

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211651Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	211651
Priority or Standard	Priority
Submit Date(s)	April 6, 2018
Received Date(s)	April 6, 2018
PDUFA Goal Date	December 6, 2018
Division/Office	DOP1/OHOP
Review Completion Date	October 10, 2018
Established Name	Talazoparib
(Proposed) Trade Name	TALZENNA®
Pharmacologic Class	Poly (ADP-ribose) polymerase (PARP) inhibitor
Code name	PF-06944076 (formerly BMN 673 or MDV3800)
Applicant	Pfizer, Inc.
Formulation(s)	Oral capsule
Dosing Regimen	1mg taken orally once daily with or without food
Applicant Proposed Indication(s)/Population(s)	TALZENNA is a poly-ADP ribose polymerase (PARP) inhibitor indicated for the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.
Recommendation on Regulatory Action	<i>Approval</i>
Recommended Indication(s)/Population(s) (if applicable)	TALZENNA is a poly- (ADP -ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation	8
Additional Reviewers of Application.....	8
Glossary.....	9
1 Executive Summary	11
1.1. Product Introduction.....	11
1.2. Conclusions on the Substantial Evidence of Effectiveness	11
1.3. Benefit-Risk Assessment	13
1.4. Patient Experience Data.....	18
2 Therapeutic Context	20
2.1. Analysis of Condition.....	20
2.2. Analysis of Current Treatment Options	21
3 Regulatory Background	25
3.1. U.S. Regulatory Actions and Marketing History.....	25
3.2. Summary of Presubmission/Submission Regulatory Activity	25
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	27
4.1. Office of Scientific Investigations (OSI)	27
4.2. Product Quality	28
4.3. Clinical Microbiology	29
4.4. Devices and Companion Diagnostic Issues	29
5 Nonclinical Pharmacology/Toxicology.....	30
5.1. Executive Summary	30
5.2. Referenced NDAs, BLAs, DMFs.....	33
5.3. Pharmacology.....	33
5.4. ADME/PK.....	36
5.5. Toxicology.....	39
5.5.1. General Toxicology.....	39
5.5.2. Genetic Toxicology.....	47
5.5.3. Carcinogenicity.....	49

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

5.5.4. Reproductive and Developmental Toxicology	49
5.5.5. Other Toxicology Studies	52
6 Clinical Pharmacology.....	54
6.1. Executive Summary	54
6.2. Summary of Clinical Pharmacology Assessment.....	59
6.2.1. Pharmacology and Clinical Pharmacokinetics	59
6.2.2. General Dosing and Therapeutic Individualization.....	60
6.3. Comprehensive Clinical Pharmacology Review	62
6.3.1. General Pharmacology and Pharmacokinetic Characteristics.....	62
6.3.2. Clinical Pharmacology Questions.....	65
7 Sources of Clinical Data and Review Strategy	75
7.1. Table of Clinical Studies.....	75
7.2. Review Strategy.....	77
8 Statistical and Clinical and Evaluation	77
8.1. Review of Relevant Individual Trials Used to Support Efficacy.....	77
8.1.1. EMBRACA	77
8.1.2. Study Results.....	92
8.1.3. Assessment of Efficacy Across Trials.....	115
8.1.4. Integrated Assessment of Effectiveness.....	115
8.2. Review of Safety.....	116
8.2.1. Safety Review Approach	116
8.2.2. Review of the Safety Database	116
8.2.3. Adequacy of Applicant’s Clinical Safety Assessments	118
8.2.4. Safety Results.....	119
8.2.5. Analysis of Submission-Specific Safety Issues.....	134
8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability.....	134
8.2.7. Safety Analyses by Demographic Subgroups.....	135
8.2.8. Specific Safety Studies/Clinical Trials.....	137
8.2.9. Additional Safety Explorations.....	137
8.2.10. Safety in the Postmarket Setting.....	138
8.2.11. Integrated Assessment of Safety.....	139

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

SUMMARY AND CONCLUSIONS	139
8.3. Statistical Issues	139
8.4. Conclusions and Recommendations	140
9 Advisory Committee Meeting and Other External Consultations.....	142
10 Pediatrics	143
11 Labeling Recommendations	144
11.1. Prescription Drug Labeling	144
11.2. Patient Labeling	151
12 Risk Evaluation and Mitigation Strategies (REMS)	152
13 Postmarketing Requirements and Commitment	153
14 Division Director (DHOT)	155
15 Division Director (OCP)	156
16 Division Director (OB)	157
17 Division Director (Clinical)	158
18 Office Director (or designated signatory authority).....	159
19 Appendices	160
19.1. References	160
19.2. Financial Disclosure	160
19.3. Nonclinical Pharmacology/Toxicology.....	161
19.4. OCP Appendices (Technical documents supporting OCP recommendations).....	161
19.4.1. Summary of Pharmacometrics Review	161
19.4.2. Sponsor’s Population Pharmacokinetics and E-R Analysis	162
PPK Analysis	162
Exposure-Response (E-R) Analysis	166
19.4.3. Appendix.....	168
19.5. Additional Clinical Outcome Assessment Analyses.....	169

Table of Tables

Table 1: Available Therapy for the Proposed Patient Population	21
Table 2: OSI Findings in the EMBRACA Study	27
Table 3: Inhibition of PARP Enzymes by Talazoparib.....	33
Table 4: In Vitro Chromosomal Aberration Assay	48
Table 5: In Vivo Bone Marrow Micronucleus Analysis.....	49
Table 6: Summary of Fetal Rat Malformation and Variations	51
Table 7. Summary of General Pharmacology and Pharmacokinetic Characteristics of Talazoparib	62
Table 8. Summary of Efficacy Outcomes in Study PRP-001.....	66
Table 9. Summary of Safety Outcomes Used to Determine Dose Escalation and Maximum Tolerated Dose of Talazoparib (Study PRP-001).....	67
Table 10. IC ₅₀ Values for Talazoparib Inhibition of CYP Activities in Human Liver Microsomes ..	71
Table 11. IC ₅₀ Values for Talazoparib Inhibition of UGT Activities in Human Liver Microsomes .	71
Table 12. Talazoparib Induction of Mean mRNA and Activity Levels of CYP Enzymes.....	72
Table 13. In Vitro Data for the Inhibition of OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2-K, and BSEP Mediated Transport by Talazoparib and Reference Inhibitor.....	73
Table 14. In Vitro Data for the Inhibition of BCRP and P-gp Mediated Transport by BMN 673ts and Reference Inhibition	74
Table 15: Listing of Clinical Trials Relevant to this NDA/BLA.....	76
Table 16: Modifications to RECIST 1.1 criteria.....	85
Table 17: Schedule of Safety Assessments	87
Table 18: Censoring rules for PFS Analysis	90
Table 19: Summary of Financial Disclosures for the EMBRACA study	94
Table 20: Major protocol deviations in EMBRACA study	96
Table 21: EMBRACA Baseline Demographics.....	97
Table 22: EMBRACA Baseline Disease Characteristics.....	98
Table 23: Concordance and Discordance of Stratification Data between eCRF and IVRS/IWRS in EMBRACA	100
Table 24: Subsequent neoplastic treatment received in >1% of talazoparib arm	101
Table 25: PFS-IRF Results	103
Table 26: PFS-IRF Event and Censoring Summary	104
Table 27: Investigator-assessed PFS Results.....	106
Table 28: PFS-IRF subgroup analyses.....	108
Table 29: PFS-IRF Sensitivity Analyses	111
Table 30: OS Efficacy Results	112
Table 31: ORR results	114
Table 32: Talazoparib exposure in Sponsor-initiated studies.....	117
Table 33: Overview of Safety in EMBRACA.....	118
Table 34: Deaths on EMBRACA study (data cutoff 9/15/2017).....	119
Table 35: SAEs that occurred in >1 patient in either treatment arm of EMBRACA	126
Table 36: AE leading to permanent discontinuation in >1 patient in talazoparib arm	127
Table 37: TEAEs that occurred in >10% of patient in either treatment arm of EMBRACA	132

