100 µM) was screened against a panel of 168 radioligand binding and enzyme assays covering a diverse panel of enzymes, receptor transporters, and ion channels	In vitro, niraparib bound to the human dopamine transporter (DAT; IC_{50} = 51 nM), norepinephrine transporter (NET; IC_{50} = 239 nM), serotonin transporter (SERT; IC_{50} = 363 nM) and monoamine oxidase (MAO-B; IC_{50} = 751 nM). In addition, niraparib also bound to rat calcium channel L-type, benzothiazepine (IC_{50} = 3220 nM)
Study Title/Number: Niraparib radioligand binding & Cellular assays/PD012 In vitro: niraparib (0.01-10 µM) was evaluated for radioligand binding activity and in cellular assays against the dopamine transporter (DAT) and the norepinephrine transporter (NET) in human CHO-K1 cell(rhDAT) and MDCK cell (rhNET)	Niraparib bound to DAT (IC_{50} = 63 nM) and NET (IC_{50} = 192 nM) and inhibited uptake of dopamine (EC_{50} = 24 nM) and norepinephrine (EC_{50} = 130 nM) in cells.
In vivo follow-up to secondary pharmacology screen	
Brain monoamine levels	
Study Title/Number: Pharmacological effects of L-001946812 on monoamines in the mouse/PD014 In vivo: Pharmacological effects of niraparib on	Niraparib did not induce typical biochemical changes associated with amine transporter blockers when compared to amphetamine. However, niraparib increased intracellular

Type of Study	Major Findings
brain monoamines were also evaluated in female ICR mice (n=4) by i.p. with vehicle (70% PEG200/3%DMSO), 20-40 mg/kg niraparib, or positive control amphetamine (10 mg/kg). The levels of monoamine/metabolite were subsequently measured in the striatum, hippocampus, and cortex by HPLC with electrochemical detection (ECD)	dopamine levels in the cortex without significantly effecting dopamine release, suggesting niraparib may be pharmacologically active in brain.
Locomotor behavior	
Study Title: Evaluation of locomotor activity with niraparib/PD013 In vivo: effect of niraparib on locomotor activity was also evaluated in female CD-1 mice administered vehicle (i.p. 70% PEG 200/30% DMSO), niraparib (i.p. 20, 30, or 40 mg/kg), or positive control d-amphetamine (i.p. 1, 3.3, or 10 mg/kg)	Results indicate that niraparib decreased distance traveled compared to vehicle control. Niraparib did not cause psychostimulant effects in this study when compared to amphetamine.

Safety Pharmacology

Study Title/Number: Electrophysiological evaluation on hERG channel current stably expressed in CHO cells/TT#07-4734

Methods: The effect of niraparib (3, 10, and 30 µM; n=3-5) on in vitro hERG current was evaluated by using stably transfected HEK293 cells and the whole cell patch clamp method.

Results: Niraparib inhibited hERG current with an IC_{50} value of 10 µM and IC_{20} value of 3.8 µM. Therefore, niraparib is considered a low-potency potassium channel blocker.

Study Title/Number: Effect of MK-4827 on cardiovascular function in anesthetized dogs/ TT#07-5300

Methods: In a non-GLP study, male vagotamized beagle dogs (n=3) were used to assess the cardiovascular effects of intravenous administration of 1, 3, and 10 mg/kg niraparib (MK-4827) in a vehicle of 100% deionized water (10 mL per dose). Heart rate, mean arterial pressure, and electrocardiographic parameters (PR, QRS, and QT/QTs intervals) were monitored predose and during each 30-minute infusion period.

Results: Intravenous administration of niraparib to dogs over 30 minutes at 1, 3 and 10 mg/kg resulted in an increased range of arterial pressures of 13-20, 18-27 and 19-25% and increased range of heart rates of 2-11, 4-17 and 12-21% above pre-dose levels, respectively. No treatment-related changes in blood flow or PR and QTc intervals were observed. The only ECG changes observed in dogs following

administration of niraparib was an increase in QRS interval (6% compared to predose) at the highest dose level (10 mg/kg).

Table 9-5 Cardiovascular effects of MK-4827 following IV dose in anesthetized dogs

Dose (mg/kg)	Heart rate increase (mean % above baseline)	Range of % change above baseline	Arterial pressure increase (mean % above baseline)	Range of % change above baseline	Plasma concentration (µM)	Free drug concentration (µM) based on 72% binding in dogs
1	5	13-20	16	2-11	1.2	0.336
3	9	18-27	21	4-17	3.9	1.09
10	17	19-25	20	12-16	15.3	4.28

Study Title/Number: Effect of MK-4827 on neurological function in conscious mice/TT#07-5362

Methods: In a non-GLP study, male conscious CD-1 mice (n=5) were used to assess neurological function using a functional battery of tests including behavior, neural reflexes, spontaneous activity, and thermoregulation at 0.5, 1, 2, 5, and 24-hour postdose. Mice were administered either a single oral dose of vehicle (0.5% (w/v) methylcellulose) or 100 mg/kg niraparib.

Results: Niraparib had no effect on neurological function during the 24-hour postdose period.

9.4. ADME/PK

Type of Study	**Major Findings**
Absorption	
Study Title/Number: Pharmacokinetics of MK-4827 in Sprague Dawley rats and Beagle dogs following intravenous and oral administration/ PK001 Male Sprague-Dawley rats (n=4), Single IV at 3 mg/kg and oral gavage at 5 mg/kg	Rat T_{max}= 2 hours; Vd_{ss} =6.9 L/kg; Orally bioavailability= 27%; $T_{1/2}$=3.4 hours; Clearance = 28 mL/min/kg; IV $AUC_{0\text{-}inf}$=5.7 µM•hr; Oral$AUC_{0\text{-}inf}$: 2.5 µM•hr

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Male Beagle dogs (n=3), Single IV at 1 mg/kg and oral gavage at 3 mg/kg</td><td>Dog T_{max}= 0.5 hour; Vd_{ss}= 12.3 L/kg; Orally bioavailability= 57%; $T_{1/2}$= 5.7 hours; Clearance = 31 mL/min/kg; IV $AUC_{0\text{-}inf}$= 1.8 µM•hr; Oral $AUC_{0\text{-}inf}$= 3.0 µM•hr</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Study Title/Number: In vitro studies with MK-4827/PK002

Plasma protein binding in rat, dog, human and monkey plasma</td><td>The mean values for unbound fraction in rat, dog, monkey and human plasma were 16, 28, 17 and 17%, respectively.</td></tr>
<tr><td>Study Title/Number: In vivo CNS penetration of MK-4827 and in vitro drug metabolism studies in monkeys/PK004

Male Rhesus monkeys (n=2) were orally administered single-dose of 10 mg/kg (5 mL/kg) niraparib.</td><td>Niraparib exhibited CNS penetration with a mean CSF to plasma ratio of 18% for AUC and 31% (1 monkey with 10% and 1 monkey with 52%) for C_{max}) in Rhesus monkeys. The C_{max} in CSF was 0.23 µM with an $AUC_{0\text{-}inf}$ of 1.9 µM•hr. The C_{max} and $AUC_{0\text{-}inf}$ in plasma were 0.77 µM and 10.8 µM•hr, respectively.</td></tr>
<tr><td>Metabolism</td><td></td></tr>
<tr><td>Study Title/Number: In vitro studies with MK-4827/PK002

The in vitro metabolism characteristics of niraparib were assessed in human liver microsomes. The oxidative metabolism of [^{14}C]MK-4827 in liver microsome from rats, dogs and human were also evaluated.</td><td>

In human liver microsomes and hepatocytes, the turnover of niraparib was very slow (<10%) over an incubation period of 2 hours.
All human metabolites of niraparib were observed in rats.

<table>
<tr><th>Rat</th><th>Dog</th><th>Human</th></tr>
<tr><td>M1</td><td>M1</td><td>M1</td></tr>
<tr><td>M2</td><td>M2</td><td>M2</td></tr>
<tr><td>M3</td><td>M4</td><td>M3</td></tr>
<tr><td>M5</td><td>M5</td><td>M8</td></tr>
<tr><td>M6</td><td>M6</td><td>M10</td></tr>
<tr><td>M7</td><td>M7</td><td></td></tr>
<tr><td>M8</td><td>M9</td><td></td></tr>
<tr><td>M10</td><td>M10</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Study Title/Number: In Vivo excretion and metabolism of [^{14}C]MK-4827/ PK003

Excretion of niraparib was evaluated in vivo following IV administration of [^{14}C]-MK-4827 to bile duct-cannulated rats (3 mg/kg) and dogs (2 mg/kg).</td><td>o In rats, the total radioactivity recovered in the excreta represented 79% of the dose with similar amounts of radioactivity recovered in bile, urine, and feces (24-30%, respectively) over a 120 hour collection period. Numerous oxidative and conjugated metabolites (i.e., M1, M2, M4-M6, M8, and M10-M22) were observed in the excreta, with no single metabolite accounting for more than 5% of the dose.
o In dogs, the total radioactivity recovered in the excreta represented 80% of the dose with 53% excreted in urine, 18% in bile, and 9% feces over a 120 hour collection period. The most prevalent metabolite (M1) is a carboxylic acid generated from amide hydrolysis, and accounted for 52% of the recovered dose. In addition, metabolites M10 and M20 were also observed in the excreta.
o The major circulating metabolites in both rats and dogs were the acid metabolite (M1) and its glucuronide conjugate (M10).</td></tr>
<tr><td>TK data</td><td></td></tr>
<tr><td>Rat: 90-Day repeat-dose toxicology study (oral gavage administration once daily (Study Number 12-2328)
Dose levels: 0, 5, 10, or 30/20 mg/kg at dose volume 5 mL/kg (final concentrations at 0, 1, 2 or 6/4 mg/mL)
Sample analysis: on Days 1 and 90 at 1, 2, 4, 6, 8, and 24 hours post dose and at 2 hours post dose for control group.</td><td><u>Rat</u>
T_{max}: 4-6 hours in males; 2-8 hours in females

<table>
<tr><th>Day</th><th>Sex</th><th>Dose level (mg/kg)</th><th>C_{max} (ng/mL)</th><th>AUC_{all} (ng•h/mL)</th></tr>
<tr><td>1</td><td>M</td><td>5</td><td>89.7</td><td>1100</td></tr>
<tr><td></td><td></td><td>10</td><td>399</td><td>4100</td></tr>
<tr><td></td><td></td><td>30/20</td><td>1430</td><td>16600</td></tr>
<tr><td>1</td><td>F</td><td>5</td><td>259</td><td>2020</td></tr>
<tr><td></td><td></td><td>10</td><td>484</td><td>4700</td></tr>
<tr><td></td><td></td><td>30/20</td><td>1240</td><td>17700</td></tr>
<tr><td>90</td><td>M</td><td>5</td><td>235</td><td>3030</td></tr>
<tr><td></td><td></td><td>10</td><td>530</td><td>6830</td></tr>
<tr><td></td><td></td><td>30/20</td><td>1320</td><td>15800</td></tr>
<tr><td>90</td><td>F</td><td>5</td><td>364</td><td>3170</td></tr>
<tr><td></td><td></td><td>10</td><td>417</td><td>3920</td></tr>
<tr><td></td><td></td><td>30/20</td><td>1920</td><td>20500</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Accumulation: Slight accumulation of niraparib (< 3-fold).

Gender difference: Females had slightly higher AUCs for niraparib than males.

Dose proportionality: C_{max} and AUC of niraparib were greater than dose proportional with each dose escalation in males. In females, C_{max} and AUC of niraparib were slightly less than dose proportional from 5 to 30 mg/kg.</td></tr>
<tr><td>Dog: 90-Day repeat-dose toxicity study (oral gavage administration once daily (Study Number 12-3110)
Dose levels: 0, 1.5, 4.5, or 12 mg/kg at dose volume 5 mL/kg (final concentrations at 0, 0.3, 0.9, or 2.4 mg/mL)
Sample analysis: on Days 1 and 90 at 0.5, 1, 2, 4, 6, 8, and 24 hours post dose and at 1 hours post dose for control group.</td><td><u>Dog</u>
T_{max}: 2-4 hours in males; 1-2 hours in females

<table>
<tr><th>Day</th><th>Sex</th><th>Dose level (mg/kg)</th><th>C_{max} (ng/mL)</th><th>AUC_{all} (ng•h/mL)</th></tr>
<tr><td>1</td><td>M</td><td>1.5</td><td>31.5</td><td>234</td></tr>
<tr><td></td><td></td><td>4.5</td><td>101</td><td>721</td></tr>
<tr><td></td><td></td><td>12</td><td>378</td><td>2690</td></tr>
<tr><td>1</td><td>F</td><td>1.5</td><td>38.3</td><td>274</td></tr>
<tr><td></td><td></td><td>4.5</td><td>137</td><td>918</td></tr>
<tr><td></td><td></td><td>12</td><td>361</td><td>2580</td></tr>
<tr><td>90</td><td>M</td><td>1.5</td><td>33.3</td><td>261</td></tr>
<tr><td></td><td></td><td>4.5</td><td>111</td><td>855</td></tr>
<tr><td></td><td></td><td>12</td><td>276</td><td>2410</td></tr>
<tr><td>90</td><td>F</td><td>1.5</td><td>34.3</td><td>285</td></tr>
<tr><td></td><td></td><td>4.5</td><td>94.2</td><td>857</td></tr>
<tr><td></td><td></td><td>12</td><td>246</td><td>2180</td></tr>
</table>

Accumulation: None.

Gender difference: None.

Dose proportionality: Generally, dose proportional increases in C_{max} and AUC.</td></tr>
</table>

9.5. Toxicology

9.5.1. General Toxicology

Study title/ number: A 90-Day oral (gavage) toxicity study in rats with a 28-day recovery period/ 12-2328

Key Study Findings

- 30/20 mg/kg (6/4 mg/mL) niraparib resulted in early deaths due to bone marrow toxicity. Clinical signs included thin appearance, red stain on muzzle, irregular breathing/rales/dry breathing, pallor (whole body), hunched posture, and decreased activity.
- Toxicologically significant hematology findings included decreased red blood cell mass (hemoglobin, % hematocrit), red blood cell counts, reticulocyte levels, white blood cells, lymphocytes, monocytes, and neutrophils but increased platelet count.
- Target organs of toxicity included bone marrow, male reproductive organs (testis, epididymis), kidneys, harderian glands, liver, lymphoid organs (spleen, lymph node, and thymus), adrenal gland, skin and subcutis, and heart.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 5, 10, or 30/20* mg/kg once daily *Note: the dose was reduced to 20 mg/kg from Days 34 to 90
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose in deionized water
Species/Strain:	Sprague Dawley rats

Number/Sex/Group:	10/sex/group (main), 5/sex/group (vehicle and high dose recovery groups); and 3-6 F/group (toxicokinetic)
Age:	9 weeks old
Satellite groups/ unique design:	none/no unique design
Deviation from study protocol affecting interpretation of results:	No

Table 9-6 Observations and Results in Rat Toxicity Study (Changes from Control)

Parameters	**Major findings**
Mortality	HD 1 female (TK group), found dead (Day 77) 1 female, moribund (Day 85) Cause of mortality: Marked bone marrow toxicity
Clinical Signs	<u>Found dead (HD)</u> Thin appearance, red stain on muzzle, irregular breathing/rales/dry breathing, and decreased activity <u>Early Sacrifices (HD)</u> Pallor (whole body), hunched posture, thin appearance, and decreased activity <u>Scheduled sacrifices (HD)</u> Salivation, pallor, thin appearance and breathing irregular from Week 4-Week 8
Body Weights	HD: ↓10% and 11% compared to control in males and females on Week 5 and Week 12, respectively. Body weight recovered after a 28-day recovery period.
Feed Consumption	In males, significant decreases in food consumption were noted at HD (30 mg/kg) during Weeks 2 to 4 (12-16%). After the HD was

	lowered to 20 mg/kg, food consumption in these males was comparable to concurrent controls. In females, significant decreases in food consumption were noted during Weeks 1 to 6 (11-16%). Food consumption was comparable to control during the recovery period.
Ophthalmoscopy	Unremarkable, performed pretest and prior to terminal and recovery necropsy
Hematology	MD: ↓11% red blood cells but↑24% platelet count in males HD: ↓11% reticulocytes and ↓24-53% in hemoglobin, % hematocrit, red blood cells, white blood cells, absolute lymphocytes, and absolute monocytes in both males and females. ↓35% neutrophils in males. ↑2X-fold compared to control in platelet, and ↑30-34% MCV and MCH in both males and females. Due to marked lower red cell mass and reticulocytes counts compared to control group in Month 1, male rats at 30 mg/kg were not dosed from Days 29 to 33. The dose was reduced to 20 mg/kg from Days 34 to 90. All findings recovered after a 28-day recovery period.
Coagulation	↑ mean prothrombin time and activated partial thromboplastic time by >15% in females at HD. Changes were recovered after a 28-day recovery period.
Clinical Chemistry	○ Increases in creatinine (100%) and phosphorus (15%) levels at MD and HD in males ○ Decreases blood urea nitrogen at all dose levels in males (14-21%), and at MD and HD in females (100%) ○ Dose-dependent decreases in triglycerides in males at MD and HD l (18-46%). ○ At high dose level, ↓globulin levels (17-20%) and ↑albumin:globulin ratio (11-12%) in both males and females. ↑11% potassium levels in females

	○ All findings recovered after a 28-day recovery period.
Urinalysis	At HD in both sexes, ↑60-80% urine volume, which was still observed (35% to 3X-fold over control) at the end of recovery period.
Gross Pathology	*Main* Early sacrifices (1F, HD) Pale color in femoral bone marrow; Pale color in lungs and bronchi Scheduled sacrifices Small adrenal (1F, HD) Dilated pelvis in kidneys (1M, MD); Small testes (1M, HD); Small thymus(1M, HD) Pale color in ovaries (1F, HD) Recovery Small testes in male rat (2M, HD)
Organ Weights	○ Dose-dependent increases in adrenal weight (10-26%) and kidney weight (10-18%) in males rats at MD and HD. ○ Decreases in thymus weight were observed in females at LD, MD, and HD (9-16%). ○ At end of recovery, findings in organ weights at HD included epididymis (-20%), kidney (21%), spleen (28%), testes (-25%), and thymus (47%) in males and pituitary (-10%), spleen (23%), uterus, and cervix (21%) in females.
Histopathology **Adequate battery:** Yes	*Main* Early sacrifices (1F at HD) Bone marrow: marked femoral depletion

	Liver: slight hepatocellular/reticuloendothelial pigment cells slight bilateral vacuolation in adrenal minimal single cell necrosis <u>Scheduled sacrifices (10/sex in control, LD, MD, HD)</u> Bone marrow: minimal to marked femoral depletion (1M at MD, 8 M at HD ; 2F at HD) minimal to moderate sternal depletion (5M and 2F at HD) Testes: minimal to marked germ cells depletion (9M at HD) mild testis dilation (1M at HD) Epididymides: minimal to moderate reduced sperm (6M at HD) mild intraluminal cell debris (1M at HD) mild tubular degeneration/atrophy (1M at MD) Kidneys: mild tubular dilation (1F at HD) minimal hyaline cast (1F at HD) minimal tubular basophilia (1M at HD) moderate chronic nephropathy (1M at HD) Harderian glands: mild abscess (1M at HD) mild inflammatory cell infiltration (1M at HD) Liver: minimal hepatocellular/reticuloendothelial pigment (1F at HD) mild hepatocellular vacuolation (1M at HD) minimal extramedullary hemopoiesis (2M and 1F at HD) Spleen: minimal lymphoid tissue depletion (5M and 1F at HD)

	minimal red pulp depletion (3M at HD) mild increased extramedullary hemopoiesis (1M at HD) Adrenal: minimal necrosis (1F at HD) Lymph node (axillary): minimal sinuses erythrocytosis/ Erythrophagocytosis (1F at HD) Skin and subcutis: minimal hypotrichosis (1F at HD) Thymus: minimal increased involution/atrophy (1M at HD) Heart: minimal chronic cardiomyopathy (1M at HD) <u>Recovery (5/sex recovery animal at control and HD)</u> Epididymides: mild to moderate reduced sperm (3M at HD) mild intraluminal cell debris (2M at HD) Testis: minimal to moderate spermatids depletion (5M at HD) Bone marrow: minimal to mild femoral depletion (2M at HD) minimal sternal depletion (2M at HD) Spleen: minimal red pulp depletion (1M at HD) Note : minimal to mild chronic cardiomyopathy was also observed in both animals administered vehicle (1M, 1F) and niraparib at HD (1 M, 1F)
Bone marrow smear test	<u>Early sacrifices</u> Observed few hematopoietic cells present in the bone marrow smear Included lymphocytes, with few mast cells, eosinophils, segmented neutrophils, lymphoblasts, and megakaryocytes, correlating with severe ablation of hematopoietic progenitors <u>Scheduled sacrifices</u> Moderate increase in myeloid to erythroid (M:E) ratio in males at HD (2.4X-fold above control) and females at HD (2.8X-fold above control).

	Recovery Findings were trending toward recovery
TK	Refer to Section 9.4 ADME/PK Sample analysis: on Days 1 and 90 at 1, 2, 4, 6, 8, and 24 hours post dose and at 2 hours post dose for control group.

LD: low dose; MD: mid dose; HD: high dose

-: indicates reduction in parameters compared to control

Study title/ number: Niraparib (MK-4827): A 90 day oral (gavage) toxicity study in dogs with a 28-day recovery period/ 12-3110

Key Study Findings

- Toxicologically significant hematology findings included decreased reticulocytes and eosinophils but increased monocytes.
- Target organs of toxicity included male reproductive organs (testis, epididymis), bone marrow, lungs, lymphoid organs (lymph node, thymus), heart, liver, and submandibular salivary gland.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 1.5, 4.5, or 12 mg/kg once daily*

*Note: The dose levels were selected based on results from a one-month repeat-dose study in dogs (Study no. 07-6050); 15 mg/kg caused significant changes in hematology parameters and male reproductive system. A high dose level of 12 mg/kg was

	anticipated to cause target organ toxicity..
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose in deionized water
Species/Strain:	Beagle dogs
Number/Sex/Group:	4/sex/group (main); 2/sex/group (vehicle and high dose recovery group); 4-6/sex/group (toxicokinetic)
Age:	9 months old
Satellite groups/ unique design:	none/No unique study design
Deviation from study protocol affecting interpretation of results:	No

Table 9-7 Observations and Results in Dog Toxicity Study (Changes from Control)

Parameters	**Major findings**
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Feed consumption	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	○ Decreases in reticulocytes were observed in males (37%) at MD and HD ○ Increases (>50%) in absolute monocytes were observed in females at MD and HD ○ Decreases (≥29%) in absolute eosinophils were observed in females at LD to HD ○ Changes in absolute monocytes and eosinophils were still observed but trend toward reversibility following a 28-

	day recover period.
Coagulation	Unremarkable
Clinical Chemistry	○ Dose-dependent increases (10-30%) in phosphorus levels were observed in males at MD and HD. ○ Dose-dependent decreases (-11 to -28%) in triglycerides were observed in females at MD and HD. ○ Decreases in cholesterol levels were observed in females at LD to HD (8 to 17%) ○ Changes in phosphorus (5%), triglyceride (-34%), and cholesterol (-31%) levels were still observed in recovery animals
Urinalysis	Unremarkable
Gross Pathology	Scheduled sacrifices Adhesion and discolored lung (2M), cyst in pituitary (1F) were observed at 12 mg/kg Recovery Discolored in lungs were still observed at end of a 28-day recovery necropsy in females administered 12 mg/kg niraparib.
Organ Weights	Scheduled sacrifices Treatment-related organ weight changes (relative to body weight) that were statistically significant and dose-dependent were limited to thyroid and spleen. Decreases in thyroid and spleen ranged from 14-29% and 25-28% in males from LD to HD, respectively. Recovery Males exhibited an 11% decrease in thyroid weight at the high dose of 12 mg/kg.
Histopathology **Adequate battery:** Yes	Scheduled sacrifices (4/sex at control, LD, MD, HD) Testes: marked hypospermatogenesis (1M at HD)

	mild increased multinucleate cell degeneration (2M at LD) minimal segmental hypoplasia (1M at MD) Epididymides: moderate to marked reduced sperm (3M at HD) Sternal marrow: mild hypocellular (2M and 1F at HD) Lungs: mild mixed leukocyte infiltration (2M at HD) mild Type 2 pneumocyte hyperplasia (1M at HD) minimal pleural fibrosis (1M at LD and 1M at HD) minimal mesothelial hyperplasia (1M at HD) minimal artery intimal proliferation (1M at MD) Axillary lymph nodes: mild sinus erythrocytosis (2M at LD; 1M at MD; and 1M at HD)) Heart: minimal hemorrhage (1M at HD) Liver: minimal to mild hemorrhage (3M at HD) minimal biliary hyperplasia (1M at LD) Submandibular salivary gland: minimal mineral (1F at HD) Thymus: minimal lymphocyte hypocellularity (1M at HD) Urinary bladder: minimal mineral (1M at HD) <u>Recovery (2/sex at control and HD)</u> Lungs: minimal pleural fibrosis (1F at HD) moderate lung dilation (1F at HD) moderate lung inflammation (1F at HD)
Bone Marrow Smear Test	Niraparib-related bone marrow smear findings were limited to minimal increases in myeloid to erythroid ratio in both sexes at HD with minimal decreases in erythroid precursors in few animals. These changes reflected suppression of erythropoiesis

	by niraparib. Changes were trending toward recovery at the end of a 28-day recovery period.
TK	Refer to Section 9.4 ADME/PK Sample analysis: on Days 1 and 90 at 0.5, 1, 2, 4, 6, 8, and 24 hours post dose and at 1 hour post dose for control group

LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters compared to control.

General toxicology; additional studies

Results of one-month general toxicity studies in rats and dogs are summarized below.

Study title/number: One-month oral toxicity study in rats with a two-week recovery period/07-9826

Methods: A one-month repeat-dose toxicity study (GLP) with a 2-week recovery period was conducted in both male and female Sprague Dawley rats. Rats received daily oral niraparib (Lot# 005R002, 99.6% purity) at doses of 5, 10, or 50 mg/kg (n = 15/sex/group [main] of these, 5/sex/group [recovery]).

Results: At the high dose level of 50 mg/kg in male rats, 5 out of 15 male rats (33%) were found dead on study Days 16, 17, 20, 22, and 31 for a total of 5 out of 30 rats (17%). Findings in clinical signs were mainly observed in animals administered 50 mg/kg niraparib and were similar to results from a 90-day repeat-dose toxicity study, except for findings of discharge from eye and/or nose and unformed feces. Animals that died on study experienced slight myocardial and liver degeneration, slight to marked multiple organ atrophy, depletion and necrosis in small intestine, lymphoid organs (thymus, spleen, and lymph nodes), salivary gland, testes, and bone marrow. Hematology parameter findings were primarily observed in animals administered 50 mg/kg niraparib and were similar to results observed in the 90-day repeat-dose toxicity studies. Changes in clinical chemistry parameters were minimal and lower in magnitude than observed in the 90-day repeat-dose toxicity study. Macroscopic and microscopic findings were similar between one-month and 90-day repeat-dose toxicity in rats. The results from the one-month repeat-dose toxicity study in rats show that niraparib targets the hematopoietic/lymphatic systems, heart, male reproductive systems, small intestine, liver, adrenal gland, hardenian glands, and skin. All findings in all targets organs, except harderian glands and skin, were still observed at the end of recovery necropsy with less severity.

Study title/number: One-month oral toxicity study in dogs with 15-day recovery period /07-6050

Methods: A one-month repeat-dose toxicity study (GLP) with 15-day recovery period was conducted in both male and female Beagle dogs. Dogs received daily oral niraparib (Lot# 005R002, 99.6% purity) at doses of 3, 6, or 15 mg/kg (n = 3/sex/group [main]; of these, 2/sex/group [recovery]).

Results: There were no unscheduled deaths; all animals survived to the end of the study. Hematology findings were primarily observed at doses ≥ 6 mg/kg in females and 15 mg/kg in males and were similar to results observed in the 90-day repeat-dose toxicity study. Macroscopic findings included cysts in ovary at ≥ 6 mg/kg in 2/6 females, and it was still observed in two females at end of recovery period. Microscopic findings in the dogs show that niraparib targets the male reproductive organ (testis). Minimal decreased in the amount of spermatogenic epithelium was observed in one male at 15 mg/kg. At end of recovery, immature prostate was presented in one male at 6 mg/kg. Slight decreased in the amount of spermatogenic epithelium was still observed in one males administered 6 mg/kg and 2 males administered 15 mg/kg. In addition, decreases in testis and prostate size were observed in one male at 15 mg/kg at the end of recovery necropsy.

9.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial reverse mutation assay with niraparib/ AE24LF.502ICH.BTL

Key Study Findings:

- Niraparib was negative with all tester strains in the presence and absence of S9 activation in the bacterial reverse mutation assay.

GLP compliance: Yes

Test system: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and Escherichia coli strain WP2 *uvr*A; +/-S9 up to 5000 µg/plate

Study is valid: *Yes*

In Vitro Assays in Mammalian Cells

Study title/ number: In vitro Mammalian chromosome aberration assay in Chinese hamster ovary (CHO) cells/AE24LF.331ICH.BTL

Key Study Findings:

- Niraparib was positive for the induction of structural chromosome aberrations and negative for the induction of numerical chromosome aberrations in CHO cells in both the non-activated and S9-activated test systems.

GLP compliance: Yes

Test system: Chinese hamster ovary (CHO) cells; up to 15 µg/mL (-S9) and up to 80 µg/mL (+S9)

Study is valid: Yes

Results:

Table 9-8 Summary of Chromosome aberration assay in non-activated and S9 activated cells

Treatment µg/mL	S9 Activation	Treatment Time	Mean Mitotic Index	Cells Scored		Aberrations Per Cell (Mean +/- SD)		Cells With Aberrations	
				Numerical	Structural			Numerical (%)	Structural (%)
DMSO	-S9	4	13.3	300	300	0.010	±0.100	0.7	1.0
Niraparib									
5	-S9	4	9.0	300	150	0.280	±0.696	0.7	21.3**§
10	-S9	4	7.9	300	150	0.353	±0.935	1.3	20.7**§
15	-S9	4	7.3	300	150	0.387	±0.749	1.3	26.7**§
DMSO	+S9	4	11.3	300	300	0.020	±0.140	1.0	2.0
Niraparib									
10	+S9	4	8.0	300	300	0.030	±0.171	2.0	3.0
30	+S9	4	7.9	300	150	0.180	±0.506	1.3	13.3**§
45	+S9	4	5.5	300	150	0.360	±0.658	2.0	28.0**§
CP, 5	+S9	4	5.1	300	150	0.540	±0.783	0.7	38.0**
DMSO	-S9	20	11.2	300	300	0.007	±0.082	0.3	0.7
Niraparib									
1	-S9	20	10.2	300	150	0.127	±0.389	1.3	11.3**§
2	-S9	20	9.9	300	150	0.320	±0.559	1.0	28.7**§
3	-S9	20	6.1	300	150	0.447	±0.782	0.7	30.7**§
MMC, 0.1	-S9	20	5.9	300	150	0.340	±0.674	1.0	26.0**

Treatment: Cells from all treatment conditions were harvested 20 hours after the initiation of the treatments.
Aberrations per Cell: Severely damaged cells were counted as 10 aberrations.
Percent Aberrant Cells: *, $p \leq 0.05$; **, $p \leq 0.01$; using Fisher's Exact test.
§ The Cochran-Armitage test was positive for a dose response.

(Copied from the Applicant's submission)

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Assay for micronucleus induction in rat bone marrow from a 1-month oral toxicity study/ TT#07-8803

Key Study Findings:

- Niraparib was clastogenic in females at ≥ 10 mg/kg and in males at 10 mg/kg.

GLP compliance: Yes

Test system: Rat bone marrow from 1 month oral repeat-dose toxicity study: 0, 5, 10, or 50 mg/kg females; 5 and 10 mg/kg males

Study is valid: Yes

Results:

Table 9-9 Summary results for micronucleus induction in rat bone marrow from a one-month oral toxicity study

Treatment Dose	Sacrifice Time (Hr)	Females				Males			
		Total PCE	Total MN-PCE	MN-PCE per 1000 PCE (±SE)[a]	% PCE (± SE)[a,b]	Total PCE	Total MN-PCE	MN-PCE per 1000 PCE (±SE)[a]	% PCE (±SE)[a,b]
0.5% Methylcel 5 mL/kg/day	24	20,000	31	1.6 ± 0.4	56.6± 2.6	20,000	44	2.2 ± 0.4	55.8 ± 2.3
MK-4827 5 mg/kg/day	24	10,000	23	2.3 ± 0.7	60.6± 2.3	10,000	25	2.5 ± 0.7	55.4 ± 4.9
MK-4827 10 mg/kg/day	24	10,000	55	5.5 ± 0.9*	62.2± 3.0	10,000	51	5.1 ± 1.4*	54.9 ± 1.6
MK-4827 50 mg/kg/day	24	10,000	352	35.2 ± 9.3**	58.8± 3.6	N/A[c]	N/A[c]	N/A[c]	N/A[c]
Mitomycin C 0.6 mg/kg	24	N/A	N/A	N/A	N/A	10,000	71	7.1 ± 1.6	57.4 ± 5.9
Mitomycin C 1.6 mg/kg	24	N/A	N/A	N/A	N/A	10,000	393	39.3 ± 7.1	59.1 ± 5.9

PCE = Polychromatic erythrocytes.
MN-PCE = Micronucleated PCE.
N/A = Not applicable.
Mitomycin C-treated animals are from an exploratory study and were dosed once and harvested approximately 24 hours later.
Vehicle and test-article treated animals are dosed daily for the duration of the study and sampled one day after the last treatment.
Data shown are from 5 animals per treated group per sex and 10 animals per vehicle control group per sex, except for Mitomycin-C dosed animals, where 5 males per dose group were scored.
0.5% (w/v) methylcellulose in deionized water is abbreviated as 0.5% Methylcel.
[a] Group mean ± standard error.
[b] PCE as a percent of 1000 total erythrocytes.
[c] Not scored due to marked suppression of bone marrow.
* Statistically significant p≤0.05 compared to the relevant control group using a pair-wise comparison with Dunnentt's adjustment for multiple comparisons (females only).
** Statistically significant p≤0.01 compared to the relevant control group using a pair-wise comparison with Dunnentt's adjustment for multiple comparisons (females only).

(Copied from Applicant's submission)

9.5.3. Carcinogenicity

No studies conducted to support the current indication

9.5.4. Reproductive and Developmental Toxicology

No studies conducted to support the current indication

9.5.5. Other Toxicology Studies

Phototoxicity:

Phototoxicity was evaluated because niraparib has an ultraviolet (UV) absorption peak at 312 nm with an extinction coefficient of 16314 L/mol/cm. This coefficient is above the no-concern threshold of 100 L $mol^{-1}cm^{-1}$.

Study Title/Number: Neutral red uptake phototoxicity assay of niraparib in BALB/c 3T3 mouse fibroblasts/20065701

The objective of this GLP-compliant study was to evaluate the phototoxic potential of niraparib (0.1 to 5.62 µg/mL) as measured by the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to niraparib and ultraviolet radiation (+UVR), as compared with the viability of fibroblasts exposed to niraparib in the absence of ultraviolet radiation (-UVR). Promethazine (0.1 to 178 µg/mL) was used as the positive control. Promethazine cytotoxicity and phototoxicity criteria were met, indicating that the assays were valid.

Result: Per OECD guideline, niraparib has phototoxic potential under the conditions tested.

Table 9-10 Summary results of phototoxicity in BALB/c 3T3 mouse fibroblasts

Definitive Assays							
Test Material	IC_{50} (µg/mL) –UVR	IC_{50} (µg/mL) +UVR	PIF	MPE	Phototoxic Potential	UVR Survival (%)	OD_{540}
Promethazine	87.454	1.104	79.303	0.509	Phototoxic	88	0.964
Niraparib (Assay 1)	-	0.800	>PIF 7.035	0.333	Phototoxic	93	0.922
Niraparib (Assay 2)	-	0.745	>PIF 7.551	0.415	Phototoxic	91	0.914

+UVR: Phototoxicity: with UVR exposure.
–UVR: Cytotoxicity: without UVR exposure.
–: IC_{50} not achieved.
PIF: Photoirritancy Factor The criterion for "phototoxic" is PIF > 5.
MPE: Mean Photo Effect. The criterion for "phototoxic" is MPE > 0.15.
UVR % Survival: OECD criterion is > 80%.
OD_{540}: OECD criterion is ≥ 0.400
PIF>1: The test article was phototoxic (+UVR) but not cytotoxic (-UVR) , and the exact PIF cannot be calculated, although it is clear that some level of phototoxic potential exists. In this case, a ">PIF" was calculated and the highest testable test article concentration (-UVR) was used for calculation.

(Copied from Applicant's submission)

Study Title/Number: Repeat dose phototoxicity study to determine the effects of oral administration of niraparib on eyes and skin in pigmented rats/ 20072663

The objective of this GLP-compliant study was to determine the potential phototoxic effects of niraparib when administered at 0, 10, 50, or 100 mg/kg (10 mL/kg; n =5) by oral administration once daily for 3 consecutive days on the eyes and skin of Long-Evans pigmented rats, followed by exposure to ultraviolet B, ultraviolet A, and visible light from a xenon lamp. Niraparib was compared with 8-methoxypsoralen (8-MOP) at 15 mg/kg (n =3) as the positive control. The control vehicle is 0.5% methocel A4C in R.O. deionized water.

Results: All rats survived until scheduled euthanasia. There was no evidence of cutaneous phototoxicity elicited by a single exposure to UVR approximately 2 hours after the third and final consecutive daily oral administration of niraparib at doses up to 100 mg/kg. Decreases in body weight were observed at doses of 50 mg/kg and 100 mg/kg (with and without UVR exposure) niraparib during dose Days 1-3. In addition, there were no test article-related ocular findings indicative of phototoxicity. Rats treated with positive control, 8-MOP, showed diffuse corneal edema in both eyes and erythema and edema on the cutaneous of skin, indicating phototoxicity in the eyes and skin.

9.6. Nonclinical Pharmacology/Toxicology Appendix

9.6.1. References

Murai, J, SN Huang, BB Das, A Renaud, Y Zhang, JH Doroshow, J Ji, S Takeda, and Y Pommier, 2012, Trapping of PARP1 and PARP2 by clinical PARP inhibitors, Cancer Res, 72(21): 5588-5599.

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/s/

WIMOLNUT N MANHENG
03/13/2017

TODD R PALMBY
03/13/2017

JOHN K LEIGHTON
03/13/2017

10 Clinical Pharmacology

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10.1. Executive Summary

The applicant seeks approval of niraparib for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum based therapy. The dosing regimen of niraparib is 300 mg administered once a day by mouth without regard to food. The primary evidence of efficacy supporting the proposed dosage regimen was based on progression-free survival (PFS) demonstrated in a randomized, double-blind, placebo-controlled trial (NOVA). In the NOVA trial, patients were first stratified by their germline BRCA mutation status and subsequently randomized to niraparib, a PARP inhibitor, at the proposed dosage regimen or placebo. A median PFS in the gBRCAmut Cohort of 21.0 and 5.5 months was observed for niraparib and placebo, respectively, with a hazard ratio of 0.26 (p-value <0.0001). A median PFS in the non-gBRCAmut Cohort of 9.3 and 3.9 was observed for niraparib and placebo, respectively, with a hazard ratio of 0.45 (p-value <0.0001). Although frequent dose interruptions (66%), and reductions (69%) occurred at the proposed dose, the toxicity of niraparib appears clinically manageable through laboratory monitoring and with the applicant's proposed dose modification scheme.

The clinical pharmacology review focused on evaluating the acceptability of the proposed dosage regimen, dose modification scheme, patient selection strategy, drug-drug interaction potential, and the dosing recommendation for patients with organ dysfunctions.

Recommendations

The Office of Clinical Pharmacology recommends the approval of the NDA 208447 from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The effectiveness of niraparib was demonstrated in the NOVA trial. A median PFS in the gBRCAmut Cohort of 21.0 and 5.5 months was observed for niraparib and placebo, respectively, with a hazard ratio of 0.26 (p-value <0.0001). A median PFS in the non-gBRCAmut Cohort of 9.3 and 3.9 was observed for niraparib and placebo, respectively, with a hazard ratio of 0.45 (p-value <0.0001). Refer to section 6.3.2 for further details.
General dosing instructions	The proposed dosage regimen of niraparib 300 mg administered by mouth once daily without regard to food is acceptable.

	Despite frequent dose interruptions, and reductions at the proposed dose, the safety profile of niraparib appears clinically manageable with the applicant's proposed dose modification scheme. For example, most myelosuppression events were mitigated with dose reduction or interruption without any evidence of decreased efficacy. However, exploratory analyses assessing the relationship between exposure and the observed increase in heart rate and blood pressure were inconclusive. Niraparib can be dosed without regard to food as the co-administration of a standard high fat, high calorie meal resulted in approximately 22% decrease and 7% increase in C_{max} and AUC_{last}, respectively. This change in exposure is considered not clinically significant.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Patients with gBRCA mutations experienced the highest net increase in PFS compared to placebo at 15.5 months compared to 5.4 months for those without gBRCA mutations. Additional exploratory analyses showed the benefit of niraparib over placebo in biomarker-defined subgroups based on BRCA and homologous recombination deficiency (HRD) status. Therefore, the proposed indication in the overall population irrespective of the BRCA mutation or HRD status appears appropriate. There are uncertainties regarding the starting dose for patients with moderate hepatic impairment. A PMR will be requested to determine the starting dose in this patient subpopulation.
Drug-drug interactions	The risk for a drug-drug interaction is considered low. Niraparib is metabolized by carboxylesterases and subsequently UDP-glucuronosyltransferases (UGT) into inactive metabolites. Niraparib exhibits weak induction activity for CYP1A2 at clinically irrelevant concentrations. The risk for transporter

	mediated drug-drug interactions with niraparib also appears low.
Labeling	Overall, the proposed label is acceptable after Applicant agreed to the FDA's revisions. Clinical pharmacology labeling recommendations are highlighted in section 10.1

Post-Marketing Requirements (PMR)

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☒ PMR	A safe starting dose in patients with moderate hepatic impairment	There were insufficient data to characterize the exposure and safety of niraparib in patients with moderate hepatic impairment.	The trial should be an open-label, non-randomized, phase 1 design of a single oral dose of 300 mg niraparib in sufficient number of patients with healthy liver and moderate hepatic impairment. The PK parameters along with safety data will be used to determine the appropriate starting dose for this patient subpopulation

10.2. Summary of Clinical Pharmacology Assessment

Niraparib is a small molecule (MW: 510.6 g/mol) inhibitor of the PARP-1, -2 at IC_{50} values of 0.82 ng/mL, and 0.67 ng/mL, respectively. All dedicated clinical pharmacology trials included in this application were conducted exclusively in oncology patients.

Niraparib exhibited a linear PK in terms of dose proportionality and time-invariant properties at dose levels ranging from 30 up to 400 mg administered once daily, with an average terminal half-life of approximately 36 hours. The mean accumulation ratio is 2.4 at the clinical dose following three weeks of repeated daily dosing. At the clinical dose, the geometric mean [% coefficient of variation (CV)] at steady state C_{max} and AUC_{tau} were 1.28 [41.2] µg/mL and 19.7 [40.6] µg*hr/mL, respectively.

10.2.1. Pharmacology and Clinical Pharmacokinetics

Absorption: Niraparib is extensively absorbed within three hours following oral administration at the proposed dose with an absolute bioavailability of approximately 73%. The median [range] time to maximal plasma concentration, T_{max} for niraparib was 3.5 hours [2.0-4.2] for patients treated at the indicated dose of 300 mg following 21 days of repeated daily administration. No clinically impactful food effect was observed. The PK of niraparib is unlikely to be altered in the presence of gastric acid reducing agents, since its aqueous free base solubility ranges from 0.7 to 1.1 mg/mL in media with pH ranging from 1.1 to 9.0.

Distribution: Niraparib exhibits concentration-independent binding to human plasma proteins with an average fraction unbound of 0.17 at concentrations ranging from 1 to 50 µM. *In vivo*, niraparib and its metabolites partition more into plasma compared to erythrocytes as indicated by a blood to plasma ratio of 0.6. The apparent volume of distribution (Vd/F) was estimated as 1074 L using population pharmacokinetic (popPK) analysis.

Metabolism: In humans, niraparib is primarily metabolized via amide hydrolysis by carboxylesterases forming the inactive metabolite M1, a carboxylic acid derivative of the parent drug. M1 is subsequently glucuronidated by UGTs to form M10, which has three isomers. It is unknown which isoform of carboxylesterase (e.g., CES1 primarily expressed in the liver vs CES2 expressed both in the intestine and liver) hydrolyzes niraparib. In serum, unchanged niraparib accounts for 2.4% of the exposure of the total circulating radioactive moieties.

Excretion: The average steady state terminal half-life was approximately 36 hours. After a single oral dose, the estimated mean [%CV] renal and apparent systemic clearance of unchanged niraparib was 1.41 [23.1] and 17.2 [26.1] L/hr, respectively. Overall, the amount of radioactive niraparib-derived materials excreted in urine and feces account for 40% and 32% of the administered dose, respectively, over a 144-hour collection period. There was approximately 19% and 11% of the administered dose recovered as unchanged niraparib in feces and urine, respectively.

10.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosage regimen of niraparib 300 mg administered by mouth once daily without regard to food is acceptable. Please refer to section 6.3.2 for details.