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Table 38 Laboratory Abnormalities in $\geq 25\%$ of Patients in EMBRACA.....	133
Table 39: TEAEs >10% in any age subgroup on the talazoparib arm.....	135
Table 40: Covariates Included in the PPK Analysis (and the Final model).....	163
Table 41. Summary of Population Pharmacokinetic Parameters.....	163
Table 42. Multivariate Analysis of Cox Proportional Hazard Model for PFS in Study 301	167
Table 43. Final Model for Anemia and Thrombocytopenia.....	167
Table 44. Summary of Studies Included in the Population PK Analysis.....	168
Table 45: EORTC-QLQ-C30 Subscales and Items.....	171
Table 46: EORTC-QLQ-BR23 Subscales and items	171

Table of Figures

Figure 1. Exposure-Response for Safety Analysis for Anemia, Thrombocytopenia, and Neutropenia 67

Figure 2. The Effect of Renal Impairment on Talazoparib Exposure. 68

Figure 3: EMBRACA Study Design 79

Figure 4: Patient Disposition 95

Figure 5: Kaplan-Meier Plots of IRF-assessed PFS (DCO: September 15th, 2017)..... 105

Figure 6: Kaplan-Meier Plots of investigator and IRF-assessed PFS 107

Figure 7: Kaplan-Meier plot of overall survival (DCO September 15th, 2017)..... 113

Figure 8. The Effect of Renal Impairment on Talazoparib Exposure 162

Figure 9. Prediction- and Variance-Corrected VPC Plots (Left) and Standardized Visual Predictive Check (Right) for the Final Model 169

Figure 10: EORTC-QLQ-C30 Completion*, denominator is number of patients eligible (on-going treatment)..... 174

Figure 11: Mean score for EORTC-QLQ-C30 domain scores (Physical and Role function) by visit and by type of missing data patterns 175

Figure 12: Changes from baseline scores for EORTC-QLQ-C30 Physical function and Role function score, higher values indicate better outcomes..... 176

Figure 13: Distribution of raw scores by visit for EORTC-QLQ-C30 physical and role function items..... 178

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Fatima Rizvi
Nonclinical Reviewer	Claudia P Miller
Nonclinical Team Leader	Tiffany Ricks
Office of Clinical Pharmacology Reviewer(s)	Amal Ayyoub, Nan Zheng
Office of Clinical Pharmacology Team Leader(s)	Hong Zhao, Jingyu Yu
Clinical Reviewer	Suparna Wedam
Clinical Team Leader	Laleh Amiri-Kordestani
Statistical Reviewer	Stella Karuri
Statistical Team Leader	Lijun Zhang
Associate Director for Labeling	William Pierce
Cross-Disciplinary Team Leader	Laleh Amiri-Kordestani
Division Director (DHOT)	John K Leighton
Division Director (OCP)	Nam Atiqur Rahman
Division Director (OB)	Rajeshwari Sridhara
Division Director (OHOP)	Julia Beaver
Office Director (or designated signatory authority)	Gideon Blumenthal

Additional Reviewers of Application

OPQ	Xiao Hong Chen
Microbiology	Kumar Janoria
OPDP	Kevin Wright
OSI	Yang-Min Ning
OSE/DEPI	Carolyn McCloskey
OSE/DMEPA	Tingting Gao / Chi-Ming Tu
OSE/DRISK	Till Olickal
Other	Francisca Ryes Turcu

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

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRCA	BReast CAncer susceptibility gene
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

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

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

1 Executive Summary

1.1. Product Introduction

Talazoparib (TALZENNA®) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2, which play a role in DNA repair. In vitro studies with cancer cell lines that harbored defects in DNA repair genes, including BRCA 1 and 2, have shown that talazoparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, decreased cell proliferation, and apoptosis. Talazoparib anti-tumor activity was observed in human patient derived xenograft breast cancer tumor models that expressed mutated or wild-type BRCA 1 and 2.

The proposed indication for talazoparib is:



The recommended indication for talazoparib is:

- *TALZENNA is a poly- (ADP -ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2 negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.*

1.2. Conclusions on the Substantial Evidence of Effectiveness

This recommendation for the regular approval of talazoparib, according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), is based on efficacy and safety data from a single randomized study comparing talazoparib to physician's choice therapy (PCT: capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. All patients were required to have a known deleterious or suspected deleterious gBRCA mutation and must have received no more than 3 prior cytotoxic chemotherapy regimens for metastatic or locally advanced disease. Patients were required to have received treatment with an anthracycline and/or a taxane (unless contraindicated) in the neoadjuvant, adjuvant, and/or metastatic treatment setting. First-line treatment for advanced or metastatic disease with no prior adjuvant chemotherapy was allowed if the investigator determined that 1 of the 4 chemotherapy choices in the control arm would be an appropriate treatment option for the patient. Prior treatment with hormonal therapy was not required for patients with HR-positive disease. The trial demonstrated a statistically significant and clinically meaningful improvement

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

in blinded independent central review (BICR) assessed progression-free survival (PFS) for patients randomized to talazoparib (estimated median PFS 8.6 months) versus PCT (estimated median PFS 5.6 months), with a hazard ratio of 0.54 (95% CI: 0.41, 0.71; $p < 0.0001$). Subgroup and sensitivity analyses all support the primary efficacy endpoint results. OS analysis was not mature at the time of the PFS analysis.

Talazoparib was generally tolerable with adverse reactions manageable with dose reduction, temporary treatment discontinuation, and/or standard medical care. Adverse reactions (incidence >20%) include fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, decreased appetite. The safety profile is acceptable for this patient population with a serious and life-threatening disease. The key adverse events of special interest (AESIs) with talazoparib and other PARP inhibitors include myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML), pneumonitis, and new primary malignancies. There was one case of AML in the talazoparib treatment arm of EMBRACA and a total of two cases across the talazoparib safety database in patients with solid tumors. There were no cases of pneumonitis in the EMBRACA study. Three primary new malignancies were reported in 3 patients in the talazoparib arm of EMBRACA. None of the events were considered related to study drug by the investigator. MDS/AML and myelosuppression have been included in the “Warnings and Precautions” section of the label so that clinicians can monitor patients appropriately. All disciplines agreed that talazoparib had a favorable risk-benefit profile and did not identify any outstanding issues that precluded approval.

1.3. **Benefit-Risk Assessment**

Breast cancer is the second leading cause of cancer death among women and the fourth leading cause of cancer death overall. In 2018, it is estimated that there will be 268,670 newly diagnosed breast cancer cases in the United States, and that 41,400 people will die from breast cancer. Approximately 5% of breast cancers are associated with a mutation in the breast cancer susceptibility gene (BRCA1 and/or BRCA2 gene). Approximately 70% of BRCA1 mutated breast cancers present as triple negative breast cancer (TNBC). In contrast, breast cancer patients carrying mutations in the BRCA2 gene are more likely to be positive for expression of the estrogen receptor (ER) and progesterone receptor (PgR) and approximately 20% are triple-negative.