Organ dysfunctions

Based on popPK results, no starting dose adjustment is needed in patients with mild to moderate renal impairment or patients with mild hepatic impairment. PopPK analyses suggested that there are no difference in the exposure among 221 patients with mild (CrCL between 60 and 89 mL/min), 81 with moderate renal impairment (CrCL between 30 and 59 mL/min), and 210 patients with normal renal

function (CrCL 90 mL/min or greater). Similar results were noted between patients with normal hepatic function (N=351) and those with mild hepatic impairment (N=27). There were only two patients with moderate (total bilirubin > 1.5 and up to 3 x ULN and any AST) or severe (total bilirubin > 3 x ULN and any AST) hepatic impairment according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

As the exact isoform of carboxylesterase enzyme that hydrolyzes niraparib to an inactive metabolite is unknown, there is insufficient evidence to exclude niraparib selectivity for CES1, which is predominantly expressed in the liver. Alterations in the expression or/and function of CES1 have been observed in liver tissue samples of patients with hepatic dysfunction. The influence of genetic polymorphisms in CES on niraparib pharmacokinetics was not evaluated by the applicant. Thus, there is uncertainty regarding the disposition and consequently safety as well as the tolerability of niraparib in patients with hepatic dysfunction.

Effects of BRCA/HRD status

Niraparib met the primary endpoint of prolonging PFS versus placebo in all 3 defined primary patient populations. Specifically, patients experienced significant improvement in PFS compared to placebo: 15.5 months for gBRCA mutations and 5.4 months for non-gBRCA mutations. Additional exploratory analyses showed the benefit of niraparib over placebo in biomarker-defined subgroups based on BRCA mutations and HRD status. Therefore, the proposed indication in the overall population irrespective of the BRCA mutation or HRD status appears to be appropriate. Refer to section 6.3.1 and 6.3.2 for a discussion on the effects of genetic subtypes on treatment outcome.

Outstanding Issues

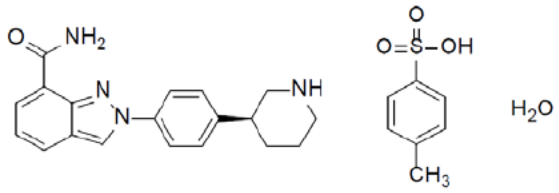
The application did not include sufficient information to adequately characterize the PK and safety of niraparib in patients with moderate hepatic impairment. A PMR will be issued to determine the appropriate starting dose in this subpopulation.

10.3. Comprehensive Clinical Pharmacology Review

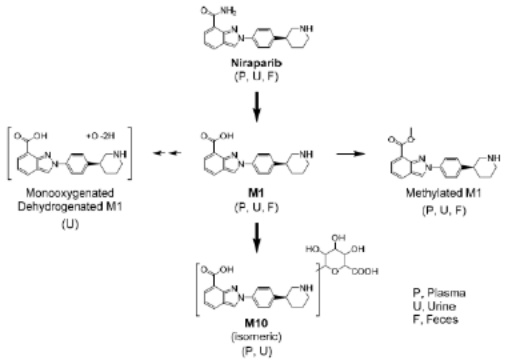
10.3.1. General Pharmacology and Pharmacokinetic Characteristics

A comprehensive summary of the clinical pharmacology and pharmacokinetics properties is outlined in table 10-1.

Table 10-1. Summary of clinical pharmacology and pharmacokinetics

Physicochemical properties	
Chemical structure and molecular weight	 Niraparib tosylate monohydrate, 510.61 g/mol
Aqueous solubility	The solubility of niraparib ranges from 0.7 to 1.1 mg/mL at 37 °C at pH below its pKa of 9.95. In simulated gastric fluid with and without enzymes, the solubility remains unchanged at 1.2 and 1.1 mg/mL, respectively. Consequently, the co-administration of gastric acid elevating agents is not expected to impact the disposition of niraparib, as its solubility is relatively constant within the expected physiological gastric pH range.
Pharmacology	
Mechanism of action	Niraparib exhibits anti-tumor activity via selective inhibition of PARP-1, -2 enzymes with IC_{50} values of 0.82 ng/mL and 0.67 ng/mL, respectively.
Active moieties	The parent compound is the only pharmacologically active moiety.
QT/QTc prolongation	*In vitro*, niraparib inhibited the delayed rectifier, rapid potassium current (I_{Kr}) ion channel in a hERG assay with an IC_{50} value of 2.16 µg/mL. No large changes in the mean QTc interval (>20 ms) were detected in patients following the treatment of niraparib 300 mg once daily.
Pharmacokinetic characteristics	
Bioanalytical assay	Validated bioanalytical assays were developed to measure the concentrations of niraparib and major metabolite M1 in the clinical studies included in the application. See appendix.
Steady state exposure at	Following 21 days at the proposed regimen, the geometric mean [%

<table>
<tr><td>the proposed regimen</td><td colspan="3">coefficient of variation (CV)] steady state C_{max}, C_{min}, and AUC_{tau} was 1.28 [41.2] µg/mL, 0.61 [43.1] µg/mL, and 19.7 [40.6] µg*hr/mL, respectively. The mean terminal half-life was 36 hours.</td></tr>
<tr><td>Range of effective dose or exposure</td><td colspan="3">The recommended dose is 300 mg by mouth once daily. Ensuing dose modifications (interruptions and/or reductions to 200 and 100 mg once daily) for management of adverse events (thrombocytopenia, anemia, neutropenia), all patients reached their respective stable maintenance dose after a few months of treatment with niraparib.</td></tr>
<tr><td>Dose proportionality</td><td colspan="3">Niraparib exhibited approximately dose proportional increase in AUC and C_{max} at doses ranging from 30 to 400 mg daily.</td></tr>
<tr><td>Accumulation</td><td colspan="3">An accumulation ratio of 2.4 was observed following repeated daily doses of niraparib over three weeks at the proposed dosing regimen.</td></tr>
<tr><td>Variability</td><td colspan="3">At steady state, the intersubject variability (CV%) in C_{max} and AUC_{tau} were approximately 41%.</td></tr>
<tr><td colspan="4">Absorption</td></tr>
<tr><td>Bioavailability</td><td colspan="3">The absolute bioavailability of niraparib is 72.7%.</td></tr>
<tr><td>Tmax</td><td colspan="3">The median (range) steady state T_{max} at the clinical dose 3.5 (2.0 – 4.2) hours.</td></tr>
<tr><td rowspan="2">Food effect</td><td>$AUC_{0-\infty}$ (GMR, 90%CI)</td><td>C_{max}(GMR, 90%CI)</td><td>T_{max} (hours)</td></tr>
<tr><td>110.1
(99.7%-121.6%)</td><td>78.5
(69.5%-88.6%)</td><td>Fed:
6.1 (1.2 – 23)
Fasted:
3.1 (1.7 – 6.1)</td></tr>
<tr><td colspan="3">No clinically relevant food effect was observed from co-administration of niraparib with a high fat, high calorie meal. Specifically, the single dose AUC_{last} increased by less than 7% while a 22.5% reduction was observed in C_{max} in the fed state compared to fasting. The median T_{max} increased from 3.1 hours to 6.1 hours reflecting a reduction in the rate of absorption of niraparib without impacting the extent as evidenced by the similar exposures observed for both fed and fasting states. The intersubject variability of niraparib PK parameters is not altered with co-administration of a high fat meal.</td></tr>
</table>

Distribution	
Volume of distribution	Niraparib has an apparent volume distribution of 1220 L as estimated using the data from the mass balance study. Based on the popPK analysis, the estimated total apparent volume of distribution was 1074 L. Approximately 83% of niraparib was bound to plasma proteins in a concentration independent manner. Systemically, niraparib is more partitioned into plasma compared to red blood cells (e.g., B/P ratio = 0.6)
Substrate of transporter systems	Niraparib is a substrate of P-gp and BCRP *in vitro*.
Elimination	
Terminal elimination half-life and clearance	The average (range) steady state terminal elimination half-life of niraparib at the proposed dose was 36 (33 – 51) hours. The single dose renal clearance of niraparib is 1.4 L/hr, which approaches the product of GFR and unbound fraction of niraparib, suggesting passive filtration as the main route of renal excretion. Comparatively, the apparent total systemic clearance was 8.4 L/hr after a single oral dose of 300 mg, which increases to 16.2 L/hr at steady state.
Metabolism	**Figure 10-1. Metabolic pathways of niraparib in humans**  Source: NDA208447, eCTD 2.7.2 Summary of Clinical Pharmacology Studies, Figure 6, Page 29 Niraparib is first hydrolyzed to an inactive carboxylic acid derivative, M1, which undergoes subsequent glucuronidation by UGT to form an isomeric acyl glucuronide moiety (M10 and three isomers) (Figure 10-1). As illustrated in figure 1, M1 can also undergo methylation. Although the methylated derivative of M1 was not observed in the applicant's preclinical data, it only accounted for 2.5% of the systemic niraparib radioactivity in

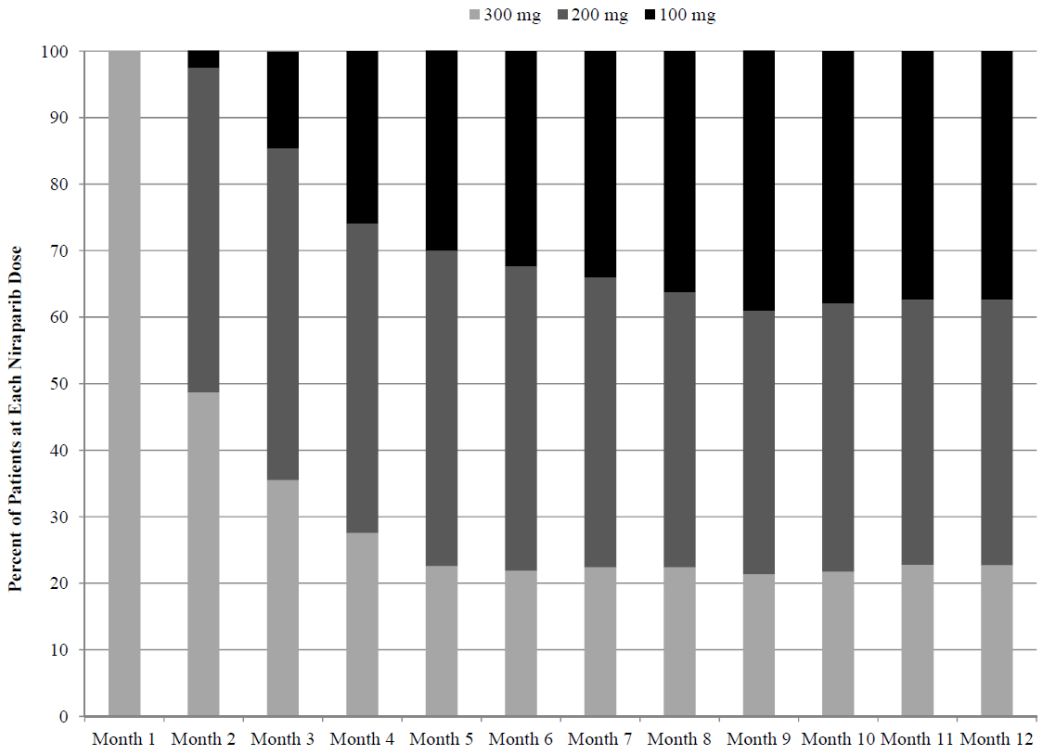
	plasma. M1 and its isomeric glucuronides respectively accounted for 9.3% and 56% of the systemic niraparib-derived radioactive exposure compared to 2.4% for unchanged niraparib. Although carboxylesterase is ubiquitous, there is no information on which isoform (e.g., CES1 primarily expressed in the liver vs CES2 expressed both in the intestine and liver) hydrolyzes niraparib. Of note, niraparib undergoes extensive biotransformation as indicated by the low parent to total radioactive moiety ratio of approximately 3%. In case niraparib exhibits substrate selectivity for CES1, genetic polymorphisms as well as hepatic dysfunction may alter its systemic exposure and negatively impact patient safety. Refer to section 6.3.2.
Excretion	Niraparib has a steady state terminal half-life of approximately 36 hours at the recommended dose and regimen. Overall, the amount radioactive niraparib excreted in urine and feces account for 40% and 32% of the administered dose, respectively, after a 144-hour collection. There was approximately 19% and 11% of the administered dose recovered as unchanged niraparib in feces and urine, respectively.
Drug interaction liability	The potential for clinically relevant drug-drug interactions with niraparib is considered low. No CYP450 enzyme inhibition or significant induction was observed with niraparib. *In vitro*, niraparib is a BCRP, and P-gp substrate. It also exhibits weak inhibitory activity for OCT1 and weak induction potential for CYP1A2, but inhibits BCRP at clinically relevant concentrations. The clinical relevance of these *in vitro* results is unknown.

10.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The effectiveness of niraparib is substantiated primarily by the efficacy results from study PR-30-5011-C, a phase 3, randomized, blinded, placebo-controlled trial (NOVA). However, there remain some uncertainties regarding the potential effectiveness of a lower starting dose based on the results. Notably, the majority (e.g., approximately 75%) of patients stabilized on reduced doses, e.g., 200, and 100 mg daily within 4 treatment cycles, without negatively impacting treatment outcome (Figure 10-2, and Figure 10-3).

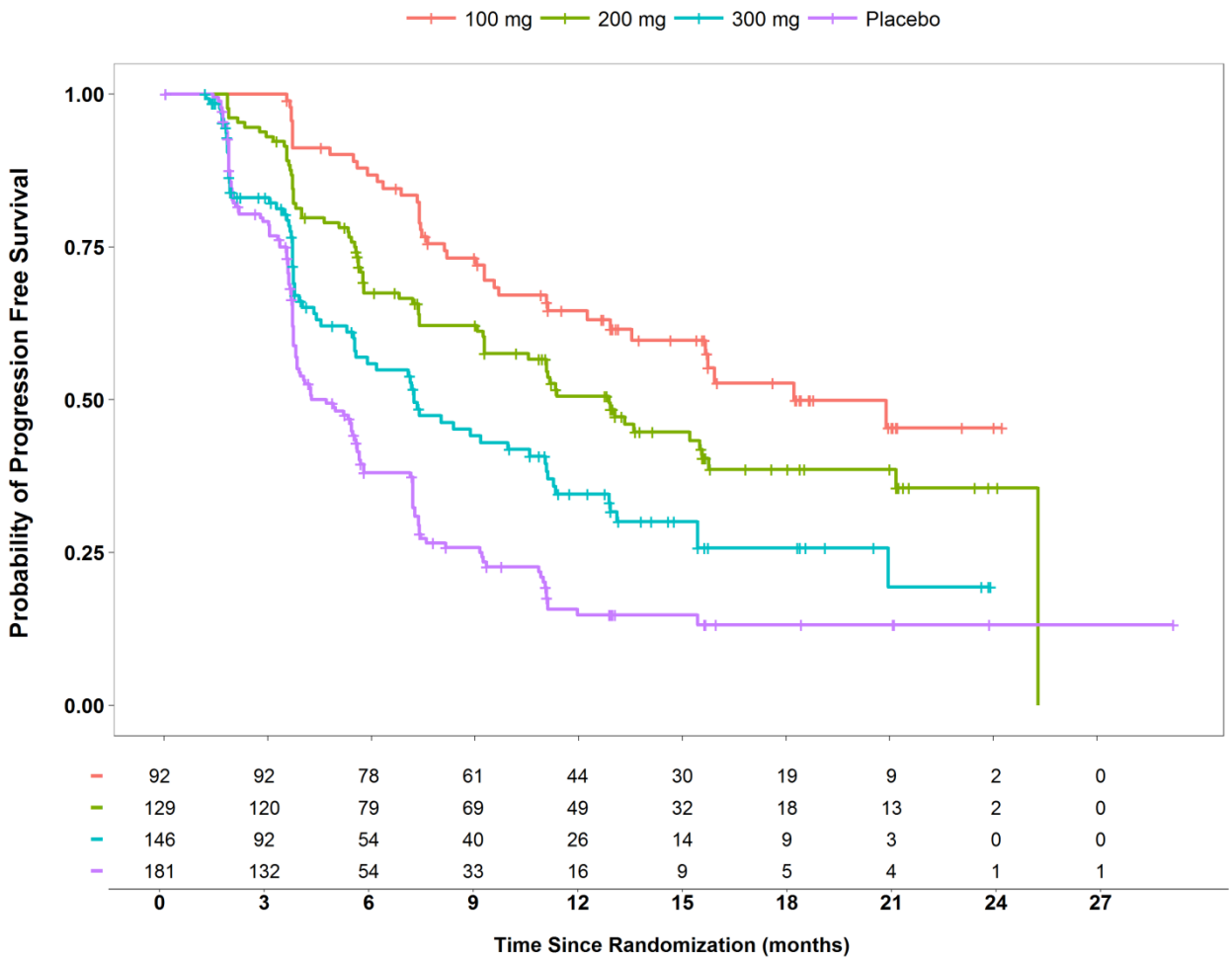
Figure 10-2. Niraparib dose level by treatment month



Source: NDA208447, eCTD 2.7.3 summary of clinical efficacy, figure 4, page 37.

Although the contribution of the starting 300 mg dose during the first few cycles to the treatment outcome cannot be ignored, dose reductions used to manage toxicity did not appear to adversely impact treatment efficacy (Figure 10-3). Of note, there are limited inferences or conclusions that can be reliably drawn from this exploratory analysis. Refer to the statistical review for further details on the safety and efficacy analyses.

Figure 10-3. KM estimates of PFS by maximum duration on dose for all treated patients



Source: modified from NOVA CSR figure 14.2.1.6

Furthermore, there is evidence of potential anti-tumor activity at lower doses (e.g., 80 mg to 200 mg daily) as illustrated by the ≥50% inhibition of PARP activity in circulating PBMCs of patients at steady state (e.g., by day 5 of cycle 1). Nonetheless, the proposed dose modification strategy was proven effective in managing the adverse events and triaging patients to their tolerable maintenance dose.

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

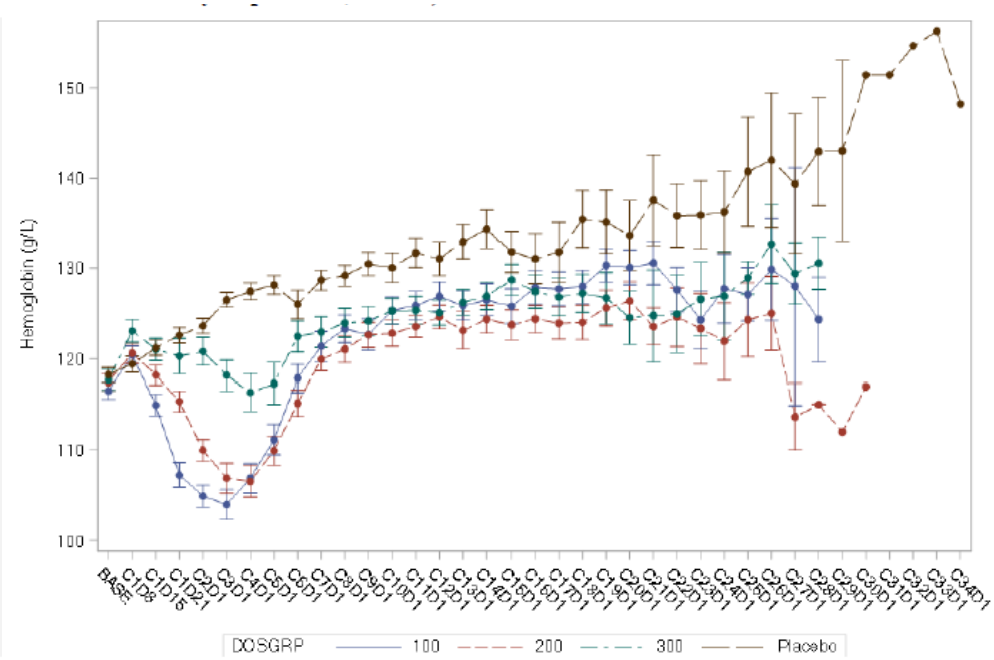
Yes. The proposed dosing regimen and dose modification strategy are appropriate for the intended population.

Niraparib met the primary endpoint of prolonging PFS versus placebo in all 3 defined primary patient populations. Specifically, patients with gBRCA mutations experienced the highest net increase in PFS

compared to placebo at 15.5 months compared to 5.4 months for those without gBRCA mutations. Additional exploratory analyses showed the benefit of niraparib over placebo in biomarker-defined subgroups based on BRCA and HRD status. Therefore, the proposed indication in the overall population irrespective of the BRCA mutation or HRD status appears to be appropriate.

The appropriateness of the proposed dose relies on the results of study PN001 in which the 300 mg once daily regimen was identified as the MTD. No alternative doses or regimens were explored in subsequent trials for niraparib as monotherapy. As illustrated in Figure 10-2, approximately 75% of patients did not remain on the proposed dosing regimen. However, the rate of dose modification was substantially reduced by the fifth treatment cycle as most patients remained on a stable dose (e.g., roughly 30% on 100 mg, 47% on 200 mg, and 23% on 300 mg). As shown in Table 10-2, dose modifications reduced grade 3 and 4 incidence of thrombocytopenia and neutropenia to lower than 3 percent after cycle 3. However, the incidence of grade 3 or higher anemia remained merely unchanged (18.5% for all cycles vs 16.9% after cycle 3) despite significant dose reductions and interruptions which occurred in the first few treatment cycles.

Figure 10-4. Mean (±SE) hemoglobin (g/L) by cycle (all patients on the final dose, safety population; n=546)



Source: Applicant's response to information request (Jan 23, 2017, sequence number: 0020), Page 19

SE = Standard Error

Table 10-2. Grade 3 or 4 adverse reactions are manageable with dose reductions

	Any Grade	Grade 3/4	Any Grade
Event, no (%)	Dose Reductions (N=367)	Events That Occurred After Cycle 3 (N=296)	Dose Discontinuations (N=367)
Thrombocytopenia[a]	148 (40.3)	7 (2.4)	12 (3.3)
Anemia[b]	68 (18.5)	50 (16.9)	5 (1.4)
Neutropenia[c]	32 (8.7)	8 (2.7)	7 (1.9)
Fatigue[d]	20 (5.4)	9 (3.0)	12 (3.3)
Hypertension	5 (1.4)	-	1

Source: Applicant's application orientation meeting slides

As shown in Figure 10-2, the number of patients on a final dose of 300 mg, 200 mg, and 100 mg niraparib was 96, 141, and 130, respectively. The hemoglobin nadir occurred between cycle 3 and 4 amongst these groups, and was lower in patients whose final dose ended up being 100 mg or 200 mg than for those who remained on 300 mg. The hemoglobin level recovered by cycles 6 and the peak recovery from anemia occurred slightly later (cycle 6 vs cycle 3 to 4) (Figure 10-4). This late effect of hemoglobin recovery explained why the anemia incidence remained high after cycle 3. This was because it takes about 90 days, the life of a RBC, for the initial drug effect to wash out and the full impact of the dose reduction to be observed. Therefore, dose modifications in addition to blood transfusions were able to mitigate the anemia related toxicities of niraparib in the trial.

Exposure-response for efficacy

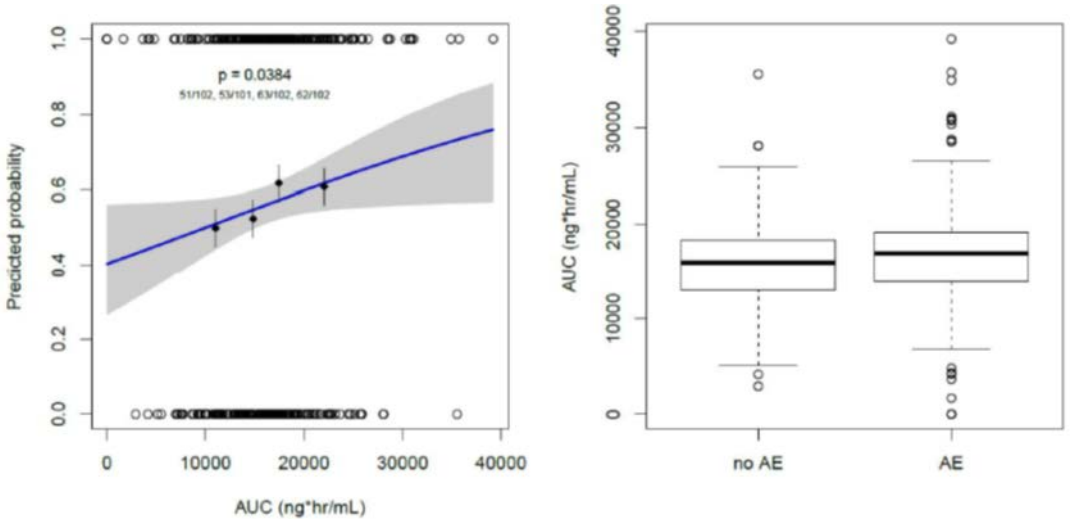
The applicant conducted exposure-survival analysis to quantify the relationship between PFS and niraparib AUC. Due to frequent dose interruptions and reductions, such analysis has a very limited value; therefore it was not used to support dose selections. The apparent negative exposure-efficacy correlation is artificial. First, most AEs leading to discontinuation occurred early. Second, the majority of patients in NOVA had dose reductions and therefore patients with longer PFS were more likely to have received one or two dose reductions/interruptions and have lower average daily exposures. Third, frequent dose interruptions in some patients may compromise the time-to-event analysis. For example, patient 034003-00002 and 048003-00009 have PFS values of 20.8 and11.3 months, but their corresponding average daily dose is unusually low: 8.2 and 33.2 mg, respectively.

Exposure-response for safety

Exposure-safety relationship between any grade and grade 3 or 4 thrombocytopenia and average daily exposure at the time of first event was assessed with a logistic regression analysis. There was a positive

relationship between niraparib AUC and any grade thrombocytopenia (Figure 10-5). The delayed effect on anemia precludes a meaningful ER analysis for this AE. Results from ER analysis for safety should be interpreted with caution as thrombocytopenia often occurred earlier than other AEs. The subsequent dose reduction caused by thrombocytopenia may confound the ER relationships for other safety events.

Figure 10-5. Predicted probability of any grade thrombocytopenia by AUC (Left Panel) and box plots of AUC by AE status (Right Panel)



Source: Applicant's response to information request (Jan 23, 2017, sequence number: 0020), page 3

Although the proposed dosing regimen appears initially high, its potential effects on the efficacy results cannot be ruled out. There were no reported treatment-related deaths in the trial. Given the demonstrated benefit and manageable safety profile, a PMR trial to investigate alternative dosing regimen is not warranted despite the high frequency of dose modifications over the first few treatment cycles.

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

No. Based on the applicant's popPK results, an alternative dosing regimen or management strategy is not required to adjust for the effects of intrinsic factors such as age, sex, ethnicity, genetics, body weight, and organ impairment (mild to moderate renal impairment, mild hepatic impairment). However, there are uncertainties regarding the starting dose for patients with moderate hepatic impairment. The metabolism of niraparib can potentially be altered by both genetic polymorphism in carboxylesterase and hepatic impairment. A PMR will be requested to determine the starting dose in this patient subpopulation. Refer to section 6.2.2 for further details.

Genetic Polymorphisms in CES and UGT

Niraparib is metabolized primarily by carboxylesterases (CES) to form a major inactive metabolite, M1 which is subsequently glucuronidated by UDP-glucuronosyltransferases (UGT) to form the inactive metabolite, M10 (see Section 6.3.1 for details on metabolism and metabolites). The influence of CES or UGT polymorphisms on niraparib pharmacokinetics was not evaluated by the applicant. Regarding UGT, the impact of UGT polymorphisms is likely to be limited, as it is involved in the conversion of the inactive metabolites M1 to M10. Whether CES polymorphisms impact the exposure of niraparib cannot be ruled out. Given the demonstrated benefit and manageable safety profile, a postmarketing study to evaluate the impact of genetic polymorphisms on niraparib is not necessary at this time.

BRCA mutations and HRD status

A total of 553 patients with (gBRCAmut Cohort) or without (non-gBRCAmut Cohort) deleterious or suspected deleterious germline BRCA 1/2 mutations were enrolled in NOVA based on local germline BRCA testing results initially and based on centrally performed BRACAnalysis test (Myriad) subsequently (Protocol Amendment 3). Treatments were randomly assigned 2:1 within the gBRCAmut and non-gBRCAmut Cohorts. In addition, DNA was isolated from formalin fixed, paraffin embedded (FFPE) tumor tissue of patients in the non-gBRCA Cohort to test for homologous recombination deficiency (HRD) using the myChoiceHRD test (Myriad). The test is a next-generation sequencing (NGS)-based assay designed to assess genomic instability, including loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions, and in parallel, to detect and classify large rearrangements and sequencing variants in the BRCA1 and BRCA2 genes (in a similar manner to BRACAnalysis). HRD-positive tumors were further categorized as HRD-positive with somatic BRCA mutations or HRD-positive without somatic BRCA mutations (HRD-positive/BRCA wildtype). Although only tumor tissue of patients enrolled in the non-gBRCA Cohort was analyzed for HRD, any tumor that has a HRD score ≥42 or has a deleterious or suspected deleterious BRCA1/2 mutation (germline or somatic) would have been considered HRD-positive via this test. PFS was independently evaluated in the gBRCAmut and non-gBRCAmut Cohorts. Within the non-gBRCAmut Cohort, PFS was evaluated in a hierarchical manner: first in a group of patients with HRD-positive tumors, and if the results were statistically significant, then in the overall non-gBRCAmut Cohort (that includes the HRD-positive group).

Maintenance treatment with niraparib showed increased PFS compared to placebo in all 3 prospectively defined primary patient populations (Table 10-3).

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Table 10-3. Progression-free survival based on IRC assessment in the 3 primary efficacy populations

	gBRCAmut Cohort N=203		**Overall non-gBRCAmut Cohort (HRD-positive, -negative, or unknown) N=350**		**Non-gBRCAmut Cohort (HRD-positive subgroup) N=162**	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)	Niraparib (N=106)	Placebo (N=56)
Median PFS (95% CI)	21.0 (12.9, NE)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
Hazard Ratio (HR) (95% CI)[a]	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	
p-value[b]	<0.0001		<0.0001		<0.0001	

Note: Source - NOVA Clinical Study Report; NE=not estimated; [a] Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors; [b] Based on stratified log-rank test using randomization stratification factors.

Results of exploratory analysis of PFS conducted by the applicant were consistent with the PFS results observed in the primary efficacy populations and included the following:

- Pooled analysis (ITT): Median PFS (95% CI) in the niraparib arm (N=372) was 11.3 months (9.6, 13.5) versus 4.7 months (3.8, 5.6) in the placebo arm (N=181) with HR (95% CI) 0.38 (0.303, 0.488).
- For patients assigned to the gBRCAmut Cohort: HR (95% CI) 0.39 (0.226, 0.660) for BRCA1 (N=84 in niraparib and 43 in placebo) and HR (95% CI) 0.12 (0.046, 0.332) for BRCA2 (N=50 in niraparib and 18 in placebo) variants.
- Non-gBRCAmut Cohort and patients with BRCA mutations (germline or somatic): The non-gBRCAmut Cohort included patients with diverse tumor molecular characteristics. Results suggest that patients experience benefit from niraparib compared to placebo regardless of biomarker status. However, differences in the potential magnitude of benefit were noted among the biomarker-defined subgroups, the lowest incremental benefit being observed in the HRD-negative subgroup to the highest in germline or somatic BRCA mutation subgroup (Table 10-4).

Table 10-4. Progression-free survival based on IRC assessment in exploratory subgroups based on HRD and BRCA status

	Non-gBRCAmut Cohort						Non-gBRCAmut and gBRCAmut Cohorts	
	HRD-negative tumors N=134		HRD-positive tumors with somatic BRCA mutation N=47		HRD-positive tumors with BRCA wildtype N=115		BRCA mutations (germline or somatic) N=250	
	Niraparib (N=92)	Placebo (N=42)	Niraparib (N=35)	Placebo (N=12)	Niraparib (N=71)	Placebo (N=44)	Niraparib (N=173)	Placebo (N=77)
Median PFS (95% CI)	6.9 (5.6,9.6)	3.8 (3.7,5.6)	20.9 (9.7,NE)	11 (2,NE)	9.3 (5.8,15.4)	3.7 (3.3,5.6)	20.9 (13.1,NE)	5.7 (3.9,7.4)
Hazard Ratio (95% CI)	0.58 (0.361,0.922)[a]		0.27 (0.081,0.903)[b]		0.38 (0.231,0.628)[b]		0.26 (0.177,0.393)[a]	
p-value	0.0226[c]		0.0248[c]		0.0001[c]		0.0003[d]	

Note: Source - NOVA Clinical Study Report; NE=not estimated; [a] Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors; [b] Niraparib:Placebo, based on Cox Proportional Hazards Model; [c] Based on stratified log-rank test using randomization stratification factors; [d] Based on combining p-values from stratified log-rank test using randomization stratification factors with Fisher's combination test; Tumor HRD status was inconclusive/ missing/ canceled in 36 patients in niraparib and 18 in placebo arms and the median PFS was 8 months (95% CI: 3.8, NE) and 7.3 months (95% CI: 1.9, NE), respectively.

Niraparib met the primary endpoint in all 3 defined primary patient populations and in all exploratory subgroups, including those who are HRD-negative. Therefore, the proposed indication in the overall population (based on response to platinum-based chemotherapy) irrespective of the BRCA mutation or HRD status appears to be appropriate. The presence of deleterious or suspected deleterious BRCA mutations appear to represent the strongest molecular determinant of the magnitude of potential benefit of niraparib compared to placebo in the population tested. Although tumor HRD-positive status (without BRCA mutations) may also inform about the magnitude of the potential benefit, it appears to be less sensitive than BRCA mutations as a predictive biomarker. Differences in PFS benefit observed

across biomarker-defined subgroups suggest that a complementary diagnostic for BRCA and HRD status determination may be appropriate.

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

No. There is no evidence for potential clinically relevant drug-drug or drug-food interactions with niraparib.

Drug-drug interaction

Niraparib is a substrate of BCRP and P-gp. Neither the parent compound nor its primary metabolite is a substrate, inhibitor, or inducer of CYP450 enzymes at clinically relevant concentrations. *In vitro*, niraparib inhibits BCRP at an IC_{50} value of 1.21 µg/mL. With 83% of niraparib bound to plasma proteins, the unbound steady state concentration is below the IC_{50} value for BCRP, which suggests low risk of a DDI between niraparib and a sensitive BCRP substrate. Hence, a dedicated DDI study or dose adjustment is not required to further mitigate this issue.

Food-drug interaction

No clinically relevant changes in niraparib exposure were observed with co-administration of a high fat meal (Table 10-5). Intrasubject variability also remained unaltered in the presence of food.

Table 10-5. Statistical evaluation of niraparib exposure parameters

Parameter	LS Mean Test (Fed)	LS Mean Reference (Fasted)	LS Mean Ratio (Fed/Fasted)	90% Confidence Intervals
C_{max} (ng/mL)	531.3	677.1	78.5	69.5% - 88.6%
$AUC_{0\text{-last}}$ (ng*hr/mL)	24018.1	22488.6	106.8	97.8% - 116.6%
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	26231.3	23822.2	110.1	99.7% - 121.6%

Source: PR-30-5011-C CSR, page 10, Table 2.

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Clinical Pharmacology Appendices (Technical documents supporting OCP recommendations)

10.3.3. Summary of Bioanalytical Method Validation and Performance

The concentrations of niraparib and M1 (the intermediate moiety resulting from the amide hydrolysis of niraparib) in plasma and urine were assayed in several clinical trials. As outlined in Table 10-6, four methods were developed and validated for the analysis of niraparib in plasma; three methods for phase 1 studies (1 for trial PN001, and 2 for trial PR-30-5015-C) and two for later phase studies (1 for trial PR-30-5011-C and another for sub-study PR-30-5011-C-FE). The concentration of the primary metabolite was only quantified in the mass balance study PR-30-5015-C. The primary assay methodology used was high performance liquid chromatographic-tandem mass spectrometry. All the assays for niraparib in plasma and urine were validated and met in-study performance criteria requirements according to the bioanalytical guidance. The linear range of the calibration curves span from 1 to 500 ng/mL for the analysis of niraparib in plasma except for study PN001 which had a range of 1 to 1000 ng/mL. The range for the standard curves were appropriate based on the PK of niraparib at the clinical dose, which has an average steady state C_{max} [%CV] of 1.28 [41.2] µg/mL.

The results of the applicant's incurred sample analysis conform to guidance requirements for niraparib in plasma and urine. The primary metabolite failed the ISR criteria in plasma as only 63% of the samples were within the 20% difference of the original analysis results. Since this moiety is pharmacologically inactive, the regulatory implications of the aforementioned ISR results for M1 appear minimal.

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Table 10-6. Bioanalytical Methods Validated for the Clinical Development of Niraparib

Study No.	Description	Biological Matrix	Analytical Site	LC/MS/MS Method	Calibration Range (ng/mL)	Validation Report	Bioanalytical Report
Phase 1 Studies							
MK-4827 001 (PN001)	Dose escalation study with expansion cohorts	Human Plasma	Merck	DM-932	Niraparib: 1 to 1000	DM-932	PN001: BA report for MK-4827 clinical protocol 001
		Human Urine	Merck	DM-935	Niraparib: 50 to 25,000	DM-935	
PR-30-5015-C	Absolute BA and AME	Human Plasma	(b) (4)	AVSBA279	Niraparib: 1 to 500 M1: 1 to 500	Niraparib\VAL\174	FIN314
		Human Urine		AVSBA281	Niraparib: 1 to 100 M1: 1 to 100	Niraparib\VAL\175	FIN314
		Human Plasma		148-001.04	^{14}C-Niraparib: 0.115 to 10.3 (dpm/mL)	148/002V	148/001
Phase 3 Study							
PR-30-5011-C-FE	Food effect substudy of phase 3 study in patients with platinum sensitive, recurrent ovarian cancer	Human Plasma	(b) (4)	BAC-KB-L006	Niraparib: 1 to 500	KB-0019-RB-CV	KB-0027-RB-CS-RPT-01
PR-30-5011-C	Main study of phase 3 study in patients with platinum sensitive recurrent ovarian cancer	Human Plasma	(b) (4)	BAC-KB-L010	Niraparib: 1 to 500 M1: 1 to 500	KB-0044-RB-CV	KB-0027-RB-CS-RPT-01

Source: NDA208447; eCTD 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, page 15-16, Table 2

10.3.4. Clinical Pharmacokinetics Characteristics

Rationale for dose selection and appropriateness of proposed dosage regimen

The proposed dosage regimen for niraparib was selected based on the safety results of the first-in-human study, PN001, where daily doses ranging from 30 to 400 mg were assessed for tolerability. Niraparib was tolerated at up to the 400 mg daily dose level at which 2 out 6 patients experienced a DLT (neutropenia incidence of grade 3 or higher), thus the preceding dose level, 300 mg, was identified as the MTD according to the protocol design. As shown in Table 10-7, in the dose escalation phase, objective response was observed at all doses above 60 mg, which is further supported by the

pharmacodynamics results showing ≤50% inhibition of PARP activity at doses above 80 mg in circulating PMBCs (Figure 10-6). The evidence for this endpoint was based on preclinical data suggesting that greater than 50% inhibition of PARP activity in circulating PBMCs correlates with 90% inhibition of PARP activity within tumor tissues and anti-proliferative effects. Since the pharmacokinetic properties of niraparib is linear and dose proportional for doses ranging from 100 to 300 mg daily, the proposed starting dose of 300 mg daily in conjunction with the dose reduction strategy for toxicity management is supported by the safety and efficacy data. Based on the early phase data, patients with dose reductions down to 100 mg daily would still remain in a clinically active dosing range.

Table 10-7. Best overall response in part A of study PN001 (ITT Population)

TYPE OF RESPONSE[1]	30 mg (N=6)	40 mg (N=3)	60 mg (N=7)	80 mg (N=6)	110 mg (N=5)	150 mg (N=6)	210 mg (N=6)	290 mg (N=5)	300 mg (N=10)	400 mg (N=6)	Total (N=60)
CR - Rate n (%)											
PR - Rate n (%)			1 (14.3)	1 (16.7)	2 (40.0)	1 (16.7)	1 (16.7)	1 (20.0)	3 (30.0)	1 (16.7)	11 (18.3)
SD - Rate n (%)	2 (33.3)	3 (100.0)	2 (28.6)		1 (20.0)	1 (16.7)	4 (66.7)	1 (20.0)	1 (10.0)	4 (66.7)	19 (31.7)
PD - Rate n (%)	3 (50.0)		2 (28.6)	5 (83.3)	2 (40.0)	2 (33.3)	1 (16.7)	2 (40.0)	6 (60.0)		23 (38.3)
Unk - Rate n (%)	1 (16.7)		2 (28.6)			2 (33.3)		1 (20.0)		1 (16.7)	7 (11.7)
RECIST Objective Response (CR+PR) - N	6	3	7	6	5	6	6	5	10	6	60
Rate n (%)	0 (0.0)	0 (0.0)	1 (14.3)	1 (16.7)	2 (40.0)	1 (16.7)	1 (16.7)	1 (20.0)	3 (30.0)	1 (16.7)	11 (18.3)
95%CI (%)	(0.0,45.9)	(0.0,70.8)	(0.4,57.9)	(0.4,64.1)	(5.3,85.3)	(0.4,64.1)	(0.4,64.1)	(0.5,71.6)	(6.7,65.2)	(0.4,64.1)	(9.5,30.4)
RECIST Disease Control (CR+PR+SD) - N	6	3	7	6	5	6	6	5	10	6	60
Rate n (%)	2 (33.3)	3 (100)	3 (42.9)	1 (16.7)	3 (60.0)	2 (33.3)	5 (83.3)	2 (40.0)	4 (40.0)	5 (83.3)	30 (50.0)
95%CI (%)	(4.3,77.7)	(29.2,100)	(9.9,81.6)	(0.4,64.1)	(14.7,94.7)	(4.3,77.7)	(35.9,99.6)	(5.3,85.3)	(12.2,73.8)	(35.9,99.6)	(36.8,63.2)
Ovarian Response (RECIST [CR+PR] and/or CA125) - N		1	3	2	3	2	2	3	7	3	26
Rate n (%)		0 (0.0)	1 (33.3)	1 (50.0)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	3 (42.9)	1 (33.3)	9 (34.6)
95%CI (%)		(0.0,97.5)	(0.8,90.6)	(1.3,98.7)	(9.4,99.2)	(0.0,84.2)	(0.0,84.2)	(0.8,90.6)	(9.9,81.6)	(0.8,90.6)	(17.2,55.7)
Prostate Response (RECIST [CR+PR] and/or PSA) - N				1		1		1	1	1	5
Rate n (%)				0 (0.0)		0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
95%CI (%)				(0.0,97.5)		(0.0,97.5)		(0.0,97.5)	(0.0,97.5)	(0.0,97.5)	(0.0,52.2)

Source: Study PN001 CSR, section 12.2.1, page 621

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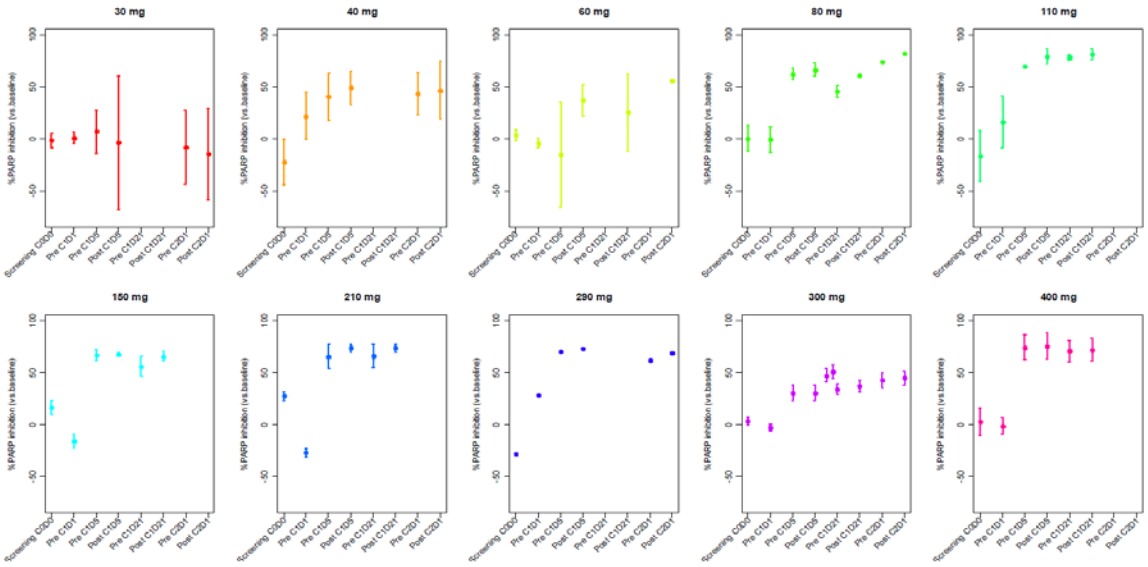
Figure 10-6. Percent PARP inhibition in PBMC across time for each dose level (mean ± SE)

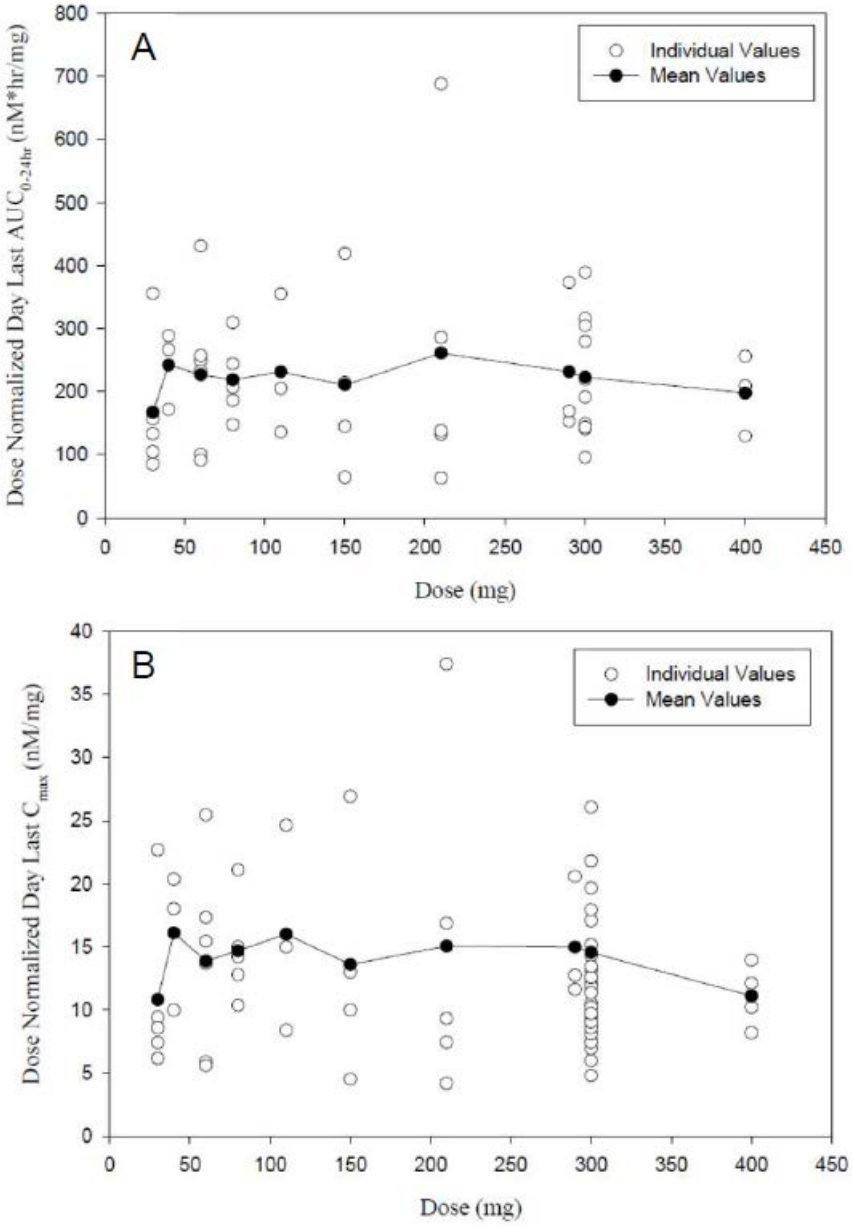


Source: Study PN001 CSR, Appendix 16.2.5.2, page 768

Dose linearity, proportionality, and stationary PK assessment

Niraparib exhibits approximate dose proportional pharmacokinetics properties for doses ranging from 30 to 400 mg administered daily. Using a power model, the slope estimate (90%CI) for single dose C_{max} and AUC were both approximately 1.1 (0.9, 1.2). Similar results were obtained for the steady state C_{max} and AUC, 0.8 (0.6, 1.1) (based on the applicant's analysis results from a Clinical Pharmacology Information Request (IR), also verified by reviewer). Although the 90% CI obtained for the single and multiple dose PK parameters did not fall within the pre-specified criteria, the PK of niraparib cannot be (statistically) declared more or less than dose proportional. Both 90% CI ranges contains unity, which does suggest dose proportionality; although more samples would be required per dose levels to explicitly substantiate this claim. Exploratory plots of dose normalized AUC at steady state, and double logarithmic plots of C_{max} or AUC vs Dose in Figure 10-7. Dose normalized AUC0-24h (A) and Cmax (B) on Day Last following multiple dose administration of niraparib to cancer patients (Figure 10-7, Figure 10-8, Figure 10-9) further illustrate the dose linearity and proportionality PK properties from 30 to 400 mg. In the trial, the applicant has proposed dose reductions from 300 to 100 mg to mitigate clinical adverse events. This proposed dose modification is justified as the exposure of niraparib decreases linearly with reduction in dose (Figure 10-8, Figure 10-9).

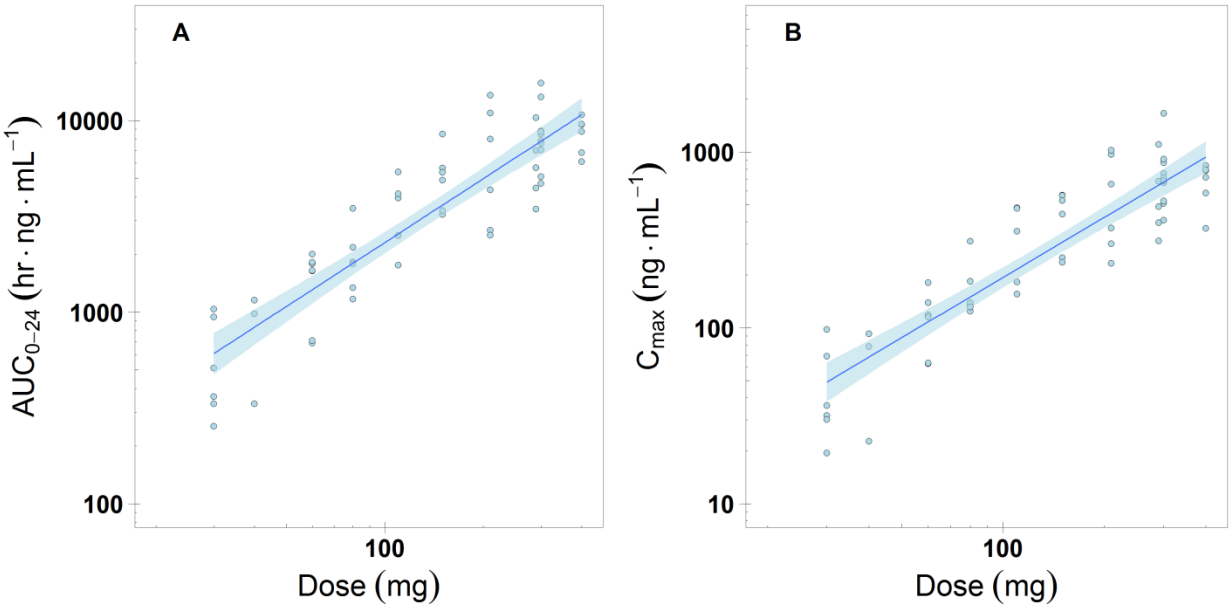
Figure 10-7. Dose normalized AUC0-24h (A) and Cmax (B) on Day Last following multiple dose administration of niraparib to cancer patients



Source: PN001 CSR MK-4827-001 Pharmacokinetic Analysis Figures 26 and 28.

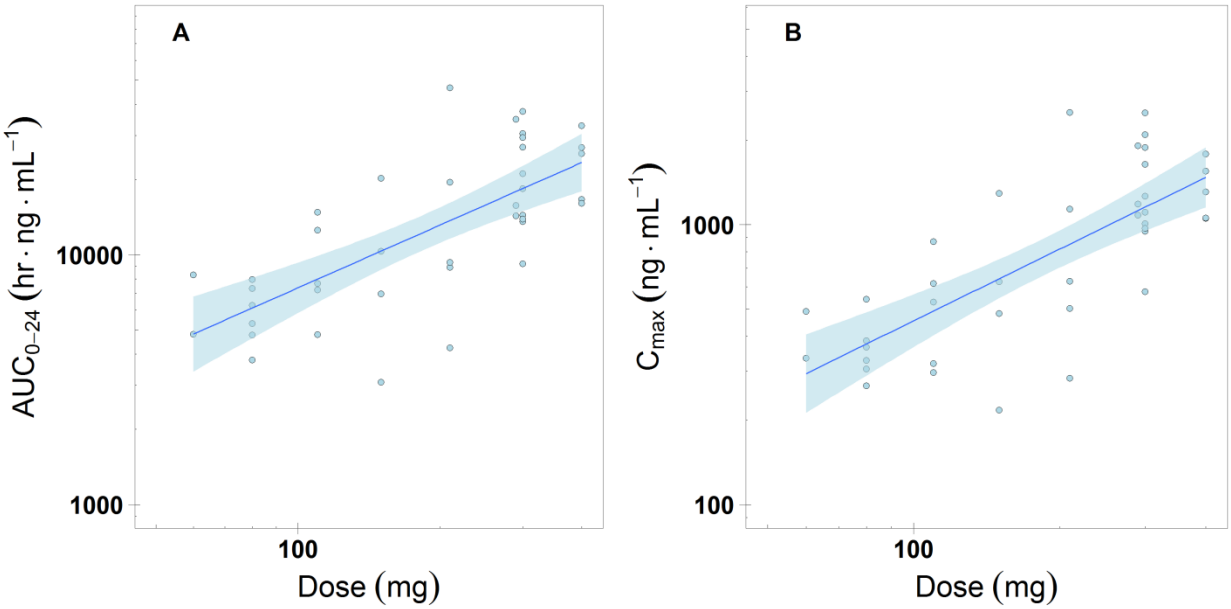
This figure was supplied by the sponsor to illustrate the dose linearity properties of niraparib at steady state across daily doses ranging from 30 to 400 mg.

Figure 10-8. Log-log plot of niraparib AUC0-24(A), Cmax (B) on day 1 from 30 to 400 mg



Light blue shaded areas reflect the confidence interval around the linear regression line overlaid onto individual exposures (light blue points) at the following dose levels (30, 40, 60, 80, 110,150, 210, 290, 300, and 400 mg)

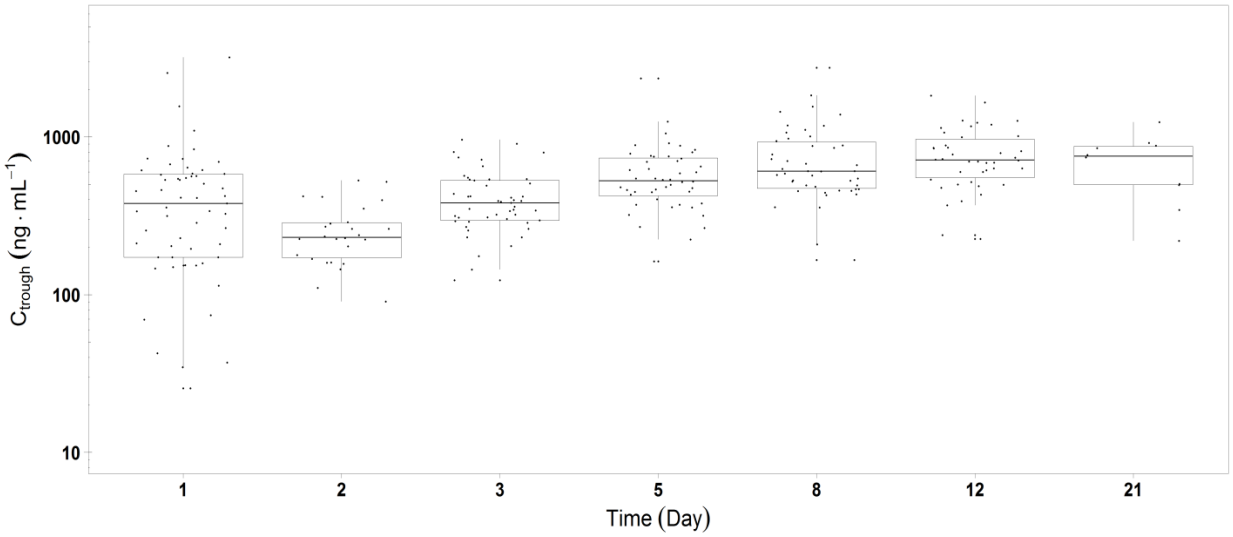
Figure 10-9. Log-log plot of AUC0-24(A), and Cmax (B) from 30 to 400 mg daily after 21 days of repeated daily dosing of niraparib



Light blue shaded areas reflect the confidence interval around the linear regression line overlaid onto individual exposures (light blue points) at the following dose levels (30, 40, 60, 80, 110,150, 210, 290, 300, and 400 mg)

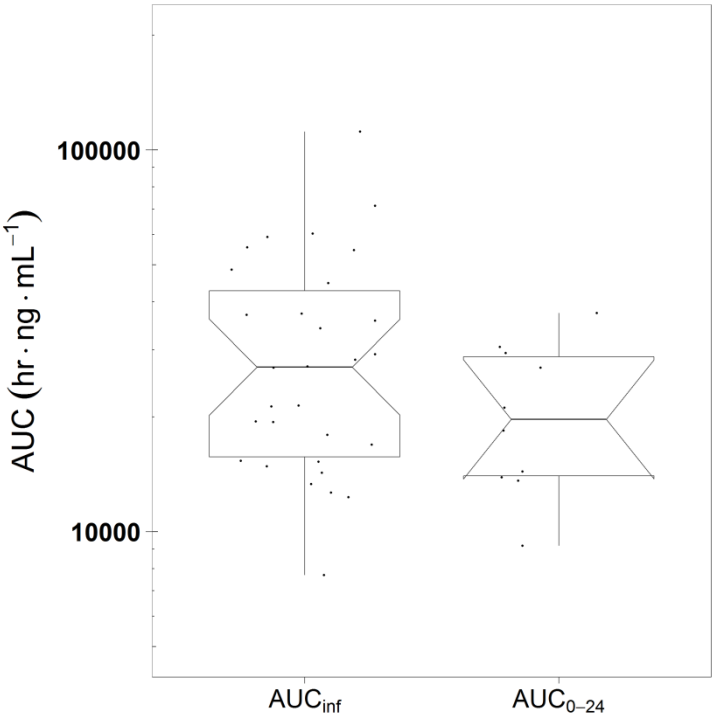
Niraparib exhibits stationary PK properties as illustrated in figures 5 and 6. The trough concentration at the proposed dosage regimen reaches and remains at steady state from day 5 to day 21 (Figure 10-10). The single dose AUC extrapolated to infinity, AUC_{inf} (n=30) compared to the steady state AUC measured over a single dosing interval, AUC_{0-24} (n=10) appear to be similar, albeit there is a trend toward a higher AUC_{inf} (Figure 10-11). Overall, niraparib appears to exhibit approximately dose proportional, linear, and stationary (time-independent) pharmacokinetic characteristics.

Figure 10-10. Semi-logarithmic plot of niraparib trough concentrations from over 21 days of 300 mg daily dosing



Boxplots illustrating the distribution of trough observations (jittered points) of all subjects treated at 300 mg from the dose escalation study PN001 on all available collection days.

Figure 10-11. Notch boxplot comparing the single dose AUCinf and steady state AUC0-24 after 21 days of repeated daily dosing of 300 mg niraparib



Boxplots illustrating estimated AUC extrapolated to infinity (using food effect data and study PN001), and steady state AUC at the 300 mg dose.

In vitro characterization of niraparib PK

Following a two-hour incubation in human liver microsomes and hepatocytes, minimal turnover was observed with niraparib. Subsequent cytochrome P450 phenotyping studies suggest that the oxidative metabolism of niraparib primarily occurred via CYP1A2 and CYP3A4/5 as well as a minor involvement of CYP2D6. However, *in vivo*, the metabolites formed did not fully support the *in vitro* results. Niraparib primarily undergoes amide hydrolysis by carboxylesterase and glucuronidation via UGTs.

Drug-drug interaction potential

Niraparib exhibited mild induction potential toward CYP1A2 (Table 10-8) at clinically irrelevant concentrations (20 µM to generate 50% of the positive control, omeprazole 50 µM). Niraparib did not exhibit inhibition or induction (besides CYP1A2) potential towards any of the cytochrome P450 enzyme isoforms.

Transporters

In vitro, niraparib and its carboxylic acid derivative, M1, are substrates of P-gp and BCRP. Niraparib is an inhibitor of BCRP with an IC_{50} value of 1.21 µg/mL. Niraparib and M1 are not substrates or inhibitors of OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, or BSEP. Niraparib and M1 are not significant inhibitors of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or BSEP at the tested concentrations.

Table 10-8. Effects of niraparib on CYP1A2 mRNA and enzyme activity in cryopreserved human hepatocytes

Treatment	[µM]	Subject											
		DMQ				DJV				527			
		RNA		Activity		RNA		Activity		RNA		Activity	
		Fold[a]	% PC[b]	Fold[a]	% PC[b]	Fold[a]	% PC[b]	Fold[a]	% PC[b]	Fold[a]	% PC[b]	Fold[a]	% PC[b]
Omeprazole	50	31.6	100	21.9	100	35.9	100	18.4	100	22.6	100	6.0	100
MK-4827	0.1	1.2	0.6	1.6	3.0	1.2	0.6	1.4	2.3	1.1	0.6	0.9	n.d.
	0.5	2.0	3.1	2.1	5.2	1.3	1.0	2.8	10.1	1.5	2.1	1.3	5.5
	1	2.0	3.3	2.4	6.7	1.8	2.2	1.5	3.0	2.2	5.6	1.1	2.3
	5	3.7	8.8	7.8	32.4	2.3	3.7	3.0	11.7	2.4	6.6	1.8	16.4
	10	3.3	7.6	7.5	30.8	2.5	4.4	2.9	10.9	2.4	6.5	1.7	13.8
	20	6.0	16.4	11.4	50.2	3.7	7.7	2.8	10.1	4.2	14.6	1.9	17.2

[a] Fold – represents the mean fold change of treated samples compared to vehicle control samples.
[b] % PC – represents the percent of induction relative to positive control omeprazole (50 µM) corrected for vehicle control.
n.d. – not determined; percentage was less than zero since response was less than vehicle control.

Source: Report PK002: Page 16, Table 3

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10.3.5. **Population PK analysis**

The applicant conducted a population PK analysis using data from 2 clinical studies: Phase 3 NOVA study (PR-30-5011-C) and Phase 1 dose escalation study (PN001) in patients with advanced solid tumors.

Objectives: the population PK analysis has the following objectives:

- Characterize the PK of niraparib in cancer patients
- Identify patient factors and laboratory parameters (for example, age, weight, hepatic and renal function) that may influence niraparib disposition.
- Investigate the PKPD relationship between concentration/exposure and efficacy and safety of niraparib.

Data: A total of 4150 niraparib concentrations from 512 adult subjects patients were included in the population PK/PD analyses. In the dataset, there were 408 subjects from the Phase 3 main study and associated substudies (QTc and FE) and 104 subjects from the Phase 1 study (PN001). Demographic characteristics for subjects included in the population PK analysis are summarized in Table 10-9.

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Table 10-9: Demographics of Subjects in the Population PK Dataset

Variable	N=512 Mean (range)
Baseline Demographic information	
Body weight (kg)	71.7 (43.4-135.1)
Age (yrs)	60 (33-83)
Creatinine clearance (mL/min)	87.3 (32.6-235.9)
Serum alanine aminotransferase, U/L	24 (6-111)
Serum aspartate aminotransferase, U/L	26 (9-109)
Alkaline phosphatase, U/L	96 (28-1334)
Bilirubin, umol/L	3.15 (0.36-30.24)
Albumin, g/L	33 (0.04-52)
Neutrophil count (/mm^3)	7.1 (0.6-33)
Hemoglobin, g/L	96 (9.3-152)
Platelets (10^9 L)	237 (85-648)
Lactate dehydrogenase (U/L)	274 (74-2339)
Categorical Covariates	
Study Phase	Phase 1 = 104 (20%) Phase 3 = 408 (80%)
Gender (M=0/F=1)	31 (6.05%)/481 (93.95%)
Race (White=0,Black=1,Asian=2, Native Hawaiian=3, if missing or unknown = 99)	0=459 (89.65%)/ 1=9 (1.76%) / 2=13 (2.54%) / 99=31 (6.05%)
CRCL category (Normal=0, if CRCL >=90 mL/min; Mild=1, if CRCL >=60 and < 90 mL/min; Moderate=2, if CRCL >=30 and < 60 mL/min)	Normal (0) = 210 (41.02%) Mild (1) = 221 (43.16%) Moderate (2) =81 (15.82%)
Age category (Group 1 = 18-<65; Group 2= 65-<75; Group 3= >=75)	Group 1 = 337 (65.82%) Group 2 = 150 (29.3%) Group 3 = 25 (29.3%)

Sources: Applicant's report: Population Pharmacokinetic and Pharmacodynamic Modeling of Niraparib, Page 35

Population PK Model Development

Base Model: The concentration-time data of niraparib was best described with a two-compartment model with first order absorption and first order elimination. The model was parameterized with apparent oral clearance (CL/F), apparent central (V2/F) and peripheral (V3/F) volumes,

intercompartmental clearance (Q/F) and absorption rate constant (KA). Inter-subject variability (ETA) was determinable on all parameters except KA and a proportional error model was used to describe the residual variability.

The base PK model estimates are summarized in Table 10-10 . According to the base model, the typical value for niraparib CL/F was estimated to be 16.2 L/h and the V2/F was estimated to be 290 L. The typical value estimates for Q/F and V3/F were 53.5 L/h and 784 L, respectively. The typical value of KA was estimated to be 0.288 hr^{-1}. Inter-subject variability (IIV) was moderate to high and was 58.1% for V2/F, 52.6% for CL/F, 138% for V3/F and 51.1% for Q/F. IIV was not estimated for KA. A proportional residual error was implemented and was estimated as 37.8% CV.

Table 10-10: **Pharmacokinetic Parameters in the Base Population Model**

	FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL LBOUND	UBOUND		DESCRIPTOR/ VARIABILITY
THETA						
1	0.288	10.3%	0.230	0.346		1KA
2	16.2	3.54%	15.1	17.3		2CL
3	290	10.6%	230	350		3V
4	784	11.8%	603	965		4V3
5	53.5	6.99%	46.2	60.8		5Q
OMEGA						INTERINDIVIDUAL VARIABILITY
1,1	0.00	...	...	...	CV =	...
2,2	0.277	3.97%	0.255	0.299	CV =	52.6%
3,3	0.337	7.98%	0.284	0.390	CV =	58.1%
4,4	1.91	14.2%	1.38	2.44	CV =	138%
5,5	0.261	22.1%	0.148	0.374	CV =	51.1%
SIGMA						RESIDUAL VARIABILITY
1,1	0.143	1.36%	0.139	0.147	CV =	37.8%

*Indicates 95% confidence interval that includes zero

%RSE is percent relative standard error (100% x SE/EST)

Source: Applicant's report: Population Pharmacokinetic and Pharmacodynamic Modeling of Niraparib, Page 36

Covariate Models:

After establishment of the base model, the effects of patient factors were assessed for their influence on the disposition of niraparib. Patient factors examined include age (AGE), race, baseline body weight (WT), age group, ethnicity (ETH), baseline and on study lab parameters including, serum creatinine clearance (CLCR) calculated using Cockcroft-Gault equation, serum albumin (ALB), serum alanine aminotransferase (ALT), serum aspartate, aminotransferase (AST), serum alkaline phosphatase (ALP), total bilirubin (BILI), neutrophil count (NEUT), hematocrit (HCTBL), hemoglobin (HGBBL), gBRCA mutation (gBRCA), HRDpos (HRD), Eastern Cooperative Oncology Group score (ECOG), number of previous platinum therapies (NPT), duration of previous platinum therapy (DPT), cumulative duration of previous platinum therapy (DPT2), time interval between previous platinum therapy and niraparib dose (IPN), meal consumption (MEAL), Grade 1 and 3 thrombocytopenia fatigue, anemia (ANE1, ANE3), nausea (NAU1, NAU3), vomiting and neutropenia. A correlation, by visual inspection, was not evident for any of the covariates and CL/F, V2/F, V3/F, and Q/F

Final Model

Based on the results above, the Applicant concluded that the final model would be the same as the base model. Outliers were then identified as concentrations with WRES≥10.

The parameter estimates of the final model were summarized below in the Table 3. The interindividual variability for CL/F, V2/F, Q/F, and V3/F were moderate to high and were approximately 38.7% to 103% CV.

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Table 10-11: **Bootstrap Parameter Estimates for the Final Population Model**

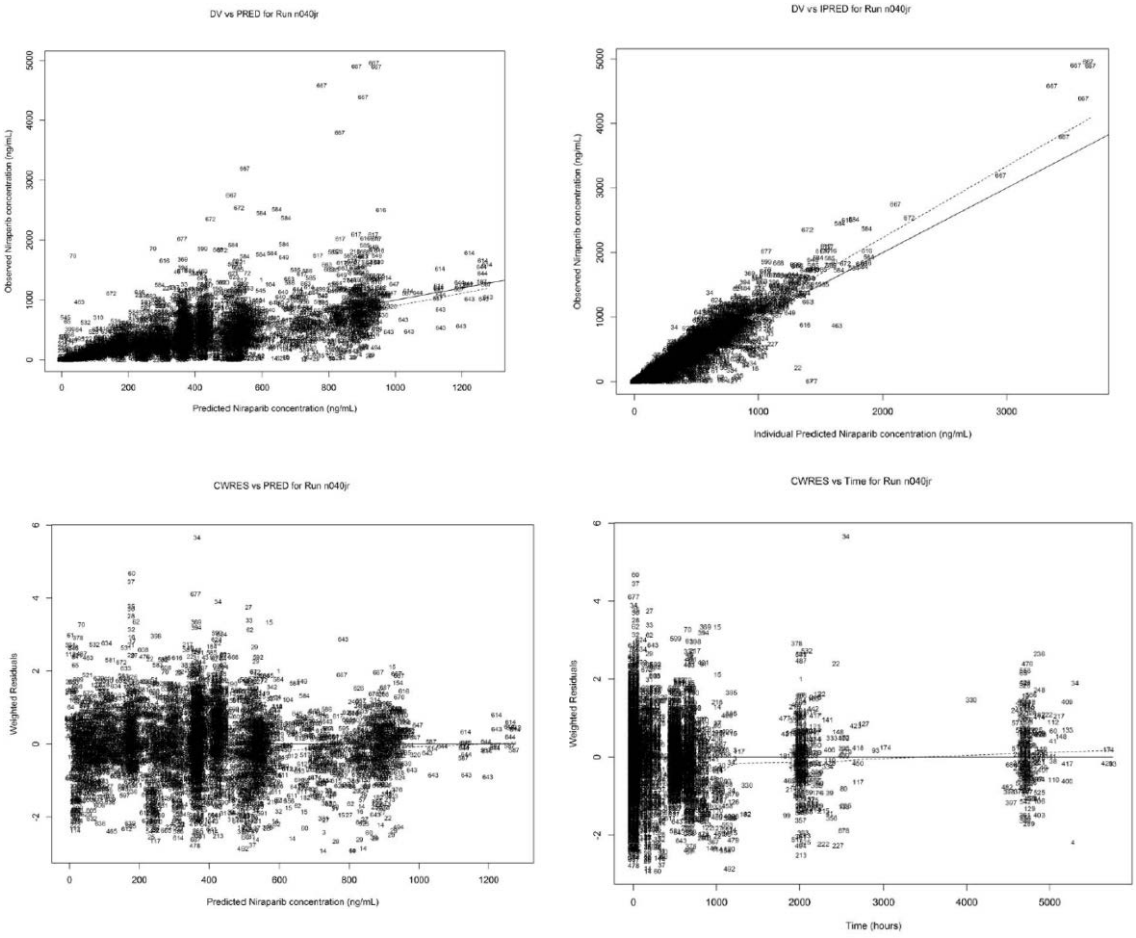
	FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL LBOUND	UBOUND	DESCRIPTOR/ VARIABILITY
THETA					
1	0.272	10.3%	0.217	0.327	1KA
2	17.2	2.35%	16.4	18.0	2CL
3	267	10.8%	210	324	3V
4	644	9.94%	519	769	4V3
5	53.6	7.00%	46.3	61.0	5Q
OMEGA					INTERINDIVIDUAL VARIABILITY
1,1	0.00	...	...	...	CV = ...
2,2	0.150	6.73%	0.130	0.170	CV = 38.7%
3,3	0.375	8.56%	0.312	0.438	CV = 61.2%
4,4	1.06	13.7%	0.776	1.34	CV = 103%
5,5	0.254	22.9%	0.140	0.368	CV = 50.4%
SIGMA					RESIDUAL VARIABILITY
1,1	0.136	1.43%	0.132	0.140	CV = 36.9%

Source: Applicant's report: Population Pharmacokinetic and Pharmacodynamic Modeling of Niraparib, Page 38

Model Evaluation

The goodness-of-fit plots for the final model are shown in Figure 10-12.

Figure 10-12. Goodness-of-fit Plot for the Niraparib Final Model



Source: Applicant's report: Population Pharmacokinetic and Pharmacodynamic Modeling of Niraparib, Page 40-43

Reviewers Comments:

The applicant's final population PK model for niraparib was able to describe the observed niraparib concentrations observed in the primary Phase 3 studies as evidenced by the goodness of fit plots. Therefore, the estimated exposure up to the time of event of interest by the population PK analysis can be used for the subsequent exposure-survival and exposure-safety analysis.

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/s/

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11 Statistical and Clinical and Evaluation

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11.1.1. Table of Clinical Studies

Table 11-1 Studies Relevant to the Efficacy and Safety Review of NDA 208447

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Primary Endpoint(s)	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
PR-30-5011-C (NOVA)	Randomized , double-blind, placebo controlled trial with 2:1 randomization	Maintenance therapy with Niraparib or placebo 300 mg PO q d	PFS by blinded central review (IRC)	Until disease progression/ death or unacceptable toxicity	553	Patients with platinum-sensitive recurrent serous ovarian cancer in PR/CR to most recent platinum-based chemotherapy	Patients enrolled from 128 sites in 15 countries, including the US.
Studies to Support Safety							
PR-30-5020-C (QUADRA)	Open-label treatment	Niraparib 300 mg PO q d continuous 28-day cycles	ORR	Until disease progression/ death or unacceptable toxicity	311	Patients with advanced, relapsed (≥ 3 prior lines of therapy) high grade serous epithelial ovarian cancer	39 sites in US

PR-30-5011-C2-FE	Open-label fasted vs. fed crossover with treatment extension	Niraparib 300 mg single dose PO; for extension 300 mg PO q d	Assess effect of high-fat meal on the PK of single dose 300 mg niraparib in patients with ovarian cancer	Median on study duration: 42 days	17	Patients with previously treated recurrent ovarian cancer with no standard therapy options.	6 sites in US
PR-30-5011-C1-QTC	Open-label ECG evaluation with treatment extension	Niraparib 300 mg PO q d	Assess effect of niraparib on cardiac repolarization measured by mean change in QTcF after baseline adjustment.	Median on study duration: 152 days	26	Patients with previously treated recurrent ovarian cancer	4 sites in US
PN001	Open-label, multiple ascending dose study of niraparib	Daily oral administration ; 30 mg up to 400 mg q d	Safety, MTD	Until unacceptable toxicity or PD	104	Patients with advanced solid tumors or hematologic malignancies	3 (US, UK)

11.1.2. Review Strategy

Data Sources

The electronic submission including Protocols, Statistical Analysis Plan (SAP), Clinical Study Reports (CSRs), and SAS transport datasets in SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) format for the NDA submission are located in the following network paths:

- Original submission: \\cdsesub1\evsprod\nda208447\0003\

These sources were utilized to perform the clinical and statistical review of this application.

Data and Analysis Quality

The clinical study protocol for the NOVA study was submitted to Independent Ethics Committees and/or Institutional Review Boards (IRB) for review. Written approvals were required prior to initiation of the study. The Office of Scientific Integrity (OSI) conducted clinical inspections of five sites, including the Sponsor, Tesaro.

Table 11-2 depicts the sites that were inspected by the Office of Scientific Investigations and shows the final inspection classification for each site. The conclusion for each of the individual sites was that the inspections revealed no significant deficiencies. The inspection of the Sponsor, Tesaro, revealed no significant deficiencies. The overall conclusion for the OSI inspection is that the data submitted to the FDA in support of Study PR-30-5011-C appear reliable. See also full OSI Inspection Summary dated 2/28/17 from Dr. Lauren Iacono-Connors.

Table 11-2 Clinical Inspection Summary

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Jonathan Berek Site 1015 300 Pasteur Drive HG-333 Stanford, CA 94305	Protocol PR-30-5011-C Subjects: 14	February 13-17, 2017	Preliminary Classification NAI
CI#2: Ursula Matulonis (Site 1009) Dana-Farber Cancer Institute	Protocol PR-30-5011-C Subjects: 9	January 24-30, 2017	Preliminary Classification NAI

450 Brookline Ave. Boston, MA 02215			
CI#3: Ursula Matulonis (Site 1009B) Beth Israel Deaconess Medical Center 330 Brookline Ave. Boston, MA 02215	Protocol PR-30-5011-C Subjects: 2	February 6-7, 2017	Preliminary Classification NAI
CI #4: Michel Fabbro (Site 33002) 208 av. des Apothicaires Montepellier, Herault 342987 France	Protocol PR-30-5011-C Subjects: 20	February 13-17, 2017	Preliminary Classification NAI
CI#5: Mansoor Mirza (Site 45003) Department of Oncology 5073 Righospitalet Copenhagen Ø, Capital 2100 Denmark	Protocol PR-30-5011-C Subjects: 26	February 13-17, 2017	Preliminary Classification NAI
CI#6: Sponsor: Tesaro, Inc. 1000 Winter Street Suite 3300 Waltham, MA 02451	Protocol PR-30-5011-C Site numbers: 001009, 001009B, 001015, 033002, 045003	January 4- 20, 2017	Preliminary Classification NAI

Key to Compliance 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 field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

11.2. Review of Relevant Individual Trials Used to Support Efficacy

11.2.1. PR-30-5011 (NOVA)

Trial Design and Endpoints

Trial NOVA was a double-blind, 2:1 randomized, placebo-controlled trial to evaluate the efficacy and safety of niraparib as maintenance treatment for patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had received at least 2 platinum-based regimens and were in response to their last platinum-based chemotherapy.

The trial was designed to independently evaluate efficacy of niraparib in 2 patient cohorts: one cohort included patients with a deleterious germline BRCA mutation or genetic variant or a suspected deleterious mutation (gBRCAmut); the other cohort included patients without a germline BRCA mutation (non-gBRCAmut). See Figure 11-1 for study schema. Patients were randomized (2:1) to receive niraparib 300 mg or matched placebo once daily within each cohort in continuous 28-day cycle. Randomization was stratified by time to progression after the penultimate platinum therapy (6 to <12 months versus ≥12 months); use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes versus no); and best response during the most recent platinum regimen (complete response versus partial response).

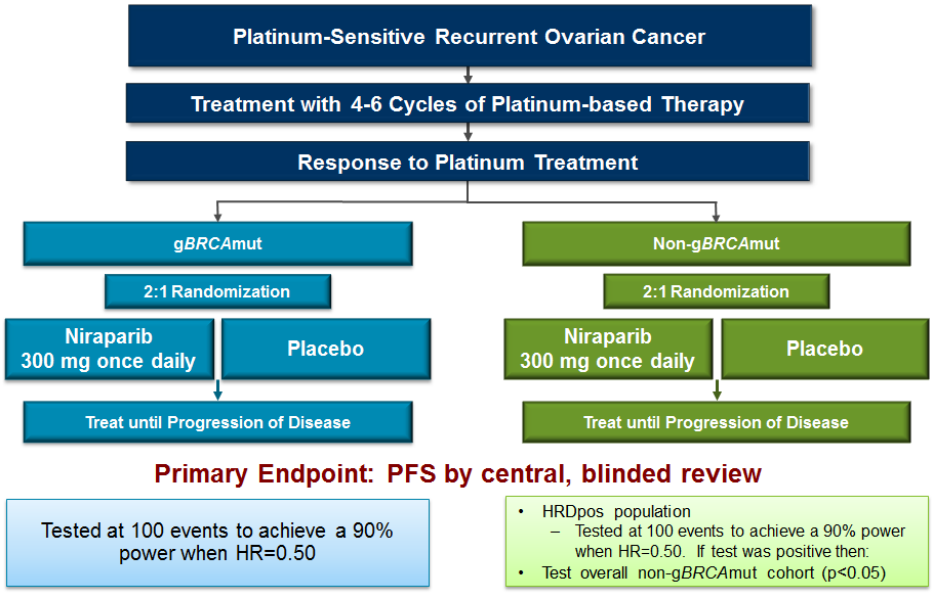

Figure 11-1 Trial NOVA Schema (Applicant's Figure)

Patients were to receive their assigned treatment until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up, whichever occurred first. After treatment

discontinuation, survival information would continue to be collected. Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 was used for tumor assessment via CT or MRI scan; such scans were required at the end of every 2 cycles through Cycle 14, then every 3 cycles until progressive disease occurred. Patient-reported outcomes (PROs) were to be collected in a coordinated fashion with RECIST tumor imaging during the treatment period. Once the patient discontinued study treatment, assessment of PROs was to be performed at the time of discontinuation and then 8 weeks (+/- 2 weeks) later, which was the final PRO assessment, regardless of subsequent treatment.

Reviewer comment: Overall, the study design was reasonable, including the choice of placebo control, since many patients with platinum-sensitive relapsed disease are monitored off therapy after response to 6-8 cycles of platinum-based chemotherapy. Since initiation of the NOVA study, bevacizumab was approved in this (similar) treatment space, however this was not the case at the time that the NOVA study was designed. The use of PFS as the primary study endpoint is what is currently used for many trials designed in this patient population.

Trial Objectives

The primary objective of trial NOVA was to compare progression free survival (PFS) between niraparib and placebo in each pre-specified patient population. The secondary objectives were to evaluate overall survival (OS), time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), chemotherapy-free interval (CFI), progression-free survival 2 (PFS2), and patient-reported outcomes (PROs). Disease progression was assessed by both the site investigators and by a blinded central independent radiologic and clinical oncology review committee (IRC). The primary efficacy analysis was based on PFS assessments determined by IRC.

Central Blinded Review

Efficacy response data was reviewed by an independent review committee (IRC) as prospectively defined in the study protocol. The committee was comprised of a minimum of 3 radiologists and 1 oncologist (a blinded, independent clinical reviewer). The radiology review was conducted in 2 steps, a primary review and a global review. During the primary review, 2 independent radiologists separately read scans for a patient on a time point-by-time point basis and provided an overall tumor response assessment at each time point according to RECIST v.1.1. Following completion of the primary radiology review, the same 2 radiologists separately completed a global review across all time points for the patient. At this time, each reviewer was permitted to update any of his/her previous time point overall tumor assessments, according to RECIST 1.1. Adjudication was required if the 2 independent radiologists' results for the global radiology review were in disagreement on progressive disease (PD vs. Non-PD) for at least one time point.

Following completion of the IRC radiology review, data from all patients underwent review by an independent IRC Oncologist. This central blinded clinical review included assessment of final IRC RECIST assessment conducted by the IRC radiologists, as well as relevant clinical data including diagnostic tests such as histology, cytology, ultrasound, endoscopy, PET results; progression by CA-125 levels according to Gynecologic Cancer Intergroup (GCIG) criteria; and clinical signs and symptoms of disease progression unlikely to be related to non-malignant/ iatrogenic causes (i.e. intractable cancer pain, malignant bowel obstruction/dysfunction, unequivocal worsening of ascites/ effusions, and CA-125 progression). The central blinded oncologist (clinician) reviewed the clinical and radiographic data supporting clinical progression and determined if a patient had protocol-defined clinical progression, and at which time point. The blinded oncologist did not have access to hematologic adverse event data. The blinded oncologist also could not provide an opinion on the presence or timing of radiographic progression, and could not select "target" lesions from clinical sources (physical exam) unless these lesions were also documented in clinical data by the investigator, in which case, they could be assessed qualitatively and incorporated into the IRC oncologist assessment.

For the purpose of the primary PFS endpoint, the date of progression was determined using information from IRC radiology review, central blinded clinician review, and investigator review. An algorithm outlined below in Table 11-5, shows how the date of progression was determined in the primary PFS analysis.

Reviewer comment: Although the use of an IRC to assess imaging response according to RECIST criteria is typical in oncology trials, the Applicant's use of the additional step in the review process (the global review) was less common. The Applicant did not ask for input from the Agency prior to utilizing this process in the NOVA trial. During the review of the NDA, the review team requested the Applicant to submit their analysis of PFS by IRC assessment, without inclusion of the global assessment process/ determinations. The results of the primary endpoint assessment with and without the global review are described in the assessment of the efficacy analyses.

Eligibility Criteria

Key Inclusion:

1. Female patients ≥ 18 years of age.
2. Agree to undergo analysis of gBRCA status, with testing completed prior to randomization.
3. Histologically diagnosed ovarian, fallopian tube, or primary peritoneal cancer.
4. High grade (or Grade 3) serous or high grade predominantly serous histology or known to have gBCRAm.
5. Must have completed at least 2 previous courses of platinum-containing chemotherapy (e.g., carboplatin, oxaliplatin, or cisplatin):

- For the penultimate (next to last) platinum-based chemotherapy course prior to enrollment:
    - Patient must have platinum sensitive disease after this treatment; defined as achieving a CR or PR and disease progression > 6 months after completion of last dose of platinum therapy (documented as 6-12 or > 12 months, source documentation required).
- For the last chemotherapy course prior to being randomized:
    - Patients must have received a platinum-containing regimen for a minimum of 4 cycles.
    - Patients must have achieved a partial or complete response.
    - Following the last regimen, patients must have either CA-125 in the normal range or a CA-125 decrease by more than 90% during their last regimen which is stable for at least 7 days (i.e., no increase > 15%).
- Patients must be randomized within 8 weeks after completion of final dose of the platinum-containing regimen.

6. Agreement to complete PROs during study treatment and at 1 additional time point 8 weeks following study treatment discontinuation.
7. Formalin fixed, paraffin-embedded archival tumor available from primary or recurrent cancer required.
8. ECOG 0-1.
9. Adequate organ function:
    - ANC ≥ 1500/µL
    - Platelets ≥ 100,000/µL
    - Hemoglobin ≥ 9 g/dL
    - Serum creatinine ≤ 1.5 x ULN or CrCl ≥ 60 ml/min
    - Total bilirubin ≤ 1.5 x ULN or direct bilirubin ≤ 1 x ULN
    - AST and ALT ≤ 2.5 x ULN unless liver metastases, in which case ≤5 x ULN

Additional Inclusion for Food-Effect Sub-Study: With the exception of inclusion criteria 2, 4, 5, 6, 7, and 8 (above), all main inclusion criteria apply. In addition, the following criteria apply to the FE sub-study only:

1. Entry criteria broadened to include patients with ovarian cancer regardless of platinum sensitivity and burden of disease as long as no standard therapy exists or patient refused standard therapy.

2. ECOG 0-2.

3. Must be able to eat a high fat meal and fast for 12 hours.

Key Exclusion:

1. Drainage of ascites during last 2 cycles of last chemotherapy

2. Palliative radiotherapy within 1 week encompassing > 20% bone marrow.

3. Persistent > Grade 2 toxicity from prior cancer therapy.

4. Symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled", CNS disease must have undergone treatment [radiation therapy (RT) or chemotherapy] at least 1 month prior. Patient must not have any new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids). Scan to confirm absence of brain metastases not required. Patients with spinal cord compression may be considered if have received definitive treatment and have been clinically stable for 28 days.

5. Major surgery within 3 weeks or not recovered from effects of surgery.

6. Invasive cancer other than ovarian cancer ≤ 2 years prior to randomization.

7. Patients considered poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disorder, or active uncontrolled infection. Examples include uncontrolled ventricular arrhythmia, recent myocardial infarction (within 90 days), uncontrolled major seizure disorder, unstable spinal cord compression, SVC syndrome, psychiatric disorder that prohibits obtaining informed consent.

8. Patients must not have received a transfusion (platelets or red blood cells) within 4 weeks

9. Immunocompromised patient (splenectomy allowed).

10. Known active hepatic disease (Hepatitis B or C).

11. Prior treatment with PARP inhibitor.

12. Patients with baseline QTc interval > 470 msec.

13. Patients receiving concomitant medication that prolong QTc and are unable to discontinue that medication.

Reviewer comment: The eligibility criteria for enrollment into the NOVA study were reasonable for a maintenance therapy setting in ovarian cancer. The selection of only patients achieved partial or complete response to their most recent platinum-based chemotherapy is in line with other trials in this setting. The requirement for normal CA-125 or decrease of CA-125 level by 90% for enrollment is less typical, but allowed for this parameter to be followed as part of disease assessment while patients were on study, and it was used in a small number of patients to help determine disease progression (by clinical parameters).

Statistical Analysis Plan

Sample Size Considerations

The gBRCAmut and non-gBRCAmut cohorts were considered as two independent cohorts and alpha level was set as one-sided 0.025 for each cohort. Randomization was conducted separately within each cohort.

In the gBRCAmut cohort, approximately 100 PFS events were needed to detect a HR of 0.50 (corresponding to an increase from 4.8 to 9.6 months in median PFS) with 90% power using a log-rank test at a one-sided 2.5% level of significance. A total enrollment of 180 gBRCAmut patients was planned.

Number of events needed for the PFS analysis in the non-gBRCAmut HRD positive subgroup was determined based on the same PFS assumption used for the gBRCAmut cohort Table 11-3. In the overall non-gBRCAmut cohort, to detect a HR of 0.5, 140 PFS events were needed to provide more than 95% power, at a 1-sided alpha of 0.025. It was assumed that approximately 40% of the non-gBRCAmut cohort was expected to be classified as HRD positive. A total of 310 patients were planned to be enrolled in the non-gBRCAmut cohort in order to ensure that a sufficient number of events would be obtained in the HRD+ group. Analyses for both of the cohorts were to be conducted at the same time.