Metastatic breast cancer (MBC) is incurable. Thus, the treatment of patients with MBC is palliative in nature. Endocrine therapy is preferable to chemotherapy for patients with hormone receptor (HR)-positive metastatic breast cancer (MBC), provided there is no visceral crisis. Other treatment options for patients with HR-positive MBC include endocrine therapy in combination with CDK 4/6 inhibitors. Most patients with HR-positive MBC will eventually require cytotoxic chemotherapy either as initial treatment or following endocrine therapy. FDA-approved endocrine therapies available for HR-positive MBC include tamoxifen, anastrozole, letrozole, toremifene, exemestane, and fulvestrant. In addition, everolimus has been approved in combination with exemestane, palbociclib has been approved in combination with letrozole or fulvestrant, abemaciclib has been approved in combination with fulvestrant, and ribociclib has been approved in combination with letrozole.

For patients with triple negative MBC, there is no single preferred first line chemotherapy. Sequential monotherapy with single-agent chemotherapy is preferred, with combination chemotherapy reserved for patients with rapid clinical progression, life threatening visceral metastases or need for rapid symptom and/or disease control. For patients previously treated with an anthracycline and a taxane in the adjuvant or metastatic setting, FDA-approved cytotoxic chemotherapy options include gemcitabine, capecitabine, ixabepilone, and eribulin.

Olaparib is a PARP inhibitor approved on January 12, 2018 by the FDA for the treatment in patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Olaparib had not been approved by the time EMBRACA was initiated and completed accrual; therefore, it was not available to be used as a control for the study.

The safety and efficacy of talazoparib was demonstrated in one clinical trial, EMBRACA. EMBRACA (NCT01945775) was an open-label, randomized study comparing talazoparib 1 mg to physician's choice therapy (PCT: capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. All patients must have received no more than 3 prior cytotoxic chemotherapy regimens for metastatic or locally advanced disease. Patients were required to have received treatment with an anthracycline and/or a taxane (unless contraindicated) in the neoadjuvant, adjuvant, and/or metastatic treatment setting. First-line treatment for advanced or metastatic disease with no prior adjuvant chemotherapy was allowed if the investigator determined that 1 of the 4 chemotherapy choices in the control arm would be an appropriate treatment option for the patient. Prior treatment with hormonal therapy was not required for patients with HR-positive disease. The trial demonstrated a statistically significant and clinically meaningful improvement in blinded independent central review assessed progression-free survival (PFS) for patients randomized to talazoparib (estimated median PFS 8.6 months) versus PCT (estimated median PFS 5.6 months), with a hazard ratio of 0.54 (95% CI: 0.41, 0.71; $p < 0.0001$). BICR-assessed PFS was analyzed in the following subgroups: stratification factors (TNBC vs non-TNBC, prior number of lines of chemotherapy for locally advanced/metastatic disease, history of CNS metastases), race, age, gender, region, ER/PR status and BRCA status by central testing. The estimated hazard ratio for these subgroups showed no evidence of a PFS detriment from talazoparib. Improvement in PFS was seen in both patients that were HR-positive and HR-negative. Subgroup and sensitivity analyses all support the primary efficacy endpoint results. With exception of patients with ER-negative/PR-positive disease, patients in all other subgroups had a PFS advantage in the talazoparib treatment arm. However, there were only 10 patients in the ER-negative/PR-positive disease subgroup so definitive conclusions cannot be drawn.

Patients were required to have a gBRCAm to be randomized onto study in the EMBRACA study. Ninety five percent of patients were centrally confirmed to have a deleterious or suspected deleterious gBRCAm using a clinical trial assay; out of which 354 (82%) were confirmed using the BRACAnalysis CDx[®]. A PMA supplement was submitted to CDRH for the BRACAnalysis CDx device. PFS results for the 354 patients with BRACAnalysis CDx test results were comparable to the PFS results of the 431 patients enrolled in the EMBRACA study. The data from this study support the reasonable assurance of safety and effectiveness of the BRACAnalysis CDx test when used in accordance with indications for use.

Results based on investigator-assessed PFS and ORR (in patients with measurable disease) also support the primary endpoint. OS results are not mature at this time and appear to be similar in both arms; however, a benefit in OS may not be seen given effect of subsequent therapies. Of note, although crossover was not allowed on study, 20 patients (14%) in the PCT treatment arm received subsequent therapy with the PARP inhibitor olaparib compared to 2 patients (1%) in the talazoparib arm. The final OS results for EMBRACA will be submitted when available as part of a post marketing commitment.

Two patient-reported outcomes (PRO) instruments were used in the EMBRACA trial, the EORTC QLQ-C30 questionnaire and the EORTC-QLQ-

BR23 questionnaire. PRO endpoints were exploratory, with no formal statistical testing and no control of type I error rate prespecified. EMBRACA was an open label trial with varied treatment schedules and administration in the control arm, making interpretation of the PRO results difficult. PRO results were not included in the product label.

The safety profile of the talazoparib was adequately assessed in the submitted application. Talazoparib was generally tolerable with adverse reactions manageable with dose reduction, temporary treatment discontinuation, and/or standard medical care. Adverse reactions (incidence >20%) include fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, decreased appetite. The safety profile is acceptable for this patient population with a serious and life-threatening disease. The key adverse events of special interest (AESIs) with talazoparib and other PARP inhibitors include myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML), pneumonitis, and new primary malignancies. There was one case of AML in the talazoparib treatment arm of EMBRACA and a total of two cases across the talazoparib safety database in patients with solid tumors. There were no cases of pneumonitis in the EMBRACA study. Three primary new malignancies were reported in 3 patients in the talazoparib arm of EMBRACA. None of the events were considered related to study drug by the investigator. MDS/AML and myelosuppression have been included in the "Warnings and Precautions" section of the label so that clinicians can monitor patients appropriately. The safety profile is acceptable for this patient population with a serious and life-threatening disease and provides an alternative treatment option compared to chemotherapy.

All disciplines agreed that talazoparib had a favorable risk-benefit profile and did not identify any outstanding issues that precluded approval. A companion diagnostic for talazoparib will be contemporaneously approved. The favorable risk benefit assessment supports approval of talazoparib in the intended population.

Talazoparib (TALZENNA®) is recommended for approval for the following indication:

- TALZENNA is a poly- (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2 negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Breast cancer is the second leading cause of cancer death among women and the fourth leading cause of cancer death overall. In 2018, it is estimated that there will be 268,670 newly diagnosed breast cancer cases in the United States, and that 41,400 people will die from breast cancer. Approximately 5% of breast cancers are associated with a mutation in the breast cancer susceptibility gene (BRCA)1 and/or BRCA2 gene. 	<ul style="list-style-type: none"> Breast cancer is a serious and life-threatening condition. Metastatic breast cancer is incurable. There is an unmet medical need to develop therapies for these cancers.
Current Treatment Options	<ul style="list-style-type: none"> The treatment of MBC is palliative in nature with a goal to prolong survival and improve quality of life by reducing cancer-related symptoms. Endocrine therapy is preferable to chemotherapy for patients with HR-positive MBC, provided there is no visceral crisis. Other treatment options for patients with HR-positive MBC the CDK 4/6 inhibitors. Most patients with HR-positive MBC will eventually require cytotoxic chemotherapy either as initial treatment or following endocrine therapy. For patients with triple negative MBC, there is no single preferred first line chemotherapy. Sequential monotherapy with single agent chemotherapy is preferred with combination chemotherapy reserved for patients with rapid clinical progression, life threatening visceral metastases, or need for rapid symptom and/or disease control. Olaparib is a PARP inhibitor approved by the FDA for the treatment in patients with deleterious or suspected deleterious gBRCAm, HER2- 	<ul style="list-style-type: none"> Cytotoxic chemotherapy is the current recommendation for patients that have HR-positive MBC that has progressed on endocrine based therapy and for patients with triple negative MBC. For patients with a deleterious or suspected deleterious gBRCAm, HER2-negative MBC, olaparib is a treatment option.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>negative MBC who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.</p>	
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> • The clinical data from an open-label, randomized phase 3 trial (EMBRACA) in patients with gBRCAm, HER2-negative locally advanced or metastatic breast cancer demonstrates an improvement in median PFS for talazoparib compared to PCT. The estimated median PFS in the talazoparib arm was 8.6 months compared to 5.6 months in the chemotherapy arm (HR =0.54, 95% CI: (0.41, 0.71); p<0.0001). • OS results were immature at the time of analysis with only 38% of deaths having occurred. • Objective response rate (ORR) was 50% in the talazoparib arm compared with 18% in the PCT arm for patients with measurable disease at baseline. 	<ul style="list-style-type: none"> • The PFS benefit derived from talazoparib is statistically significant and clinically meaningful.
<p><u>Risk and Risk Management</u></p>	<ul style="list-style-type: none"> • The most common adverse reactions experienced by at least 20% of patients in the EMBRACA study included fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, decreased appetite. • Talazoparib is intended to be prescribed by oncologists. • MDS/AML, myelosuppression and embryo-fetal toxicity are included in the Warnings and Precautions section of the label • Laboratory and vital sign monitoring is recommended before and during treatment. 	<ul style="list-style-type: none"> • The safety profile of talazoparib is acceptable for the intended population. • The safe use of talazoparib can be managed through accurate labeling and routine oncology care. • No REMS is indicated.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
<input type="checkbox"/>	Clinical outcome assessment (COA) data, such as	Section 8.2.6, 19.5
<input checked="" type="checkbox"/>	<input type="checkbox"/> Patient reported outcome (PRO) <input checked="" type="checkbox"/>	
<input type="checkbox"/>	<input type="checkbox"/> Observer reported outcome (ObsRO)	
<input type="checkbox"/>	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	<input type="checkbox"/> Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Laleh Amiri-Kordestani, MD

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Breast cancer is the second leading cause of cancer death among women and the fourth leading cause of cancer death overall. In 2018, it is estimated that there will be 268,670 newly diagnosed breast cancer cases in the United States, and that 41,400 people will die from breast cancer. Approximately 5% of breast cancers are associated with a mutation in the breast cancer susceptibility gene (BRCA1 and/or BRCA2 gene). Approximately 70% of BRCA1 mutated breast cancers present as triple negative breast cancer (TNBC). In contrast, breast cancer patients carrying mutations in the BRCA2 gene are more likely to be positive for expression of the estrogen receptor (ER) and progesterone receptor (PgR) and approximately 20% are triple-negative.

Although there are phenotypic differences in breast cancers resulting from BRCA1 or BRCA2 mutations, mutations in either gene result in tumors that are deficient in homologous recombination. Given the small size of the BRCA mutated subpopulation in breast cancer, firm conclusions cannot be drawn, as information comparing the outcome of this subpopulation with the overall breast cancer population is based on reports from a few small studies.

Metastatic breast cancer (MBC) is incurable. Thus, the treatment of patients with MBC is palliative in nature. Endocrine therapy is preferable to chemotherapy for patients with hormone receptor (HR)-positive metastatic breast cancer (MBC), provided there is no visceral crisis. Other treatment options for patients with HR-positive MBC include endocrine therapy in combination with CDK 4/6 inhibitors. Most patients with HR-positive MBC will eventually require cytotoxic chemotherapy either as initial treatment or following endocrine therapy (ies). FDA-approved endocrine therapies available for HR-positive MBC include tamoxifen, anastrozole, letrozole, toremifene, exemestane, and fulvestrant. In addition, everolimus has been approved in combination with exemestane, palbociclib has been approved in combination with letrozole or fulvestrant, abemaciclib has been approved in combination with fulvestrant and ribociclib has been approved in combination with letrozole.

For patients with triple negative MBC, there is no single preferred first line chemotherapy. Sequential monotherapy with single-agent chemotherapy is preferred, with combination chemotherapy reserved for patients with rapid clinical progression, life threatening visceral metastases or need for rapid symptom and/or disease control.

For patients previously treated with an anthracycline and a taxane in the adjuvant or metastatic setting, FDA-approved cytotoxic chemotherapy options include gemcitabine, capecitabine,

ixabepilone, and eribulin.

Olaparib is a PARP inhibitor approved by the FDA for the treatment in patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.

2.2. Analysis of Current Treatment Options

Listed in Table 1 are FDA-approved treatment options for patients with HER2-negative MBC that have received prior chemotherapy.

Table 1: Available Therapy for the Proposed Patient Population

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments					
Olaparib	in patients with deleterious or suspected deleterious gBRCAm, HER2-negative MBC, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.	2018	300 mg orally BID continuous	Compared to physician's choice: Median PFS 7.0 mos vs 4.2 mos ORR: 52.1% vs 22.7%	Nausea, fatigue, vomiting, diarrhea, anemia, leukopenia, neutropenia, diarrhea, respiratory tract infection, decreased appetite, headache
Capecitabine	in MBC patients, resistant to both paclitaxel and an anthracycline-containing regimen	2001	1250 mg/m ² twice daily orally for 2 weeks followed by a one-week rest period in	Single arm study: ORR 25.6%	Diarrhea, hand/foot syndrome, myelosuppression

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

			3-week cycles		
Ixabepilone	In combination with capecitabine for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane OR monotherapy for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine	2007	40 mg/m ² infused intravenously every 3 weeks	Combination vs capecitabine alone: Median PFS: 5.7 mos vs 4.1 mos ORR: 34.7% vs 14.3% Monotherapy single arm study: ORR: 12.4% by independent review and 18.3% by investigator assessment	Peripheral neuropathy, myelosuppression
Eribulin	MBC who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease.	2010	(b) (4) mg/m ² intravenously on Days 1 and 8 of a 21-day cycle	Compared to physician's choice: Median OS: 13.2 mos vs 10.6 mos	Peripheral neuropathy, myelosuppression, QT prolongation
Everolimus	Postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole	2012	10 mg orally once daily	Combination vs placebo+exemestane: Median PFS: 7.8 mos vs 3.2 mos ORR: 12.6% vs 1.7%	Pneumonitis, infections, stomatitis, angioedema
Palbociclib	For the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with: an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women; or fulvestrant in	2014, 2015, 2016	(b) (4) mg once daily for 21 days followed by 7 days off treatment	Palbociclib+letrozole vs letrozole alone: Median PFS: 24.8 mos vs 14.5 mos ORR: 55.3% vs 44.4% Palbociclib+fulvestrant vs fulvestrant: Median PFS: 9.5 mos vs 4.6 mos ORR: 24.6% vs 10.9%	Myelosuppression, fatigue

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

	women with disease progression following endocrine therapy.				
Ribociclib	In combination with an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with HR-positive, (HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy	2017, 2018	600 mg orally once daily for 21 days followed by 7 days off treatment	Ribociclib+letrozole vs letrozole: Median PFS: NR vs 14.7 mos ORR: 52.7% vs 37.1% Ribociclib +fulvestrant vs fulvestrant: Median PFS: 20.5 mos vs 12.8 mos ORR: 40.9% vs 28.7%	QT prolongation, hepatotoxicity, myelosuppression
Abemaciclib	In combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy OR as monotherapy for the treatment of adult patients with HR-positive, HER2-negative	2017	in combination with fulvestrant: 150 mg orally twice daily as monotherapy: 200 mg orally twice daily	Abemaciclib+fulvestrant vs fulvestrant: Median PFS: 16.4 vs 9.3 mos ORR: 48.1% vs 21.3% Monotherapy single arm study: ORR: 17.4% by independent review and 19.7% by investigator assessment	Diarrhea, myelosuppression, hepatotoxicity, venous thromboembolism

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

	advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting				
Other Treatments					
Vinorelbine	Not FDA approved for breast cancer. Included in NCCN guidelines.	N/A	25 mg/m2 intravenously Day 1 weekly or 30 ^{(b) (4)} mg/m2 intravenously on Days 1 and 8 of a 21-day cycle	In patients previously treated with anthracycline and taxane ORR 25% has been reported	Hepatotoxicity, neurologic toxicity, constipation, pulmonary toxicity
Gemcitabine	Single agent not FDA approved for breast cancer. Included in NCCN guidelines.	N/A	800-1200 mg/m2 on Days 1, 8 and 15 of a 28-day cycle	In patients, previously treated with anthracycline and taxane ORR 23%-42% have been reported	Myelosuppression, hepatotoxicity, Hemolytic-Uremic Syndrome

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Talazoparib is currently not approved or marketed in any country worldwide.