Table 11-3 Sample Size Calculation

	gBRCAmut cohort	Non-gBRCAmut cohort	
		HRD+ subgroup	Entire Cohort
PFS HR targeted (corresponding medians assumed)	HR=0.5 (4.8 vs. 9.6 months)	HR=0.5 (4.8 vs. 9.6 months)	HR=0.5 (4.8 vs. 9.6 months)
Alpha (1-sided)	0.025	0.025	0.025
Power	90%	90%	>95%
# of PFS events needed	100	100	140
Sample Size Planned	180	120	310

[Source: NOVA SAP]

Analysis Sets

The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all patients randomized into the study. Patients were to be classified according to assigned treatment group, regardless of the actual treatment received. Each cohort had its own ITT population.

A per-protocol population was defined as all patients randomized who did not have major protocol deviations that might significantly impact the interpretation of efficacy results.

The safety analysis population would include all patients who receive any amount of study drug. Analysis of safety data would be performed according to the actual treatment a patient has received.

Efficacy Measures

The primary efficacy endpoint, PFS, was defined as the time from randomization to disease progression per IRC or death from any cause, whichever occurred first. Disease progression was assessed by RECIST v1.1 as well as by clinical criteria. The clinical criteria were defined by elevated CA-125 levels according to Gynecologic Cancer Intergroup (GCIG) criteria and clinical signs of ovarian cancer disease progression. Thus, disease progression was determined if at least one of the following three criteria was met:

1. Tumor assessment by CT/MRI showed PD according to RECIST v.1.1 criteria.
2. Additional diagnostic tests (e.g., histology/cytology, ultrasound techniques, endoscopy, PET) identified new lesions or determined that existing lesions qualified from unequivocal PD and CA-125 progression, according to GCIG criteria (Table 11-4).
3. Definitive clinical signs and symptoms of PD unrelated to nonmalignant or iatrogenic causes ([1] intractable cancer-related pain; [2] malignant bowel obstruction/worsening dysfunction; or [3] unequivocal symptomatic worsening of ascites or pleural effusion) and CA-125 progression according to GCIG criteria (Table 11-4) were present.

It was noted that CA-125 progression alone was not to be considered disease progression. In order to declare PD using the criteria 2 and 3 above, both investigator and central independent clinician must agree on the progression of disease. The criteria used to determine CA-125 progression are depicted in Table 11-4.

Table 11-4 CA-125 Progression[1]

	Post-Baseline Results *(Requires 2 CA-125 results ≥ 7 days apart,* **within ±** *14 days of clinical documentation)*		
Baseline	**Last value prior to < 14 days to PD**	**Initial and if applicable confirmation (± 14 days to PD)**	**Confirmation (≥14 Days to PD)**
> ULN	Within normal range	≥ 2 x ULN	≥ 2 x ULN
> ULN	Missing or > ULN	≥ 2 x nadir	≥ 2 x nadir
≤ ULN	Any (missing or not)	≥ 2 x ULN	≥ 2 x ULN

[1] According to Gynecologic Cancer Intergroup (GCIG) criteria

[Source: NOVA SAP]

For the purpose of the primary endpoint, the date of progression was to be determined using information from central radiology review, the central blinded clinician, and the investigator. For radiology progression date, the central review was to be used. For clinical progression, both the central blinded clinician and investigator must agree on the progression status, and the actual clinical progression date was to be determined by the investigator. Table 11-5 shows how the date of progression was determined.

Table 11-5 Determination of Disease Progression Date in the Primary PFS Analysis

Central Reviewers		Investigator	Date of PD
Radiologist	Blinded Clinician		
PD	PD	Clinical PD	Earliest of Radiology and Investigator
PD	No PD	Clinical PD	Radiology
PD	PD	Non-PD	Radiology
PD	No PD	Non-PD	Radiology
Non-PD	PD	Non-PD	No PD
Non-PD	No PD	Clinical PD	No PD
Non-PD	PD	Clinical PD	Investigator

[Source: NOVA SAP]

Secondary endpoints included OS, PFS2, CFI, TFST, TSST, and patient reported outcomes. No multiplicity adjustment for the secondary endpoints has been pre-specified in the study protocol or SAP.

Overall Survival was defined as the time from randomization to death from any cause. Patients known to be alive were to be censored at the last known survival follow-up date.

Chemotherapy-free Interval was defined as the time from last platinum dose until initiation of next anticancer therapy (excluding maintenance therapy). If no anticancer therapy was initiated, CFI was to be censored on the last date of treatment on the current study.

Time to first subsequent therapy was defined as the date of randomization to the earlier of the start date of first follow-up anti-cancer treatment or death.

Time to second subsequent therapy was defined as the date of randomization to the earlier of the start date of second follow-up anti-cancer treatment or death.

Progression-free survival 2 was defined as the date of randomization in the current study to the earlier date of assessment of progression on the next anti-cancer therapy following study treatment or death by any cause. If progression could not be determined, the start date of the second line of subsequent anti-cancer therapy (the second line of treatment after completion of either niraparib or placebo) was to be used as a surrogate for date of PD. If date of progression, date of death, and start date of the second line of subsequent anti-cancer therapy were unknown, then PFS2 was to be censored at the stop date of the first line of subsequent anti-cancer therapy. If the stop date was unknown, PFS2 was to be censored on the last contact date. Determination of progression was to be by site physician clinical and radiographic assessment.

Patient-reported outcomes were evaluated using three instruments: Functional Assessment of Cancer

Therapy – Ovarian Symptom Index (FOSI), EQ-5D-5L, and neuropathy questionnaire. See Review of Patient-Reported Outcomes Section and Appendix 2 for detailed patient-reported outcomes review.

Reviewer comments

Per the statistical analysis plan, there was no multiplicity adjustment for secondary endpoint analyses.

Only one analysis of OS was planned in the SAP and it was at the time of primary PFS analysis. Further survival data are still being collected, and updated descriptive survival analyses may be submitted with longer follow-up.

Efficacy Analysis Methods

The primary analysis of PFS was based on central blinded assessments and prospectively planned to occur when approximately 100 PFS events occurred in both the gBRCAmut cohort and the HRD+ subgroup of non-gBRCAmut cohort. PFS was to be summarized using Kaplan-Meier survival curves, and compared between the two treatment arms using a log-rank test stratified by the randomization stratification factor, i.e., use of bevacizumab in conjunction with the penultimate or last platinum regimen, time to progression after the penultimate platinum therapy before study enrollment, and best response during the last platinum regimen, as collected in the IVRS system. The hazard ratio with a two-sided 95% confidence interval was derived from a stratified Cox proportional hazards model with same three stratification factors used in the stratified log-rank test. PFS was to be analyzed in the gBRCAmut cohort and non-gBRCAmut cohort separately, at 1-sided alpha 0.025. Within the non-gBRCAmut cohort, a hierarchy testing procedure was applied, where PFS was tested in the HRD+ subgroup first, if statistically significant, a test of PFS was to be performed for the entire non-gBRCAmut cohort.

PFS was to be censored following the rules below in the primary analysis:

1. If no adequate post-baseline radiological assessments, patients are censored at the date of randomization unless death occurred within 17 weeks of randomization (in which case the death is an event) or clinical PD is determined.

2. Patients known to be alive and known not to have started new (non-protocol) anti-cancer treatment, who are progression-free, and who have a baseline and at least 1 post-dosing radiological assessment, are censored at the date of the last radiological assessment that verified lack of PD.

3. Patients starting new anti-cancer treatment prior to progression or death are censored at the date of last radiological assessment documenting no progression prior to the new treatment.

4. Documentation of progression or death after an unacceptably long interval (> 17 weeks, i.e., 2 consecutive missed or indeterminate overall response assessments) since the last radiological assessment will be censored at the date of last radiological assessment documenting no progression.

5. Discontinuation of study treatment due to disease progression according to the investigator that was later overturned during central blinded review will be censored on the date of last radiological assessment.

Several sensitivity analyses were specified in the statistical analysis plan, as summarized in

Table 11-6.

Table 11-6 PFS Sensitivity Analyses Pre-specified in the SAP

S1	An IRC-PFS analysis excluding patients with major protocol deviations
S2	An IRC-PFS analysis using unstratified log-rank test along with Cox regression modeling using treatment only
S3	PFS per investigator assessment
S4	An IRC-PFS analysis using only RECIST v1.1 as progressions
S5	An IRC-PFS analysis treating censors due to subsequent anti-cancer treatment, discontinuation due to any reason, missed tumor assessments as events.
S6	An IRC-PFS analysis using the scheduled assessment date to show progression if the off-scheduled assessment was after the previous scheduled date. This was to be done only for progression, not for censored observations.

Reviewer comments
The review team performed more sensitivity analyses for PFS:
S1) an IRC-PFS analysis without considering global review update in radiology assessment of tumor response status
S2) an IRC- PFS analysis considering patients censored due to progression per investigator but not confirmed by IRC as PFS events at the next scheduled assessment time
S3) in the non-gBRCAmut HRD+ subgroup, using a Cox regression model adjusted by unbalanced baseline covariates to estimate IRC-PFS hazard ratio
S4) a PFS analysis using programmatically re-derived tumor data from investigator based raw lesion measurement following RECIST v.1.1.
Results are summarized in the section of FDA's PFS sensitivity analyses.

OS, PFS2, TFST, TSST, and CFI were to be analyzed in the same manner as for the primary efficacy PFS. As sensitivity analyses, an un-stratified log-rank test and associated Cox regression model were to be performed.

Protocol and SAP Amendments

The original protocol (dated: 21 March 2013) was amended 6 times during the study for clarification and changes in analysis. The key revisions based on the protocol amendments are outlined in Table 11-7.

Table 11-7 Protocol Amendment Summary

Amendment (final date)	Major Changes
1 (03 May 2013)	• Disease progression was originally required to be confirmed objectively by blinded central review in conjunction with RECIST v.1.1. Clinical criteria were added to the means of confirmation (i.e., RECIST, clinical criteria, and blinded central review) to ensure that progressive disease could be determined objectively and with certainty. • QTc Analyses was added. • PROs were to continue to be collected even after a patient discontinued treatment, regardless of progression status.
2 (03 Mar 2014)*	• The Integrated BRACAnalysis® was specified as the diagnostic test to determine germline BRCA mutation status, prior to this local BRCA tests could be used. • To maintain objectivity, PRO evaluations were to be administered prior to conducting any other study procedures at the study visit • Patients who were benefitting from treatment could continue to receive their assigned treatment as long as the treating physician considered treatment to be acceptable, or until they were discontinued from the treatment or study as specified in the protocol.
3 (09 Apr 2014)	• Exclusion criterion 11 for immunocompromised patients was modified to allow patients with a splenectomy to enroll, as they were vaccinated and not immune compromised. • A table was added to clarify assignment of patients to study cohorts, based on their Myriad Integrated BRACAnalysis® test results. • The description of the Integrated BRACAnalysis® was updated to include that DNA from the submitted sample(s) was going to be stored and could be used at a later time for additional biomarker testing, including the potential to bridge to candidate companion diagnostic assays.
4 (04 Dec 2014)	• In addition to germline BRCA testing, text was added in this amendment to indicate that patients would be tested (centrally) to classify their HRD status, and to indicate the timing of that testing. • It was further specified that HRDpos patients in the non-gBRCAmut cohort would be evaluated first for PFS, followed by all non-gBRCAmut patients. • Statistical methods were updated to indicate that superiority of niraparib relative to placebo in PFS would be evaluated in the gBRCAmut cohort using a 1-sided alpha equal to 0.025. In addition, if the treatment effect was significant in the non- gBRCAmut HRDpos group, PFS would then be tested in the full non-gBRCAmut cohort. • Concordance of a candidate companion HRD diagnostic test compared with the HRD diagnostic test used in this study would be assessed, if needed, and baseline samples for HRD analyses were to be collected and archived for possible bridging the study's HRD test to a candidate companion HRD diagnostic test. • The sample size for evaluation of PFS was expanded to include the original 180

	gBRCAmut patients, and up to 310 patients randomized to the non-gBRCAmut cohort. Sample size increase, including statistical assumptions, was explained in the Sample Size Considerations section of the protocol.
5 (11 Sept 2015)	• Guidance on monitoring patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML was added to the protocol.
6 (09 Mar 2016)	• Definitions of the non-gBRCAmut subgroups were clarified: HRDpos/sBRCAmut and HRDpos/ BRCAwt, with further clarification of the hierarchical analyses to be performed by cohort and subpopulations (i.e., statistical analysis of primary endpoint [PFS] for non-gBRCAmut patients, with test for HRDpos group first, followed by a test of the overall non-gBRCAmut if the first test was statistically significant). o Changes were made to ensure that the gBRCAmut cohort would not be overpowered to detect a small PFS difference and to provide evidence needed to determine whether there might have been a differential response to niraparib in the patient population with gBRCAmut tumors vs HRDpos/sBRCAmut tumors vs HRDpos/BRCAwt. This amendment reduced power of the gBRCAmut cohort from >95% to 90% and allowed for analysis for both of the cohorts simultaneously. The new sample size for this test was determined to be approximately 100 PFS events in the gBRCAmut cohort, to maintain 90% power. • Secondary objectives were added: TFST and TSST. TFST was defined as the date of NOVA study randomization to the start date of the first subsequent anti-cancer therapy. TSST was defined as the date of NOVA study randomization to the start date of the second subsequent anti-cancer therapy. • PK assessments would not include the major niraparib metabolite, M1. • An interim analysis of the gBRCAmut cohort, planned to follow approximately 85 PFS events, was deleted from the protocol, since the timing of these events would approximately coincide with the current planned analysis of data.

*Amendment 2 was not issued and changes outlined in this amendment were included in Amendment 3.

Reviewer comment: With the first protocol amendment, the Sponsor modified the criteria for defining disease progression to extend beyond RECIST radiographic criteria, to include certain clinical criteria which are utilized by clinicians to determine disease progression in patients with ovarian cancer. These include the use of rising CA-125 by GCIG criteria and reliance upon the presence of certain clinical signs and symptoms of PD which are characteristic in patients with ovarian cancer. These included the occurrence of intractable cancer-related pain, malignant bowel obstruction/worsening dysfunction, and/or unequivocal symptomatic worsening of ascites or pleural effusion. It is notable that the use of these criteria could potentially create a more "real world" experience in how disease status/ progression was assessed. The results of how many patients actually were determined to have PD based upon the clinical criteria are shown in Table 11-15. Overall, only 9 patients across all cohorts were determined to have PD by clinical criteria, and these were evenly distributed across treatment arms and cohorts. Therefore, it is unlikely that the application of clinical criteria would have impacted the integrity of the trial or our interpretation of the study results.

The first version of statistical analysis plan was released on 18 December 2015, and amended twice thereafter. The major changes in each amendment are summarized in Table 11-8. All amendments to SAPs were performed prior to the database lock (lock date: 18 June 2016) and unblinding to the treatment assignment.

Table 11-8 SAP Amendment Summary

SAP version (Final Date)	Major Changes
Version 2 (18 May 2016)	• Modified the analysis method for patients who were incorrectly stratified during randomization to present them under the stratum assigned during randomization • Clarified the exploratory nature of the pooled analyses of non-gBRCAmut HRD+ subgroup and gBRCAmut cohort and the pooled analyses of somatic BRCAmut of the non-gBRCAmut cohort and gBRCAmut cohort.
Version 3 (17 Jun 2016)	• With the questions arising during the ADaM Programming, censoring rules for the secondary endpoint PFS-2 were updated. • A table was included to clarify cohort assignment based on Myriad report • The analysis regarding the concordance of a candidate CDx gBRCA mutation test with the centralized BRACAnalysis® diagnostic test to identify gBRCAmut patients using archived samples was removed.

11.2.2. Study Results

Compliance with Good Clinical Practices

The clinical study protocol for study PR-30-5011-C was submitted to Independent Ethics Committees (IEC) and/or Institutional Review Boards (IRB) for review. Written approvals were required prior to initiation of the study.

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

Patient Disposition

Patient disposition at the time of data cut off for the NOVA study is shown in Table 11-9. More patients had discontinued from placebo than from niraparib at that time, attributed mainly to disease progression. More patients discontinued treatment from niraparib (n=50) due to adverse event than from placebo (n=3), which reflects the recognized toxicity profile of niraparib. The details, including adverse events leading to treatment discontinuation are explained further in the safety review.

Table 11-9 Patient Disposition NOVA Study

Disposition	gBRCA		Non-gBRCA	
Randomized	**Niraparib N=138 (%)**	**Placebo N=65 (%)**	**Niraparib N=234 (%)**	**Placebo N=116 (%)**
Randomized but not treated	**2 (1)**	**0**	**3 (1)**	**2 (2)**
Ongoing at data cutoff	**47 (34)**	**4 (6)**	**46 (19)**	**12 (10)**
Discontinued from treatment	**89 (65)**	**61 (94)**	**185 (79)**	**102 (88)**
Adverse event	17 (12)	1 (2)	33 (14)	2 (2)
Disease progression	63 (46)	49 (75)	129 (55)	98 (84)
Withdrawal by subject/patient decision	8(6)	8 (12)	11 (5)	1 (1)
Terminated by Sponsor/patient risk	0	2 (3)	2 (1)	0
Protocol deviation	0	0	2 (1)	0
Other*	1 (1)	1 (2)	8 (3)	1 (1)

*Other included PD believed by investigator, investigator request, patient request, symptomatic progression in absence of radiographic progression.

Protocol Violations/Deviations

Overall, there were 36 patients (6.5%) on the NOVA study with major protocol deviations. The breakdown by treatment arm and cohort are shown in Table 11-10. The majority of deviations across treatment arms and cohorts were related to eligibility criteria, with most having to do with the time interval between progression and the penultimate platinum regimen. Given that the intent of this specific inclusion criterion was to isolate patients with platinum sensitive disease at the time of initiating the platinum regimen immediately prior to entry onto the NOVA study, it seems that, if anything, violation of this criterion would only have had a (potentially) negative impact on study results, since some of the patients enrolled may actually have had platinum resistant disease. Given that the primary study endpoint was met and was robust, it does not seem that this deviation had a notable effect on the

study overall. Likewise, the remaining protocol deviations in are also unlikely to have an impact on the study results.

In Table 11-9, there were 2 patients (both in non-gBRCA, niraparib arm), listed as discontinuing therapy due to protocol violations. Only 1 of these 2 patients had a major protocol violation, listed in as "non-compliance with study therapy". The other patient discontinued niraparib therapy due to a "minor violation" related to prohibited concomitant use of ondansetron, as well as other issues that were not fully elucidated in the datasets.

Table 11-10 Protocol Deviations NOVA Study

Protocol deviation	gBRCA		Non-gBRCA	
	Niraparib N=138 (%)	Placebo N=65 (%)	Niraparib N=234 (%)	Placebo N=116 (%)
Patients with at least 1 major protocol deviation	11 (8)	1 (1.5)	16 (7)	8 (7)
Eligibility criteria	9 (7)	0	15 (6)	5 (4)
Inclusion criterion 5a – Progression ≥ 6 months after penultimate platinum	6 (4)	0	2 (0.8)	4 (3)
Inclusion criterion 5b- No measurable lesion > 2 cm	0	0	9 (4)	0
Inclusion criterion 9a – ANC ≥1500 not met	2 (1.5)	0	3 (1)	1 (0.8)
Exclusion criterion 7- other malignancy was met	1 (0.7)	0	0	0
Exclusion criterion 9 – blood transfusion within 4 weeks	0	0	1 (0.4)	0
Non-compliance with study therapy	1 (0.7)	0	1 (0.4)	1 (0.8)
Dispensed incorrect study medication kit	1 (0.7)	0	0	2 (1.7)
Misallocated to cohort randomized to gBRCAm, central testing did not confirm	0	1 (1.5)	0	0

Reviewer comment: Overall, the number of major protocol deviations was small, but there were slightly more in niraparib treated patients. The protocol deviation of importance was the time interval from progression after the penultimate platinum regimen, where this could be an issue if there were a large number of patients who actually progressed within 6 months of the last platinum regimen (platinum-resistant disease), rather than the protocol specified interval of ≥ 6 months (platinum-sensitive). This could have potentially selected for a group of patients with a poorer prognosis. However, on the NOVA study, there were actually more patients (though small numbers overall) with violations of this criterion on the niraparib arm than on the placebo arm. If any bias was introduced by this, it would have favored the placebo arm. Based upon the robust study results, it does not appear that imbalance between arms had an impact on the study results overall.

Table of Demographic Characteristics

The baseline demographics by study arm and disease cohort are shown in Table 11-11. They were overall well balanced between treatment arms, and between the gBRCA and non-gBRCAm cohorts. The median age among all patients who received niraparib was 61 years, and among those who received placebo was 60 years. The majority of patients were white. Approximately 40% of all patients were enrolled in the US or Canada and 60% enrolled in Europe and Israel. The highest enrolling countries in Europe included Germany, Denmark, Spain, France, and Great Britain.

Table 11-11 Baseline Demographics NOVA Study

Demographic	gBRCAmut cohort n= 203		Non-gBRCAmut cohort N=350			
			HRD positive N=162		Entire cohort N=350	
	Niraparib N=138 n(%)	Placebo N= 65 n(%)	Niraparib N=106 n(%)	Placebo N=56 n(%)	Niraparib N=234 n(%)	Placebo N=116 n(%)
Age						
Mean (SD)	56.9 (9.3)	57.2 (9.2)	61.8 (9.4)	59.1 (8.9)	62 (9.4)	59 (9.6)
Median	57	58	62	59	63	60
Range	36,83	38, 73	40, 83	38, 82	33, 84	34, 82
18-64y	110 (80)	49 (75)	63 (59)	40 (71)	130 (56)	69 (59)
≥ 65y	28 (20)	16 (25)	43 (41)	16 (29)	104 (44)	47 (41)
≥ 75y	4 (3)	0	8 (8)	9 (16)	19 (8)	16 (14)
Race						
White	123 (89)	55 (84)	89 (84)	49 (88)	201 (86)	101 (87)
Black	1 (0.7)	1 (2)	3 (3)	1 (2)	4 (2)	1 (1)
Asian	2 (1.4)	3 (6)	5 (5)	2 (4)	10 (4)	4 (3)
American Indian/ Alaska	1 (0.7)	0	0	0	0	0
Hawaiian/ Pacific Islander	0	0	0	0	0	0
Unknown	11 (8)	6 (8)	9 (8)	4 (6)	19 (8)	10 (9)
ECOG						
0	91 (66)	48 (74)	71 (67)	43 (77)	160 (68)	78 (67)
1	47 (34)	17 (26)	35 (33)	13 (23)	74 (32)	38 (33)
BMI (kg/m^2), n						
Mean (SD)	26.0 (5.7)	26.8 (6.0)	26.1 (6.0)	26.1 (4.4)	26.2 (5.7)	26.4 (5.3)
Median	24.7	25.5	25.0	25.6	25.0	25.6
Range	13.9-44.6	19.0-50.4	17.6-43.8	19.3-36.5	13.9-45.6	18.0-50.4
Geog. region						
US, Canada	53 (38)	28 (43)	44 (42)	22 (39)	96 (41)	44 (28)
Europe, Israel	85 (62)	37 (57)	62 (58)	34 (61)	138 (59)	72 (62)

Reviewer comment: The demographic characteristics of patients were generally well balanced between the study arms and between the gBRCA and non-gBRCA cohorts. In the gBRCA cohort, the majority of patients (75-80%) were between 18-64 years of age, whereas there were more patients (40%) across arms in the non-gBRCA cohort who were ≥ 65 years of age. This is at least in part due to the fact that patients carrying a gBRCA mutation typically present with malignancies at younger age. The majority of patients across all cohorts were white, which is also expected with a population of women diagnosed with ovarian cancer and carrying a gBRCA mutation. Although the demographics of the patients in the trial, particularly for the gBRCA cohort, are representative of a population of ovarian cancer patients with gBRCA mutations, it is notable that patients with ovarian cancer who carry a gBRCA mutation are not as prevalent in the general population as are those without a gBRCA mutation (non-gBRCA). For example, it is estimated that the incidence of deleterious germline BRCA mutation (gBRCAm)-associated ovarian cancer is approximately 10-15% of all cases of ovarian cancer, this corresponds to an annual incidence of approximately 2000 cases per year in the US. (Pal 2005, Zhang 2011). In the NOVA trial, 37% of the ITT population was comprised of patients with gBRCA mutation. Therefore the gBRCA mutation cohort is overrepresented in this trial, as compared to the general population.

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

Baseline disease characteristics for the NOVA study are shown in

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Table **11-12**. Most patients (>80%) across all cohorts had an ovarian primary tumor, with serous histology. More than 60% of patients in all cohorts had fewer than three metastatic sites of disease. Except for some minor variability, about half of patients were in complete response to their last platinum regimen, with the other half having a PR (and therefore, "measurable disease" by RECIST criteria). Approximately 60% of patients in the gBRCA cohort had received two prior lines of platinum (with 40% receiving more than 2 prior platinum regimens). This number was higher in the non-gBRCA patients, where 70% had received 2 prior platinum regimens, compared with 30% receiving more than 2 platinum regimens. The reason for this is unclear, but it does corroborate the results for number of other chemotherapy regimens received. In the gBRCA cohort, more than half of patients received 3 or more prior chemotherapy regimens (including platinum), whereas only 30-40% of patients in the other cohorts had received 3 or more prior regimens. Although there was variability across the non-gBRCA cohort, this may indicate that patients in the gBRCA cohort were overall more heavily pretreated than the non-gBRCA patients enrolled on the study, regardless of study arm. Finally, across all cohorts, 27% of patients had received prior bevacizumab.

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Table 11-12 Baseline Disease Characteristics NOVA Study

	gBRCA n=203		Non-gBRCA N=350			
			HRD pos N=162		Entire cohort N=350	
	Niraparib N=138 (%)	Placebo N=65 (%)	Niraparib N=106 (%)	Placebo N=56 (%)	Niraparib N=234 (%)	Placebo N=116 (%)
Primary tumor						
Ovarian	122 (88)	53 (82)	88 (83)	49 (88)	192 (82)	96 (83)
Primary peritoneal	7 (5)	6 (9)	10 (9)	4 (7)	24 (10)	8 (7)
Fallopian tube	9 (7)	6 (9)	8 (8)	3 (5)	18 (8)	11 (9)
Missing	0	0	0	0	0	1 (1)
Histologic subtype						
Serous	122 (88)	59 (91)	103 (97)	55 (98)	225 (96)	114 (99)
Endometrioid	8 (6)	3 (4.5)	1 (1)	1 (2)	3 (1)	0
Mucinous	0	0	0	0	0	0
Other/ Missing/ Not available	8 (6)	3 (4.5)	2 (2)	0	6 (2)	1 (1)
# metastatic sites						
<3	89 (64)	40 (62)	71 (67)	37 (66)	157 (67)	79 (68)
≥3	49 (36)	25 (38)	35 (33)	19 (34)	77 (33)	37 (32)
gBRCA variant						
BRCA1	85 (62)	43 (66)	NA	NA	NA	NA
BRCA2	51 (38)	18 (28)	NA	NA	NA	NA
BRCA1/2	9 (7)	4 (6)	NA	NA	NA	NA
Response to last platinum (IVRS)						
CR	71 (51)	33 (51)	59 (56)	27 (48)	117 (50)	60 (52)
PR	67 (49)	32 (49)	47 (44)	29 (52)	117 (50)	56 (48)
Interval from penultimate platinum (IVRS)						
6-12 m	54 (39)	26 (40)	33 (31)	23 (41)	90 (38)	44 (38)
≥ 12 m	84 (61)	39 (60)	73 (69)	33 (59)	144 (62)	72 (62)
Number of lines of prior platinum						
1	1	0	0	0	0	0
2	79 (57)	37 (57)	75 (71)	40 (71)	174 (74)	87 (75)
>2	58 (43)	28 (43)	31 (29)	16 (29)	60 (26)	28 (25)
Missing	0	0	0	0	0	1
Number of lines of prior chemotherapy						
1	1 (1)	0	0	0	0	0
2	70 (51)	30 (46)	66 (62)	35 (63)	155 (66)	77 (66)
3	40 (29)	20 (31)	26 (26)	10 (18)	55 (23)	17 (15)
4	13 (9)	10 (15)	7 (6)	5 (9)	11 (5)	12 (10)
≥5	14 (10)	5 (8)	7 (6)	6 (10)	13 (6)	9 (7)

Missing	0	0	0	0	0	1 (2)
Prior Bevacizumab (IVRS)						
Yes	33 (24)	17 (26)	31 (29)	8 (14)	62 (26)	40 (34)
No	105 (76)	48 (74)	75 (71)	48 (86)	172 (74)	76 (66)

Reviewer comments

- *It is noted that the HRD+ subgroup in the non-gBRCAmut cohort was not defined based on a stratification factor, and an approximately 10% difference was observed in the distributions of the three stratification factors between the two arms. The review team has performed a sensitivity analysis for PFS in this subgroup to adjust for these three factors, and the results are consistent to the primary findings (see FDA's PFS sensitivity analyses).*
- *The stratification factor data used in the primary PFS analysis were collected from IVRS. The review team has compared stratification data per IVRS and CRFs. The discordance rate of data from the two sources is low (in total only 7 patients with discordance), thus the source of stratification factor data should not affect the results.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Niraparib therapy is administered orally on a daily basis, with continuous dosing, making treatment compliance potentially difficult to assess accurately. In the current application, treatment compliance was assessed based upon pill counts, calculated according to number of pills dispensed compared to the number of pills returned at each clinic visit, and reported as a percent compliance. The Sponsor defined that a patient was "compliant" if she took at least 80% of the assigned doses, and less than 120% of the assigned doses. The analysis of treatment compliance by arm and cohort are shown in Table 11-13, and described as percentages.

Table 11-13 Treatment Compliance NOVA Study

	Niraparib safety population N=367		**Placebo safety population N=179**	
	gBRCA n=136 %	Non-gBRCA N=231 %	gBRCA n=65 %	Non-gBRCA N=114 %
Overall compliance assessable, n	135	229	65	113
Median	91	89	99	99
Mean (SD)	87 (14)	87 (14)	98 (6)	98 (4)
Min, max	19, 107	27, 120	59, 113	81, 109

Analysis performed using the ADEX analysis dataset.

Reviewer comment: It seems that a true assessment of treatment compliance is difficult in the setting of an orally dosed medication, particularly due to reliance upon pill count as the metric of whether patients actually took their doses as scheduled. However, despite the limitation in interpreting these data, on its face, it appears that patients were overall relatively "compliant" with the prescribed regimen. Compliance was higher in the placebo group, which can, in part, be attributed to the higher rate of dose delays due to adverse event in patients taking niraparib. Finally, the Sponsor's use of a range for defining compliance to be inclusive of up to 120% is puzzling, given that it does not seem that any patients should have had compliance over 100%. The inclusive range of 80- 120% seems to detract from the overall validity of the analysis, and there is no rationale for the use of this range described in the protocol

Subsequent Therapies

Subsequent anti-cancer therapy information is summarized in Table 11-14 for the three patient cohorts separately. Overall, more patients treated with placebo on the NOVA study went on to receive subsequent anticancer therapy, regardless of cohort. Fewer patients receiving subsequent therapy in the niraparib arm may be partially due to fewer patients experiencing disease progression on that arm, at the time of the analysis. The most common specific agents received are shown and include carboplatin with our without another agent, taxanes, and anthracyclines. Only patients in the gBRCA cohort received subsequent therapy with another PARP inhibitor, olaparib, which is an approved product in for patients with gBRCAm advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

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Table 11-14 Subsequent Anticancer Therapies

	gBRCAm n=203		Non-gBRCA			
			HRD+ N=162		Entire non-gBRCA cohort N=350	
Subsequent chemotherapy agents	**Niraparib N=138 (%)**	**Placebo N=65 (%)**	**Niraparib N=106 (%)**	**Placebo N=56 (%)**	**Niraparib N=234 (%)**	**Placebo N=116 (%)**
Patients receiving any subsequent anticancer therapy	54 (39)	42 (65)	48 (45)	41 (73)	130 (56)	81 (70)
Chemotherapy	51 (37)	41 (63)	48 (45)	39 (70)	127 (54)	78 (67)
Hormonal therapy	1 (1)	2 (3)	4 (2)	3 (5)	10 (4)	6 (5)
"Other"	14 (10)	10 (15)	8 (5)	20 (36)	20 (9)	12 (10)
Specific subsequent anticancer agents						
Carboplatin or Carboplatin combination	34 (25)	21 (32)	22 (21)	21 (38)	63 (27)	41 (35)
Taxane	17 (18)	12 (18)	18 (17)	13 (23)	31 (13)	25 (22)
Anthracycline (Doxil)	22 (16)	14 (22)	17 (16)	18 (32)	52 (22)	32 (28)
Gemcitabine	10 (7)	14 (22)	19 (18)	10 (18)	41 (18)	24 (21)
Olaparib	11 (8)	10 (15)	0	0	1 (0.5)	0
Bevacizumab	9 (7)	7 (11)	11 (10)	11 (20)	28 (12)	20 (17)
Niraparib	0	0	0	1 (2)	0	2 (2)

Reviewer comment: More patients on placebo in all cohorts received subsequent anticancer therapy, with the most common agent received being platinum. This phenomenon is likely related to the improved PFS and therefore disease control experienced by patients treated with niraparib, as compared with placebo.

Efficacy Results – Primary Endpoint

The primary analysis of PFS was performed in the gBRCAmut and non-gBRCAmut cohort independently at a significance level of 1-sided 0.025. Within the non-gBRCAmut cohort, the HRD+ subgroup was tested first and followed by the entire cohort. Table 11-15 presents the results of primary analysis for PFS per IRC assessment on the ITT population, using the cutoff date of 30 May 2016. There was a statistically significant improvement in PFS for patients in the niraparib arm compared to patients in the placebo arm in all three pre-specified patient groups.

Table 11-15 Progression-Free Survival Analysis per IRC assessment

	gBRCAmut cohort		**non-gBRCAmut cohort**			
			HRD+ subgroup		**Entire Cohort**	
	Niraparib (n=138)	**Placebo (n=65)**	**Niraparib (n=106)**	**Placebo (n=56)**	**Niraparib (n=234)**	**Placebo (n=116)**
# of PFS events	58	44	56	45	125	88
rPD[1]	55	43	56	42	123	84
cPD[2]	1	1	0	2	2	3
Death	2	0	0	1	0	1
Median in months (95% CI)	21.0 (12.9, NR)	5.5 (3.8, 7.2)	12.9 (8.1, 15.8)	3.8 (3.5, 5.7)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)
HR (95% CI)[3]	0.26 (0.17, 0.41)		0.37 (0.24, 0.58)		0.45 (0.34, 0.61)	
P-value[4]	<0.0001		<0.0001		<0.0001	

[1] rPD= radiographic disease progression per disease progression criterion #1 as defined in Section 7.2.1
[2] cPD=clinical disease progression per disease progression criteria #2 and #3 as defined in Section 7.2.1
[3] based on stratified Cox proportional hazards model using randomization stratification factors
[4] based on stratified log-rank test using randomization stratification factors
NR=Not Reached
[Source: response to information request dated as 12 December 2016]

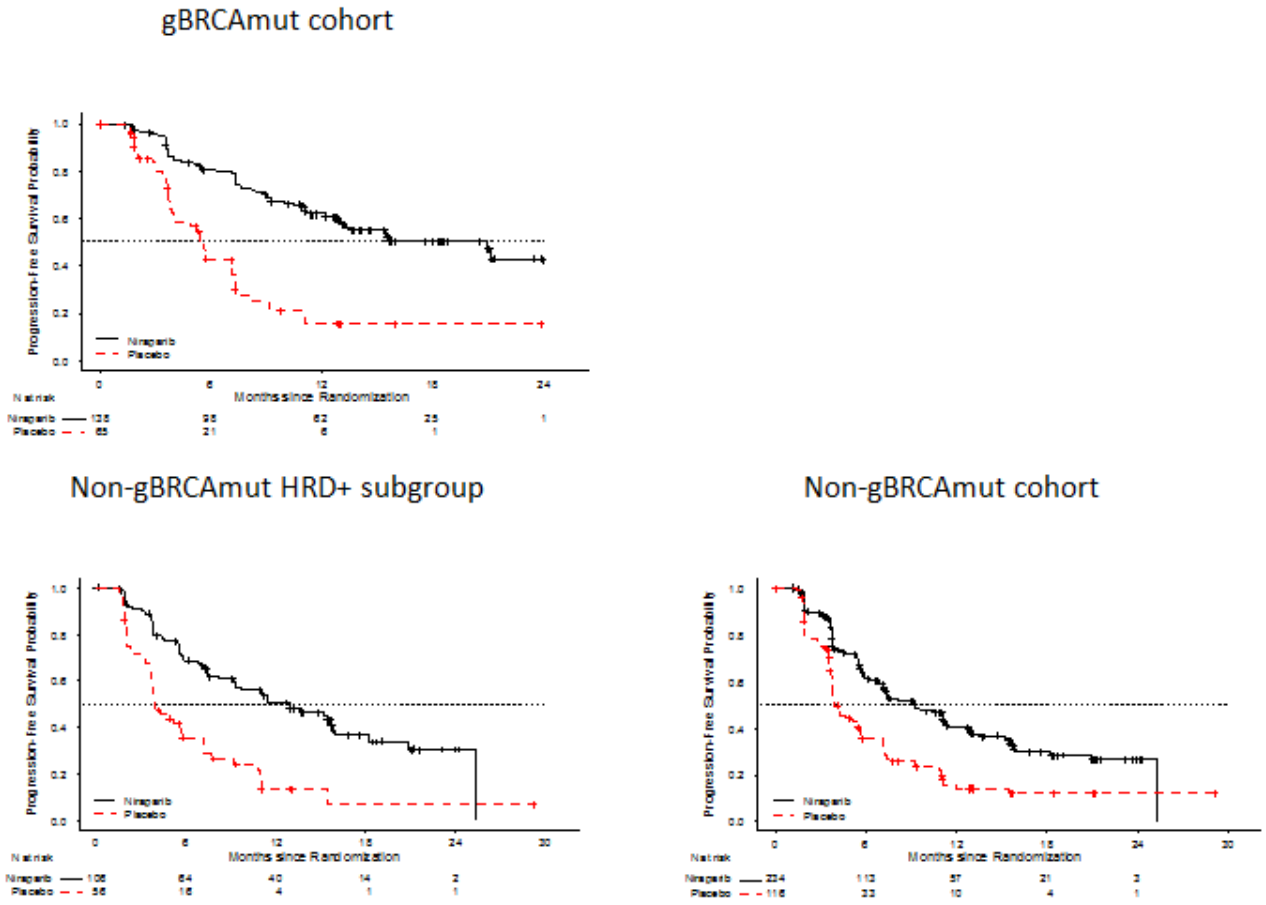

Figure 11-2 Kaplan-Meier Curves for PFS per IRC Assessment

Reviewer comment: The PFS results for each of the 3 pre-specified cohorts reached statistical significance, with the largest improvement in PFS median being in the gBRCA cohort, where the point estimate of PFS median for the niraparib arm is 21 months. As shown in Figure above, the number of patients at risk around the median estimate is small and the Kaplan-Meier curve is almost a plateau since month 16. Therefore, the estimate of median for niraparib arm may not be robust and reliable. The non-gBRCAm cohort had the smallest improvement in PFS median over placebo, at approximately 6 months, which is still considered to be clinically meaningful in this disease setting.

The review team performed an exploratory analysis for all-comers (ITT) by pooling the two independent cohorts together, and the results are shown in Table 11-16. The Sponsor performed this exploratory analysis, as well. The hazard ratio of IRC-PFS was 0.42 (95% CI: 0.34, 0.53). The Kaplan-Meier curves are in Figure 11-3

Table 11-16 IRC-PFS Results in the Pooled Dataset, FDA's Exploratory Analysis

	Pooled Dataset	
	Niraparib (n=372)	**Placebo (n=181)**
# of PFS events	183 (49%)	132 (73%)
rPD[1]	178	127
cPD[2]	3	4
Death	2	1
Median in months (95% CI)	11.3 (9.6, 13.6)	4.7 (3.8, 5.6)
HR (95% CI)[3]	0.42 (0.34, 0.53)	

[1] rPD= radiographic disease progression per disease progression criterion #1 as defined in Section 7.2.1
[2] cPD=clinical disease progression per disease progression criteria #2 and #3 as defined in Section 7.2.1
[3] based on stratified Cox proportional hazards model using cohort as the stratification factor

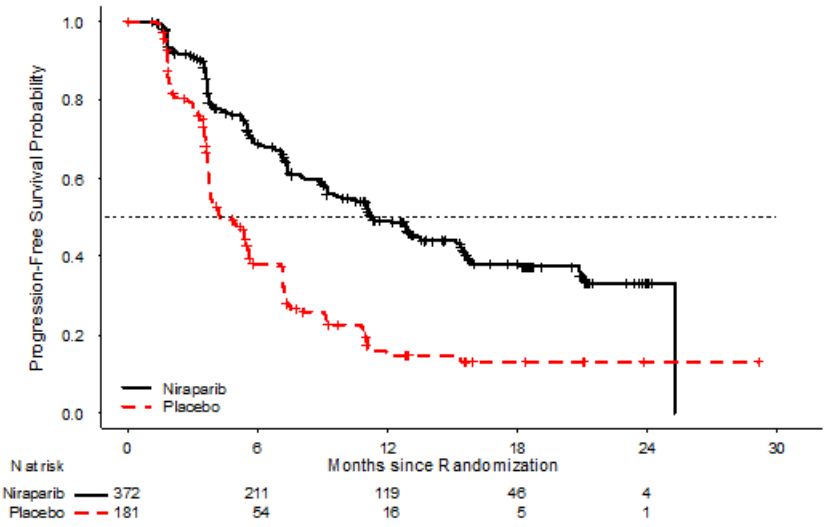

Figure 11-3- Kaplan-Meier Curves for PFS per IRC Assessment, in the Pooled Dataset

Reviewer comment: Interpretation of the pooled analysis result should be done with care, as the prevalence rate of gBRCAmut in the pooled dataset may not reflect the real world prevalence, since only about 10-15% of cases of ovarian cancer occur in patients with gBRCA mutation, yet approximately 37% of patients in the ITT population on the NOVA study had underlying gBRCA mutation. It is suspected that the PFS improvement of niraparib over placebo may be less in a true "all-comers" population than that seen on the NOVA study, but how much less is unknown.

The applicant performed multiple sensitivity analyses for PFS to evaluate the impact of protocol deviations, missing visits, treatment discontinuation, and non-protocol anti-cancer therapy before disease progression, et al. Results are in line with the primary findings and are shown in Table 11-17 .

Table 11-17 Applicant's PFS Sensitivity Analyses

gBRCAmut cohort			Non-gBRCAmut cohort					
			HRD+ subgroup			Entire Cohort		
Niraparib Median (months)	**Placebo Median (months)**	**HR (95% CI)**	**Niraparib Median (months)**	**Placebo Median (months)**	**HR (95% CI)**	**Niraparib Median (months)**	**Placebo Median (months)**	**HR (95% CI)**
S1: IRC-PFS excluding patients with major protocol deviations								
21.0	5.5	0.28 (0.18, 0.43)	12.9	3.7	0.32 (0.21, 0.50)	9.3	3.8	0.43 (0.32, 0.59)
S2: Unstratified IRC-PFS								
21.0	5.5	0.30 (0.20, 0.45)	12.9	3.8	0.37 (0.24, 0.56)	9.3	3.9	0.50 (0.38, 0.65)
S3: PFS per investigator assessment								
14.8	5.5	0.27 (0.18, 0.40)	11.4	4.0	0.34 (0.23, 0.52)	8.7	4.3	0.53 (0.41, 0.68)
S4: Radiographic PD only IRC-PFS								
21.0	5.5	0.26 (0.17, 0.41)	12.9	3.8	0.39 (0.25, 0.60)	9.3	3.9	0.46 (0.34, 0.62)
S5: Limited censoring IRC-PFS								
11.2	5.4	0.35 (0.23, 0.50)	9.3	3.8	0.42 (0.28, 0.63)	5.9	3.8	0.66 (0.51, 0.85)
S6: IRC-PFS using scheduled assessment dates								
21.0	5.5	0.26 (0.17, 0.41)	12.9	3.8	0.38 (0.24, 0.59)	9.2	3.8	0.45 (0.34, 0.61)

[Source: CSR Tables 27, 30, and 32]

FDA's PFS sensitivity analyses

The review team conducted additional sensitivity analyses to evaluate the robustness of the primary findings of PFS. The results are summarized in Table 11-18.

Sensitivity Analysis 1: This analysis was conducted to determine the impact of the "global review update" of the central blinded review utilized in the primary PFS analysis. This was performed using information provided by the Applicant in response to an information request sent by the FDA, and the purpose was to ascertain what the results of the PFS analysis would have been in the absence of the

global review updates, and to ascertain whether bias could have been inserted into the study results based upon the use of the global update process. The global review of central radiographic assessments changed the disease progression status for 14 patients (PD vs. censor) and 66 patients' progression or censoring date. This sensitivity analysis used timepoint-by-timepoint radiographic assessment data only, and did not consider the change made by global review from central radiologists.

Sensitivity Analysis 2: Approximately 12% of patients randomized across both cohorts were censored in the primary IRC-PFS analyses due to disease progression determined by investigator but not confirmed by central review and no further follow-up disease assessment. This might lead to informative censoring. This sensitivity analysis considered those patients as PFS events at the next scheduled assessment time.

Sensitivity Analysis 3: In the non-gBRCAmut cohort, HRD status was not a stratification factor. Therefore, some disease characteristics are not balanced between the two treatment arms in the non-gBRCAmut HRD+ subgroup. In this sensitivity analysis, a hazard ratio of IRC-PFS in the HRD+ subgroup was estimated from a Cox regression model adjusted by use of bevacizumab in conjunction with the penultimate or last platinum regimen, time to progression after the penultimate platinum therapy before study enrollment, and best response during the last platinum regimen. .

Sensitivity Analysis 4: A PFS analysis used programmatically re-derived tumor data from investigator based raw lesion measurements following RECIST v1.1 (the re-derived data were provided by the Applicant in response to a FDA information request).

Sensitivity Analysis Conclusion: Estimates of hazard ratios in these sensitivity analyses are consistent with those in the primary analysis across the three populations. It has been noted that the point estimate of PFS median on the niraparib arm varies in the gBRCAmut cohort, and the lack robustness for the median point estimate in this cohort has been discussed in the primary PFS analysis. Overall, the results of sensitivity analyses support the primary PFS findings.

Table 11-18 FDA's PFS Sensitivity Analyses

	gBRCAmut cohort			**Non-gBRCAmut cohort**					
				HRD+ subgroup			**Entire Cohort**		
	Niraparib Median (months)	Placebo Median (months)	HR (95% CI)	Niraparib Median (months)	Placebo Median (months)	HR (95% CI)	Niraparib Median (months)	Placebo Median (months)	HR (95% CI)
SA1	16.1	5.8	0.27 (0.17, 0.42)	11.1	3.8	0.39 (0.25, 0.60)	8.0	3.9	0.46 (0.34, 0.61)
SA2	13.6	5.4	0.27 (0.18, 0.41)	11.1	3.8	0.36 (0.24, 0.55)	7.4	3.8	0.47 (0.36, 0.62)
SA3	-	-	-	12.9	3.8	0.34 (0.22, 0.51)	-	-	-
SA4	14.1	5.5	0.29 (0.19, 0.43)	11.2	4.0	0.34 (0.22, 0.51)	8.5	4.3	0.51 (0.40, 0.67)

FDA's analysis of discordance between IRC and INV assessment of disease progression

Per the study design, disease status was assessment by both IRC and INV. The primary PFS analysis was based on the IRC assessment, with the INV-based PFS as a supportive analysis. An analysis of discordance rate between the different cohorts is shown in Table 11-19. The discordance rate between IRC and INV assessment in terms of PFS status (event vs. censoring) was 17% in the niraparib arm and 11% in the placebo arm for the gBRCAmut cohort. In the non-gBRCAmut cohort, the discordance rate was 20% and 15% for the niraparib arm and placebo arm, respectively.

Table 11-19 Discordance Rate of PFS Event Status between IRC and INV Assessment

	gBRCAmut Cohort		**Non-gBRCAmut Cohort**			
			HRD+ Subgroup		**Entire Cohort**	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
Overall discordance rate, n(%)	23 (17%)	7 (11%)	15 (14%)	8 (14%)	48 (20%)	17 (15%)
PFS event by IRC, n(%)	58 (42%)	44 (68%)	56 (53%)	45 (80%)	125 (53%)	88 (76%)
PFS event by INV, n(%)	55 (40%)	44 (68%)	53 (50%)	44 (79%)	120 (51%)	86 (74%)
Censored by INV, n(%)	3 (2%)	0	3 (3%)	1 (2%)	5 (2%)	2 (2%)
Censored by IRC, n(%)	80 (58%)	21 (32%)	50 (47%)	11 (20%)	109 (47%)	28 (24%)
Censored by INV, n(%)	60 (43%)	14 (22%)	38 (36%)	4 (7%)	66 (28%)	13 (11%)
PFS event by INV, n(%)	20 (15%)	7 (11%)	12 (11%)	7 (13%)	43 (18%)	15 (13%)

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints included overall survival, time to first subsequent therapy, time to second subsequent therapy, chemotherapy-free interval, progression-free survival 2, and patient-reported outcomes. It has been noted that there was no multiplicity adjustment pre-specified in the study protocol and SAP; therefore, no statistical conclusions can be made based on these analyses and no formal inference could be drawn.

Overall Survival

Overall survival was a secondary efficacy endpoint. No specific hypothesis testing plan was pre-specified for survival analysis. OS was compared between the two arms at the time of primary PFS analysis as the other secondary endpoints. As of the clinical cutoff date 30 May 2016, 94 patients (24 in the gBRCAmut cohort and 70 in the non-gBRCAmut cohort) out of the total 553 randomized patients have died. Results of OS analyses in the three patient populations are summarized in Table 11-20 and Kaplan-Meier curves are shown in **Figure 11-4.**

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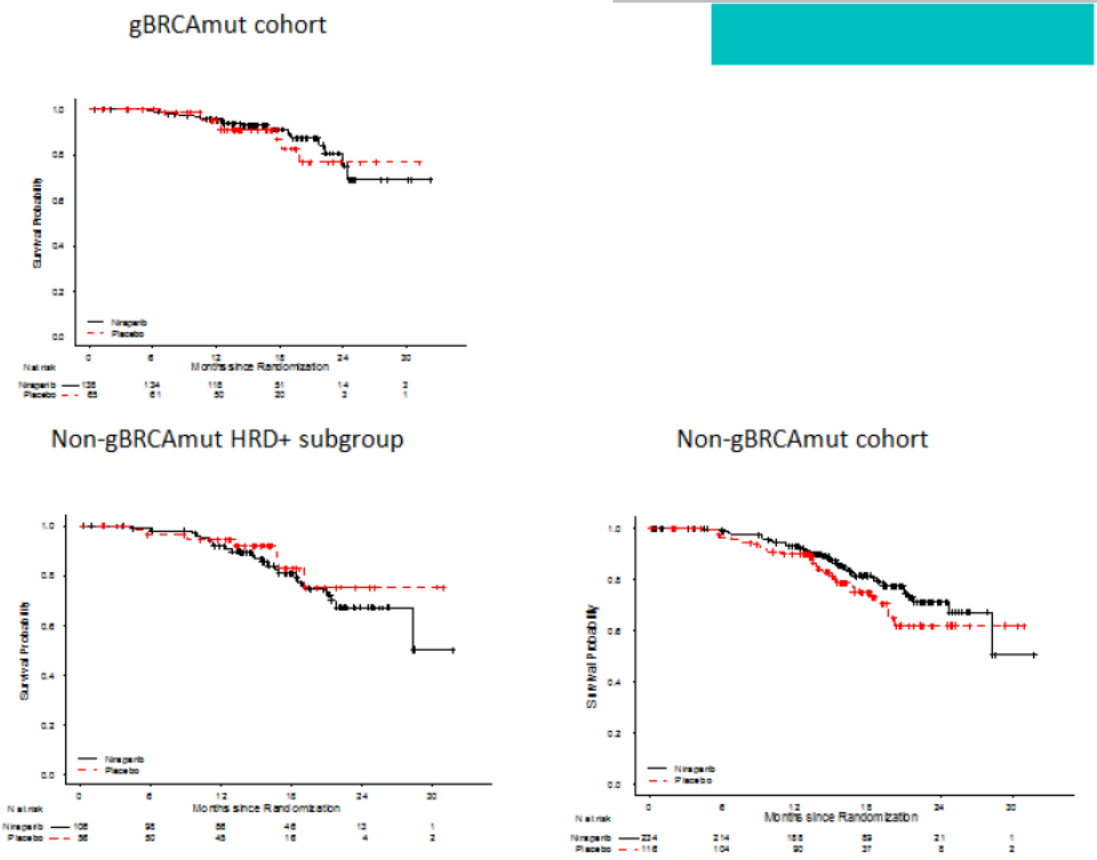


Figure 11-4 Kaplan-Meier Curves for Overall Survival

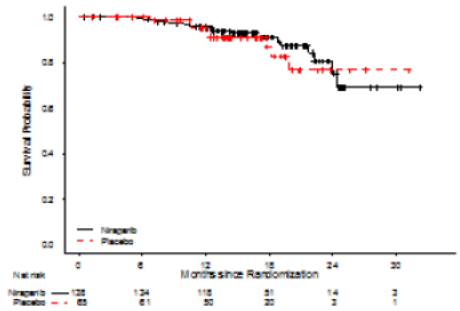
Table 11-20 Results of Overall Survival

	gBRCAmut cohort		non-gBRCAmut cohort			
			HRD+ subgroup		Entire cohort	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
# of deaths	16 (12%)	8 (12%)	23 (22%)	7 (13%)	43 (18%)	27 (23%)
Median (95% CI) (months)	NR (24.5, NR)	NR	NR (28.3, NR)	NR	NR (28.3, NR)	NR (20.2, NR)
HR (95% CI)[1]	0.92 (0.37, 2.32)		1.39 (0.57, 3.42)		0.72 (0.44, 1.18)	

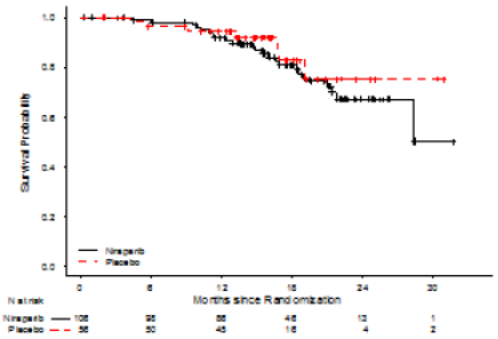
[1]based on Cox proportional hazards model stratified by randomization stratification factors
NR=not reached
[Source: CSR Tables 15 and 14.2.4.1]

Reviewer comment: In the non-gBRCAmut HRD+ subgroup, the point estimate of hazard ratio is 1.39 but with a wide 95% confidence interval include 1. It is noted that this is a small subgroup analysis and only approximately 20% of patients have died at the time of analysis. Due to limited overall survival information, no definitive conclusion could be drawn on overall survival. Further survival data are still being collected, and updated descriptive survival analyses may be submitted with longer follow-up.

gBRCAmut cohort



Non-gBRCAmut HRD+ subgroup



Non-gBRCAmut cohort

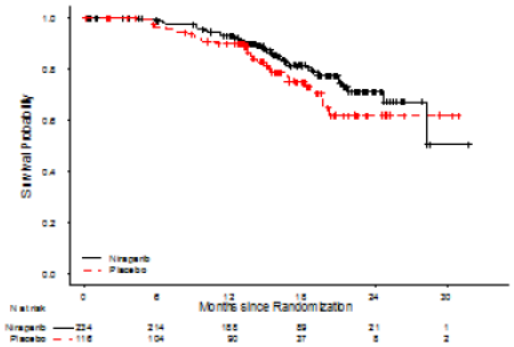


Figure 11-5 Kaplan-Meier Curves for Overall Survival

Similar to the pooled PFS analysis, the review team performed an exploratory OS analysis for all comers by pooling the two independent cohorts together. The hazard ratio of OS was 0.73 (95% CI: 0.48, 1.11). The K-M curves for OS for the pooled population are shown in Figure 11-5.

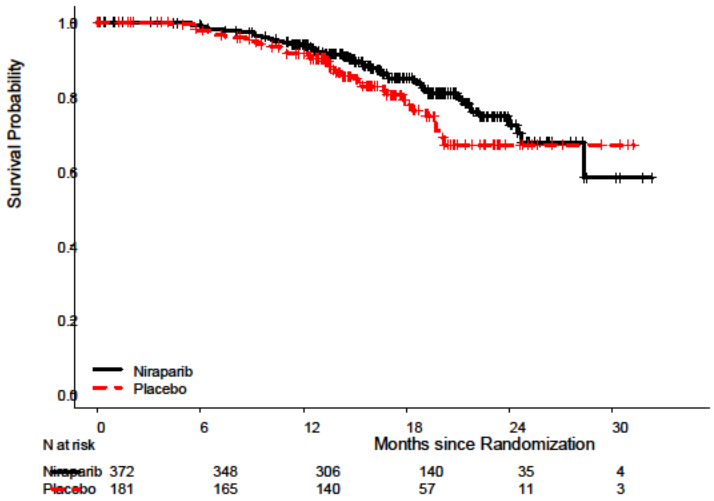


Figure 11-6 Kaplan-Meier Curves for Overall Survival, in the Pooled Dataset

Progression-Free Survival 2

PFS2 was defined as the time from treatment randomization to the earlier date of assessment of progression on the next anticancer therapy or death by any cause. As of the clinical data cutoff date, a total of 64 PFS2 events have occurred in the gBRCAmut cohort, 158 in the overall non-gBRCAmut cohort, and 64 in the non-gBRCAmut HRD+ subgroup. Analysis results for PFS2 are summarized in Table 11-21 .

Table 11-21 Analysis Results of Progression-Free Survival 2

	gBRCAmut cohort		non-gBRCAmut cohort			
			HRD+ subgroup		Entire cohort	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
# of PFS2 events	39 (28%)	25 (38%)	38 (36%)	23 (41%)	102 (44%)	56 (48%)
Median (95% CI) (months)	25.8 (20.3, NR)	19.5 (13.3, NR)	22.3 (18.6, NR)	17.6 (12.9, NR)	18.6 (16.2, 21.7)	15.6 (13.2, 20.9)
HR (95% CI)[1]	0.48 (0.28, 0.82)		0.65 (0.37, 1.12)		0.69 (0.49, 0.96)	

[1] Based on stratified Cox proportional hazards model using randomization stratification factors. [Source: CSR Tables 37, 38, 14.2.5.1]

Reviewer comment: As noted, PFS2 was defined as time from treatment randomization to the earlier date of disease progression on the next anticancer therapy following study treatment or death due to any cause. The Sponsor noted that 50-70% of data for patients across the treatment arms and cohorts were censored for this reporting, as of data cutoff. Therefore, the data are immature. In addition, interpretation of this endpoint is confounded by the variability in the subsequent anticancer treatments patients went on to receive after study discontinuation and by the variability in tumor assessment intervals post-progression, since there was no required or fixed assessment interval in the protocol for PFS2. As a result, no definitive conclusions can be made from the analysis of this endpoint in the context of this application. Likewise, analyses of other secondary endpoints including time to first and second anticancer therapies are difficult to interpret, particularly since the clinical meaning of these endpoints in this disease setting is unclear.

Time to First Subsequent Therapy and Time to Second Subsequent Therapy

Results for time to first subsequent therapy and second subsequent therapy are summarized in Table 22.

Table 11-22 Analysis Results of Time to First Subsequent Therapy and Time to Second Subsequent Therapy

	gBRCAmut cohort		**non-gBRCAmut cohort**			
			HRD+ subgroup		**Entire cohort**	
	Niraparib (n=138)	**Placebo (n=65)**	**Niraparib (n=106)**	**Placebo (n=56)**	**Niraparib (n=234)**	**Placebo (n=116)**
Time to first subsequent therapy						
# of events	58 (42%)	43 (66%)	53 (50%)	43 (77%)	138 (59%)	87 (75%)
Median (95% CI) (months)	21.0 (17.5, NR)	8.4 (6.6, 10.6)	15.9 (12.4, NR)	6.0 (1.7, 9.8)	11.8 (9.7, 13.1)	7.2 (5.7, 8.5)
HR (95% CI)[1]	0.31 (0.21, 0.48)		0.36 (0.23, 0.57)		0.55 (0.41, 0.72)	
Time to second subsequent therapy						
# of events	33 (24%)	23 (35%)	31 (29%)	19 (34%)	85 (36%)	49 (42%)
Median (95% CI) (months)	25.8 (22.4, NR)	20.5 (16.0, NR)	NR (20.3, NR)	20.8 (15.4, NR)	21.1 (18.5, NR)	20.3 (15.1, NR)
HR (95% CI)[1]	0.48 (0.27, 0.85)		0.66 (0.36, 1.23)		0.74 (0.52, 1.07)	

[1] Based on stratified Cox proportional hazards model using randomization stratification factors.
[Source: CSR Tables 33, 34, 14.2.11, and 14.2.12]

Chemotherapy-Free Interval

Results for chemotherapy-free interval are summarized in Table 11-23.

Table 11-23 Analysis Results of Chemotherapy-Free Interval

	gBRCAmut cohort		non-gBRCAmut cohort			
			HRD+ subgroup		Entire cohort	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
# of events	54 (39%)	42 (65%)	48 (45%)	41 (73%)	130 (56%)	81 (70%)
Median (95% CI) (months)	22.8 (17.9, NR)	9.4 (7.9, 10.6)	18.2 (14.2, 24.3)	7.7 (6.3, 10.6)	12.7 (11.0, 14.7)	8.6 (6.9, 10.0)
HR (95% CI)[1]	0.26 (0.17, 0.41)		0.31 (0.19, 0.49)		0.50 (0.37, 0.67)	

[1] Based on stratified Cox proportional hazards model using randomization stratification factors.
[Source: CSR Tables 35, 36, and 14.2.8]

Reviewer comment: It is noted that the starting time for chemotherapy-free interval calculation was the date of last platinum therapy prior to randomization instead of randomization date like other endpoints. As the length of interval between date of last platinum therapy and date of randomization varies among patients, this may introduce bias to the analysis and the results may be uninterpretable. In addition, similar to the endpoints of time to first and second subsequent therapies, the clinical meaning of the endpoint of chemotherapy-free interval is unknown.

Patient-Reported Outcomes

Please refer to the review of Patient-Reported Outcomes performed by Lynn Howie and Lijun Zhang.

Additional Analyses Conducted on the Individual Trial

Exploratory subgroup analyses of IRC-PFS by demographics and baseline disease characteristics are presented in Table 11-24. In addition, exploratory analyses in various mutational subgroups were performed, as shown in Table 11-25.

Table 11-24 Subgroup Analyses of IRC-PFS per Baseline Characteristics

	Niraparib		Placebo		IRC-PFS HR (95% CI)*
	n of events/ N of patients	Median (months)	n of events/ N of patients	Median (months)	
gBRCAmut cohort					
Age					
<65	47/110	15.5	32/49	7.2	0.32 (0.20, 0.51)
≥65	11/28	NR	12/16	3.7	0.23 (0.10, 0.55)
ECOG PS					
0	38/91	21.0	32/48	5.8	0.31 (0.19, 0.51)
1	20/47	15.7	12/17	5.0	0.23 (0.11, 0.49)
Region					
USA and Canada	19/53	NR	17/28	5.8	0.26 (0.13, 0.52)
Europe, Israel	39/85	15.7	27/37	5.4	0.31 (0.18, 0.51)
TTP before enrollment					
6-12 months	31/54	10.5	19/26	3.9	0.36 (0.20, 0.65)
≥12 months	27/84	NR	25/39	7.2	0.23 (0.13, 0.41)
Use of Bev					
Yes	15/33	15.5	14/17	4.1	0.17 (0.07, 0.39)
No	43/105	21.0	30/48	7.2	0.34 (0.21, 0.55)
BOR on last platinum regimen					
CR	29/71	21.0	21/33	5.8	0.35 (0.19, 0.62)
PR	29/67	15.5	23/32	5.3	0.24 (0.13, 0.43)
Number of prior platinum regimens					
2	29/79	NR	25/37	5.8	0.26 (0.15, 0.46)
>2	29/58	13.6	19/28	5.4	0.32 (0.18, 0.60)
Non-gBRCAmut cohort					
Age					
<65	75/130	7.4	52/69	4.2	0.58 (0.40, 0.83)
≥65	50/104	11.1	36/47	3.8	0.40 (0.26, 0.62)
ECOG PS					
0	90/160	7.4	59/78	4.3	0.56 (0.40, 0.78)
1	35/74	11.2	29/38	3.7	0.38 (0.23, 0.63)
Region					
USA and Canada	48/96	9.3	35/44	3.9	0.47 (0.30, 0.73)
Europe, Israel	77/138	9.3	53/72	4.2	0.51 (0.36, 0.73)
TTP before enrollment					
6-12 months	55/90	5.9	37/44	3.6	0.42 (0.27, 0.65)
≥12 months	70/144	11.3	51/72	5.6	0.51 (0.35, 0.73)
Use of Bev					

Yes	35/62	7.1	25/30	3.9	0.43 (0.25, 0.73)
No	90/172	9.6	63/86	3.8	0.52 (0.37, 0.71)
BOR on last platinum regiment					
CR	60/117	11.0	43/60	7.2	0.62 (0.42, 0.92)
PR	65/117	7.5	45/56	3.6	0.33 (0.22, 0.50)
Number of prior platinum regimens					
2	89/174	9.3	66/87	4.2	0.53 (0.38, 0.73)
>2	36/60	9.2	22/28	3.7	0.39 (0.22, 0.67)

*based on unstratified Cox proportional hazards model

Table 11-25 IRC-PFS Subgroup Analyses by Mutation Type

	Niraparib		Placebo		IRC-PFS HR (95% CI)*
	n of events/ N of patients	Median (months)	n of events/ N of patients	Median (months)	
Non-gBRCAmut HRD+ somatic mutation	15/35	20.9	7/12	11.0	0.27 (0.08, 0.90)
Non-gBRCAmut HRD+ wild type	41/71	9.3	38/44	3.7	0.37 (0.22, 0.61)
Non-gBRCAmut HRD-	54/92	6.9	35/42	3.8	0.58 (0.36, 0.92)
Non-gBRCAmut HRD Unknown	15/36	8.0	8/18	7.3	0.54 (0.19, 1.50)
Tumor BRCAmut[1]	73/173	20.9	51/77	5.7	0.26 (0.18, 0.39)
HRD+ by myChoice HRD™ test[2]	114/244	15.4	89/121	5.2	0.30 (0.22, 0.41)

*HR is based on Cox proportional hazards model stratified by randomization stratification factor.
[1] tumor BRCAmut was defined as BRCA mutation in tumor, including germline and somatic mutation. This cohort included patients in the gBRCAmut cohort and the somatic BRCA mutation subgroup of the non-gBRCAmut cohort
[2]HRD+ by myChoice HRD™ test included patients in the gBRCAmut cohort and the non-gBRCA cohort HRD+ subgroup.

Reviewer comments

All the subgroup analyses are considered exploratory or hypothesis generating and no formal inference may be drawn. No apparent outliers were observed in the subgroup analyses.

11.3. Integrated Review of Effectiveness

11.3.1. Assessment of Efficacy Across Trials

Primary Endpoints

The NOVA trial, PR-30-5011-C was the single trial used to support the efficacy of niraparib as a maintenance therapy for patients with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer who had received at least 2 platinum-based regimens and were in response to their last platinum-based chemotherapy. An integrated review of efficacy across trial was not conducted; however, as has been described in the efficacy analysis of the NOVA trial, the results of the PFS endpoint were robust across cohorts and even in the overall ITT population, as depicted in Table 11-15 and Table 11-16.

Secondary and Other Endpoints

See discussion of secondary endpoints for the NOVA trial, described above.

Subpopulations

Exploratory subgroup analyses for PFS by demographics and baseline disease characteristics were conducted and are shown in Table 11-24 and 25. No formal conclusions can be made about any specific subpopulation, but overall, the robustness of the PFS improvement for niraparib over placebo was basically consistent across multiple subpopulation analyses, including ECOG PS, use of prior bevacizumab, region of enrollment, and platinum-free interval.

11.3.2. Integrated Assessment of Effectiveness

Although there were additional studies submitted in the application in support of safety outcomes, the only study designated to support the effectiveness of niraparib in any context was the NOVA study, which has already been discussed in this review. It is notable that no efficacy data was included in any of the study reports from the OCT pool studies (including QUADRA and PN001). The Sponsor conducted integrated efficacy analyses, by "pooling" results from the 2 main cohorts (gBRCA and non-gBRCA) in the NOVA study, and as noted in prior sections (including Table 11-16), the PFS results in the two cohorts were supportive of each other, even though the efficacy was most robust in the gBRCA cohort.

11.4. Review of Safety

11.4.1. Safety Review Approach

The main focus of the safety review for this application is on study PR-30-5011-C (NOVA), however, the Sponsor also conducted a pooled analysis of four additional studies which enrolled patients with ovarian, fallopian tube, and primary peritoneal cancers. Safety data from these four studies, shown in Table 11-26, were pooled to form the "Ovarian Cancer Therapy Pool" or OCT Pool, and data from these pooled studies were assessed separately from the NOVA study to provide additional safety information

on niraparib. The OCT pool did not include the NOVA study, nor were any integrated analyses, combining the NOVA study and the OCT pool, conducted. The key study in the OCT pool was the QUADRA study (PR-30-5020-C), which was a single-arm, open-label study of niraparib monotherapy in patients with advance, relapsed high grade serous ovarian, fallopian tube, or primary peritoneal cancer who had received ≥ 3 prior lines of therapy. Two NOVA sub-studies, the QT study and the food effect study were also included, as well as the initial dose finding study (PN001). When including all patients who received niraparib, there were 367 patients on NOVA and 384 patients in the OCT pool, for a total of 751 patients to comprise the overall safety database.

11.4.2. Review of the Safety Database

Overall Exposure

The NOVA study comprised the key exposure data in support of the application, and 367 patients were exposed to the proposed dose of 300 mg daily on that study. Supportive data from the OCT pool included an additional four studies with 384 patients. Patients in the OCT pool received varying dosing regimens and durations, as shown in Table 11-26.

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Table 11-26 Niraparib Exposure in OCT Pool

	Niraparib dose	Niraparib schedule/ study design	Indication	Number patients exposed
QUADRA (PR-30-5020-C)	300 mg daily	Continuous dosing Open-label	Ovarian cancer with ≥ 3 prior lines of therapy	291
PN001	Dose finding; range 30 mg- 400 mg q d	Continuous dosing	Advanced solid tumors and hematologic malignancies	50
FE Study (NOVA Sub Study)	300 mg single dose; 300 mg daily	Single dose; 14-day cross over study with extension Open-label	Similar to NOVA, but patients could have any platinum status, response to platinum, or disease burden. Had to have no standard therapy available	17
QTc Study (NOVA Sub study)	300 mg daily	Open-label ECG evaluation with treatment extension	Similar to NOVA, but patients could have any platinum status, response to platinum, or disease burden. Had to have no standard therapy available	26
Total				384

Relevant characteristics of the safety population:

The primary source for safety data came from the NOVA study, but the OCT pool added an additional cohort of patients, most of whom also had ovarian cancer, and the majority of these patients also received the proposed dose of 300 mg daily niraparib. The baseline characteristics for patients treated on the NOVA Study were shown in Table 11-11 and

Table 11-12.

Adequacy of the safety database:

The NOVA study included 372 patients who received treatment with niraparib 300 mg daily, and these patients comprised the primary focus of the safety review. There were 7 patients (5 niraparib and 2 placebo) who did not experience an adverse event, therefore the safety population on the NOVA study included 367 patients who were treated and experienced and adverse event on treatment. Additional supportive safety data from the 367 patients in the OCT pool were supportive. The overall safety database was considered to be adequate.

11.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

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

Categorization of Adverse Events

The safety and tolerability of niraparib was based upon assessment of patient deaths, adverse events, serious adverse events, laboratory assessments, and vital sign measurements. Adverse events were graded according to the NCI CTCAE version 3.0 and coded using Medical Dictionary for Regulatory Affairs (MedDRA) version 17.0. Adverse events were categorized by System Organ Class (SOC) and Preferred Term (PT).

Routine Clinical Tests

The schedule of assessments on the NOVA study, as outlined in the protocol, is shown in Figure 11-6. The figure depicts the frequency of laboratory testing, vital signs, and adverse event monitoring. The protocol specified that if dosing was interrupted or modified due to hematologic toxicity at any point during the study, the frequency of CBC blood draws was subsequently increased to a weekly schedule (if it had been less frequently) for at least 4 weeks after occurrence of the event. This was due to the high proportion of patients experiencing hematologic adverse events such as neutropenia, but it was also a method by which to more efficiently identify patients who could be at risk for, or were experiencing myelodysplasia and/or leukemia.

Cycle[1]	Screening	1				2	Subsequent Cycles[2]	Study Treatment Discontinuation (visit within 7 days of last dose)	Post Treatment Assessments
Day	-28 to -1	1[3]	8	15	21	1	Cycle n, Day 1		
Randomization	X[8]								
Physical examination	X	X		X		X	X	X	
Vital signs, height,[9] weight	X	X		X		X	X	X	
ECOG performance status	X	X				X	X	X	
Adverse event monitoring	X	X		X		X	X	X[10]	
Concomitant medications	X	X		X		X	X	X	
Coagulation/serum chemistry	X	X[11]		X		X	X	X	
CBC[12]	X	X	X	X	X	X	X	X	
Serum CA-125[13,14]	X	X				X	X	X	
Urinalysis[15]	X								
12-lead ECG[16]	X	X				X		X	

[7] Negative serum pregnancy test required within 72 hours from first dose of study treatment for females of childbearing potential; repeated every 3 months for duration of study (ie, Cycle 4, Cycle 7, etc).
[8] Randomization must occur within 72 hours prior to first dose.
[9] Height obtained at screening only.
[10] SAEs recorded up to 30 days after study treatment discontinuation.
[11] If Screening laboratory testing (serum chemistry, CBC, coagulation) performed within 72 hours of Day 1, repeat testing not required.
[12] If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the adverse event resolves, and to ensure safety of the new dose, weekly blood draws for CBC will be also be required for an additional 4 weeks after the adverse event has been resolved to the specified levels, after which monitoring every 4 weeks may resume.
[13] CA-125 levels must be normal at screening or > 90% decrease as compared with baseline prior to last platinum-based chemotherapy course. Abnormal CA-125 levels during study do not represent disease progression; however, they may prompt imaging if clinically indicated. CA-125 sample within 72 hours of dose on Cycle 1/Day 1.
[14] For determination of CA-125 progression, at least 2 CA-125 values at least 1 week apart are required for confirmation (Section 6.1).
[15] Urinalysis parameters must include: specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen, and bilirubin.

Cycle[1]	Screening	1				2	Subsequent Cycles[2]	Study Treatment Discontinuation (visit within 7 days of last dose)	Post Treatment Assessments
Day	-28 to -1	1[3]	8	15	21	1	Cycle n, Day 1		
Triplicate ECGs (selected sites only)		X[17]							
Tumor sample[18]	X								
Blood sample for PK		X[19,20]				X	X[21]		
Tumor Assessment (RECIST)[22]	X						X	X	X
Chest CT/MRI[23]	X								
FOSI, EQ-5D-5L, neuropathy questionnaire[24]	X						X	X	X

[16] Patients will have a 12-lead ECG at Screening, Baseline (predose, within 30 minutes), 2 hours postdose on Day 1(within 30 minutes), Cycle 2/Day 1, (predose, 2 hours postdose, within 30 minutes) and upon study treatment discontinuation. Note that the ECG is to be completed prior to the PK blood draw.
[17] At selected sites, a subset of patients (approximately 24) will undergo triplicate ECG testing on Day 1 only at baseline (predose) and 1, 1.5, 2, 3, 4, 6 and 8 hours postdose. Triplicate ECGs should be performed between 2-5 minutes apart and should be performed prior to blood draws for PK.
[18] Formalin fixed, paraffin-embedded tumor sample (primary or metastatic site) consisting of 100 micron thickness of sections (≥ 80 micron minimum) or unsectioned paraffin block.
[19] Blood samples for PK collected on Cycle 1/Day 1 and Cycle 2/Day 1 collected predose (within 30 minutes) and 2 hours postdose (within 30± 15 minutes Note: The exact time of the PK blood draw will be recorded and ECG monitoring is to be completed prior to the PK blood draw.
[20] At selected sites, a subset of patients (approximately 12) undergoing intensive PK on Day1 will have samples collected at baseline (within 30 minutes predose) and 1, 1.5, 2, 3, 4, 6 and 8 hours (± 2 minutes at all time points) postdose. Note: The exact time of the PK blood draw will be recorded and the ECG monitoring is to be completed prior to the PK blood draw.
[21] Additional blood samples for PK on Cycle 4/Day 1 and Cycle 8/Day 1 will be collected at predose (trough) within 30 minutes only.
[22] RECIST tumor assessment via CT or MRI scan of abdomen/pelvis and clinically indicated areas required at baseline, then after every 2 cycles (ie, 8 weeks with a window of ± 7 days from date of visit) through Cycle 14 (56 weeks), then after every 3 cycles (12 weeks with a window of ± 7 days) until study treatment discontinuation; at this point, a final follow-up set of imaging is required. PET/CT may be used according to RECIST guidelines. Cycle timing will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for clinical progression and does not meet the criteria specified in the protocol, scans and CA-125 testing should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment.
[23] Chest CT/MRI if not done as part of RECIST tumor assessment at Screening. If the chest CT/MRI is clear at screening, repeat chest imaging is not required in the absence of lesions to be followed or in the absence of clinical indication requiring follow-up.

Figure 11-7 Schedule of Assessments

11.4.4. Safety Results

An overview of the key safety events on the NOVA study are depicted in Table 11-27 and these will be discussed in detail later in the review.

Table 11-27 Safety Overview NOVA Study

	Niraparib N=367			Placebo N= 179		
	gBRCAm	**Non-gBRCA**	**Total**	**gBRCAm**	**Non-gBRCA**	**Total**
	N=136 (%)	N=231 (%)	N=367 (%)	n=65 (%)	N=114 (%)	N=179 (%)
G1-4 AE	136 (100)	231 (100)	367 (100)	61 (94)	110 (96)	171 (96)
G3-4 AEs	108 (80)	164 (71)	272 (74)	14 (22)	27 (24)	41 (23)
SAEs	42 (31)	68 (29)	110 (30)	7 (11)	20 (18)	27 (15)
AE leading to discontinuation	18 (13)	36 (16)	54 (15)	1 (2)	3 (3)	4 (2)
AEs leading to Death	0	0	0	0	0	0

Deaths

There were no adverse events with an outcome of death within 30 days on either treatment arm in the NOVA study. Overall, only about 20% of deaths had occurred across all cohorts at the time of data cutoff, as shown in Table 11-20, but all of them occurred during the follow-up period beyond 30 days after study discontinuation.

Serious Adverse Events

Serious adverse events occurring in ≥ 1% of patient on either arm of the NOVA study are depicted in Table 11-28. A total of 137 patients overall experienced at least one serious adverse event, with 30% of niraparib treated patients experiencing a serious adverse event and 15% of niraparib treated patients experiencing a serious adverse event. Several events, including bowel obstruction, abdominal pain, effusion, ascites and metastases were most likely related to the underlying ovarian cancer rather than to niraparib, per se. One patient treated with placebo in the non-gBRCAm, HRD+ cohort was diagnosed

with breast cancer while on study, which was considered to be a serious adverse event and lead to study discontinuation.

Table 11-28 Serious Adverse Events ≥ 1% on NOVA Study

Adverse Event	**Niraparib N=367 (%)**	**Placebo N=179 (%)**	**Total N=546 (%)**
Patients with SAE	**110 (30)**	**27 (15)**	**137 (25)**
Thrombocytopenia	41 (11)	0	41 (7)
Anemia	14 (4)	0	14 (3)
Bowel obstruction	8 (2)	4 (2)	12 (2)
Abdominal pain/discomfort/distention	3 (1)	2 (1)	5 (1)
Constipation	4 (1)	1 (1)	5 (1)
Urinary tract infection	3 (1)	2 (1)	5 (1)
Pleural effusion	3 (1)	2 (1)	5 (1)
Fever	4 (1)	0	4 (1)
Neutropenia (including febrile neutropenia)	4 (1)	0	4 (1)
Ascites	2 (0.5)	2 (1)	4 (1)
Nausea	1 (0.3)	3 (2)	4 (1)
Ileus	2 (0.5)	2 (1)	4 (1)
Metastases to CNS	0	2 (2)	2 (0.3)
Breast cancer	0	1 (1)	0

Dropouts and/or Discontinuations Due to Adverse Effects

On the NOVA study 54 patients (15%) discontinued niraparib due to an adverse event and only 4 patients (2%) discontinued placebo due to an adverse event. Adverse events leading to dose interruption and dose reduction occurred in substantially more patients treated with niraparib, and are shown in Table 11-29. This analysis was particularly concerning upon initial review, calling into question whether the Sponsor's proposed dose of 300 mg daily for niraparib was appropriate. An in-depth analysis of the dosing for niraparib, including dose-response for efficacy and safety endpoints, was conducted by the Clinical Pharmacology reviewers. Although it is notable that dose reductions and

interruptions were necessary for more than half of patients treated with niraparib, these modifications were almost exclusively due to cytopenias, including thrombocytopenia, anemia, and neutropenia. It was found in the analysis that the majority of modifications occurred within the first few months on therapy (90% occurred by Cycle 4). In most cases, patients requiring dose reductions in particular, were typically able to reach a stable, tolerable dose by the 4th cycle, and were often able to stay on that dose for the duration of therapy, often for many months.

Table 11-29 Dose Modifications and Discontinuations on NOVA Study

	Niraparib			**Placebo**		
	gBRCAm n=136 (%)	**Non-gBRCA n=231 (%)**	**Total n=367 (%)**	**gBRCAm N=65 (%)**	**Non-gBRCA N=114 (%)**	**Total N=179 (%)**
Any AE leading to discontinuation.	18 (13)	36 (16)	**54 (15)**	1 (2)	3 (3)	**4 (2)**
AE leading to dose interruption	93 (68)	151 (65)	**244 (66)**	10 (15)	16 (14)	**26 (15)**
AE leading to dose reduction (200 mg qd)	108 (79)	175 (76)	**253 (69)**	3 (5)	7 (6)	**9 (5)**
AE leading to second dose reduction (100 mg qd)	54 (40)	74 (32)	**128 (35)**	1 (2)	3 (3)	**4 (2)**

Reviewer comment: Based upon the analyses conducted by both the clinical and clinical pharmacology teams, and in light of the compelling efficacy seen with niraparib therapy, it was determined that the proposed starting dose of 300 mg daily is the acceptable dose. Product labeling provides adequate guidance to clinicians on when and how to institute when dose reductions and interruptions, based upon toxicities, most of which are hematologic.

Significant Adverse Events

Myelodysplastic Syndrome/Acute Myelogenous Leukemia

The potential for development of MDS and/or AML after treatment with PARP inhibitors has been described (Kim, 2015) and was known to be a risk for patients receiving niraparib therapy. The protocol for the NOVA study, in particular, had specific guidance for investigators to follow in the event of emergence of prolonged cytopenias or other indicators of possible development of MDS/AML. In particular, it was recommended that patients be referred for hematology consultation to undergo bone marrow analysis for morphology and cytogenetics in the event of any suspicious/ prolonged hematologic laboratory abnormalities.

On the NOVA study, there were 5 patients treated with niraparib (1.4%) who developed MDS or AML, and there were 2 cases diagnosed in patients who received placebo (1.1%). There 2 additional patients in the niraparib safety database who were also diagnosed with MDS/AML, one patient on the food-effect portion of the NOVA study, and one patient on the QUADRA study. In total, the overall incidence of MDS or AML out of 751 patients treated with niraparib in the entire safety database was 0.9%.

The Table 11-30 depicts an overview of the characteristics of the diagnoses in all 9 patients diagnosed with MDS/AML. Only 1 patient (placebo, NOVA) was actually diagnosed with AML. The remaining 8 patients had MDS at the time of diagnosis. Three of the 9 patients (33%), including both placebo patients, had died at the time of data cutoff. All patients had been treated with at least 2 prior chemotherapy regimens, including one patient with 13 prior lines of therapy. Most of the patients received prior anthracyclines and/or alkylating agents. Only one patient had documented exposure to radiation therapy. The duration of therapy with niraparib prior to diagnosis with MDS/AML was highly variable and ranged from 15- 559 days. In total, 3 niraparib patients and 1 placebo patient diagnosed with MDS/AML had underlying gBRCA mutation. The remaining patients either did not have an underlying gBRCA mutation, or the status was unknown. None of the patients from the non-gBRCA cohort were documented to be HRD-positive.

Only 4 of the 9 patients had documented cytogenetic abnormalities (2 niraparib, 2 placebo), but these were consistent with therapy-related MDS/AML, in that they involved chromosomes 5 or 7.

Reviewer comment: It is notable that the incidence of MDS/AML in the niraparib database was compared (by the review team) to the incidence seen the olaparib database, since both agents are PARP inhibitors indicated for the treatment of ovarian cancer patients, including those with gBRCA mutation. On olaparib, the incidence of MDS/AML was 0.8% overall out of 2618 patients exposed, and it was 2.2% on the randomized, placebo-controlled trial, Study 19. Bearing in mind the limitations of comparing between agents and studies, it was encouraging that the incidence in the niraparib database appears to be in line with this similar agent, and does not appear to be worse. As clinicians gain more experience with the use of PARP inhibitors, awareness of this risk will continue to increase, and potentially methods to mitigate the risk may come to be available. At this point in time, clinicians must weigh this (and all risks) of niraparib therapy when making treatment decisions for individual patients.

Table 11-30 MDS and AML Cases in the Safety Database

#	Stu-dy	Patient ID/ Age	Arm	Cancer under treatment	BRCA stat.	Days on nirap/ placebo	Prior chemo agents received for cancer in question	Prior XRT? y/n	Dx	Cyto-genetics (if done)	Outcome
1	NOVA	001003-00008 69y	placebo	Ovarian	gBRCA mut	140	1.cisplatin/ carboplatin/ paclitaxel 2.abagovomab 3.carboplatin 4.carboplatin/ doxorubicin 5.carboplatin/ doxorubicin	No	**AML**	**17p-, 5q-**	Death
2	NOVA	033002-00013 60y	placebo	Primary peritoneal	Non-gBRCA HRD neg	111	1.carboplatin/ paclitaxel 2.carboplatin/ liposomal doxorubicin 3.carboplatin/ gemcitabine (after discon from NOVA study)	No	**MDS**	**7p-**	Death
3	NOVA	001024-00004 59y	Niraparib	Primary peritoneal	gBRCA mut	334	1. carboplatin/ cisplatin/ paclitaxel 2. Topotecan 3. carboplatin 4. carboplatin/ bevacizumab	Yes	**MDS**	Data not provided	Death

4	NOVA	033002-00025 64y	Niraparib	Ovarian	gBRCAm	308	1.paclitaxel/ carboplatin 2.liposomal doxorubicin/ carboplatin 3.gemcitabine/ carboplatin 4.carboplatin 5.liposomal doxorubicin/ carboplatin	No	**MDS**	**5q-, monosomy 7**	Ongoing
5	NOVA	034005-00003 58 y	Niraparib	Ovarian	Non-gBRCA HRD not determined	559	1.carboplatin/ paclitaxel/ bevacizumab 2.bevacizumab maintenance 3. carboplatin/ paclitaxel 4.carboplatin/ liposomal doxorubicin	No	**MDS** IPSS-R score - 5 (high risk)	Not reported	Ongoing
6	NOVA	047002-00001 46 y	Niraparib	Ovarian	gBRCAm	371	1.carboplatin/ paclitaxel 2.carboplatin/ liposomal doxorubicin	No	**MDS** (RAEB-2) with trilinear dysplasia	**5p-, monosomy 7, monosomy 21, add 8(p11) x2**	Ongoing
7	NOVA	972003-00001 64 y	Niraparib	Ovarian	Non-gBRCA / HRD neg	217	1.carboplatin/ paclitaxel 2.liposomal doxorubicin/carboplatin 3.carboplatin/gemcitabine	No	**MDS** (IPSS score not avail)	Not reported	Ongoing

8	NOVA-FE	001007-00002	Niraparib	ovarian	FE study-no documented gBRCA or HRD status.	23	1.carboplatin/ paclitaxel 2.Xyotax (paclitaxel form) 3.carboplatin 4.LY573636 5.gemcitabine/ ARQ 197 6.BB-1091 7.Tivozanib 8.Tivozanib (listed separate by Sponsor) 9.U31565-A-U101 10.carboplatin 11.paclitaxel 12. liposomal doxorubicin 13.IMGN 853	Unknown	**MDS**	Not reported	Ongoing
9	QUADRA	001426-404 63 y	Niraparib	ovarian	Non-gBRCA (HRD unk)	15	1.carboplatin/ paclitaxel 2.carboplatin/gemcitabine 3.arimidex 4.carboplatin+liposomal doxorubicin 5.bevacizumab+ cyclophosphamide	Unk.	MDS	Not reported	Ongoing

Discussion of the narratives for the 9 patients diagnosed with MDS/ AML are presented as follows:

1. 001003-0008- NOVA study, placebo arm, gBRCAm. AML.
   69 year old white female stage IIIC HGS primary peritoneal cancer 3/08. Also previous diagnosis of breast cancer. On study dates were 10/9/14 until 2/25/15. She received 4 prior lines of platinum, as well as other anticancer therapy including taxanes, anthracyclines, mAb

(abagovomab). No prior XRT. Prior duration of therapeutic regimens was 1205 days. She had a history of myelosuppression, and CBC at screening reported as "below normal ranges". Treatment with placebo was interrupted on 2/25/15 (C6) due to G1 thrombocytopenia (also had diarrhea, flank pain, nausea and leukopenia in the same timeframe), and was never restarted. On 3/24/15, neutropenia was G3, thrombocytopenia G2 and treatment remained interrupted. 4/3/15, thrombocytopenia worsened to G3. (b) (6), bone marrow biopsy revealed acute myeloid leukemia (AML) with 80% blasts in the marrow. 50% of the leukocytes expressed CD34, CD117, CD33, dim CD13 and CD7. FISH showed mixed lineage leukemia (MLL), no evidence of MLL rearrangement. Cytogenetics: complex karyotype with **loss of 17p and deletion of 5q**, associated with poor prognosis. This was considered to be therapy-related AML vs. AML with myelodysplastic changes. On (b) (6), she was hospitalized. Initiated therapy for AML with azacitidine on (b) (6). Discharged from hospital (b) (6). Readmitted on (b) (6) with fever, diarrhea, vomiting from rotavirus. Discharged (b) (6). On (b) (6) she fell at home and sustained a subarachnoid hemorrhage. She was hospitalized and mental status declined. She was unable to follow commands or control bowel/ bladder. (b) (6), chest CT showed infiltrating aspergilloma. On (b) (6), went to palliative care. On (b) (6), she died. Cause of death on narrative listed as complications from subarachnoid hemorrhage and traumatic brain injury. Neutropenia was ongoing at time of death.