3.2. Summary of Presubmission/Submission Regulatory Activity

April 12, 2013: End of Phase 2 (EOP2) Meeting to obtain feedback on the nonclinical and clinical development programs to support an NDA in BRCA 1/2 mutant breast cancer.

- Several comments were provided regarding eligibility criteria, choice of control arm, choice of endpoints, and targeted improvement for median PFS for the proposed phase 3 study. Further feedback was to be provided when results were available from the phase 2 study, which could help inform the design of the phase 3 study.

January 8, 2014: Type C Meeting to obtain feedback on comparability assessment plan for the optimized drug substance manufacturing process and updated specifications.

February 25, 2015: Type C Meeting to obtain feedback on the dissolution method and comparability of 4 × 0.25 mg vs 1 mg capsules, biowaiver for 0.5 and 0.75 mg capsules, additional manufacturing site, clinical plan for generating sufficient experience with DP Generation 3.1, bracketing approach, number of registration batches to support MAA/NDA.

July 27, 2016: Meeting to obtain feedback on the QT study protocol and SAP.

- In general, the proposed QT study protocol was acceptable.

September 15, 2016: Type C Meeting Written Feedback to obtain feedback on clinical pharmacology and non-clinical toxicology questions submitted in follow-up to the EOP2 meeting on April 12, 2013.

- The proposed clinical pharmacology studies for renal impairment, hepatic impairment and DDI appeared reasonable.

November 30, 2016: Type C Meeting to obtain feedback on the acceptability of the ABRAZO and EMBRACA statistical analysis plans to support an NDA filing

- The SAP appeared reasonable. Whether the results of ABRAZO and EMBRACA could support an NDA was to be a review issue.

March 17, 2017: Type C Meeting to obtain feedback on the dissolution method acceptability, comparability of 4 × 0.25 mg vs 1 mg capsules, use of different capsule color in registration batches

July 7, 2017: pre-NDA meeting to reach consensus on the key efficacy and safety data to be submitted in support of the proposed application and on the content and logistics of the

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

proposed NDA

- The proposed efficacy and safety data for the NDA submission appeared adequate.

October 2, 2017: CDRH Written Feedback for Q171484 BRACAnalysis CDx to obtain agreement on the overall strategy for the PMA supplement submission for Myriad BRACAnalysis test.

- CDRH agreed with the proposed strategy for PMA submission

October 31, 2017: Type C Meeting Written Feedback to obtain feedback regarding the rationale for specified and unspecified impurity acceptance criteria in the drug substance

February 5, 2018: Type B pre-NDA Meeting Written Feedback to gain agreement on the efficacy and safety data to be submitted in support of the proposed indication, the appropriateness of a priority review request and the proposal for the safety update report

April 6, 2018: NDA 211651 submitted to the FDA

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to perform site inspections as part of review of this NDA. Reference is made to the Clinical Inspection Summary by Max Ning, MD, PhD. The classification given to the three sites inspected are given in Table 2.

Table 2: OSI Findings in the EMBRACA Study

Inspection	Site # and # of Subjects	Inspection Date	Final Classification
Sara Hurvitz UCLA Department of Medicine: Hematology-Oncology 10945 Le Conte Ave, Ste 3360 Los Angeles, CA 90095	Site #: 0127 # of subjects: 11	June 4-8, 2018	NAI
Louis Fehrenbacher Kaiser Permanente 975 Sereno Dr Vallejo, CA 94589	Site #: 1321 # of subjects: 10	May 5-24, 2018	VAI
Kyung-Hun Lee Seoul National University Hospital 101 Daehak-ro Jongno-gu Seoul 03080 Republic of Korea	Site #: 1366 # of subjects: 10	July 16-20, 2018	VAI

NAI = No deviation from regulations; VAI = Deviation(s) from regulations

Reviewer Comment: *Based on preliminary classification from the OSI review, the primary efficacy endpoint of PFS as determined by the clinical investigators was verified with the source records generated at the inspected clinical sites. In addition, there was no evidence of underreporting of adverse events including serious adverse events. Overall, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the proposed indication. Two of the three sites (site 1321 and 1366) were found to have GCP compliance deviations which were not felt to have a significant impact on the benefit-risk assessment of the product in study subjects or have placed study subjects at undue risk.*

Inspection of site 1321 found a number of inspectional observations, which led to a Form 483

being issued. These are summarized as follows: five of the ten enrolled subjects had recordkeeping discrepancies between the source document for adverse events (AEs) end date and electronic case report forms (eCRFs) and two subjects had inaccurate doses and/or no end dates of concomitant medicines reported on the eCRFs. To address the compliance deficiencies, the investigator implemented a number of measures including evaluation of AE data management, revision of workflow for AE assessment collection and data submission, revision of concomitant log for clarity, and additional research staff training on the new workflow and operating procedures.

Inspection of site 1366 found evidence of late submissions of some CT/MRI scans to the central radiology review facility. Almost all the late submissions occurred within 1-3 weeks after the scans were performed. This is beyond the time frame as specified in Study Imaging Manual, which required post-baseline scans to be submitted within 3 days of image acquisition. In the written response to the Form FDA 483 issued for the late submissions, Dr. Lee acknowledged the observation, provided reasons for this deviation, and stated to report all delayed submissions to the local IRB. Dr. Lee also specified his actions to comply with investigational plan.

4.2. Product Quality

The chemical name of talazoparib tosylate is (8S,9R)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3H-pyrido[4,3,2-de]phthalazin-3-one 4-methylbenzenesulfonate (1:1). The chemical formula of talazoparib tosylate is C₂₆H₂₂F₂N₆O₄S, and the relative molecular mass is 552.56 Daltons. Talazoparib tosylate is a white to yellow solid. Talazoparib capsules for oral use are available as a 0.25 mg hard hypromellose (HPMC) capsule that contains 0.363 mg talazoparib tosylate equivalent to 0.25 mg talazoparib free base or as a 1 mg HPMC capsule that contains 1.453 mg talazoparib tosylate equivalent to 1 mg talazoparib free base.

Inactive ingredients: silicified microcrystalline cellulose (sMCC). The white/ivory and white/light red opaque capsule shells contain HPMC, yellow iron oxide, red iron oxide and titanium dioxide; and the printing ink contains shellac, black iron oxide, potassium hydroxide, ammonium hydroxide, and propylene glycol.

The drug product specifications consist of appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, water content, and microbial limits. The dissolution specification was evaluated by biopharmaceutics reviewer, Dr. Qi Zhang. Microbial test was reviewed by Dr. Kumar Janoria. Based on the primary and supportive stability data, a shelf life of 24 months, as proposed by the applicant was granted to 0.25 mg and 1 mg. Talazoparib capsules packaged in HDPE bottles and (b) (4) closures (b) (4) when stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F).