Reviewer comment: Patient treated on placebo arm. History of gBRCA mutation, prior breast cancer and primary peritoneal cancer. Prior therapies for cancers included anthracycline, taxanes, and monoclonal antibodies within the 6 years from the time of diagnosis or peritoneal cancer and on-study date. Reported to have had prior myelosuppression and had counts below normal range at time of on-study. Developed worsening cytopenias during study, and had therapy interrupted due to G1 thrombocytopenia and other AEs on 2/25/15. Therapy was never restarted. She was diagnosed with therapy-related AML (cytogenetics showed loss of 17p and deletion of 5q). Initiated azacitadine, but subsequently fell and sustained a subarachnoid hemorrhage (presumably related to the underlying thrombocytopenia). She never recovered mental status. Developed infection with aspergillus, with continued neutropenia and thrombocytopenia. Died on (b) (6). Agree with sponsor that cause of death was from sequelae from subarachnoid hemorrhage, but secondary cause should be considered to be complications from therapy-related AML.

2. 0033002-00013- NOVA study, placebo arm, non-gBRCA/HRD neg. MDS.
60 year old female (unknown race) diagnosed with stage IIIA primary peritoneal cancer in 9/12. Underwent TAH/BSO and extensive abdominal surgery. She received 2 lines of platinum based chemotherapy (carbo/taxol and carbo/doxorubicin). She had a prior history of myelosuppression prior to study. She had not received prior XRT. Other medical history was notable for only migraines, depression, hemorrhoids. She started on NOVA study (placebo arm)

when in PR from carbo/doxorubicin regimen on 10/22/14. Baseline platelets were reported as normal, and ANC was below normal range (G1). Her course during study was significant for only G1-2 asthenia, G1 peripheral neuropathy, epistaxis (G1), bulimia nervosa (G1), G1 dyspnea, and G1 abdominal distention (no action with study drug taken). She was taken off study on 2/9/15 (after C4) due to disease progression. She was treated with platinum + gemcitabine after PD and discontinuation from NOVA study, from 8/15-10/15. During that therapy and after it was discontinued (approximately 10/15) she developed neutropenia (G1-3), leukopenia, and thrombocytopenia (G1-3). The chemotherapy regimen at that time was delayed d/t cytopenias. On (b) (6) she underwent bone marrow biopsy, which revealed G4 myelodysplastic syndrome (MDS). Specific details included that cytogenetic analysis revealed a clonal population with **del of short arm of chromosome 7**. Karyotype ranked in the middle groups of allogeneic abnormalities for MDS. On 11/25/15, she initiated therapy with azacitadine for MDS. She received no further therapy for peritoneal cancer, but reportedly died due to progressive peritoneal cancer on (b) (6) (almost (b) (6) after coming off the NOVA study).

Reviewer comment: Given that this patient was not treated with niraparib, this was clearly not the cause for her diagnosis with MDS. It seems that her main (only) risk for therapy related MDS was prior exposure to anthracycline, as she did not have documented gBRCA mutation.

3. 001024-00004- NOVA study, niraparib arm, gBRCAm. MDS.
59 year old white female started on niraparib arm 2/14/15. She was originally diagnosed with Stage IIA primary peritoneal cancer (HGS) 1/2108 and found to have gBRCA2 mutation. This patient also had a history of breast cancer diagnosed and treated in 1989. For the peritoneal cancer, she received 3 lines of platinum therapy. Other therapies included taxanes, topoisomerase inhibitor (topotecan), carboplatin and cisplatin and monoclonal antibody (bevacizumab). She also received pelvic radiation. Total duration for these regimens was 1381 days. She began niraparib on study on 2/12/14. Study baseline platelet count, WBC, and ANC were within normal limits. She received her last dose of study treatment on 1/11/15, and treatment was discontinued at that point due to disease progression. There is no mention of MDS/ AML in the narrative for the time she was on study therapy. There did not appear to be history of cytopenias during therapy (reported as AEs or in assessing lab values), with the exception of intermittent G1 thrombocytopenia. (b) (6) months after discontinuation, she died of MDS- on (b) (6).

Reviewer comment: No real data provided in the narrative to provide insight about the proximal history leading up to the AML diagnosis, as patent was off study at the time the diagnosis occurred and details were not provided.

4. 033002-00025- NOVA study, niraparib arm, gBRCAm. MDS.
64 year old female (unknown race) diagnosed with Stage IIIC high grade serous ovarian cancer 5/27/09. She received 5 lines of platinum-based chemotherapy, including paclitaxel+ carboplatin, doxorubicin + carboplatin (two separate times approx. 4 years apart), gemcitabine + carboplatin, and single agent carboplatin. The total duration of prior chemotherapy was 624 days. She had not received prior XRT. She began niraparib on the NOVA study on 6/1/15. She had a history of myelosuppression with previous chemotherapy regimens. On C1D21 ((b) (6)) she was found to have G4 thrombocytopenia which required interruption of niraparib treatment and was accompanied by G1 gingival hemorrhage. She received platelet transfusion. Niraparib was resumed on 7/9/15 at reduced dose (200 mg). On 8/8/15, she was found to have G3 neutropenia, and niraparib was interrupted. The neutropenia resolved by 8/13/15 and niraparib was again restarted with another dose reduction (100 mg). She continued therapy for several more months, until 4/2/16 when she was diagnosed with G1 MDS. She discontinued study treatment due to the MDS on 5/2/16, and at that point had received 11 cycles of therapy with niraparib. Cytogenetic analysis **revealed 5q**-, **monosomy 7**, and abnormality of chromosome 12. No information on whether the patient received therapy for MDS was reported. The MDS was ongoing at the time of last contact with the Sponsor, but specific date was not given.

Reviewer comment: This patient had received multiple lines of chemotherapy including anthracycline and platinum prior to initiating niraparib. Per the report, she had hemoglobin below normal range at baseline, however, her course during therapy with niraparib was complicated by thrombocytopenia and neutropenia requiring dose interruptions and the maximum allowable dose reductions. Cytogenetic analysis of the MDS clone(s) revealed 5q-, monosomy 7, and abnormal chromosome 12, which are consistent with expected aberrations seen in therapy-related MDS and/or AML. Given the duration of therapy with niraparib (11 cycles) and the cytogenetic abnormalities consistent with therapy-related MDS, a contribution of niraparib to the development of MDS in this patient cannot be ruled out, and is likely.

5. 034005-00003- NOVA study, niraparib arm, non-gBRCA, HRD unk. MDS.
58 year old white female with Stage IIIC high grade serous ovarian cancer diagnosed 6/30/11. She received 4 prior lines of therapy, including carboplatin for 3 lines, paclitaxel for 2 lines, bevacizumab, and liposomal doxorubicin. Total duration of prior therapies was 885 days. She had no history of myelosuppression, and received no prior XRT. She began niraparib on the NOVA study on 10/2/14, with normal baseline hematologic parameters. During C2, she experienced G1 anemia and lymphopenia, which persisted during C3 and C4. She continued on niraparib for 20 cycles, and presented to start C21 D1 on 4/12/16. At that time, she was found to have G2 anemia and G3 thrombocytopenia, which resulted in treatment interruption. Follow-up CBC one week later 4/19/16 showed G3 anemia and G2 thrombocytopenia. On 4/26/16, she was found to have G3 neutropenia, G2 anemia, and G1 thrombocytopenia (130K). On 5/5/16, she was diagnosed with G3 myelodysplastic syndrome (MDS with IPSS score 5.0, high-risk), and was withdrawn from the study and treatment with niraparib on 5/11/16. At the

time of the most recent follow-up on 6/1/16, she had not received any therapy for MDS or for her ovarian cancer.

Reviewer comment: This patient also received several lines of chemotherapy, including anthracycline, prior to initiation of niraparib. However, she remained on niraparib for approximately 18 months, receiving 20 cycles, which is longer than most patients on the present study. She had no prior radiation therapy and did not carry a gBRCA mutation. Given the timing of the onset of MDS after 20 cycles with niraparib, it seems likely that development of MDS in this patient was related to niraparib.

6. 047002-00001- NOVA study, niraparib arm, gBRCAm. MDS.
46 year old white female diagnosed with gBRCA-2 mutation, Stage IIIC high grade serous ovarian cancer on 6/27/12. She received 2 lines pf platinum therapy including carboplatin + paclitaxel and carboplatin + doxorubicin. Total duration of prior therapy was 277 days. She had a history of prior myelosuppression, but had received no prior XRT. She began on the NOVA study and received first dose of niraparib on 3/11/14. Baseline hematologic parameters were within normal limits. On C4 D1 (6/2/14), she was found to have G1 anemia, which worsened to G2 on (b) (6) (prompting RBC transfusion). During C5, anemia had improved to G1. However, when she presented for C6 ((b) (6)), she was found to have G4 anemia (hemoglobin 5.5 g/dL) and G1 thrombocytopenia. She had niraparib dose reduced to 200 mg daily, and was again transfused. She continued to have intermittent G1 anemia and thrombocytopenia and G1-2 neutropenia for the next several cycles, without any further dose delays or reductions. She started C15 on (b) (6), and developed G2 anemia again requiring transfusion. Platelet count subsequently worsened to G2, and gastroscopy and abdominal ultrasound were performed, but were found to be unremarkable for source of bleeding. Study treatment was subsequently discontinued on (b) (6), and reason for discontinuation was G2 thrombocytopenia (55K). She was also experiencing fever and diarrhea at that time, and was hospitalized for work up. On (b) (6), she had G2 anemia and G3 thrombocytopenia. Bone marrow biopsy was performed (b) (6) and she was diagnosed with MDS (RAEB 1-2) with 10% blasts. On (b) (6), she developed G3 abdominal pain requiring hospitalization. On (b) (6), bone marrow aspiration showed 30- 40% dysplastic megakaryocytes, and 12-13% blasts. The diagnosis was MDS (RAEB-2) with trilinear dysplasia. Cytogenetics showed deletion **5p, monosomy 7, monosomy 21,** and add 8(p11)x2. On 5/11/15, she initiated azacitadine for MDS. On (b) (6), she developed fistula between the small and large bowel, requiring colonic resection. She completed azacitadine on 6/26/15. She also received additional cisplatin chemotherapy in 4/16 for progressive ovarian cancer. At the time of most recent contact (9 months after study discontinuation), both ovarian cancer and MDS were ongoing.

Reviewer comment: This patient had a cancer with underlying gBRCA mutation. She was on niraparib for 15 cycles, and her course was complicated by recurrent anemia and thrombocytopenia as early as C2. She had received prior anthracycline therapy, but had no history of XRT. The cytogenetic abnormalities seen with her MDS (namely del 5p and monosomy 7) are the typical aberrations seen in treatment related MDS/ AML. Given these factors, the contribution of niraparib to the development of MDS in this case seems likely.

7. 972003-00001- NOVA study, niraparib arm, non-gBRCAm, HRD neg. MDS.
64 year old white female diagnosed with stage IV HGS ovarian cancer 1/14/10. She received 3 lines of platinum therapy, as well as therapy with taxanes, anthracyclines and antimetabolites. Specific regimens were carboplatin+ taxol 3/10-10/10, liposomal doxorubicin + carboplatin 8/11-9/12, gemcitabine + carboplatin from 4/14- 11/14. She did not receive prior XRT. Total duration of prior therapy was 675 days. She did have prior history of myelosuppression with previous regimens. She began therapy with niraparib on the NOVA study on 12/28/14. Baseline platelets and hemoglobin were reported to be in normal range. She missed doses during C2 due to elective surgery. (b) (6), she underwent elective surgical repair of abdominal aortic aneurysm. She was noted to have G2 anemia during C3, and also during C3, she developed G3 surgical wound infection requiring hospitalization and antibiotic therapy (niraparib was continued). Anemia fluctuated between G2-3, but on C4, she underwent dose reduction of niraparib due to anemia, and the anemia resolved to normal range hemoglobin after the dose reduction. During C5, she had G2 creatinine elevation and missed several doses of niraparib during C6 due to vomiting. On 7/20/15, she was found to have disease progression (end of C7), and was taken off study drug on 8/1/15. She had regular follow ups until withdrawal on 5/29/16 due to unblinding. She had received subsequent therapy with platinum after discontinuing niraparib therapy from 8/15- 1/16. She was diagnosed with MDS after discontinuing her last platinum regimen (due to progressive ovarian cancer), and the diagnosis of MDS was made on 2/8/16. The narrative states that the diagnosis of MDS was confirmed on (b) (6) by bone marrow biopsy, but not information on cytogenetics or IPSS-R score were available.

Reviewer comment: Many specific details of this patient's MDS diagnosis are missing, particularly cytogenetics. She did not have a documented gBRCA mutation or a history of XRT. She experienced intermittent anemia during therapy with niraparib. Although the contribution of niraparib in this patient's case of MDS is unclear, it cannot be excluded as a cause of the event.

8. 001007-00002- NOVA Food-effect study, non-gBRCA. MDS.
64 year old white female enrolled on the FE study of NOVA. Patient had history of ovarian cancer, high-grade serous, stage IIIC originally diagnosed 9/25/06. She did not have documented gBRCA mutation or HRD mutation. She had received 13 prior anticancer therapies before enrolling in the FE study (and briefly on the main study) of NOVA and had a history of prior anemia. The specific prior therapies included carboplatin+ paclitaxel x 2. LY573636, gemcitabine + ARQ197, BB-10901, tivozanib, U31565-A-U101, carboplatin, taxol, liposomal doxorubicin, IMGN 853. She initiated therapy with niraparib 300 mg on 7/22/13, then received the Day 8 dose on 7/29/13, completing the FE portion of the study. She began C1D1 on 8/5/13, with daily dosing of niraparib. Per the patient's CRF, she received her last dose of niraparib on 8/13/13 and discontinued from study on 9/3/13 (due to patient decision). She was reported to have G2 anemia during the treatment period with niraparib, as well as G4 neutropenia and G3 thrombocytopenia. She was diagnosed with MDS by bone marrow biopsy and aspirate on (b) (6). The biopsy showed trilineage dysplasia with ringed sideroblasts. Peripheral blood showed WBC 3100, hemoglobin 9.8, platelets 60K with occasional myelocytes by no blasts.

Reviewer comment: In the case of this particular patient, she received less than one month of therapy with niraparib, including that she only received weekly dosing for one of the 4 weeks. It was reported that she had a history of anemia prior to study enrollment, though details are lacking. Nevertheless, her counts worsened quickly during the short period on niraparib, including that she developed G3-4 cytopenias during treatment. Her reason for discontinuation from study 2 months after initiation was listed as "patient decision", which is uninformative. She was then diagnosed with MDS one month later. Although it is unknown what the minimum amount of exposure (to PARP-inhibitors and other agents known to cause MDS/AML) is that may be considered to be "causative" for the onset of MDS, it seems that this patient's particular case is unlikely to be related to niraparib and more likely to be related to the multiple other therapies she received previously, many of which also have associations with MDS/ AML.

9. 001426-404- QUADRA study, niraparib, non-gBRCA. MDS.
63 year old WF with Stage IIIC HGS ovarian cancer diagnosed 3/09, and had no underlying BRCA mutation. She received 3 lines of platinum therapy as follows: carboplatin+ paclitaxel, carboplatin + gemcitabine, arimidex, carboplatin + liposomal doxorubicin, bevacizumab + cyclophosphamide. This patient had a prior history of myelosuppression requiring G-CSF. Prior anticancer therapies included 7 years of treatment including platinum and bevacizumab. She apparently was only on niraparib therapy for 15 days, after which it was discontinued. She then was diagnosed with MDS one month after study discontinuation. No details on cytogenetics, therapy for MDS, or outcome are given.

Reviewer comment: In the case of this patient, the timing and duration of therapy with niraparib (15 days) make it unlikely that the MDS developed as a result of niraparib than as a result of the patient's multiple other therapies. However, at this time, it is unknown how little exposure to niraparib or other PARP-inhibitors can cause the inciting event that may lead to MDS.

Secondary malignancies other than MDS/AML

In the safety database, there were 5 reports on secondary malignancies other than MDS/AML in niraparib treated patients, shown in **Table 11-31**. All cases were on the NOVA or NOVA-FE studies. Three of them were skin cancers and two were in patients with gBRCAm. The other cancers included an auditory meningioma and an undifferentiated sarcoma. All patients had received other chemotherapy agents at some point in their ovarian cancer history.

Table 11-31 Secondary Malignancies in Niraparib-treated Patients

No.	Study	Patient ID	Age	Study treatment	BRCA status	HRD status	Secondary cancer	Time to onset (study day)
1	NOVA	001010-0003	64	niraparib	gBRCAm	-	Skin- BCC	284
2	NOVA	001030-0001	60	niraparib	Non-gBRCAm	HRD+	Auditory meningioma	295
3	NOVA	001032-0003	52	niraparib	gBRCAm	-	Skin- BCC	65
4	NOVA	033002-00017	62	niraparib	Non-gBRCAm	HRD+	Undifferentiated sarcoma	48
5	NOVA-FE	001004-00003	-	niraparib	-	-	Skin- SCC	134

Reviewer comment: The contribution of niraparib to these malignancies is unclear, but secondary malignancies besides MDS/AML have been documented after therapy with other PARP inhibitors, particularly skin cancers, and there could be a mechanistic contribution of niraparib in some of these cases of secondary cancers. Overall, given that most of the cancers are skin cancers, which are common in the general population it did not appear that the incidence of these events rose to the level that warranted a warning to be described in the product label.

Cardiovascular Adverse Events

NOVA

A safety signal associated with niraparib use has been the occurrence hypertension, including hypertensive crisis. In addition, other cardiovascular events including and angina and arrhythmias have been observed. Specific cardiovascular events and arrhythmias on the NOVA study are depicted in **Table 11-32**. These safety findings arise from niraparib's binding to several receptors which would affect the cardiovascular system, including norepinephrine, serotonin, and dopamine transporters, acting to inhibit the uptake of norepinephrine and dopamine.

Table 11-32 Cardiovascular Adverse Events on NOVA Study

	Niraparib	Placebo
	Total N=367 N (%)	N=179 N (%)
G1-3 Hypertension	75 (20)	10 (6)
Any G1	31 (8)	1 (0.5)
Any G2	56 (15)	4 (2)
Any G3	34 (9)	5 (3)
Hypertensive crisis (G4)	2 (0.5)	0
SAE of Hypertension	1 (0.3)	0
Prior Bevacizumab	15 (4)	3 (2)
Arrhythmia (G1-4)	34 (9)	3 (2)
Arrhythmia (G3-4)	0	1 (0.5)
Tachycardia (G1-4)	32 (9)	3 (2)
Palpitations (all grades)	39 (11)	3 (2)
G1 palpitations	36 (10)	3 (2)
G2 palpitations	6 (2)	0
Hot flashes		
G1-4	35 (10)	11 (6)
G3-4	3 (1)	0

Hypertension of grades 1-3 was documented as an adverse event in 20% of patients on the NOVA study, compared with 6% on placebo. There were 2 events of hypertensive crisis in niraparib treated patients, one of which involved patient presentation to the ER with systolic blood pressure >200 and chest pain, requiring intravenous antihypertensive medications. The Applicant has attempted to attribute some of the hypertensive events on niraparib treated patients to prior use of bevacizumab, and although approximately 25-30% of all patients on the NOVA study had received prior bevacizumab, only 4% of those who experienced hypertension of any grade had documentation of prior bevacizumab exposure, making this an unlikely to be the explanation in most cases.

Arrhythmias grade 1-4 occurred in 9% of patients treated with niraparib and only 2% of patients on placebo. The majority of the arrhythmias were sinus tachycardia or tachycardia (unspecified) and were

Grade 1-2 in severity, meaning they were asymptomatic and did not require urgent intervention. There were also two patients on niraparib who experienced grade 1 ventricular arrhythmia/tachycardia on niraparib, which is defined as asymptomatic and not requiring intervention. Neither of these events were deemed by the Applicant to be serious adverse events nor did they result in death or treatment discontinuation, so narratives were not provided for these patients. Finally, there were two niraparib-treated patients who experienced serious adverse events of tachycardia/ sinus tachycardia on the NOVA study, which are included in the group of patients experiencing G1-4 tachycardia in **Table 11-32**. The narratives for these two patients are described as follows:

1) PR-30-5011-C-001024-00004- SAE of Grade 2 tachycardia. Also experienced anxiety, and non-cardiac chest pain. 59 year old WF gBRCAm with Stage IIA primary peritoneal cancer (HGS) diagnosed 1/08. Treated with 3 lines of prior platinum therapy, as well as taxanes, monoclonal antibody, and topoisomerase inhibitor. She also had a past medical history significant for breast cancer, anxiety, hypertension. She began niraparib therapy 2/14/14. She remained on therapy until 1/11/15, when it was discontinued due to disease progression. Her course on therapy was complicated by G2 nausea, G3 LFT abnormalities, G1-2 electrolyte abnormalities including hypokalemia and hypomagnesemia requiring supplementation. On the day of study drug discontinuation (b) (6)), she presented to the emergency room with G2 anxiety, G1 non-cardiac chest pain (serious), and G2 serious tachycardia requiring hospital admission, and G1 pyrexia. Following hospital admission that day, EKG revealed sinus rhythm (heart rate not specified) and non-specific T wave abnormality. Chest X-ray revealed no cardiopulmonary process and troponin <0.1. The non-cardiac chest pain and pyrexia resolved that same day. Treatment with niraparib was interrupted due to the events. On (b) (6), CT scan revealed disease progression in the form of a new lesion at the site of the appendix. The SAE of anxiety and tachycardia had resolved. She was discharged from the hospital and had therapy permanently discontinued due to progressive disease. On (b) (6), eight months after study discontinuation, she died due to myelodysplastic syndrome. The details of her diagnosis of MDS are discussed with the narrative discussions for MDS/AML.

2) PR-30-5011-C-011001-00008- SAE of Grade 2 sinus tachycardia. 65 year old white female non-gBRCAm with Stage IV ovarian cancer treated with 2 prior platinum regimens. Other past medical history was significant for anxiety, hypertension, tachycardia, dyslipidemia, type 2 diabetes, insomnia. She was taking Ramipril for hypertension, metformin, and simvastatin. On C1 D15 she presented for her scheduled CBC and was found to have heart rate of 150 bpm and report of recent memory impairment, so she was sent to the emergency department for evaluation. She was hospitalized with G2 sinus tachycardia with “abnormal ECG findings which were considered to be not clinically significant”. All other tests were normal. No action was taken with niraparib treatment and no therapy was given for the tachycardia. She was discharged from the hospital the following day when the tachycardia had improved to “nonserious G2 sinus tachycardia”. She had no further episodes of tachycardia described in her narrative.

Reviewer comment: There was initial concern, upon assessment of the incidence of arrhythmias, that niraparib may have had arrhythmogenic potential to an extent that had been inadequately described by the Applicant. Further assessment of individual cases on the NOVA study and in the OCT pool, indicate that the majority of arrhythmias were sinus tachycardia, which required no intervention. Despite this, prescribing physicians will need to be aware of this drug's potential to cause tachycardia as well as hypertension, and will need to consider a patient's underlying medical history and comorbidities when administering this agent. Proper monitoring of vital signs by physicians and focused history and physical exam will be important to detect signs and symptoms of arrhythmias, hypertension (including hypertensive crisis) and ischemia, so that prompt treatment can be administered. Proper risk-benefit assessment will be particularly important, with regard to these possible risks.

Consistent with the finding of arrhythmias was the documentation of patients reporting palpitations more frequently on the niraparib arm (11% vs. 2% on placebo). One patient experienced an episode of angina pectoris on niraparib on the NOVA study (not shown in **Table 11-32**), but no patients on NOVA were diagnosed with MI. Finally, patients also reported hot flashes, as a vascular event, more frequently on niraparib.

There were no events of myocardial infarction or ischemia on the NOVA study, in either arm.

OCT pool

Cardiovascular events and arrhythmias in the OCT pool are shown in **Table 11-33**. Grades 1-3 hypertension occurred in 8% of patients, which is lower than the 20% seen on the NOVA study. However, there were 5 serious adverse events of hypertension on niraparib in the OCT pool. Arrhythmias of any grade, mostly sinus or supraventricular tachycardias, occurred in 8% of patients in the OCT pool. There were also 2 patients with angina pectoris and one patient with documentation of myocardial infarction in the OCT pool, however the details of the cases were not well described by the Applicant, and narratives describing these events were not provided.

Overall, the data on cardiovascular events, namely hypertension, seen in the NOVA study and in the OCT, will be included as potential adverse reactions in product labeling for niraparib, so that prescribing physicians are aware of the potential risk, and can use their clinical judgment to weigh the risk and benefit of prescribing niraparib to individual patients based upon risk factors and comorbidities.

Table 11-33 Cardiovascular Events in the OCT Pool

	Niraparib N= 384 N (%)
G1-3 Hypertension	32 (8)
Any G1	15 (4)
Any G2	17 (4)
Any G3	11 (3)
Hypertensive crisis	0
SAE of Hypertension	5 (1)
Arrhythmia (G1-4)	30 (8)
Arrhythmia (G3-4)	1 (0.3)
Tachycardia (any)	29 (8)
Atrial fibrillation	4
Angina pectoris	2 (0.5)
Myocardial infarction*	1 (0.3)
Palpitations (all grades)	25 (7)
G1 palpitations	23 (6)
G2 palpitations	1 (0.3)
G3 palpitations	1 (0.3)
Hot flashes	1 (0.3)

*In the OCT pool, one patient on the QUADRA study (5020-C-001439-404) had report in the safety dataset of an abnormal EKG consistent with possible anterior infarct (myocardial infarction) and possible inferior infarction; however it did not appear that patient presented with any symptoms of ischemia, and she had no other related adverse events reported. No toxicity grade was assigned to this "event", no action was taken with regard to niraparib dosing, and no intervention occurred.

Atrial fibrillation in the OCT pool

There were four patients with documented atrial fibrillation in the OCT pool. Two patients (PR-30-5011-C-001004-0005 and PR-30-5011-C-001004-0005) on the food effect portion of the NOVA study experienced atrial fibrillation, which was documented in the OCT adverse event dataset. One of these was grade 1 in severity, and the other was grade 3, but neither were documented as serious adverse events or resulted in treatment discontinuation, and therefore, narratives were not provided for these patients. A third patient, PR-30-5020-C-001432-404, was also listed in the adverse event dataset as having experienced grade 1 atrial fibrillation, which was not serious, and did not have a narrative describing the event. The narrative provided by the applicant for the one remaining patient who experienced atrial fibrillation while taking niraparib is described as follows:

1. PR-30-5020-C-001415-403- Atrial fibrillation- 73 y/o white female with stage IIIC ovarian cancer diagnosed 7/07. She had received four prior lines of platinum therapy, as well as other agents. Her medical history was significant for "ongoing" atrial fibrillation as well as prior atrial flutter. Prior to starting the QUADRA study, she underwent an echocardiogram which revealed an ejection fraction of 70-75%, severely dilated left atrium, mitral valve regurgitation, mild aortic stenosis and regurgitation, and mild pulmonary hypertension. At screening, her ECG revealed sinus bradycardia. She was taking metoprolol at study baseline. She began niraparib 300 mg 10/26/15. Her baseline ECG on that day revealed atrial fibrillation. On study day 4 (10/30/15), she experienced Grade 2 nonserious atrial fibrillation, as well as Grade 3 non-cardiac chest pain and fatigue. Study treatment was interrupted due to the atrial fibrillation, fatigue, and myalgia. Atrial fibrillation resolved that same day. Niraparib was held until 11/10/15 due to the G3 fatigue, which resolved allowing for niraparib to be restarted with a dose reduction. On 11/17/15, niraparib was interrupted again due to G3 fatigue. On (b) (6), when niraparib was still being held, she presented to the emergency room with serious G2 supraventricular arrhythmia and serious G3 transient global amnesia. She was also experiencing chest pain radiating to the left arm, but had no concomitant shortness of breath, lightheadedness, or dizziness. Her blood pressure was 167/83 and heart rate was 94 bpm. EKG showed sinus rhythm with T wave inversions and anterolateral ischemia. She was hospitalized. Repeat EKG showed atypical atrial flutter, but subsequent repeat EKGs showed that she may have been fluctuating between sinus rhythm and atrial fibrillation/ flutter. CT scan of the head showed no acute intracranial process. She received metoprolol for the atrial fibrillation, hydrocodone and sublingual nitroglycerine for possible angina, and aspirin. She was monitored for transient global aphasia, which resolved the next day. She was discharged from the hospital. Niraparib was resumed at 100 mg daily on 12/1/15. EKG that day revealed atrial fibrillation, which was considered to be "stable". On cycle 4 Day 1 (1/25/16), she presented to clinical and was in atrial fibrillation on EKG with multiple premature atrial complexes. She was referred to a neurologist on 1/26/16 for follow-up of the transient global amnesia. Her blood pressure on that day was 173/103 (G3 hypertension). She complained of headaches and was confused. "No abnormalities were found on exam". No action was taken with regard to the niraparib or the blood pressure/ arrhythmia/ transient global amnesia. The patient continued on niraparib until 4/19/16, when it was discontinued due to disease progression. According to the narrative, the Investigator considered the atrial fibrillation and the transient global amnesia as unlikely to be related to study medication, but considered the SAE of supraventricular arrhythmia to be related to the study medication.

Reviewer comment: This case is concerning because although the patient was said to have had "previous history of atrial fibrillation', she seemed to be in sinus rhythm at the time of starting niraparib therapy. Through the course of therapy with niraparib, she experienced intermittent episodes of atrial fibrillation and supraventricular arrhythmia, with transient neurologic symptoms, which prompted her physician to hospitalize her. She also experienced at least one episode of documented G3 hypertension. The Sponsor did not attribute events of atrial fibrillation or transient global amnesia to niraparib, and did not even provide an assessment of attribution for the G3 hypertension. The concern is that the contribution of niraparib for the entire sequence of events experienced by this patient cannot be ruled out, and based upon niraparib's effect on multiple related receptors (including dopamine, norepinephrine, and serotonin), it is likely that niraparib was to blame for her clinical presentation. It does not seem that the physician caring for this patient had sufficient suspicion for niraparib as a causative agent for the arrhythmia(s) and hypertension, nor the possible TIA symptoms the patient experienced in conjunction with these, since she was continued on therapy (with dose reduction), despite having had these events. Although the narrative provides no further mention of subsequent vascular events, it is possible that they simply were not documented/ reported, and the patient eventually came off of niraparib due to disease progression. This patient's narrative gives cause for concern that there are likely to be other patients with certain risk factors for arrhythmias and hypertension, including a prior history or current history but "controlled", that may experience worsening or recurrence of these prior events once on niraparib. It will be important for treating physicians to be aware of the potential for adverse events including hypertension and tachycardia/ tachyarrhythmias in patients, particularly in those with prior history of either or with risk factors for developing these. Clinical judgment and risk benefit analysis in such patients will be essential prior to prescribing niraparib, for all patients, but particularly for patients such as the one described here.

Psychiatric adverse events

Since niraparib binds to dopamine, serotonin, and norepinephrine receptors, there was potential for psychiatric adverse events to occur in patients receiving niraparib. The incidence of the common psychiatric adverse events in both study arms on the NOVA study is shown in **Table 11-34**. Anxiety and insomnia were the most common psychiatric adverse events. These events have been described in niraparib product labeling.

Table 11-34 Psychiatric Adverse Events NOVA Study

	Niraparib N=367 (%)		Placebo N=179 (%)	
	G1-4	G3-4	G1-4	G3-4
Any psychiatric AE	132 (36)	4 (1)	30 (17)	2 (1)
Insomnia	100 (27)	1 (0.3)	14 (8)	0
Anxiety	42 (11)	1 (0.3)	12 (7)	1 (0.6)
Depression	20 (5)	1 (0.3)	5 (3)	1 (0.6)
Hallucinations	2 (1)	0	0	0
Psychosis	0	0	0	0
Suicide attempt	0	0	1 (0.6)	1 (0.6)

Reviewer comment: Although it is difficult to give specific guidance regarding the potential psychiatric adverse events, by ensuring that prescribers are at least aware of the potential for their occurrence is likely to mitigate some of the risk. Inclusion of these events in labeling, particularly insomnia and anxiety, could help guide physicians in prescribing niraparib to individual patients, based upon risk factors and medical/ psychiatric history.

The incidence of similar psychiatric adverse events in the OCT pool is shown in **Table 11-35**, with insomnia and anxiety being the most common events among niraparib treated patients.

Table 11-35 Psychiatric Adverse Events OCT Pool

	Niraparib N=384 (%)	
	G1-4	G3-4
Any psychiatric AE	96 (25)	4 (1)
Insomnia	68 (18)	2 (0.5)
Anxiety	24 (6)	1 (0.3)
Depression	16 (4)	0
Mania	1 (0.3)	0

Treatment Emergent Adverse Events and Adverse Reactions

The most common grade 1-4 adverse reactions (by MedDRA preferred term), which occurred in ≥ 10% of patients in at least 1 arm, are shown in Table 11-36. All patients treated with niraparib and most patients treated with placebo experienced at least 1 treatment-emergent adverse event. In the niraparib treated patients, nausea was the most common adverse event, occurring in 74% of patients, compared with 35% in placebo patients. Thrombocytopenia and anemia occurred in 61% and 50% of niraparib patients, respectively. These results are consistent with the results of the analysis of dose reductions and interruptions, where it was found that the majority of these were due to thrombocytopenia and/or anemia. Only the adverse event of abdominal pain occurred more frequently in placebo treated patients, and this may be related, to some extent, to the improved disease controlled afforded to patients treated with niraparib. Hypertension of grades 1-4 occurred in 20% of niraparib patients, compared with only 5% in placebo. This event was unique, when compared to other PARP inhibitors, and was discussed earlier in the review.

Table 11-36 Grade 1-4 Adverse Events NOVA Study ≥ 10%

	Niraparib N=367			**Placebo N= 179**		
	gBRCAm	**Non-gBRCA**	**Total**	**gBRCAm**	**Non-gBRCAm**	**Total**
Preferred term	N=136 (%)	N=231 (%)	N=367 (%)	n=65 (%)	N=116 (%)	N=179 (%)
Any AE	136 (100)	231 (100)	367 (100)	61 (94)	110 (95)	171 (96)
Nausea	105 (77)	165 (71)	270 (74)	22 (34)	40 (34)	62 (35)
Thrombocyto-penia	96 (71)	128 (55)	224 (61)	2 (3)	7 (6)	9 (5)
Fatigue/Asthenia	79 (58)	130 (56)	209 (57)	22 (34)	51 (44)	73 (41)
Anemia	72 (53)	114 (49)	186 (50)	5 (8)	7 (6)	12 (7)
Vomiting	54 (40)	72 (31)	126 (34)	10 (15)	19 (16)	29 (16)
Constipation	51 (38)	94 (41)	146 (40)	12 (18)	24 (21)	36 (20)
Leukopenia (incl. neutropenia)	49 (36)	74 (32)	123 (34)	11 (17)	9 (8)	20 (11)
Headache	48 (35)	48 (21)	96 (26)	5 (8)	15 (13)	20 (11)
Abdominal pain	45 (33)	76 (33)	121 (33)	24 (37)	46 (40)	70 (39)
Neutropenia	42 (31)	69 (30)	111 (30)	6 (9)	5 (4)	11 (6)
Hypertension	31 (23)	42 (18)	73 (20)	5 (8)	4 (3)	9 (5)
Decreased appetite	29 (21)	61 (26)	90 (25)	9 (14)	17 (15)	26 (15)
Insomnia	26 (19)	74 (32)	100 (27)	5 (8)	9 (8)	14 (8)
Dyspnea	25 (18)	50 (22)	75 (20)	3 (5)	12 (10)	15 (8)
Anxiety	19 (14)	23 (9)	42 (11)	7 (11)	5 (4)	12 (7)

Grade 3-4 adverse events are shown in Table 11-37, and similar terms were included as for Grade 1-4

events, as appropriate. Cytopenias were among the most common severe adverse events on niraparib. Severe events of hypertension, including hypertensive crisis, occurred in 9% of patients on niraparib. This particular adverse event of interest is discussed further in section 1.4.4 as a significant adverse event.

Table 11-37 Grade 3-4 Adverse Events on NOVA Study

	Niraparib N=367			**Placebo N= 179**		
	gBRCAm	**Non-gBRCA**	**Total**	**gBRCAm**	**Non-gBRCAm**	**Total**
Preferred term	**N=136 (%)**	**N=231 (%)**	**N=367 (%)**	**n=65 (%)**	**N=116 (%)**	**N=179 (%)**
Any AE	108 (80)	164 (71)	272 (74)	14 (22)	27 (23)	41 (23)
Thrombocyto-penia	51 (38)	73 (32)	124 (34)	1 (2)	0	1 (0.6)
Anemia	45 (33)	48 (21)	93 (25)	0	0	0
Neutropenia	29 (21)	43 (19)	72 (20)	2 (3)	1 (1)	3 (2)
Hypertension	13 (10)	19 (8)	32 (9)	3 (5)	1 (1)	4 (2)
Fatigue/Asthenia	11 (8)	19 (8)	30 (8)	0	0	0
Nausea	7 (5)	4 (2)	11 (3)	2 (3)	0	2 (1)
Vomiting	5 (4)	2 (1)	7 (2)	0	1 (1)	1 (0.6)
Abdominal pain	2 (2)	4 (2)	6 (2)	0	4 (3)	4 (2)
Constipation	1 (1)	1 (0.4)	2 (0.5)	1 (2)	0	1 (0.6)
Decreased appetite	0	1 (0.4)	1 (0.3)	0	1 (1)	1 (0.6)
Headache	1 (1)	0	1 (0.3)	0	0	0
Diarrhea	0	1 (0.4)	1 (0.3)	1 (2)	1 (1)	2 (1)
Insomnia	1 (1)	0	1 (0.3)	0	0	0
Anxiety	1 (1)	0	1 (0.3)	1 (2)	0	1 (0.6)

Laboratory Findings

On study laboratory abnormalities in >25% of patients on the NOVA study are shown in Table 11-38. The occurrence of cytopenias as laboratory abnormalities is consistent with the reporting of adverse events, but for some events, namely leukopenia and neutropenia, the incidence of these as laboratory abnormalities was higher than their reports as adverse events, per se, and this is a common occurrence in review of data from clinical trials.

Table 11-38 On Study Laboratory Abnormalities NOVA Study >25%

Lab parameter	Niraparib N=367		Placebo N=179	
	G1-4 (%)	G3-4 (%)	G1-4	G 3-4
Decrease in hemoglobin	313 (85)	91 (25)	100 (56)	1 (0.5)
Decrease in platelet count	261 (72)	127 (35)	37 (21)	1 (0.5)
Decrease in WBC count	241 (66)	28 (7)	67 (37)	1 (0.5)
Decrease in absolute neutrophil count	193 (53)	76 (21)	45 (25)	3 (2)
Increase in AST	133 (36)	4 (1)	41 (23)	0
Increase in ALT	104 (28)	5 (1)	27 (15)	3 (2)

Vital Signs

An analysis of on-study vital sign abnormalities, namely blood pressure, pulse rate, and temperature deviations, is shown in Table 11-39. The findings of blood pressure and pulse elevations in patients treated with niraparib, more so than placebo treated patients (particularly for Grade 3), correlates with the identified cardiovascular effects of niraparib. This analysis was performed using the vital sign dataset, which did not have parameters for recording G4 Hypertension (hypertensive crisis), therefore these events were not captured by review of vital sign data. Tachycardias were also seen more in niraparib treated patients (43% vs. 17%), which is in keeping with the identification of arrhythmia as a safety signal associated with niraparib.

Table 11-39 Vital Sign Abnormalities on NOVA Study

Vital Signs Abnormalities	Niraparib N=367		Placebo N=179	
	G1-3 N (%)	G3 N (%)	G1-3 N (%)	G3 N (%)
High systolic BP	353 (96)	88 (24)	165 (92)	30 (17)
High diastolic BP	329 (90)	46 (13)	135 (75)	5 (3)
High pulse rate (>100 bpm)	157 (43)	-	31 (17)	-
High pulse rate (>140 bpm)	4 (1)	-	0	-
Low pulse rate (< 60 bpm)	20 (5)	-	35 (20)	-
Fever (≥ 38°)	2	0	2	0

Reviewer comment: When comparing the incidence of hypertension by vital sign measurements with hypertension reported as an adverse event, there were clearly more patients experiencing hypertension than were reported as adverse events. This indicates that hypertension is likely to be more prevalent in patients treated with niraparib than has been estimated to date. This has been described in labeling since prescribing physicians will need to be aware of this common treatment side effect, as many patients receiving niraparib may require dose adjustments and/or antihypertensive medications while on therapy, including patients without history of hypertension prior to niraparib use.

In addition, the incidence of heart rate > 140 on vital sign assessment was examined, based upon the potential concern for tachycardia and tachyarrhythmias with niraparib. There were 4 patients who had documented heart rate > 140. Only 1 of these patients had report of an adverse event of G2 sinus tachycardia, which was also designated as a serious adverse event. The narrative for this patient on niraparib (011001-00008) was described with the cardiovascular adverse events on the NOVA study.

Electrocardiograms (ECGs)

Safety pharmacology studies have shown that niraparib inhibited the rapid component of the delayed rectifier potassium current (IKr) ion channel in vitro (hERG assay) with in IC50 value of 10 µM. In the 1-month and 3- month GLP toxicity studies in dogs, niraparib was administered at doses of 15 and 12 mg/kg/day. EKGs were monitored and no related EKG abnormalities were observed.

See also QT section below.

QT

The potential for QTc prolongation with niraparib was evaluated in the QTc substudy of the NOVA study (PR-30-5011-C1). This open-label study included 26 patients who received niraparib 300 mg qd. EKG monitoring for QTc was performed during C1. The conclusion from the QTc analysis was that, overall, no large changes in the mean QTc interval (> 20 msec) were detected following treatment with niraparib. See QT-IRT Review by Dr. Marathe for full summary of the QT-IRT findings.

Immunogenicity

An assessment of reactions that could indicate increased immunogenicity or allergy to niraparib was done. The safety dataset on the NOVA study and for the OCT pool was assessed for adverse events including the terms:

Allergic reaction, anaphylactoid reaction, dermatitis allergic, dermatitis contact, drug hypersensitivity, face edema, flushing, hypersensitivity, edema, lip swelling, mouth swelling, tongue swelling, peripheral swelling, pruritis, pruritis general, rash, erythematous rash, macular rash, maculo-papular rash, pruritic rash, pustular rash, skin reaction, sneezing, swelling face, throat tightness, uriticaria

On the NOVA study, any of these preferred terms occurred in 59 patients (16%) on niraparib and 24 patients (13%) on placebo. Most cases were grade 1-2 in severity on niraparib and all cases were grade 1 in severity on placebo. No events were serious. Three patients on niraparib had dose reduced and 2 patients had dose interrupted due to reactions of rash, pruritis, face swelling, and/or flushing thought to be related to niraparib. Narratives for four niraparib treated patients are discussed as follows (2 patients experiencing a grade 3 rash or anaphylactoid reaction, 1 patient requiring dose reduction due to edema, flushing, face swelling, and one patient who had dose reduction due to face edema.

- Patient 011007-00003 was a 53 year old Asian female (gBRCAm) who experienced G2 flushing, edema, facial swelling, rash, and pruritis on study day 31. These events were thought to likely be related to niraparib and resulted in dose reduction for niraparib. No narrative was provided for this patient, but no further episodes were reported after the initial event.
- Patient 011008-00007 was a 66 year old Asian female (nongBRCAm) who experienced a G3 anaphylactoid reaction after 1 year on niraparib. This was associated with hypotension, loss of consciousness, and dizziness, but was thought to be related to the use of IV contrast for CT scan. She was treated with diphenhydramine and steroids with resolution. No action was taken with niraparib dosing and it was deemed to be unrelated to niraparib.

- Patient 045004-00002 was a 55 year old white female (non-gBRCAm) who experienced a grade 1 photosensitivity reaction after approximately 3 weeks on niraparib, which resulted in study drug interruption. Dose was reduced upon restarting after resolution of the reaction. She had recurrent episodes of rash of grade 2-3 in severity thereafter. She had study treatment interruption due to rash. She discontinued niraparib therapy after approximately 8 weeks on study due to disease progression.

> *Reviewer comment: This particular event does not seem indicative of an allergic reaction, but simply a rash, which may have been related to niraparib.*

In the OCT pool, there were 33 patients out of 384 (9%) who experienced similar potentially immunogenic/ allergic events as in the NOVA study. All but 2 cases were grade 1 in severity. One patient on the QUADRA study (PR-30-5020-C-0014330-411) experienced a grade 1 rash on her chest and arms, which was thought to be related to niraparib and resolved with temporary dose interruption. The rash did not recur with reintroduction of niraparib. The second patient (PR-30-5020-C-001439-406) experienced grade 2 edema on day 1 of niraparib dosing. Although it was thought to be unrelated to niraparib, the patient was taken off study, and specific details were not provided by the Applicant.

> *Reviewer comment: There overall did not appear to be compelling data to support the propensity for niraparib to cause immunogenic/ allergic reactions. It was notable that the two patients who experienced more severe (anaphylactoid-like) reactions on NOVA were both Asian. Whether there could be a pharmacogenetic component to the reactions experienced by these two patients is certainly possible, but would need to be evaluated in a larger number of similar patients in order to be able to come to any conclusions on this contribution.*

11.4.5. **Analysis of Submission-Specific Safety Issues**

APPEARS THIS WAY ON ORIGINAL

Specific safety issues related to niraparib (including MDS/AML, cardiovascular events, and psychiatric events) have been discussed in prior sections in 1.4.4.

11.4.6. Safety Analyses by Demographic Subgroups

An analysis of common grade 1-4 adverse events by age group was conducted for patients taking niraparib on the NOVA study. The analysis is shown in Table 11-40.