Following a review of the application and past inspectional documents, per Dr Xiao Hong Chen, Ph.D. CMC technical lead review, there are no outstanding manufacturing or facility risks that

prevent approval of this application. PAI inspection for [REDACTED] (b) (4) [REDACTED] (b) (4) site was requested for this application. The manufacturing and associated facilities listed in 356 h for NDA 211651 were found to be acceptable.

4.3. **Clinical Microbiology**

Not applicable.

4.4. **Devices and Companion Diagnostic Issues**

The BRACAnalysis CDx was approved on December 19, 2014 for use as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza (olaparib). Since the initial approval, several PMA supplements have been reviewed and approved to expand the device indications for use and/or modify components of the device. The current PMA supplement has been submitted for the BRACAnalysis CDx device to update the labeling with the results of the Pfizer clinical study EMBRACA for use of talzoparib in breast cancer patients with germline deleterious or suspected deleterious mutations in BRCA1/BRCA2 genes.

Based on the review by the Center for Devices and Radiological Health (CDRH), the data in the PMA supplement for the BRACAnalysis CDx support the reasonable assurance of safety and effectiveness of the device for a new companion diagnostic claim. The effectiveness of the BRACAnalysis CDx test was based on 354 patients with deleterious or suspected deleterious germline BRCA1 or BRCA2 mutations for whom BRACAnalysis CDx test results were available. The 354 patients represented 82% of the overall randomized population. PFS results for the 354 patients with BRACAnalysis CDx test results were comparable to the PFS results of the 431 patients enrolled in the EMBRACA study. The data from this study support the reasonable assurance of safety and effectiveness of the BRACAnalysis CDx test when used in accordance with indications for use. Patients were required to have a gBRCAm to be randomized onto study in the EMBRACA study; therefore, BRACAnalysis CDx test will be approved as a companion diagnostic with this NDA.

For further details, refer to the review by Dr. Francisca Reyes Turcu in CDRH for PMA supplement (P140020/S015).

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Talzenna (talazoparib, BMN 673) is a poly (ADP-ribose) polymerase (PARP) inhibitor. PARP enzymes, particularly PARP-1 and PARP-2, are activated by DNA damage and facilitate DNA repair of single strand breaks. Suppression of PARP activity results in accumulation of unrepaired single strand breaks, which leads to formation of cytotoxic double strand breaks that need to be repaired by other mechanisms, such as homologous repair (HR). The rationale to use talazoparib in germline BRCA-mutated HER2-negative breast cancer stems from the hypothesis that BRCA-mutated cancers cells, which are HR deficient due to BRCA status, will be more susceptible to PARP inhibition, causing accumulation of DNA damage and resulting in cell death.

The applicant conducted in vitro and in vivo pharmacology studies, primarily using the tosylate salt form of talazoparib (BMN 673ts), which is representative of the clinical and commercial formulation. In vitro, talazoparib inhibited the enzymatic activity of several PARP family members, with its strongest activity against PARP-1 and PARP-2 with IC₅₀ values of 0.7 nM and 0.3 nM, respectively. Talazoparib also demonstrated activity against TNKS2 (PARP 5b), TNSK1 (PARP 5a), and PARP3, with IC₅₀ values of 4.7 nM, 13.5 nM and 22 nM, respectively. Increased cytotoxicity with talazoparib was observed in various cancer cell lines that harbored defects in DNA repair pathways compared to cancer cell lines with functional DNA repair pathways or normal primary human cells. Further examination with a prostate cancer cell line containing multiple DNA damage response mutations showed that talazoparib by itself, and more so in the presence of temozolomide (a DNA damaging agent), caused cells to accumulate in S-phase with increased amounts of DNA double strand breaks damage, which was associated with activation of caspase-3 and reduced cell growth. In addition to inhibiting PARP catalytic activity, PARP inhibitors can form PARP-DNA complexes which interfere with DNA repair, replication, and transcription. Formation of PARP-DNA complexes was assessed in vitro in cells pre-treated with a DNA damaging agent, methyl methanesulfonate (MMS), followed by talazoparib. In BRCA mutant breast cancer cells cytotoxicity by talazoparib in the presence of MMS correlated with increased accumulation of PARP-DNA complexes. In contrast, in wild type BRCA breast cancer cells, accumulation of PARP-DNA complexes was detected but did not correlate with cytotoxic susceptibility by talazoparib. In vivo, talazoparib demonstrated dose-dependent anti-tumor activity in subcutaneous xenograft models of breast cancer with or without BRCA mutations. In comparison to carboplatin, talazoparib showed greater anti-tumor efficacy in a breast cancer xenograft mouse model. Based on the pharmacology data submitted, the Established Pharmacologic Class (EPC) of talazoparib is “poly (ADP-ribose) polymerase (PARP) inhibitor.”

Talazoparib exposure (AUC) in rats and dogs increased with increasing dose and was generally dose proportional in dogs but was slightly greater than dose proportional in rats.

Pharmacokinetic analysis demonstrated females had a slightly higher AUC and C_{max} at the high dose tested in rats (1.0 mg/kg) and dogs (0.1 mg/kg). Oral bioavailability was 43 to 73%

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

following a single oral dose in rats, and the elimination half-life was 25 to 50 h. In dogs, the oral bioavailability was 60% to 87% following a single oral dose, and the elimination half-life was 55 to 89 h. Talazoparib equally partitioned in blood and plasma in dogs but had a slight preferential distribution into red blood cells in rats. Talazoparib was primarily excreted via the fecal route in rats and dogs with approximately 70% in feces and 23% in urine.

In GLP-compliant, safety pharmacology studies, talazoparib was a low-potency hERG blocker in vitro, with an estimated IC₅₀ greater than 100 μM. Talazoparib had no effects of toxicological significance on respiratory and CNS function in male rats receiving single doses up to 3 mg/kg.

Talazoparib was evaluated in GLP-compliant, repeat-dose toxicity studies conducted in rats and dogs for up to 13 weeks. Daily oral dosing in rats with talazoparib at 0.005 or 0.015 mg/kg/day for 13 weeks was tolerated. In the 0.05 mg/kg group, five rats in the main study and one in the TK satellite group were sacrificed moribund on Day 49 due to severe decreases in red cell mass and white blood cells, associated with pale ears, feet, and eyes, hypoactivity and reduced bone marrow hypocellularity and lymphoid depletion. Remaining high dose (HD) animals had a dosing holiday from Day 50 to 63 based on decreased red cell parameters which were associated with pale eyes, ears, and feet. Dosing was resumed on Day 64 at a reduced dose of 0.04 mg/kg/day. Administration of talazoparib for 13 weeks at oral doses of 0.0015, 0.005 and 0.01 mg/kg/day were tolerated in dogs. Hematopoietic toxicity, with decreased red cell mass and leukocyte populations, was observed in both species. These findings correlated with toxicity observed in bone marrow (hypocellularity, increased myeloid/erythroid ratio) and lymphoid organs (lymphocyte depletion in thymus and lymph nodes; and increased extramedullary hematopoiesis in spleen in rats only). These findings were primarily noted at doses 0.05/0.04 mg/kg in rats and 0.01 mg/kg in dogs, which are approximately 1 and 0.21 times, respectively, the exposure (AUC) in humans at the recommended clinical dose. Hematology changes were generally reversible. Consistent with these nonclinical findings, in humans, talazoparib caused hematologic toxicities, including anemia, leukopenia/neutropenia and thrombocytopenia at the recommended clinical dose of 1 mg once daily.

In rats, additional histological findings in glandular stomach and duodenum (apoptosis/necrosis) and liver (hepatocyte necrosis) were noted at 0.05 mg/kg/day (approximately 0.73 times the human exposure at the recommended dose) in the 28-day study. The 0.05/0.04 mg/kg/day dose group in the 13-week study had minimal necrosis of duodenum in one animal and single cell necrosis of hepatocytes was noted in two early decedents, with one rat having increased AST and ALT levels. Enlarged kidneys without histopathology correlates were observed in 1 or 2 rats at all dose levels either at end of dosing or end of recovery. In humans, talazoparib related GI adverse events noted were abdominal pain, constipation, diarrhea, nausea, and vomiting. Additionally, most common laboratory abnormalities included increases in AST, ALT and ALP.

Talazoparib was not mutagenic in a bacterial reverse mutation (Ames) assay but was clastogenic. As expected, based on its mechanism of action, talazoparib induced chromosomal aberration in human lymphocyte cultures in vitro and was positive at all doses tested in a stand-

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

alone in vivo rat bone marrow micronucleus assay after a single oral administration. The applicant did not conduct carcinogenicity studies with talazoparib due to its intended use in patients with advanced cancer. In clinical trials, myelodysplastic syndrome, and acute myeloid leukemia (MDS/AML) was reported in patients treated with talazoparib; an adverse reaction that has been observed as well with other FDA-approved PARP inhibitors (Rubraca, Lynparza, and Zejula). The contribution of PARP inhibitors to the development of MDS/AML is unclear as this advanced cancer population has received previous chemotherapy with platinum agents and/or DNA damaging agents, including radiotherapy.

Fertility studies with talazoparib were not conducted. In the repeat-dose toxicity studies of up to 3-month duration, daily administration of talazoparib caused non-reversible toxicity in male reproductive organs. Decrease in organ weights, luminal cellular debris, reduced sperm and degeneration/atrophy in testis and epididymis were noted at doses ≥ 0.04 mg/kg/day in rats and ≥ 0.01 mg/kg/day in dogs. These doses in rats and dogs resulted in exposures that were approximately 1.0 times and 0.18 times, respectively, the exposure (AUC) in humans at the recommended dose. In a 5-day study, follicular atresia of the ovary was observed in rats at doses ≥ 1 mg/kg/day talazoparib (approximately 9.5 times the human exposure at the recommended dose). Based on these results, Talzenna may impair fertility in males of reproductive potential. The human AUC used to calculate animal to human exposure margins was 202 ng.h/mL, which was the clinical AUC for the recommended dose, 1 mg once daily, which was provided by the applicant and confirmed by the clinical pharmacology team.

In an embryo-fetal development toxicity study, talazoparib was embryotoxic when administered to pregnant rats during the period of organogenesis. Embryo-fetal death was observed at doses ≥ 0.015 mg/kg/day, which resulted in maternal systemic exposures that were approximately 0.24 times the AUC in non-pregnant patients at the recommended dose. Talazoparib caused decreased fetal body weights and an increased incidence of fetal malformations (depressed eye bulge, small eye, split sternebra, and fused cervical vertebral arch) and structural variations including misshapen or incomplete ossification of the sternebra, skull, rib, and vertebra at a dose of 0.015 mg/kg/day. Based on these results, mechanism of action, and genotoxicity, effective contraception for females of reproductive potential during treatment and for (b) (4) months following the final dose of Talzenna was recommended (b) (4). Male patients with female partners of reproductive potential and pregnant partners are recommended to use effective contraception during treatment and for (b) (4) months following the last dose (b) (4). Additionally, lactating women are advised not to breastfeed during treatment with Talzenna and for at least 1 (b) (4) (b) (4) after the final dose. Based on the half-life of talazoparib of approximately 20 hours in humans (per the clinical pharmacology reviewer), the applicant's proposal for use of effective contraception in females and males and to not breastfeed for at least 7, 4 and 1 month after the last dose, respectively, is acceptable.

The submitted nonclinical pharmacology and toxicology data support approval of Talzenna for the proposed indications.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Primary pharmacology

In vitro, talazoparib targeted PARP family members. Talazoparib inhibited activity of PARP1, PARP2 and TNSK2 (PARP 5b) with IC₅₀ values of 0.7 nM, 0.3 nM, and 4.7 nM, respectively; and PARP3 and TNSK1 (PARP 5a) with IC₅₀ values of < 25 nM (Study # PF-06944076_02Nov17_092045). In this study, talazoparib had comparable IC₅₀ inhibition profiles against PARP1 and PARP2 when compared to other PARP inhibitors (olaparib, rucaparib, niraparib and veliparib); however, talazoparib inhibited TNSK1 and TNSK 2 activity with lower IC₅₀ values (< 15 nM) versus the other inhibitors (≥ 131 nM to > 10 μM).

Table 3: Inhibition of PARP Enzymes by Talazoparib

Enzyme	IC ₅₀ (nM)
PARP1	0.7
PARP2	0.3
PARP3	22
TNSK1 (PARP 5a)	13.5
TNSK2 (PARP 5b)	4.7
PARP6	574
PARP7	>10000
PARP8	225
PARP10	>10000
PARP11	517
PARP12	9600
PARP14	>10000
PARP15	>10000

Cytotoxicity and PARylation were evaluated to determine IC₅₀ and IC₉₀ values with talazoparib and other PARP inhibitors. The applicant selected the dose that achieved IC₉₀ PARylation inhibition to examine formation of PARP-DNA complexes with PARP inhibitors. In the presence of alkylating agent MMS, talazoparib induced PARP1 accumulation in the chromatin-bound fraction in breast cancer cell lines with wild type or mutant BRCA1. In BRCA1 mutant breast cancer cells, cytotoxicity correlated with more PARP1 accumulation in the chromatin-bound fraction. MDA-MB-436, which was more sensitive to talazoparib cytotoxicity (IC₅₀ = 1 nM), had a 36x fold-increase (drug treated/vehicle control) of PARP-DNA complexes. In comparison, HCC1954 was less sensitive to talazoparib cytotoxicity (IC₅₀ = 32 nM) and had a 12x fold-increase of PARP-DNA complexes induced by talazoparib compared to control. In contrast, WT cells had 45x and 46x fold-increase of PARP-DNA complex accumulation for JIMT1 and HCC1143 cells, respectively, despite their sensitivity to talazoparib cytotoxicity with IC₅₀ values of 34 nM

and 119 nM. In the absence of MMS, talazoparib was not as effective in forming PARP-DNA complexes.