Table 11-40 Adverse Events by Age

Adverse event by PT	**Niraparib n=367**		
Common G1-4 Adverse Events by age	**Age <50 N= 55 (%)**	**Age 50- <65 N= 183 (%)**	**Age ≥ 65 N= 129 (%)**
Anemia	25 (45)	92 (50)	65 (50)
Thrombocytopenia	33 (60)	81 (44)	85 (66)
Neutropenia	18 (33)	59 (32)	34 (26)
Nausea	41 (75)	143 (78)	86 (66)
Constipation	19 (35)	73 (40)	57 (44)
Abdominal pain	15 (27)	77 (42)	44 (34)
Vomiting	23 (42)	68 (37)	35 (27)
Diarrhea	15 (27)	37 (20)	19 (15)
Decreased appetite	11 (20)	39 (21)	43 (33)
Fatigue/ Asthenia	32 (58)	116 (63)	71 (55)
Headache	18 (33)	54 (30)	28 (22)
Insomnia	9 (16)	49 (27)	33 (26)
Anxiety	2 (4)	18 (10)	11 (9)
Hypertension	7 (13)	53 (29)	26 (20)

Reviewer comment: The assumption that perhaps patients over the age of 65 may not tolerate therapy with niraparib as well, or may experience a higher frequency of adverse did not appear to be true overall, and in some cases, including events of nausea and diarrhea, the events appeared to be reported less in patients over age 65 years compared with patients less than 50 years.

11.4.7. Specific Safety Studies/Clinical Trials

As was described in section 1.4.6, the potential for QTc prolongation with niraparib was evaluated in the QTc substudy of the NOVA study (PR-30-5011-C1). Overall, no large changes in the mean QTc interval (> 20 msec) were detected following treatment with niraparib.

11.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Nonclinical carcinogenicity studies have not been conducted with niraparib. Niraparib was not mutagenic in an Ames test, but it was clastogenic in *in vitro* and *in vivo* assays. However, as was discussed in Section 1.4.4, there were cases of MDS/AML and other solid tumors seen in niraparib treated patients with higher frequency than placebo treated patients. Given the mechanism of action of niraparib as a PARP inhibitor, there is increasing evidence that agents such as niraparib (and other PARP inhibitors) do promote of cause human cancers, including MDS, AML, and certain solid tumors. Adequate clinical suspicion and active surveillance for these events are important to identifying these events in patients, and monitoring has been described in patient labeling.

Pediatrics and Assessment of Effects on Growth

Pediatric studies have not been conducted. The Applicant requested a waiver for conducted of pediatric studies under PREA. The final determination on whether a PREA waiver will be granted is still pending at the time of this review.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This drug does not have drug abuse potential.

11.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

The following post-marketing requirement s and commitments (PMR and PMC) have been conveyed to the Applicant, along with expected due dates.

PMR 3187-1:

Conduct a dedicated pharmacokinetic trial in patients with moderate hepatic impairment to determine an appropriate starting dose of niraparib in patients with moderate hepatic impairment.

Final protocol submission: 6/2017

Trial completion: 11/2018

Final study report submission: 2/2019

PMC 3187-2:

One Post-Marketing Commitment (3/6/17) was put forth by CDRH, regarding the test.
The Sponsor (Tesaro) will need to provide the appropriate analytical and clinical validation data for the HRD test to inform product labeling for niraparib. The final wording is as follows:

Submit to FDA the appropriate analytical and clinical validation study for the in vitro diagnostic assay used to identify patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer with homologous recombination deficiency (HRD) in clinical trial entitled "A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer" to inform product labeling for both the device and for Niraparib.

Final report submission: 12/2017.

Reviewer comment: *As a result, the PMC described above will be issued to the drug sponsor, Tesaro, as well. It was determined that the NDA 208447 approval for the indication of "maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy" will be issued on the current timeline* *.*

There are 3 CMC post-marketing commitments (PMC), as follows:

PMC 3187-3:

Submit Revise as necessary in-coming material quality controls and/or formulation and/or unit operation(s) such that the current practice of releasing drug product (b) (4) *while still maintaining product quality and batch to batch consistency.*

Final report submission: 4/15/2018.

Study rationale: The applicant's current manufacturing process involves releasing drug product (b) (4) *he quality and batch to batch consistency of your drug product should be based on sound understanding of the science and well designed and controlled manufacturing process, instead of on testing.*

PMC 3187-4:

Provide method validation data for accuracy and precision using the revised assay method AM-1971 and capsules made by the manufacturing process approved in the application. The validation of the analytical method should be consistent with the ICH Q2 guidelines.

Final report submission: 4/15/2018

Study rationale: The applicant's current validation study fails to meet the acceptance criteria for accuracy and precision due to interference. Applicant has committed to submit the requested study after the application is approved and after the method description has been updated with information accepted in the NDA.

PMC 3187-5:

Provide method validation data for accuracy and precision using the revised dissolution method AM-1974 and capsules made by the manufacturing process approved in the application. Data should be presented in the form of drug release profiles collected at 5, 15, 30, 45, and 60 minutes. The validation of the analytical method should be consistent with the ICH Q2 guidelines.

Final report submission: 4/15/2018

Study rationale: The applicant's current method validation study fails to meet the acceptance criteria for accuracy and precision due to interference from the drug product. The applicant has committed to submit the requested study after the application is approved and after the method description has been updated with method description information accepted in the NDA.

11.4.10. Integrated Assessment of Safety

The primary safety database for niraparib consists primarily of the 367 patients with platinum-sensitive relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancers who are in response to the most recent platinum-based chemotherapy. Supportive safety data was drawn from the OCT pool, including an additional 384 ovarian cancer patients, for a total of 751 patients with ovarian cancer receiving niraparib. The key adverse reaction of interest with niraparib is the occurrence of MDS and AML. As has been noted, there were a total of 7 cases of MDS or AML out of the safety database including 751 patients (0.9%) This overall rate of MDS/AML with niraparib is similar to the rate seen with a similar agent, olaparib, where the reported incidence at the time of approval was 1.2%. When considering the incidence rate with niraparib, it is also important to consider the overall annual incidence of MDS/AML in the US. This is estimated to be approximately 3.3 cases per 100,000 or 0.0033%. Likewise, the incidence in a large case control study of almost 29,000 ovarian cancer patients who received prior platinum therapy was 0.3%. Given all these factors, the overall risk with niraparib is small, but has devastating consequences when it occurs, given that 3 of 9 patients (33%) diagnosed in this database had died by the time of data cutoff. Given the poor prognosis and treatment options for patient with MDS/ AML, the number of deaths in patients diagnosed with MDS/AML after niraparib therapy will certainly increase with time.

The other key safety concern with use of niraparib includes the occurrence of cardiovascular events which mainly consist of hypertension and tachycardia. As was described, approximately 20% of patients treated with niraparib on NOVA and 8% of patients in the OCT pool experienced hypertension of any grade. This did not appear to be related to prior bevacizumab use. Approximately 9% of niraparib-treated patients on NOVA and 8% in the OCT pool experienced arrhythmias of any grade, with the majority being sinus tachycardia. In the entire safety database, there was 1 patient who experienced myocardial infarction and 2 patients who experienced angina pectoris. It is acknowledged that hypertension, as well as tachycardia, can be managed medically by physicians. However, the key will be for patients to be monitored appropriately so that intervention can be given promptly to minimize more serious cardiac sequelae such as stroke and myocardial infarction that can occur, particularly in patients with underlying, preexisting risk factors for these events.

11.5. Review of Patient-Reported Outcomes

Patient reported outcomes (PRO) data were collected as part of the NOVA study. The Applicant chose to use 1) the Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index (FOSI), an eight-item subset of the FACT-Ovarian instrument that assesses ovarian cancer associated symptoms and health-related quality of life (HRQL), and 2) the EuroQol five dimensions, 5-level version questionnaire (EQ-5D-5L), an instrument used to assess generic health status and outcomes. Additionally, the

applicant generated a two-item questionnaire to assess symptoms of peripheral neuropathy in the hands and feet.

From the FDA's perspective, the FOSI is limited as a well-defined measure of ovarian cancer symptoms due to its inclusion of both symptoms and global concepts such as worry and HRQL ("I have a lack of energy," "I have been vomiting," "I have pain," "I have nausea," "I have swelling in my stomach area," "I worry that my condition will get worse," "I am content with the quality of my life right now," and "I have cramps in my stomach area") (See Appendix Patient-Reported Outcomes11.10, Figure 11-9 and Figure 11-10). The PRO data were collected as exploratory data with the stated study objective of better understanding the perspective of the patient on maintenance therapy and as supportive endpoints for the understanding of progression free survival.

Statistical Analysis Plan

Patient-reported outcomes were secondary endpoints of the NOVA trial. There was no specific hypothesis testing plan, nor were there alpha adjustments for multiple comparisons. The purpose of these analyses was descriptive.

Completion rates for each instrument were to be calculated for each planned assessment: screening/baseline, even cycles (for example cycle 2, cycle 4, etc.) for the first 14 cycles and then every third cycle thereafter while the patient was on study treatment. For those patients who discontinued treatment, PROs were to be collected at treatment discontinuation and 8 weeks after treatment discontinuation. The completion rate for each PRO assessment was defined as the number of patients who completed the questionnaires at that time point, divided by the number of patients eligible to be assessed for that study visit. Changes from baseline in continuous scores (FOSI, EQ-5D-5L index, and EQ-5D VAS) were to be analyzed descriptively by treatment group in each cohort. The individual neuropathy questionnaire items were to be described by number and percentage of patients reporting each response by treatment group. A longitudinal growth curve model was also conducted to assess the change of PRO scores over time where time was modeled categorically for the purposes of the assessments. Time to symptom worsening (TSW) on the total FOSI score was compared between two arms in each cohort and summarized using the Kaplan-Meier method. TSW was defined as the time to first decrease in FOSI score by greater than one minimally important difference (MID) threshold.

Patient-Reported Outcome Results

PRO Completion Rates

As shown in Table 11-41, per FDA's analysis, the completion rates for the FOSI, the EQ-5D-5L and the neuropathy questionnaire were higher than or close to 80% at assessments on study treatment. The 8 week post end of treatment assessment completion rate per FDA's analysis was lower than the applicant's reports as the Applicant modified the definition of the assessment after treatment discontinuation to include only participants who had discontinued treatment due to progressive disease rather than include all patients who discontinued treatment (e.g. for intolerability or for adverse events).

Table 11-41: FDA's Analysis of PRO Completion Rates at Each Assessment Time Point

	# of Expected Patients		FOSI		EQ-5D-5L		Neuropathy	
	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo
gBRCAmut cohort								
Screening	138	65	97%	95%	99%	98%	98%	98%
Cycle 2	131	64	89%	91%	91%	94%	90%	89%
Cycle 4	120	53	93%	79%	96%	79%	94%	79%
Cycle 6	104	40	92%	90%	94%	90%	93%	90%
Cycle 8	94	26	87%	81%	91%	81%	88%	81%
Cycle 10	83	15	89%	80%	90%	80%	89%	80%
EOT	89	61	79%	82%	80%	84%	78%	84%
8-wk post EOT	81	59	60%	64%	60%	64%	60%	64%
Non-gBRCAmut cohort								
Screening	234	116	97%	97%	99%	97%	98%	96%
Cycle 2	209	113	87%	88%	89%	88%	86%	86%
Cycle 4	177	95	85%	80%	87%	82%	84%	80%
Cycle 6	143	56	87%	86%	88%	89%	85%	88%
Cycle 8	116	40	90%	88%	91%	90%	88%	88%
Cycle 10	96	30	91%	93%	93%	93%	91%	93%
EOT	185	102	85%	84%	85%	84%	86%	84%
8-wk post EOT	177	101	62%	66%	62%	67%	61%	67%

EOT: end of treatment

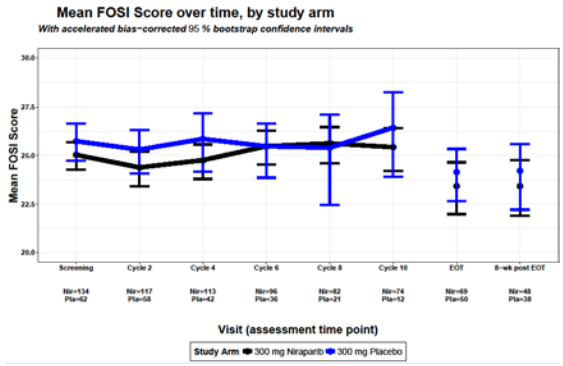
Review of PRO instrument completion rates demonstrated that the collection of PRO data in this population was feasible and the completion rate was considered adequate for further analysis. The primary reason for non-completion of these instruments was administrative failure. The completion rate decreased for the eight week post end of treatment assessment, however, and this was noted to be due to increase in patient illness/refusal for this time points. A detailed review of instrument completion data by cycle and assessment of reasons for missing data is included in the full PRO review located in Appendix 12.3.

Analysis of PRO Scores over Time

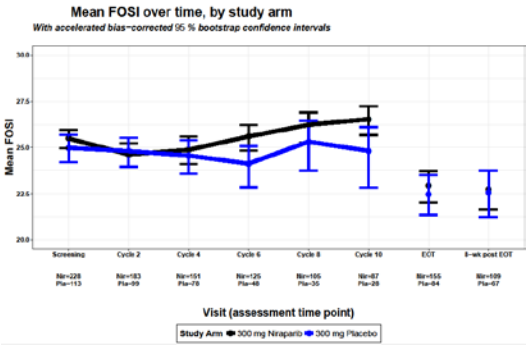
FOSI score was calculated as the summed value of item scores multiplied by 8 and then divided by the number of questions answered. FOSI is considered complete as long as at least five of the eight items are answered (i.e. over 50% of the items). FOSI score ranges from 0 to 32 and higher composite scores indicate less severe symptoms while lower scores indicate more severe symptoms.

The mean score of FOSI over time is shown in Figure 11-7 (a) for gBRCAmut cohort and (b) for non-gBRCAmut cohort, and the mean change compared to baseline over time was shown in Figure 7 (c) and (d). The analyses of the FOSI score over time did not show a consistent or compelling difference between the two treatment arms in both cohorts. Similar results were observed for EQ-5D VAS analyses as shown in Figure 11-8.

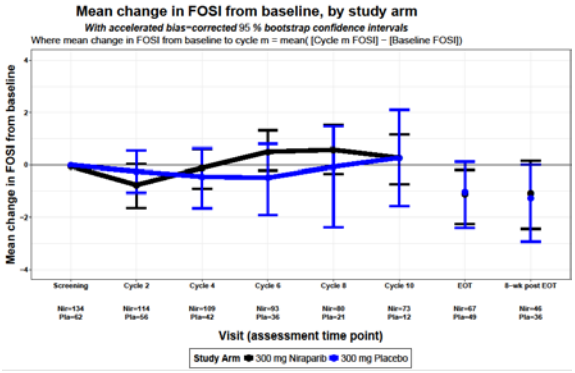
(a) FOSI Mean Over Time, in gBRCAmut Cohort



(b) FOSI Mean Over Time, in non-gBRCAmut Cohort



(c) FOSI Mean Change Over Time, in gBRCAmut Cohort



(d) FOSI Mean Change Over Time, in non-gBRCAmut Cohort

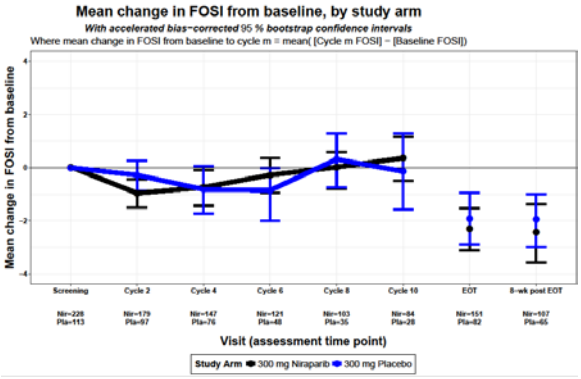


Figure 11-8: FDA's Descriptive Analyses of FOSI Score over Time

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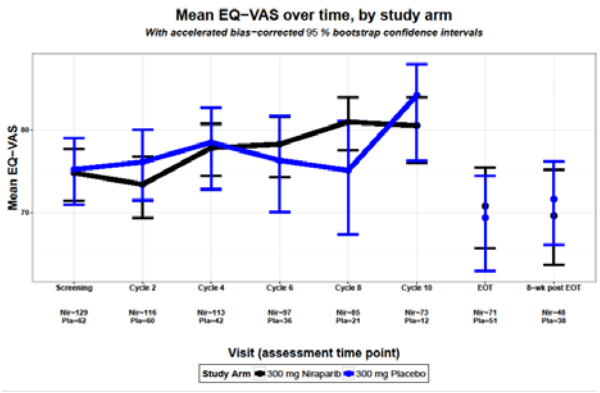
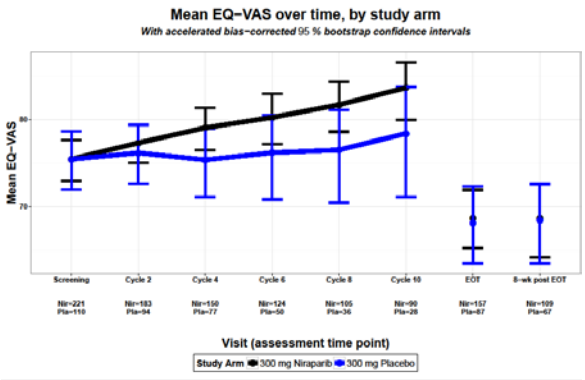
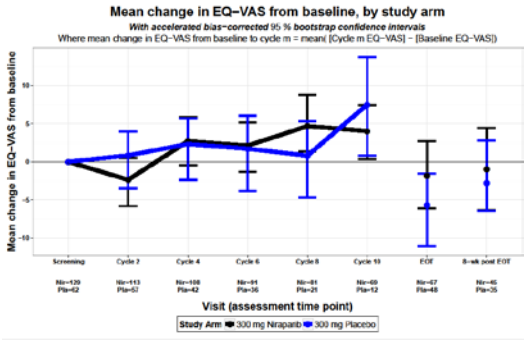
(a) EQ-5D VAS Mean Over Time, in gBRCAmut Cohort



(b) EQ-5D VAS Mean Over Time, in non-gBRCAmut Cohort



(c) EQ-5D VAS Mean Change Over Time, in gBRCAmut Cohort



(d) EQ-5D VAS Mean Change Over Time, in non-gBRCAmut Cohort

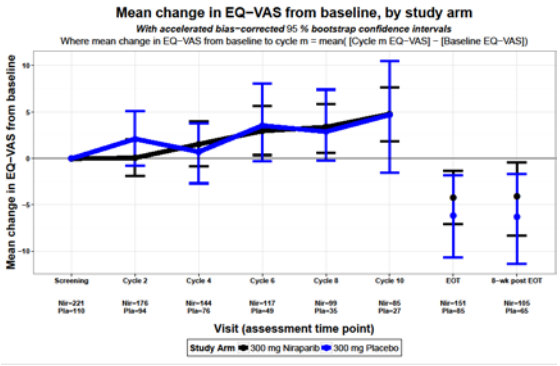


Figure 11-9: FDA's Descriptive Analyses of EQ-5D VAS Score over Time

The applicant defined Time to Symptom Worsening as the time to first decrease in FOSI score by greater than one MID threshold (i.e., 2 points). Based on this assessment, the median of TSW in the gBRCAmut cohort was 8.3 months on niraparib vs. 6.1 months on placebo, and the hazard ratio was 0.84 (95% CI: 0.56, 1.27). For the non-gBRCAmut cohort, the median TSW was 5.6 months on niraparib vs. 7.3 months on placebo, and the hazard ratio was 1.12 (95% CI: 0.85, 1.57). These analyses are of composite FOSI scores which, as previously discussed, combine selected disease and treatment symptoms along with worry and HRQL. Items such as HRQL may be confounded factors not related to disease or treatment and potentially decrease the overall score's responsiveness to changes in symptoms. Furthermore, the inclusion of non-symptom items such as worry and HRQL make the content of the instrument inconsistent with concept that the endpoint is purported to measure (Time to Symptom Worsening). Additionally, it is not clear that the MID threshold of 2 points would be considered appropriate in this maintenance setting as the MID used was determined in a study evaluating therapy for progressive metastatic disease where observation is not considered current standard of care.

The review team conducted further exploratory analyses focused on individual items of interest including symptoms such as pain, fatigue, nausea and vomiting from the FOSI as well as functional items from the EQ-5D-5L. As these analyses were intended to inform tolerability, the analysis population selected included those patients who were on study and on treatment. There are no standard analyses and data visualization methods for PRO data. Methods that provide the most informative and least misleading interpretation of PRO data continues to be an area of active investigation and development within the agency's oncology drug evaluation process. The individual PRO item analyses should be interpreted with caution given that the FOSI and the EQ-5D-5L were developed to be used in composite form; however individual items were analyzed descriptively to better understand patient symptoms and change in function while on anti-cancer therapy.

Analysis of item level responses for FOSI and EQ5D demonstrated no clear difference in symptoms between groups except for nausea and vomiting which were numerically increased in the niraparib arm starting at cycle 2. This was consistent with adverse event data in which increases in both symptoms associated with niraparib were reported. While fatigue was a clinician reported adverse event more in patients on niraparib (45.8% vs. 32.4% placebo), there was a high proportion of patients on niraparib who reported no fatigue on the FOSI PRO item. While the reason for this is not clear, the discrepancy between clinician reported and patient reported data may have been due to the wording of the item as "I have a lack of energy" with the response for no fatigue being "not at all." This double negative may have made it unclear how the patient should respond. Additionally there were proportionately more patients in the niraparib arm that reported no pain on both the EQ-5D-5L and the FOSI pain items. This was consistent with the adverse event reporting as well; however, the attribution of this effect on pain to niraparib is problematic given that the PRO item question was broad and not specific to abdominal pain, which would be expected in patients with ovarian cancer. Full individual item level analyses are located in Appendix 12.3.

Responses to the neuropathy questionnaire were not reviewed in detail and are of limited utility in evaluating an agent not expected to cause peripheral neuropathy.

In summary, PROs were systematically assessed with reasonably high completion rates. The instruments selected by the applicant have limitations for regulatory use in describing treatment effect as previously described. Evaluation of the individual item data showed increase in nausea and vomiting and decreased pain on the niraparib arm, complementing findings from the CTCAE clinician reported data. The development of standard analyses and visualization are needed to maximize the utility of longitudinal patient-reported symptom and function data in the evaluation of new therapies. Sponsors and applicants are encouraged to continue to discuss the use of appropriate instruments to assess patient outcomes in trials, and to use a pre-specified SAP that controls for multiple comparisons if considering seeking a marketing claim based on these data. Additionally, development and use of more specific and quantifiable questions from item banks or libraries for symptoms and patient function may allow the patient voice to be more clearly understood and incorporated in product labeling and regulatory decisions which seek to describe impacts that are most likely to be related to the anticancer product's effects.

SUMMARY AND CONCLUSIONS

11.6. Statistical Issues

There are no major statistical issues with the efficacy results of the pivotal study NOVA. The study met its primary objective of PFS per IRC assessment and the results appeared consistent across sensitivity analyses and no apparent outliers were observed in subgroup analyses.

11.7. Conclusions and Recommendations

The review team recommends full approval for niraparib for the following indication:

Niraparib is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

The recommendation is based primarily upon the review of the results from study PR-30-5011-C (NOVA) which was a double-blind, placebo-controlled trial in which 553 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer were randomized 2:1 to niraparib 300 mg orally daily or matched placebo within 8 weeks of last therapy. Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis CDx. Patients with deleterious or suspected deleterious germline BRCA mutation were assigned to the gBRCAm cohort (n=203) and those without gBRCAm were assigned to the non-gBRCAm cohort (n=350). The trial demonstrated a statistically significant improvement in PFS for patients treated with niraparib, as compared to placebo. These results were seen in both cohorts. The median PFS results in the gBRCAm cohort were 21.0 months vs. 5.5 months (HR 0.26, p <0.0001), and in the non-gBRCAm cohort, the median PFS results were 9.3 months vs. 3.9 months (HR 0.45, p<0.0001). An exploratory pooled analysis of the ITT population also demonstrated an improvement in median PFS of 11.3 months vs. 4.7 months (HR 0.42, 95% CI 0.34, 0.53). The FDA performed multiple sensitivity analyses of various populations (including gBRCAm, non-gBRCAm, and HRD-positive cohorts) to examine the robustness of the primary PFS analysis. Estimates of hazard ratios in these sensitivity analyses were consistent with those in the primary analysis across the three populations. Overall, the results of sensitivity analyses support the primary PFS findings.

The safety profile of niraparib was adequately assessed in the submitted database. The primary data to support the safety of niraparib as a maintenance therapy for patients in response to platinum-based chemotherapy came from the results of the NOVA study. Niraparib was generally well tolerated by patients. Common adverse events including thrombocytopenia, anemia, and nausea could be managed with dose interruption/ reduction and supportive therapies (such as anti-emetics). A large number of patients (>60%) on niraparib required dose interruption and/or reduction to manage toxicity, but it was found that the majority of patients were able to tolerate long durations of therapy after appropriate

dose modifications were instituted. The most serious adverse reaction of interest with niraparib was the occurrence of MDS and AML, which has been identified as an uncommon, but severe and life-threatening event that can occur after treatment with niraparib. This event has been well described with this and other similar agents. Clinicians will need to be aware of this potential event, in order to monitor and diagnose patients promptly and appropriately. Other adverse events, including those of hypertension, tachycardia and arrhythmias and psychiatric events such as anxiety are described in product labeling, and will be manageable with dose modifications and concomitant medications, as necessary.

Overall, there is a favorable risk-benefit profile when considering its intended use as a maintenance therapy for patients with recurrent, platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer who are in response to their most recent platinum-based chemotherapy regimen.

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APPENDICES

11.8. References

Kim, G. (2015). FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy. *Clin Cancer Res*, 21 (19), 4257-4261.

Pal, T. P.-W. (2005). BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer,* 104(12), 2807-2816.

Siegel R. (2014). Cancer statistics, 2014. CA: A Cancer Journal for Clinicians, 9-29.
Travis, L.B. (1999). Risk of leukemia after platinum-based chmeotherpay for ovarian cancer. N Engl J Med, 340(5), 351-357.

Zhang, S. R. (2011). Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecologic oncology,* 121(2), 353-357.

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11.9. Financial Disclosure

Disclosure of financial interests of the investigators who conducted the clinical trials supporting this NDA, including statements of due diligence in cases where the applicant was unable to obtain a signed form from the investigator, was submitted in the FDA form 3454. These disclosures were certified by Simona Cipra, Vice President of Clinical Operations at Tesaro. Disclosure of financial interests was submitted for the following sub-investigator:

Name	Study	Role in Study	Number of patients enrolled at site	Potential to affect outcome of study
(b) (6)	Study PR-30-5011-C (NOVA)	Sub-investigator	(b) (6)	No

Reviewer comment: Only one sub-investigator at the (b) (6) *site was listed as having significant financial disclosures. There were* (b) (6) *subjects enrolled at this study site, and therefore, this sub investigator's involvement and disclosures are unlikely to have affected the outcome of the NOVA study.*

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11.10. **Patient-Reported Outcomes**

Patient reported outcomes (PRO) data were collected as part of the NOVA study. The Applicant chose to use 1) the Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index (FOSI), an eight-item subset of the FACT-Ovarian instrument that assesses ovarian cancer associated symptoms and 2) the EuroQol five dimensions, 5-level version questionnaire (EQ-5D-5L), an instrument used to assess generic health status and outcomes. Additionally, the applicant generated a two-item questionnaire to assess symptoms of peripheral neuropathy in the hands and feet. The PRO analyses were considered exploratory with the stated study objective of better understanding the perspective of the patient on maintenance therapy and as supportive endpoints for the understanding of progression free survival.

FOSI

The FOSI is an 8-item subset of questions from the FACT-O questionnaire to measure symptom response to treatment for ovarian cancer. Patients are to respond to their symptom experience over the previous seven days using a five point verbal rating scale ranging from 0 ("not at all") to 4 ("very much"). The items included in the questionnaire are as follows: "I have a lack of energy," "I have been vomiting," "I have pain," "I have nausea," "I have swelling in my stomach area," "I worry that my condition will get worse," "I am content with the quality of my life right now," and "I have cramps in my stomach area." Higher scores indicate less severe symptoms and lower scores indicate more severe symptoms (Figure 11-9 below).

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

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
O1	I have swelling in my stomach area	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4

Figure 11-10: FOSI Questionnaire

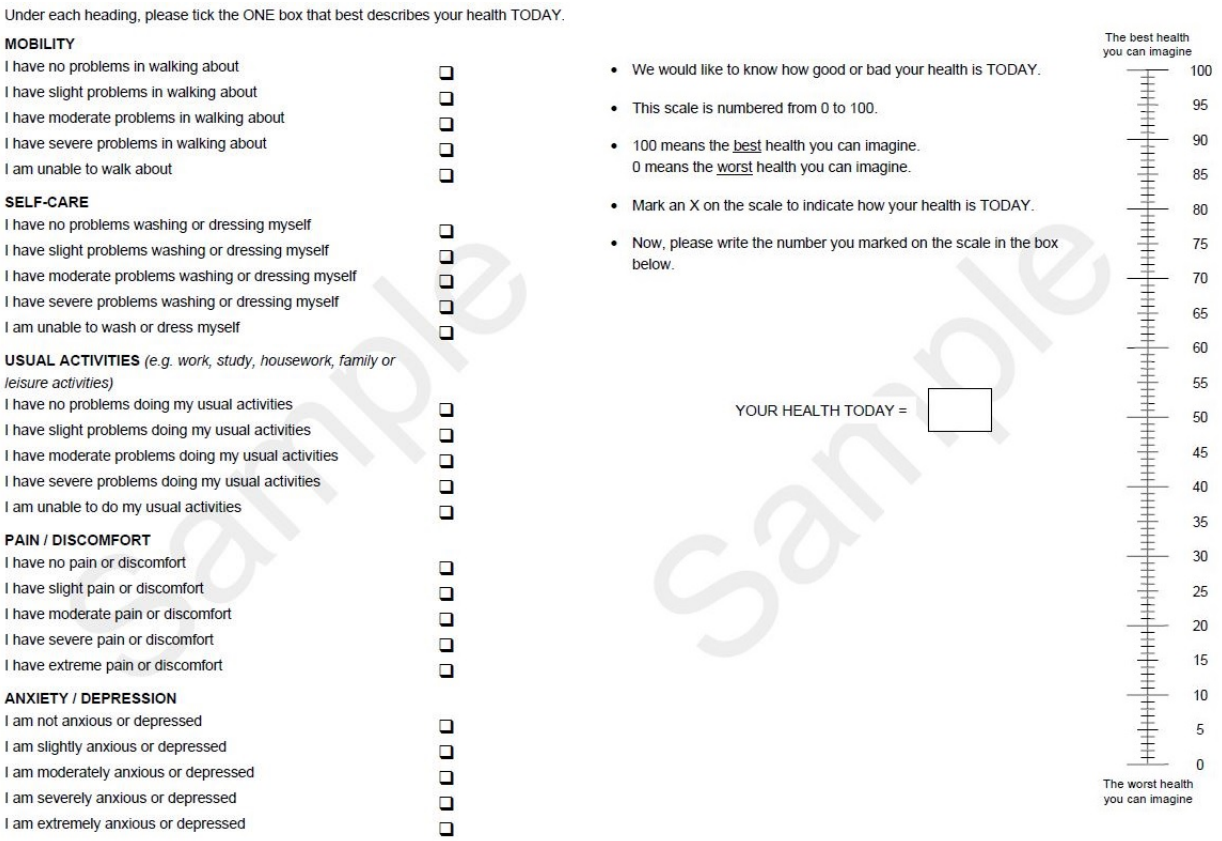
Reviewer Comments: The composite FOSI score is problematic from a regulatory perspective because it combines assessments of disease symptoms and treatment side effects with more global impacts such as quality of life and worry about prognosis. Elements more distal to disease and treatment related symptoms, such as worry and global quality of life, are influenced by multiple non-drug factors. Including these global elements in the overall score may decrease responsiveness to the effect of a drug, making the composite FOSI results difficult to interpret. Additionally, the item "I have pain," is broad and not specific (for example, could include knee pain from osteoarthritis not related to ovarian cancer or its treatment). The item "I have a lack of energy" is confusing as the response to demonstrate no symptoms is "not at all." This is a double negative and can be confusing as it is not readily apparent that this is the asymptomatic response (for example, it would be more clear if the item read "I have fatigue" and "not at all" was the response for an asymptomatic patient).

EQ-5D-5L

EQ-5D-5L is a five domain assessment of general health function that has been used for a variety of health conditions and treatments to assess generic health status for clinical and economic evaluations. Patients are to respond to their health status with items that best describe their health status for that

day. Domains include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is assessed with a response from 1 to 5 with 1 being "no problems" to 5 being "unable" to complete tasks or having "extreme" levels of pain, anxiety or depression. Scoring was completed by generating a five digit number with the response to each item. For example, health state 11111 indicates no problems on any of the five dimensions, while health state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort, and extreme anxiety or depression. EQ-5D-5L health states may be converted into a single index value. The index values, presented in country specific value sets, facilitate the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions. (Note: the index values from the EQ-5D are derived from crosswalk value sets from the EQ-5D 3L). Additionally, a visual analog scale records the respondent's self-assessed health status on a 20 cm vertical line with ticks along the line from 0 to 100 the top of the line being "best health you can imagine" and the bottom of the line being "worst health you can imagine." The respondent puts an x on the place on the line that she assesses herself to be and then records the number corresponding to the x in a box marked "your health today." See Figure 11-10.

Figure 11-11: EQ-5D-5L



Reviewer Comments: The EQ-5D-5L is a 5 item tool producing a single index value for health status. It incorporates concepts spanning pain, physical function, anxiety/depression and overall health. While the EQ-5D-5L contains items that may be useful to provide a general description of select drug and disease impacts (pain, some functional items), the pain assessment is general and may include pain that is not clearly related to disease. The intent of the EQ-5D-5L is to provide a single health utility index value for use in economic analyses. It lacks evidence of content validity for use in estimating clinical benefit for labeling claims, however, we acknowledge that the EQ-5D-5L may be useful and necessary for other regulatory authorities and/or payers.

Neuropathy Questionnaire

The applicant generated two questions to assess the patient's neuropathy over the past seven days, asking if the patient's feet (question 1) or hands (question 2) felt numb or had prickling/tingling feelings. The goal of this question was to assess the chemotherapy induced peripheral neuropathy (CIPN) status of each patient. Responses were on a 5-point verbal rating scale from 0 ("not at all") to 4 ("very much").

Responses to items on these assessments were evaluated individually with patients assessed as having CIPN if their response to question 1 (neuropathy in feet) was greater than 0 ("not at all"). For question 2, patients were assessed as having CIPN if their response was greater than 1 ("a little bit").

Reviewer Comments: The neuropathy questions have not been developed among patients with chemotherapy induced peripheral neuropathy. Responses to the neuropathy questionnaire are of limited utility in evaluating an agent not expected to cause peripheral neuropathy.

Schedule of Assessments

The study evaluated patients on treatment every four weeks with collection of PRO data and tumor imaging every eight weeks. PRO data were collected at baseline and then every two cycles (cycle = 28 days) from cycle 2 through 14 (e.g. cycle 2, 4, 6, etc.). After cycle 14, PRO data were collected every three cycles through the patient's study treatment. Although the applicant had initially proposed continuing PRO assessment after study discontinuation, the assessment plan was modified prior to the initiation of the protocol to include PRO assessment at the time to treatment discontinuation and then at one additional time point 8 weeks (± 2 weeks) after treatment discontinuation.

Statistical Analysis Plan and Methodology

Analysis of the PRO data was specified in the Statistical Analysis Plan (SAP) as a secondary endpoint. No alpha adjustments were made for multiple comparisons.

The Applicant performed the primary analysis using the ITT population as per the SAP Scores for the FOSI and EQ-5D-5L were computed as described above. Items from the neuropathy questionnaire were

handled individually as per the analysis plan. Missing data were handled based on the instructions from each instrument's manual. Missing data from the neuropathy questionnaire were not taken into account. The primary analysis was performed using the ITT population. For continuous variables, change in baseline overall score was analyzed descriptively by treatment group for each subgroup (gBRCA mutated and non-gBRCA mutated). The baseline, maintenance period containing cycles 2, 4 and 6 and post-treatment discontinuation assessments were analyzed in the applicant's report. Data from subsequent cycles were included in the appendix, however the Applicant focused on the data from the initial cycles given the decrease in completion rates over time coupled with the decrease in patients on each arm due to the 2:1 randomization scheme as well as the differences in progression free survival based on treatment arm.

The change in baseline FOSI score was analyzed descriptively by treatment group using a mixed effects growth curve model where time was modeled categorically for the purposes of the assessments. The EQ-5D-5L index was to be derived per the manual and both EQ-5D-5L index scores and EQ-VAS scores were to be analyzed in the same manner as the FOSI. Additionally, the display of the numbers and percentages of patients in each of the 5 response levels for each of the five dimensions was reported.

The number and percentage of patients reporting each response for neuropathy questionnaire items were to be displayed and association between ordinal response and treatment was to be evaluated using Pearson chi-square test.

Reviewer Comments: The Applicant indicates that the statistical plan for the PRO analyses is descriptive. The PRO analyses with composite scores were not controlled for multiple comparisons, and these analyses are considered exploratory.

Time to Symptom Worsening

Time to Symptom worsening based on the FOSI score was defined as time from randomization to the first FOSI assessment with a worsened score compared to baseline. A score was considered to be worsened if there was a change in score greater than the minimally important difference (MID) threshold. The MID is the smallest difference in score that is thought to be important. Previous studies evaluating the MID for the FOSI have considered change thresholds of 2-3 points to be the MID. This is based on data from a phase II study assessing the MID in FOSI scores from a treatment trial of patients with ovarian cancer. If the change from baseline FOSI score was greater than 1 MID, the patient was determined to be improved. If the FOSI score was within 1 MID from baseline, the patient was determined to be stable. If the change from baseline FOSI score was more than 1 MID lower, then the patient was determined to be worsened. The cumulative percentage of patients categorized as "worsened" by greater than 1 MID was determined at each time point. The number and percentage of patients with CIPN was reported by MID category by treatment group and cohort as well. Patients with no baseline and/or post-baseline FOSI assessment were censored at the date of randomization.

Reviewer comments: The FOSI contains items that are distal to disease and are not clearly symptoms of disease or treatment side effects. The composite FOSI score change over time to evaluate "symptom worsening" is of limited use as individual items include not only disease and treatment related symptoms but the more distal concepts of global QoL and worry. It is also not clear the MID threshold of 2-3 points would be considered appropriate in the maintenance setting as the MID used was determined in a treatment phase setting. In the future, data from anchor-based methods and cumulative distribution function (CDF) plots should inform the threshold for meaningful change. Obtaining patient input from structured cognitive debriefing interviews on what patients consider to be a meaningful change may also be useful to help determine an appropriate threshold for meaningful change for the condition and treatment that is being evaluated.

Health State Utility Analysis

The relationship between health state and reported health utility was retrospectively evaluated through a cross-sectional analysis of adjusted EQ-5D-5L health utility index scores. This analysis evaluates the mean health utility of patients following their baseline QoL score but prior to disease progression. The least square means estimates of the adjusted health utility index scores were presented cross-sectionally by treatment arm and compared with mean adjusted health utility index scores at baseline and at disease progression.

Reviewer comments: These assessments of utility, while we recognize are useful to other agencies and payers, are not within the scope of FDA assessment.

Disutility Analysis of Adverse Events:

A disutility analysis of adverse events (AEs) including fatigue, anemia, neutropenia and thrombocytopenia was conducted to determine which AE signs and symptoms were associated with statistically significant differences in health utility and FOSI symptoms during the stable treatment period as defined by post-baseline assessments prior to disease progression with 2-way interaction with the fixed treatment factor. These impacts were evaluated using adjusted EQ-5D HUI and FOSI scores derived from mixed models using the following covariates: histology, region, prior treatment, age, treatment, and baseline EQ-5D-5L or FOSI score. Separate models were developed to assess the contribution of AE type. Differences in the severity of AEs will be take into account by developing different disutility estimates for CTCAE grades 3 and 4 (severe or life threatening) events as compared to the overall analysis with CTCAE grades 1-4 and then stratified by treatment arms.

Reviewer comments: Anemia, neutropenia and thrombocytopenia are likely asymptomatic side effects that may not be reflected in changes in patient reported outcomes. Given the adverse event profile of niraparib, inclusion of side effects such as nausea and vomiting would be appropriate to determine if these adverse effects had an impact on the patient.

To further explore drug impacts, we analyzed individual item level responses of symptoms, function, and other patient experiences while on therapy using descriptive statistics.

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RESULTS

PRO Completion and Missing Data

Table 11-42: FDA's Analysis of PRO Completion Rates at Each Assessment Time Point

	# of Expected Patients		FOSI		EQ-5D-5L		Neuropathy	
	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo
gBRCAmut cohort								
Screening	138	65	97%	95%	99%	98%	98%	98%
Cycle 2	131	64	89%	91%	91%	94%	90%	89%
Cycle 4	120	53	93%	79%	96%	79%	94%	79%
Cycle 6	104	40	92%	90%	94%	90%	93%	90%
Cycle 8	94	26	87%	81%	91%	81%	88%	81%
Cycle 10	83	15	89%	80%	90%	80%	89%	80%
EOT	89	61	79%	82%	80%	84%	78%	84%
8-wk post EOT	81	59	60%	64%	60%	64%	60%	64%
Non-gBRCAmut cohort								
Screening	234	116	97%	97%	99%	97%	98%	96%
Cycle 2	209	113	87%	88%	89%	88%	86%	86%
Cycle 4	177	95	85%	80%	87%	82%	84%	80%
Cycle 6	143	56	87%	86%	88%	89%	85%	88%
Cycle 8	116	40	90%	88%	91%	90%	88%	88%
Cycle 10	96	30	91%	93%	93%	93%	91%	93%
EOT	185	102	85%	84%	85%	84%	86%	84%
8-wk post EOT	177	101	62%	66%	62%	67%	61%	67%

*Table provided by FDA Statistical Reviewer. The denominator used to calculate the completion rate was the number of at the time due for a cycle evaluation. The denominator for the 8 week post end of treatment visit was the number of patients who discontinued study treatment 8 weeks (+2 weeks) earlier. The Applicant analysis included only those patients who had a PRO assessment 8 weeks (±2 weeks) post ovarian cancer progression which led to a discrepancy in the proportion of patients who completed the end of treatment (EOT) assessment as compared to that reported by the Applicant.

Table 11-43: Reasons for Missing PRO Data^

FOSI Missing Data Reason	Total	
	Niraparib	*Placebo*
Screening	9/10 administrative failure 1/10 unknown	4/6 administrative failure 1/6 Spanish speaking patients 1/6 missing
Cycle 2	22/41 administrative failure 2/41 treatment discontinuation 1/41 patient failure to complete 2/41 patient upset 1/41 patient hospitalized 12/41 missing	14/21 administrative failure 2/21 treatment discontinuation 5/21 missing
Cycle 4	19/33 administrative failure 8/33 other 6/33 missing	8/25 administrative failure 12/22 treatment discontinuation 1/22 patient withdrew consent 1/25 patient too ill 3/25 missing
Cycle 6	10/22 administrative failure 4/22 other 8/22 missing	3/11 administrative failure 3/11 other 2/11 missing
8 week post progression	21/52 administrative failure 4/52 patient illness 26/52 patient refused/withdrew 1/52 missing	13/29 administrative failure 7/29 patient too ill 1/29 patient upset 1/29 patient felt inconvenient 4/29 patient refused/withdrew 3/29 missing

^Table adapted from Applicant Table 1, PRO report, pages 21-26. This table captures data regarding reason for missing data. Numbers are different from the above generated table by FDA given the discrepancy between the intended end of treatment visit vs. the Applicant's report of the 8 week "post progression" assessment.

Reviewer comments: The PRO questionnaires had a relatively high completion rate. As demonstrated in previous studies, the missing rate increases with time. The most common reason for missing data across cycles was administrative failure. The most common reason for missing data in the post treatment assessment was due to patient not feeling well. FDA results were similar to the Applicant's; however the numbers are different as the Applicant modified the definition of the assessment after treatment discontinuation to include only participants who had discontinued treatment due to progressive disease rather than include all patients who discontinued treatment (e.g. for intolerability or for adverse events).

One objective for PRO data is to describe the experience of patients who are taking the therapy under study. It is reasonable to evaluate these results over the first six months of treatment as the Applicant did. This is because while there was good responsiveness of patients even on cycles past the six month period, this reviewer noted that, due to both the differences in PFS between treatment and placebo and the 2:1 randomization, there were smaller numbers of patients who remained on the control arm for cycles 8 and beyond which may make the results less reliable.

Analysis of PRO Scores Over Time

Table 11-44: FOSI Time to Symptom Worsening by Cohort

Cohort	Parameter	Statistic	Niraparib	Placebo
g*BRCA*mut		N	(N = 138)	(N = 65)
	TSW (months)[3,4]	75th Percentile (95% CI)	NE	NE (8.71, NE)
		Median (95% CI)	8.3 (4.73, NE)	6.1 (4.63, 10.28)
		25th Percentile (95% CI)	2.8 (1.91, 3.75)	3.1 (1.87, 4.63)
	Censored Observations	n (%)	68 (49.3)	30 (46.2)
	Event Rate, Overall	n (%)	70 (50.7)	35 (53.8)
	p-value[5]			0.399
	HR, Niraparib:Placebo[6]	HR (95% CI)	0.844 (0.561, 1.271)	
Non-g*BRCA*mut Overall		N	(N = 234)	(N = 116)
	TSW (months) [3,4]	75th Percentile (95% CI)	NE (12.02, NE)	NE (11.07, NE)
		Median (95% CI)	5.6 (3.84, 6.80)	7.3 (4.60, 10.15)
		25th Percentile (95% CI)	2.0 (1.91, 2.83)	3.7 (2.40, 3.78)
	Censored Observations	N (%)	99 (42.3)	55 (47.4)
	Event Rate, Overall	N (%)	135 (57.7)	61 (52.6)
	p-value[5]			0.215
	HR, Niraparib:Placebo[6]	HR (95% CI)	1.158 (0.854, 1.570)	

Resource: Applicant analysis, Patient Reported Outcomes Report Table 9, page 100.

Reviewer comments: There was a numerically greater time to symptom worsening in the non-gBRCA patients on placebo as compared to treatment (7.3 months vs. 5.6 months), however the hazard ratio had a wide 95% confidence interval including 1. The TSW in the gBRCA arm was numerically greater in the niraparib arm as compared to placebo (8.3 months vs. 6.1 months). Additionally, as previously stated, using the composite FOSI score change over time to evaluate "symptom worsening" may be misleading as individual items include disease and treatment related symptoms as well as the more distal concepts of quality of life and worry.

The FOSI may be less responsive to drug effects because inclusion of elements distal to the impact of the drug on disease symptoms and treatment side effects are incorporated into a single score. Some of the items themselves are also problematic as previously outlined (e.g. "I have pain" is not specific; quantification may have both inter and intra-patient issues; wording of "I have a lack of energy" item is problematic given the double negative). The tables above demonstrate that there were similar baseline FOSI scores in each arm and that there were minimal changes in the overall score from visit to visit. Comparison of mean scores of the study population may obscure important individual level changes in score over time.

Given the stated limitations of the composite scores, FDA further explored items at the individual level to

better understand the patient experience. Of particular interest were items related to fatigue, pain, and nausea/vomiting. Pain is an important symptom reported by many patients as their metastatic cancer progresses and nausea and vomiting may be side effects from PARP inhibitor therapy based on experience from other studies and review of the Applicant's AE reporting.

Table 11-45: Clinician-reported Adverse Events, Any Grade, from CTCAE Analysis Provided by the Applicant

MedDRA Preferred Term	Niraparib (%)	Placebo (%)
Any TEAE	100.0	95.5
Nausea	73.6	35.2
Anemia	48.5	6.7
Fatigue	45.8	32.4
Vomiting	34.3	16.2
Abdominal pain	22.6	29.6

Resource: Applicant analysis, NOVA Clinical Study Report adapted from Table 43, pages 180-181.

Reviewer comments: To further explore the patient experience, the FDA reviewers evaluated data from patients who completed PRO assessments at screening, and their subsequent responses in cycles 2, 4, 6 and 8 to look at the change from baseline. Items of interest were FOSI: "I have pain," "I have a lack of energy," " I have nausea," "I have cramps," "I have swelling in my stomach area," "I have been vomiting" and EQ-5D-5L: Pain, Mobility, Self-Care, Usual Activities. These analyses are exploratory and further work is needed to identify the most informative visualization to describe this data.

In completing this exploratory analysis, patient responses were grouped into one of three different categories: those who responded "not at all" (score 0) were categorized as "none," those who responded "A little bit" or "Somewhat" (score 1 or 2) were categorized as "moderate," and those who responded "Quite a bit" or "Very Much" were categorized as "severe."

The tables below demonstrate the number of patients who completed the instruments at each cycle as well as the proportion of responses at each cycle. The responses for cycles 2, 4, 6, and 8 are further categorized by color within each response category based on their baseline response at the screening visit. Baseline symptoms were color coded as green (no baseline symptoms), yellow (moderate baseline symptoms) or red (severe baseline symptoms). Visualizing the data in this way demonstrates the change in response from baseline which helps to better understand the effect of the intervention.

For example, in the FOSI item, "I have pain," 138/361 (38%) patients on the niraparib arm reported moderate (yellow) pain at screening and 119/291 (41%) reported moderate pain at cycle 2. Of these 119

patients with moderate pain at cycle 2, 74 patients on niraparib reported moderate (yellow) pain at baseline and thus were stable, 36 patients with moderate pain at cycle 2 had no pain (green) at screening (representing an increase in pain at cycle 2), and 9 patients with moderate pain at cycle 2 had severe pain (red) at screening (representing a decrease in pain). The reviewer recognizes the complexity of the interpretation of this visualization. However, for a population with heterogeneous symptoms at baseline, it is important to take into account baseline symptoms at subsequent assessments in order to better understand treatment effects. These visualizations represent one of many ways these data can be presented longitudinally. Continued development of optimal analytic and visualization methods is warranted.

FOSI "I have pain"

	Screening	**Cycle 2**		**Cycle 4**	
	# of patients per score (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=361**	**N=291**		**N=254**	
Severe	19 (5)	13 (4)	4 (1)	14 (6)	3 (1)
			5 (2)		9 (4)
			4 (1)		2 (<1)
Moderate	138 (38)	119 (41)	9 (3)	100 (39)	6 (2)
			74 (25)		59 (23)
			36 (12)		35 (14)
None	204 (57)	159 (55)	2 (<1)	140 (55)	1 (<1)
			33 (11)		31 (12)
			124 (43)		108 (43)

An additional factor specific to this study which should be considered when interpreting these data is that the population had recently completed cytotoxic chemotherapy prior to enrollment. As a result, baseline scores from the screening evaluation may reflect toxicities from previous therapy that had not yet resolved. Another consideration is that, as is the case in most cancer contexts, symptoms can be related to side effects or disease progression.

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FOSI "I have pain"

	Screening	Cycle 2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=361**	**N=291**		**N=254**		**N=213**		**N=183**	
Severe	19 (5)	13 (4)	4 (1)	14 (6)	3 (1)	12 (6)	1 (<1)	6 (3)	3 (2)
			5 (2)		9 (4)		8 (4)		2 (1)
			4 (1)		2 (<1)		3 (1)		1 (<1)
Moderate	138 (38)	119 (41)	9 (3)	100 (39)	6 (2)	81 (38)	4 (2)	65 (36)	1 (<1)
			74 (25)		59 (23)		47 (22)		44 (24)
			36 (12)		35 (14)		30 (14)		20 (11)
None	204 (57)	159 (55)	2 (<1)	140 (55)	1 (<1)	120 (56)	0	112 (61)	0
			33 (11)		31 (12)		31 (15)		27 (15)
			124 (43)		108 (43)		89 (42)		85 (46)
Placebo	**N=174**	**N=151**		**N=117**		**N=84**		**N=55**	
Severe	13 (7)	19 (13)	8 (5)	12 (10)	4 (3)	8 (10)	4 (5)	6 (11)	4 (7)
			9 (6)		4 (3)		2 (3)		2 (4)
			2 (1)		4 (3)		2 (3)		0
Moderate	66 (38)	64 (42)	5 (3)	55 (47)	6 (5)	34 (40)	3 (4)	28 (51)	1 (2)
			37 (25)		28 (24)		20 (24)		17 (31)
			22 (15)		21 (18)		11 (13)		10 (18)
None	95 (55)	68 (45)	0	50 (43)	0	42 (50)	0	21 (38)	0
			10 (7)		6 (5)		6 (7)		1 (2)
			58 (38)		44 (38)		36 (43)		20 (36)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: At screening, around half of patients had reported no pain at all and fewer than 10% reported severe pain. Pain was reported with greater frequency on the placebo arm for subsequent cycles with 39-45% of patients reporting pain during cycles 2-8 on the niraparib arm compared with 50-62% of patients on the placebo arm. Among patients who reported moderate pain ("a little bit" or "somewhat") at study screening, proportionally more patients in the niraparib arm felt better and reported no pain at post-baseline on-treatment assessments when compared to placebo. Overall, the proportion of patients in the niraparib arm with no pain was numerically higher than that of placebo at on-treatment assessments. However, it was noted that this is a general pain item and does not refer specifically to abdominal pain which is more likely to be associated with ovarian cancer symptoms as with possible treatment related symptoms.

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FOSI "I have a lack of energy"

	Screening	Cycle2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=372**	**N=292**		**N=255**		**N=211**		**N=183**	
Severe	64 (17)	64 (22)	24 (8)	48 (19)	20 (8)	30 (14)	14 (7)	23 (12)	10 (5)
			35 (12)		27 (11)		15 (7)		13 (7)
			5 (2)		1 (<1)		1 (<1)		0
Moderate	219 (61)	172 (59)	23 (8)	147 (58)	20 (8)	115 (55)	14 (7)	102 (56)	12 (7)
			117 (40)		107 (42)		80 (38)		70 (38)
			31 (11)		20 (8)		21 (10)		20 (11)
None	79 (22)	57 (20)	1 (<1)	60 (24)	1 (<1)	66 (31)	4 (2)	58 (32)	5 (3)
			22 (8)		21 (8)		29 (14)		25 (14)
			34 (12)		38 (15)		33 (16)		28 (15)
Placebo	**N=175**	**N=154**		**N=119**		**N=84**		**N=55**	
Severe	33 (19)	26 (17)	13 (8)	19 (16)	9 (8)	13 (15)	8 (10)	7 (13)	5 (9)
			12 (8)		10 (8)		5 (6)		2 (4)
			1 (<1)		0		0		0
Moderate	109 (62)	101 (66)	15 (10)	70 (59)	12 (10)	49 (58)	8 (10)	36 (65)	6 (11)
			74 (48)		48 (40)		36 (43)		27 (49)
			12 (8)		10 (8)		5 (6)		3 (5)
None	33 (19)	27 (18)	0	30 (25)	0	22 (26)	0	12 (22)	0
			13 (8)		16 (13)		11 (13)		5 (9)
			14 (9)		14 (12)		11 (13)		7 (13)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: No marked differences were observed between the two treatment arms. In the niraparib arm 61% of patients were in the moderate group at screening (yellow). At cycle 2, 35 patients (12%) who were in the moderate group at baseline had worsened to the "severe" group and 8% improved to the "none" group. Most of these patients (38-42%) remained stable within this category from cycle 2 to cycle 8.

Similar results were observed in the placebo arm.

It was noted that the wording of this item may be confusing given that "I have a lack of energy" and the response "not at all" is a double negative. This may account for the discrepancy between the adverse event reporting of fatigue with higher proportions of fatigue reported in the niraparib arm based on clinician reported AE data.

FOSI "I have nausea"

	Screening	Cycle2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=362**	**N=293**		**N=255**		**N=214**		**N=180**	
Severe	13 (4)	20 (7)	4 (1)	13 (5)	1 (<1)	5 (2)	0	4 (2)	0
			10 (3)		6 (2)		4 (2)		2 (1)
			6 (2)		6 (2)		1 (<1)		2 (1)
Moderate	71 (20)	128 (44)	5 (2)	88 (35)	6 (2)	73 (34)	4 (2)	52 (29)	3 (2)
			35 (12)		25 (10)		21 (10)		18 (10)
			88 (30)		57 (22)		48 (22)		31 (17)
None	278 (77)	145 (49)	1 (<1)	156 (61)	3 (1)	136 (64)	3 (1)	124 (69)	4 (2)
			12 (4)		18 (7)		15 (7)		10 (6)
			132 (45)		135 (53)		118 (55)		110 (61)
Placebo	**N=175**	**N=151**		**N=118**		**N=84**		**N=55**	
Severe	3 (2)	5 (3)	1 (<1)	5 (4)	1 (<1)	4 (5)	1 (1)	2 (4)	0
			2 (1)		2 (2)		2 (2)		2 (4)
			2 (1)		2 (2)		1 (1)		0
Moderate	31 (18)	25 (17)	0	15 (13)	1 (<1)	12 (14)	0	7 (13)	0
			14 (9)		8 (7)		6 (7)		4 (7)
			11 (7)		6 (5)		6 (7)		3 (5)
None	141 (81)	121 (80)	1 (<1)	98 (83)	0	68 (81)	0	46 (83)	0
			9 (6)		8 (7)		6 (7)		6 (11)
			111 (74)		90 (76)		62 (74)		40 (73)

Screening score 0 (Not at all) | Screening score 1 or 2 (A little bit or Somewhat) | Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: More patients on niraparib experienced worsening nausea compared to their screening visit when compared to placebo. Most of these patients reported an increase to moderate levels of nausea with a few patients (2% or fewer) moving from no symptoms at screening to severe nausea during subsequent cycles. At screening, 77% of patients in the niraparib arm had no nausea; however, 30% of the

patients on cycle 2 who had no nausea at screening reported moderate nausea at this time point while and 2% reported severe nausea at cycle 2. The proportion reporting some level of nausea decreased slightly with subsequent cycles but was still higher than the screening rate of reporting this symptom. In the placebo arm, the report of nausea severity was relatively stable from screening to cycle 8. Given the timing and the known toxicity profile of niraparib, we can conclude this is most likely related to treatment. The increase in nausea reporting by patients on niraparib is consistent with the AE reports of nausea associated with the use of this drug.

FOSI "I have been vomiting"

	Screening	Cycle2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score n(%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=362**	**N=293**		**N=256**		**N=213**		**N=182**	
Severe	0	5 (2)	0 1 (<1) 4 (1)	3 (1)	0 2 (<1) 1(<1)	2 (<1)	0 0 2 (<1)	2 (1)	0 0 2 (1)
Moderate	23 (6)	32 (11)	0 6 (2) 26 (9)	29 (11)	0 5 (2) 24 (9)	17 (8)	0 4 (2) 13 (6)	15 (8)	0 5 (3) 10 (5)
None	339 (94)	256 (87)	0 12 (4) 244 (83)	224 (88)	0 12 (5) 212 (83)	194 (91)	0 10 (5) 184 (86)	165 (91)	0 7 (4) 158 (87)
Placebo	**N=175**	**N=153**		**N=118**		**N=84**		**N=56**	
Severe	1 (<1)	0	0 0 0	2 (2)	0 1 (<1) 1 (<1)	1 (1)	0 1 (1) 0	0	0 0 0
Moderate	11 (6)	10 (7)	0 4 (3) 6 (4)	8 (7)	0 2 (2) 6 (5)	5 (6)	0 3 (4) 2 (2)	4 (7)	0 3 (5) 1 (2)
None	163 (93)	143 (93)	1 (<1) 6 (4) 136 (89)	108 (91)	1 (<1) 4 (3) 103 (87)	78 (93)	0 3 (4) 75 (89)	52 (93)	0 2 (4) 50 (89)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: At screening, more than 90% of patients did not have any vomiting in both arms. From cycle 2 to cycle 8, reports of vomiting were numerically higher in the niraparib arm, i.e., approximately 7-10% patients who reported no vomiting at baseline reported some level of vomiting. The placebo arm had a similar trend but the percentage was lower, ranging from approximately 2-6%.

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FOSI "I have swelling in my stomach area"

	Screening	Cycle 2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score n(%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=361**	**N=289**		**N=253**		**N=212**		**N=181**	
Severe	14 (4)	16 (6)	6 (2)	9 (4)	4 (2)	9 (4)	1 (<1)	6 (3)	1 (<1)
			8 (3)		4 (2)		5 (2)		4 (2)
			2 (<1)		1 (<1)		3 (1)		1 (<1)
Moderate	79 (22)	65 (22)	5 (2)	65 (26)	5 (2)	54 (25)	6 (3)	44 (24)	3 (2)
			32 (11)		27 (11)		27 (13)		19 (11)
			28 (10)		33 (13)		21 (10)		22 (12)
None	268 (74)	208 (72)	2 (<1)	179 (70)	1 (<1)	149 (70)	0	131 (72)	1 (<1)
			22 (8)		21 (8)		11 (5)		16 (9)
			184 (64)		157 (62)		138 (65)		114 (63)
Placebo	**N=175**	**N=150**		**N=118**		**N=83**		**N=56**	
Severe	6 (3)	5 (3)	2 (1)	7 (6)	1 (<1)	7 (8)	1 (1)	4 (7)	1 (2)
			2 (1)		5 (4)		2 (2)		2 (4)
			1 (<1)		1 (<1)		4 (5)		1 (2)
Moderate	33 (19)	34 (23)	2 (1)	24 (20)	0	16 (19)	0	13 (23)	0
			13 (9)		6 (5)		7 (8)		7 (13)
			19 (13)		18 (15)		9 (11)		6 (11)
None	136 (78)	111 (74)	1 (<1)	87 (74)	1 (<1)	60 (73)	1 (1)	39 (70)	1 (2)
			12 (8)		9 (8)		8 (10)		3 (5)
			98 (65)		77 (65)		51 (61)		35 (63)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: Patient reports of feelings of stomach swelling were similar between the niraparib arm and the placebo arm.

FOSI "I have cramps in my stomach area"

	Screening	Cycle2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score n(%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=362**	**N=293**		**N=256**		**N=213**		**N=183**	
Severe	4 (1)	10 (3)	2 (<1) 5 (2) 3 (1)	11 (4)	0 7 (3) 4 (2)	5 (3)	1 (<1) 3 (1) 1 (<1)	7 (4)	0 4 (2) 3 (2)
Moderate	65 (18)	69 (24)	2 (<1) 31 (11) 36 (12)	61 (24)	1 (<1) 27 (11) 33 (13)	50 (23)	0 26 (12) 24 (11)	37 (20)	1 (<1) 18 (10) 18 (10)
None	293 (81)	214 (73)	0 16 (5) 198 (68)	184 (72)	1 (<1) 15 (6) 168 (66)	159 (74)	1 (<1) 10 (5) 148 (69)	139 (76)	1 (<1) 8 (4) 130 (71)
Placebo	**N=175**	**N=153**		**N=118**		**N=84**		**N=56**	
Severe	1 (<1)	4 (3)	1 (<1) 1 (<1) 2 (1)	3 (3)	0 1 (<1) 2 (2)	1 (1)	0 1 (1) 0	0	0 0 0
Moderate	28 (16)	25 (16)	0 11 (7) 14 (9)	22 (19)	0 4 (3) 18 (15)	19 (23)	0 6 (7) 13 (15)	13 (23)	0 6 (11) 7 (13)
None	146 (83)	124 (81)	0 11 (7) 113 (74)	93 (79)	0 13 (11) 80 (68)	64 (76)	0 8 (10) 56 (67)	43 (77)	0 5 (9) 38 (68)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: At screening there were approximately 80% patients without stomach cramping and 20% with any stomach cramping in both treatment arms. There was no consistent trend observed in changes in abdominal cramping.

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EQ-5D-5L Mobility

	Screening	Cycle2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score n(%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=367**	**N=304**		**N=266**		**N=220**		**N=189**	
Severe	5 (1)	1 (<1)	0	6 (2)	1 (<1)	3 (1)	1 (<1)	2 (1)	1 (<1)
			1 (<1)		5 (2)		2 (<1)		0
			0		0		0		1 (<1)
Moderate	107 (29)	87 (29)	5 (2)	68 (26)	1 (<1)	43 (20)	0	42 (22)	0
			55 (18)		38 (14)		28 (13)		26 (14)
			27 (9)		29 (11)		15 (7)		16 (8)
None	255 (69)	216 (71)	0	192 (72)	1 (<1)	174 (79)	1 (<1)	145 (77)	0
			28 (9)		30 (11)		30 (14)		25 (13)
			188 (62)		161 (61)		143 (65)		120 (63)
Placebo	**N=179**	**N=158**		**N=120**		**N=86**		**N=57**	
Severe	5 (3)	4 (3)	3 (2)	4 (3)	2 (2)	2 (2)	1 (1)	3 (5)	2 (4)
			1 (<1)		2 (2)		1 (1)		1 (2)
			0		0		0		0
Moderate	42 (23)	50 (32)	2 (1)	37 (31)	1 (<1)	25 (29)	1 (1)	15 (26)	0
			30 (19)		23 (19)		13 (15)		8 (14)
			18 (11)		13 (11)		11 (13)		7 (12)
None	132 (74)	104 (66)	0	79 (66)	0	59 (69)	1 (1)	39 (68)	0
			8 (5)		8 (7)		9 (10)		3 (5)
			96 (61)		71 (59)		49 (57)		36 (63)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: There was no clear change of mobility score from screening and this was similar for the two treatment arms.

EQ-5D-5L Self-Care

	Screening	Cycle2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score n(%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=367**	**N=302**		**N=266**		**N=220**		**N=189**	
Severe	1 (<1)	1 (<1)	0	1 (<1)	0	0	0	0	0
			0		1 (<1)		0		0
			1 (<1)		0		0		0
Moderate	26 (7)	19 (6)	0	21 (8)	0	14 (6)	0	7 (4)	0
			9 (3)		11 (4)		9 (4)		6 (3)
			10 (4)		10 (4)		5 (2)		1 (<1)
None	340 (93)	282 (94)	0	244 (92)	0	206 (94)	0	182 (96)	0
			11 (4)		8 (3)		7 (3)		8 (4)
			271 (90)		236 (89)		199 (90)		174 (92)
Placebo	**N=179**	**N=158**		**N=120**		**N=86**		**N=57**	
Severe	2 (1)	0	0	0	0	0	0	0	0
			0		0		0		0
			0		0		0		0
Moderate	14 (8)	15 (8)	1 (<1)	12 (10)	0	9 (10)	0	6 (11)	0
			9 (6)		6 (5)		4 (5)		0
			5 (3)		6 (5)		5 (6)		6 (11)
None	163 (91)	143 (92)	1 (<1)	108 (90)	0	77 (90)	1 (1)	51 (89)	0
			4 (3)		3 (3)		3 (3)		2 (4)
			138 (87)		105 (88)		73 (85)		49 (86)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: Approximately 90% of patients had no problems with self-care at screening in both arms and this remained similar over the course of the study.

EQ-5D-5L Usual Activities

	Screening	Cycle2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score n(%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=367**	**N=304**		**N=265**		**N=220**		**N=189**	
Severe	10 (3)	8 (3)	0	6 (2)	1 (<1)	4 (2)	1 (<1)0	2 (1)	1 (<1)
			5 (2)		3 (<1)		3 (1)		1 (<1)
			3 (1)		2 (<1)		0		0
Moderate	163 (44)	126 (41)	4 (1)	103 (39)	2 (<1)	69 (31)	0	60 (32)	0
			89 (29)		73 (28)		52 (24)		41 (22)
			33 (11)		28 (11)		17 (8)		19 (10)
None	194 (53)	170 (56)	2 (<1)	156 (59)	2 (<1)	147 (67)	2 (<1)	127 (67)	1 (<1)
			34 (11)		35 (11)		33 (15)		33 (17)
			134 (44)		119 (45)		112 (51)		93 (49)
Placebo	**N=178**	**N=158**		**N=120**		**N=86**		**N=57**	
Severe	10 (6)	4 (3)	2 (1)	3 (3)	1 (<1)	3 (3)	1 (1)	1 (2)	1 (2)
			2 (1)		2 (2)		1 (1)		0
			0		0		1 (1)		0
Moderate	73 (41)	65 (41)	6 (4)	45 (38)	4 (3)	34 (40)	3 (3)	20 (35)	2 (4)
			46 (29)		32 (27)		25 (29)		13 (23)
			13 (8)		9 (8)		6 (7)		5 (9)
None	95 (53)	89 (56)	1 (<1)	72 (60)	0	49 (57)	0	36 (63)	0
			18 (11)		18 (15)		11 (13)		13 (23)
			70 (44)		54 (45)		38 (44)		23 (40)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: There were no consistent differences between the two arms from screening through cycle 8.

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EQ-5D-5L Pain/Discomfort

	Screening	Cycle2		Cycle 4		Cycle 6		Cycle 8	
	# of patients per score n(%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)	n (%)	# of pts per score at screening (%)
Niraparib	**N=367**	**N=302**		**N=266**		**N=220**		**N=189**	
Severe	10 (3)	6 (2)	2 (<1)	3 (1)	0	3 (1)	0	2 (1)	0
			4 (1)		1 (<1)		3 (1)		1 (<1)
			0		2 (<1)		0		1 (<1)
Moderate	171 (47)	148 (49)	4 (1)	125 (47)	5 (2)	95 (43)	3 (1)	84 (44)	1 (<1)
			105 (35)		84 (32)		63 (29)		62 (33)
			39 (13)		36 (14)		29 (13)		21 (11)
None	186 (51)	148 (49)	2 (<1)	138 (52)	1 (<1)	122 (56)	0	103 (55)	0
			32 (11)		38 (14)		32 (15)		24 (13)
			114 (38)		99 (37)		90 (41)		79 (42)
Placebo	**N=179**	**N=158**		**N=120**		**N=86**		**N=57**	
Severe	9 (5)	8 (5)	4 (3)	5 (4)	2 (2)	3 (3)	1 (1)	2 (4)	1 (2)
			3 (1)		2 (2)		1 (1)		1 (2)
			1 (<1)		1 (<1)		1 (1)		0
Moderate	78 (44)	89 (56)	4 (3)	65 (54)	3 (3)	45 (52)	2 (2)	33 (58)	1 (2)
			57 (36)		43 (36)		31 (36)		25 (44)
			28 (18)		19 (16)		12 (14)		7 (12)
None	92 (51)	61 (39)	1 (<1)	50 (42)	0	38 (45)	0	22 (39)	0
			8 (5)		4 (3)		7 (8)		2 (4)
			52 (33)		46 (38)		31 (36)		20 (35)

Screening score 0 (Not at all)

Screening score 1 or 2 (A little bit or Somewhat)

Screening score 3 or 4 (Quite a bit or Very much)

Note: Denominator for the percentage calculation is the total number of patients at each assessment for each treatment arm

Reviewer comments: Similar to the data from the FOSI pain item, the screening distribution of pain or discomfort was similar between the two treatment arms. At post-screening on-treatment assessments, more patients who reported any pain were on the placebo arm. Attribution of the

improvement in pain to treatment is problematic, however, given that the PRO pain assessments were not specific to abdominal pain.

APPEARS THIS WAY ON ORIGINAL

Summary of Findings

FDA carefully reviewed the PRO data for this submission in the setting of a maintenance therapy. While the data complemented the submitted clinician reported safety data and radiographic and survival data, the inclusion of PRO results in product labeling is not recommended for multiple reasons. Prior to the NDA submission, FDA had discussed with the Applicant concerns about the limitations of the instruments used in the NOVA trial, including inability to adapt symptom measures to the particular clinical context, and use of a summary score that mixes symptoms, function, and more distal impacts, raising concerns over the responsiveness and interpretation of the composite scores. Additionally, in this study, no alpha was pre-specified and no adjustment for multiplicity was made in the SAP for the PRO analyses, limiting the ability for the Applicant to make a claim of treatment benefit. Finally, optimal descriptive longitudinal analyses and visualization is not yet known for side effects and other measures of tolerability.

FDA review of the PRO information submitted did not identify large or compelling differences in the composite score for FOSI or EQ-5D-5L . PRO data in this application primarily provide a descriptive account of the patient experience while on treatment with a maintenance therapy to delay disease progression. In this context we focused on the first 8 cycles of treatment given that the data is most reliable for these cycles given small sample sizes in the placebo arm in the later cycles.

The PRO data were collected with an acceptable rate of completion through 8 cycles of treatment. Nausea and vomiting were seen more frequently in the niraparib arm than in the placebo arm. This patient perspective was consistent and complementary to the CTCAE reporting of these adverse events.

Exploration of individual patient-reported symptoms can be informative, but in this case was limited to those symptoms incorporated into the FOSI and EQ-5D-5L which are not easily adapted and have been designed as composite scores. Future studies might benefit from employing an item library from which an unbiased selection of the important individual symptoms relevant to the disease and treatment context could be selected.

In addition to looking at individual items in the FOSI, the responses to individual items in the EQ-5D-5L results were of interest. As with FOSI and the reported adverse reactions, pain appeared to be slightly decreased on the niraparib arm. We were not able to assess the tradeoffs between disease control with this agent vs. traditional chemotherapy given that those on placebo no longer completed PRO assessments beyond the 8 week post-treatment discontinuation point. We continue to develop and refine our analyses of these data in an effort to better understand and describe the patient experience while on treatment and to use these data in the drug evaluation process.

In conclusion, PROs were assessed with reasonably high completion rates. The instruments selected by the Applicant have multiple limitations as previously described. Evaluation of the individual item data showed increase in nausea and vomiting and decreased pain on the niraparib arm, complementing findings from the CTCAE clinician reported data. However, pain questions did not target abdominal pain and the degree to which non-ovarian cancer pain affected the results is not known.

More specific and quantifiable tools such as item banks or libraries for symptoms and physical function, as well as optimal analyses to provide the most informative and least misleading PRO information remain an area of active investigation. Sponsors and applicants are encouraged to continue to discuss their PRO strategy with the FDA, and to use a pre-specified SAP with control for multiple comparisons if considering seeking marketing claims.

APPEARS THIS WAY ON ORIGINAL

Covered Clinical Study (Name and/or Number): PR-30-5011-C (NOVA)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 109		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 9		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

/s/

GWYNN ISON
03/22/2017

LYNN J HOWIE
03/22/2017

LIJUN ZHANG
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03/22/2017

12 Labeling Recommendations

12.1. Prescribing Information

Summary of Significant Labeling Changes *(High level changes and not direct quotations)*		
Section	**Proposed Labeling**	**Approved Labeling** ***(As of March 17, 2017)***
Highlights of Labeling		
Indications and Usage	ZEJULA is a poly(ADP-ribose) polymerase (PARP) (b) (4) inhibitor indicated for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy. (1)	FDA revised the established pharmacologic class to "poly (ADP-ribose) polymerase (PARP) inhibitor" and removed "platinum sensitive". To be consistent with the revisions to Section 1 below, FDA added "who are in a complete or partial response to platinum-based chemotherapy".
Dosage and Administration	• Recommended dose is 300 mg taken once daily. (2.1)	FDA added "with or without food" to be consistent with Section 2 and 17 (Patient Counseling Information).
Warnings and Precautions	• Myelodysplastic syndrome/Acute Myeloid Leukemia: MDS/AML occurred in patients exposed to ZEJULA (b) (4) and some cases were fatal. Discontinue if MDS/AML is confirmed. (5.2) • (b) (4) Test complete blood counts weekly for the first month (b) (4) monthly for the next 11 months and periodically	FDA moved the MDS/AML information from 5.2 to 5.1 to be consistent with revisions in Section 5. FDA replaced the last sentence with "Monitor patients for hematological toxicity and discontinue if MDS/AML is confirmed (5.1)". FDA revised (b) (4) to "Bone Marrow Suppression" and removed (b) (4) " to be consistent with the revisions in Section 5.2.

	[redacted] for clinically significant changes. (5.1) • [redacted] Monitor blood pressure monthly for the first year and periodically thereafter during treatment with Zejula. Manage with antihypertensive medications as well as adjustment of the Zejula dose, if necessary. (5.3) • Embryofetal toxicity: ZEJULA can cause [redacted] fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to [redacted]. (5.4, 8.1)	FDA revised the title of 5.3 to "Cardiovascular Effects" to be consistent with the revisions in Section 5.3, and added heart rate monitoring (i.e., "Monitor blood pressure and heart rate…"). FDA removed [redacted] "use effective contraception".
Adverse Reactions	Most common adverse reactions (incidence > [redacted]%) are anemia, thrombocytopenia, nausea, constipation, vomiting, fatigue, [redacted] decreased appetite, headache, and insomnia. (6.1)	FDA revised the incidence to ≥ 10% and added the required ARs to be consistent with the revisions in Section 6.1.
Use in Specific Populations	[redacted]	[redacted] FDA revised this to the following: • Lactation: Advise women not to breastfeed during treatment

		and for 1 month after receiving the final dose. (8.2) (b) (4) [redacted]
Full Prescribing Information		
1. Indications and Usage	ZEJULA™ is indicated for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.	FDA removed "platinum sensitive" while maintaining the description "who are in a complete or partial response to platinum-based chemotherapy" to remove redundancy and more precisely define the indicated population. *See Section 11.2 of this review for more information.*
2. Dosage and Administration	**2.1 Recommended Dosage** The recommended dose of ZEJULA as monotherapy is three 100 mg capsules taken orally once daily, (b) (4) [redacted] … … **2.2 Dose Adjustments for Adverse Reactions** *(see labeling for Tables 1,2,and 3)*	FDA revised to the following to improve readability and potentially prevent medication errors: "The recommended dose of ZEJULA as monotherapy is 300 mg (three 100 mg capsules) taken orally once daily". … FDA added information to inform patients that Zejula can be taken with or without food. … In Table 3, FDA revised the monitoring recommendations for complete blood counts from "(b) (4) [redacted] to "weekly for the first month". *See 11.4.3 of this review for more information.* FDA removed (b) (4) [redacted] and added cross references to the corresponding Warnings and

		Precautions subsections. (b) (4) [redacted]
5. Warnings and Precautions	**5.2 Myelodysplastic Syndrome/Acute Myeloid Leukemia** … (b) (4) [redacted] … **5.1** (b) (4) [redacted] Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia), (b) (4) [redacted]	FDA moved MDS/AML from subsection 5.2 to subsection 5.1 to reflect the clinical significance of these ARs. **5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia** … FDA added the following: "Overall, MDS/AML has been reported in 7 out of 751 (0.9%) patients treated with niraparib in clinical studies." … FDA removed (b) (4) [redacted] … *See 11.4.4 Safety Results, Significant Adverse Events, Myelodysplastic Syndrome/Acute Myelogenous Leukemia in this review for more information.* FDA revised "**5.1** (b) (4) [redacted] to "**5.2 Bone Marrow Suppression**" … FDA added: "Grade ≥3 thrombocytopenia, anemia and

	[redacted] have been reported in patients treated with ZEJULA. … [redacted] monitoring for the next 11 months of treatment and periodically after this time [redacted] [see Dosage and Administration (2.2)]. … [redacted]	neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients." … FDA revised the monitoring recommendations for complete blood counts to "weekly for the first month". *See 11.4.3 of this review for more information.* … FDA removed [redacted] … FDA added "refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics [*see Dosage and Administration (2.2)]."* FDA revised the subtitle heading to "**5.3 Cardiovascular Effects**" and added the following: "Grade 3-4 hypertension occurred in 9% of niraparib treated patients compared to 2% of placebo treated patients in Trial 1. Discontinuation due to hypertension occurred in <1% of patients." FDA added heart rate monitoring to the blood pressure recommendations.

	(b) (4)	FDA added "Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension." FDA cross referenced to additional detail in the labeling: *[see Dosage and Administration (2.2) and Nonclinical Toxicology (13.2)]*.
	5.4 Embryofetal Toxicity	FDA merged subsection 5.4 and 5.5 as follows:
	(b) (4)	**5.4 Embryo-Fetal Toxicity** "Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)].* ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) *[see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1)]*. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZEJULA *[see Use in Specific Populations (8.1, 8.3)]."* *See Section 9, Nonclinical*

		Pharmacology/ Toxicology, of this review for more information.
6 Adverse Reactions	**6.1 Clinical Trials Experience** … ZEJULA has been studied in 367 patients with platinum-sensitive recurrent ovarian cancer. Adverse reactions in (b) (4) trial led to dose interruption in (b) (4)% of patients, (b) (4) (b) (4) … *See labeling for Table 4.* …	**6.1 Clinical Trials Experience** … FDA revised this section to the following: "The safety of ZEJULA monotherapy 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in Trial 1 (NOVA)." FDA added the following: "The permanent discontinuation rate due to adverse reactions in Trial 1 was 15%. Adverse reactions led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The median exposure to ZEJULA in these patients was 250 days." FDA removed (b) (4) " FDA revised Table 4 to change the AR incidence (b) (4) to ≥10% to include ARs for neutropenia, leukopenia, palpitations, abdominal pain/distention, mucositis/stomatitis, diarrhea, dyspepsia, dry mouth, urinary tract infection, AST/ALT elevation, myalgia, back pain, arthralgia, dizziness, dysgeusia, anxiety, nasopharyngitis, dyspnea, cough, rash, and hypertension.

	…	FDA updated the AR incidence rates for some ARs [e.g., fatigue/asthenia (b) (4) 57%].
	…	To report clinically relevant laboratory abnormalities in patients treated with Zejula, FDA added Table 5 Abnormal Laboratory Findings in ≥25% of patients receiving Zejula.
	The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, (b) (4)	FDA revised this information to the following based on FDA safety analysis: "The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, epistaxis."
(b) (4)		
8. Use in Specific Populations	**8.1 Pregnancy** Risk Summary (b) (4)	**8.1 Pregnancy** FDA revised to: Risk Summary Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women [*see Clinical Pharmacology (12.1)].*

	(b) (4)	There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [*see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1)].* Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus. …
	8.2 Lactation Risk Summary	FDA revised as follows: **8.2 Lactation** Risk Summary
	(b) (4)	No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from ZEJULA, advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.
	8.3 Females and Males of Reproductive Potential	**8.3 Females and Males of Reproductive Potential**
	(b) (4)	FDA removed this information and added "ZEJULA can cause fetal harm when administered to a

	(b) (4)	pregnant woman *[see Use in Specific Populations (8.1)]*"under the Pregnancy Testing heading. FDA moved the spermatogenesis information below under an Infertility heading. …
	Contraception *Females* (b) (4)	Since niraparib is genotoxic, FDA revised contraception (b) (4) to "6 months" following the last dose of Zejula. This is based on the folliculogenesis and five serum half-lives of niraparib. FDA added the following: "Infertility *Males* Based on animal studies, ZEJULA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*." *See the Nonclinical Pharmacology Section (9.1) of this review for more information.*
	8.5 Geriatric Use (b) (4)	**8.5 Geriatric Use** FDA revised to the following: "In Trial 1 (NOVA), 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out."
	8.6 Renal Impairment … **8.7 Hepatic Impairment** **…**	FDA added the definitions and methodology for the renal and hepatic impairment categories. FDA revised the recommendations

		for moderate hepatic impairment [redacted] (b) (4) to "The safety of ZEJULA in patients with moderate to severe hepatic impairment is unknown".
11. Description	…	FDA added the niraparib tosylate monohydrate salt information and clarified the strength is based on the niraparib free-base.
12. Clinical Pharmacology	**12.2 Pharmacodynamics** **…**	FDA added information to describe the cardiovascular effects of niraparib on pulse rate and blood pressure and the potential relationship to pharmacological inhibition of the dopamine transporter (DAT), norepinephrine transporter (NET) and serotonin transporter (SERT). FDA added a cardiac electrophysiology subsection to describe the potential for QTc prolongation with niraparib. *See Section 11.4.4, Cardiovascular Adverse Events of this review for more information*.
	12.3 Pharmacokinetics **…**	FDA moved the information from Section 7 to Drug Interaction Studies in 12.3.
13. Nonclinical Toxicology	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **…**	FDA added information from repeat-dose oral toxicity studies in rats and dogs to characterize the nonclinical toxicities related to reduced sperm, spermatids and germ cells; and the dose levels at which these effects were observed.
	13.2 Animal Toxicology and/or Pharmacology **…**	FDA added information related to niraparib binding to the DAT, NET, and SERT transporters and reuptake inhibition of NE and DA.

		FDA added information related to the cardiovascular effects observed in dogs (e.g., arterial pressure increases, heart rate increases). FDA added information related to niraparib crossing the blood-brain-barrier in rats and in monkeys.
14. Clinical Studies	*See labeling for full details, tables, and figures.* … … …	… FDA added the following: "Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis CDx". … FDA added the description of the study population to Section 14 (i.e., median age, race, ECOG performance status, percent of patients in complete response to most recent platinum-based regimen, interval since the penultimate platinum regimen, percent of patients with prior bevacizumab therapy, and percent of patients with 3 or more lines of treatment). … FDA removed [redacted] (b) (4) … FDA removed [redacted] (b) (4)

	…	(b) (4) … FDA added "At the time of the PFS analysis, limited overall survival data were available with 17% deaths across the two cohorts." *See Section 11.2.2, Efficacy Results – Secondary and other relevant endpoints of this review for more information.*
16. How Supplied / Storage and Handling	…	FDA added "Each capsule contains 100 mg of niraparib free base."
17. Patient Counseling Information	…	FDA revised this section to be consistent with the revisions to the Warnings and Precautions, Use in Specific Populations (Contraception and Lactation), and the current Patient Counseling Information guidance.

12.2. Patient Labeling

APPEARS THIS WAY ON ORIGINAL

- FDA added a “What is the most important information I should know about ZEJULA?” section to the beginning of the Patient Information and populated it with the applicable information from the Prescribing Information.
- FDA revised the Patient Information to reflect revisions throughout the Prescribing Information, to relocate information to the most applicable sections, and to remove unnecessary redundancy. *See the Patient Labeling Review filed with this NDA for complete details.*

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/s/

WILLIAM F PIERCE
03/17/2017

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/s/

GEOFFREY S KIM
03/24/2017

RICHARD PAZDUR
03/24/2017

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 208447 **Applicant: Tesaro, Inc** **Stamp Date: 10/31/2016**

Drug Name: Niraparib **NDA/BLA Type: NME**

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Female only
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208447	**SDN**	3
Applicant	Tesaro	**Submission Date**	10/31/206
Generic Name	Niraparib	**Brand Name**	Zejula
Drug Class	Poly(ADP-ribose) polymerase (PARP) inhibitor		
Indication	Maintenance treatment of adult patients with recurrent, platinum sensitive, ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy		
Dosage Regimen	300mg once daily		
Dosage Form	Capsule	**Route of Administration**	Oral
OCP Division	DCPV	**OND Division**	

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Vadryn Pierre	Pengfei Song
Pharmacometrics	Fang Li	Yu Jingyu
Genomics	Anuradha Ramamoorthy	Rosane Charlab Orbach

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	12/30/2016	**74-Day Letter Date**	12/30/2016
Review Due Date	3/7/2017	**PDUFA Goal Date**	6/30/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☑ Metabolism Characterization	2	Studies PK002, and KB-0081-DV-BADB: Metabolite profiling in preclinical species (rats and dogs), and human plasma, urine, and

		feces. CYP450 phenotyping, inhibition, induction, by niraparip and M1. Plasma protein binding and blood-to-plasma partitioning were also assessed.
☑ Transporter Characterization	1	In study 15TESAP1R2, the sponsor screened for substrate, inhibition, and induction potential of niraparib and M1 for P-gp, hepatic and renal uptake transporters
☑ Distribution	2	Studies KB-0039-DA-RI, PK004 and PK002: The extent of CNS distribution in rat and monkeys was investigated in studies PK002 and KB-0039-DA-RI. The P-gp substrate potential of niraparib was assessed in study PK002.
☑ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☑ Absolute Bioavailability	1	PR-30-5015-C-ADME-PK
☐ Relative Bioavailability		
☐ Bioequivalence		
☑ Food Effect	1	PR-30-5011-C2-FE
☐ Other		
Human Pharmacokinetics		
Healthy Subjects ☐ Single Dose		
Healthy Subjects ☐ Multiple Dose		
Patients ☑ Single Dose	1	PN001
Patients ☑ Multiple Dose	1	PN001
☑ Mass Balance Study	1	Study PR-30-5015-C-ADME-PK
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☑ Genetics		PR-30-5011-C
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☑ Patients	1	PN001, Exploratory pharmacodynamics markers were assessed
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☑ Patients		
☑ QT	1	PR-30-5011-C1-QTC
Pharmacometrics		
☑ Population Pharmacokinetics	1	PopPK report pooling data from all studies was used to develop

		structural model and conduct ER analyses.			
☑ Exposure-Efficacy	1				
☑ Exposure-Safety	1				
Total Number of Studies		**In Vitro**	7	**In Vivo**	4
Total Number of Studies to be Reviewed			5		4

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Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☑Yes ☐No ☐N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☑Yes ☐No ☐N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☑Yes ☐No ☐N/A	

Filing Memo
This is optional, discuss with your TL content and format

APPEARS THIS WAY ON ORIGINAL

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208447 **Applicant: Tesaro** **Stamp Date: 10/28/16**

Drug Name: Niraparib **NDA/BLA Type: NME**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: PN001 Study Title: Phase 1 study of MK-4827 in patients with advance solid tumors or hematologic malignancies. Sample Size: 104 Arms: doses 30 mg to 400 mg (300 mg qd MTD) Location in submission: Module 2.7.4, section 5.2	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 PR-30-5011-C (NOVA)	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Randomized, placebo-controlled trial Indication: Patients with platinum-sensitive, recurrent ovarian cancer with gBRCA mutation or non-gBRCA mutant tumors who were in response to last platinum regimen. Study #2 PR-30-5020-C (QUADRA) Phase 2, open-label, single arm study to evaluate the safety and efficacy of niraparib in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 3 or 4 chemotherapy regimens.				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			PR-30-5011-C and PR-30-5011-C2 evaluated QT in 36 +20 patients. Report is in PR-30-5011-C1-CARDIAC
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

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

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 208447 **Applicant: Tesaro, Inc.** **Stamp Date: October 31, 2016**

Drug Name: Zejula (niraparib) **NDA Type: 505 (b)(1)**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The Applicant's proposed labeling will be reviewed during the NDA review.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		Acceptability of the Applicant's proposed specifications will be determined during the NDA review.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

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

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

None at this time.

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/s/

WIMOLNUT N MANHENG
12/12/2016

TODD R PALMBY
12/12/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Narratives for deaths, SAEs, d/c due to AE, certain G3-4 AEs, and AML/MDS in 14.3.3
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric waiver 1.9.1
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			We requested all CRFs (n=553), and the narratives for SAEs and deaths. We have 479 CRFS, will request if needed.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Reviewing Medical Officer Date

Clinical Team Leader Date

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/s/

GWYNN ISON
12/14/2016

LALEH AMIRI KORDESTANI
12/14/2016

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/s/

VADRYN PIERRE
12/15/2016

PENGFEI SONG
12/15/2016

JINGYU YU
12/15/2016

ROSANE CHARLAB ORBACH
12/15/2016

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/s/

LIJUN ZHANG
12/16/2016

SHENGHUI TANG
12/16/2016