The effects of talazoparib and other PARP inhibitors on DNA damage and cytotoxicity in presence or absence of DNA alkylating agent, temozolomide (TMZ), were evaluated in a prostate cancer cell line DU145 (Study# 17GR323). This cell line was selected because it harbors multiple DNA damage response (DRR) mutations and was previously used to characterize effects of PARP inhibitors. A multiparametric DRR assay used flow cytometry to assess cell cycle distribution, γ H2AX levels indicative of double strand DNA breaks, apoptosis by cleavage of caspase-3 and cell growth in a single experiment in response to a range of doses of talazoparib (2.4×10^{-6} to 20 μ M) with or without a subtherapeutic and clinically relevant exposure of TMZ (43 μ M and 128 μ M, respectively). For all these end points, the applicant determined an ACC (activity-concentration-at cut-off or derived minimal effect level) value for talazoparib, representing a point-of-departure on a dose-response curve where a response was statistically higher than background. The statistical threshold for point-of-departure was set to 3 standard deviation from negative control. Cell cycle analyses revealed that talazoparib induced accumulation in S-phase by itself after 24 h. This effect was further enhanced in the presence of TMZ. Levels of γ H2AX (mean fluorescence) were increased by talazoparib for total number of dsDNA breaks and S-phase specific DNA breaks with talazoparib ACC values of 0.87 μ M and 0.20 μ M, respectively. The maximum increase in γ H2AX (mean fluorescence) was observed when talazoparib was combined with 43 μ M TMZ, demonstrating a 2-fold increase compared to vehicle. The talazoparib ACC values determined with this combination were 0.002 μ M for total dsDNA breaks and 0.008 μ M for S-phase specific DNA breaks. Although a further increase in mean fluorescence was not noted when talazoparib was combined with 128 μ M TMZ compared to control, the dose-response occurred at lower concentrations, shifting the ACC values of talazoparib to 0.0005 μ M for total dsDNA breaks and 0.0003 μ M for S-phase specific DNA breaks. A maximum 13% increase of cleaved caspase-3 (CC3)-expressing cells was observed in talazoparib only treated cells, compared to 3.2% in control, suggesting weak apoptotic induction. Talazoparib plus increasing doses of TMZ, resulted in increased apoptosis, shifting the dose response with ACC values for talazoparib to 0.009 μ M and 0.0016 μ M when combined with 43 μ M or 128 μ M TMZ, respectively. Whereas, talazoparib alone had an ACC value of 3.84 μ M for apoptosis. Cell growth inhibition analyses showed decreased cell growth with talazoparib by itself, which was further reduced when combined with TMZ. Up to 50% reduction in cell growth was achieved with talazoparib plus high dose TMZ, which was the maximum suppression observed.

The effects of talazoparib and several related compounds on proliferation were evaluated in normal human primary cells (MRC-5) or in a panel of cancer cell lines with or without DNA repair gene mutations. Proliferation was assessed after cells were exposed for 7 days or 14 days with doses ranging from 0.128 nM to 10 μ M. Talazoparib was more cytotoxic against Capan-1 (BRCA2 mutation, pancreatic cancer) and MX-1 (BRCA1 mutation, breast cancer) with IC_{50} values of 5 nM and 0.3 nM, respectively. It was also selective for PTEN deficient breast cancer and pancreatic cancer cells, MDA-MB-468 (IC_{50} = 3.7 nM, breast cancer), LNCap (IC_{50} = 4.3 nM,

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

pancreatic cancer) and PC-3 ($IC_{50} = 4.4$ nM, pancreatic cancer); and MLH-1 mutant colorectal carcinoma cell line, HCT-116 ($IC_{50} = 10.6$ nM). In contrast, the IC_{50} values for MRC-5, or cancer cell lines that lack mutations in DNA repair genes (lung: A549, colorectal: LoVo, breast: MDA-MB-231) were higher, ranging from 258 nM to > 1 μ M. The enantiomeric isomer of talazoparib (LT-00674), which according to the applicant has weak PARP inhibition, was less cytotoxic against these cells.

The anti-tumor effect of oral talazoparib was evaluated in several subcutaneous patient-derived xenograft (PDX) models of breast cancer, expressing wild type or mutant BRCA. In BR-05-0028, administration of 0.3 mg/kg talazoparib, orally, once daily, had statistically significant anti-tumor activity by Day 67, demonstrating 108% tumor growth inhibition (TGI) compared to control; while 30 mg/kg carboplatin, administered once via intraperitoneal injection (positive control) achieved 67% TGI (Study# MDVT-20160830B). In HBCx-10 (BRCA2 mutant), a triple negative breast cancer (TNBC) PDX model, anti-tumor activity was noted starting at Day 17 of treatment with 0.07 mg/kg talazoparib, orally, twice a day (Study# CXT-356/XTS-1622). Complete regression in 6/10 mice and 4/10 partial regression were noted at 0.15 mg/kg, given orally, twice a day at end of study. Tumor growth inhibition was reported as the percent ratio between the mean tumor volume of talazoparib-treatment group compared to the control group (T/C%). In the HBCx-10 PDX model, talazoparib treatment resulted in a T/C% of 34.27% and 3.48% at 0.07 and 0.15 mg/kg, respectively.

In HBCx-6, a TNBC PDX model harboring TP53 mutation and wildtype BRCA1/2 (Study# CXT-356/XTS-1623), administration of 0.07 or 0.15 mg/kg talazoparib, orally, twice a day for 35 days resulted in a dose-dependent TGI. The T/C% values were 1.63% and 0.32% for 0.07 and 0.15 mg/kg talazoparib, respectively.

In T168, a TNBC PDX model with TP53 and BRCA1 mutations and wildtype PTEN, talazoparib achieved complete regression (10/10 mice) in both treatment groups (Study# CXT-356/XTS-1624), with T/C% values of 1.26% at 0.07 mg/kg and 0.39% for 0.15 mg/kg. In HBCx-9, a TNBC PDX model with TP53 mutation and wildtype BRCA2, RB1 and PTEN, anti-tumor activity was observed but not as robust as in other models. Nevertheless, a dose-dependent T/C% was observed of 73.8% at 0.07 mg/kg and 46.25% at 0.15 mg/kg. A dose-dependent anti-tumor activity was also observed with talazoparib with HBCx-12B PDX model, obtained from a metastasis of breast infiltrating ductal adenocarcinoma with TP53 mutation and is triple negative (Study# CXT-356/XTS-1626). When established tumors were treated for 25 days with oral talazoparib, twice a day, a 44.4% T/C% was observed with 0.07 mg/kg and 26.6% T/C% with 0.15 mg/kg. In this model, toxicity was noted at the high dose. A decrease in body weight (-20%) was observed in two mice, which was associated with dyspnea, deterioration of health and prostration on Days 25-27 leading to sacrifice. Another mouse was also euthanized on Day 32 based on neurological findings, including tilted head, inability to stand upright on its leg and turn on itself.

Overall, talazoparib showed a dose-dependent anti-tumor activity in vivo by inhibiting tumor growth with statistical significance. Pharmacokinetics were also conducted in the PDX TNBC models, demonstrating C_{max} values and AUC levels to be approximately dose proportional.

Safety pharmacology

The effects of talazoparib on human ether a-go-go-related gene (hERG) channel current were evaluated using stably transfected HEK293 cells (Study# 8229172). Due to solubility limitations, the highest concentration tested was 100 μM talazoparib, which resulted in 33.4% inhibition of hERG channel currents. Based on these results, the IC₅₀ value is > 100 μM, indicating a low risk of hERG channel inhibition.

The effect of talazoparib on respiratory parameters (tidal volume, respiration rate and minute volume) was evaluated in a GLP safety pharmacology study in male rats (Study# 8229153). In this study, animals received a single oral administration of vehicle, 0.3, 1 or 3 mg/kg talazoparib. Talazoparib decreased tidal volume. Grand covariate-adjusted means were compared across time points given that the treatment effect was significant but the treatment by time effect was not. Compared to vehicle group, the grand covariate-adjusted means for tidal volume were decreased by -9%, -11% and -12% at 0.3, 1 and 3 mg/kg talazoparib, respectively. The talazoparib-induced decrease in tidal volume did not influence overall minute volume, as it was offset by increases in respiration rates that were not statistically significant.

The effect talazoparib on nervous system function was evaluated in a GLP safety pharmacology study in male rats (Study# 8227534). Animals were administered a single oral dose of vehicle, 0.3, 1 or 3 mg/kg talazoparib. Animals were evaluated for neuronal function and reflex/activity monitoring at several time points within 24 hours after treatment. No significant adverse findings were noted with talazoparib.

5.4. ADME/PK

Type of Study	Major Findings																																																						
Absorption																																																							
Pharmacokinetics study in Sprague-Dawley rats following a single intravenous or oral gavage dose of BMN 673ts (Study# BMN673-10-072)	<p>Rat Plasma PK parameters of BMN 673fb (free base) following a single oral or IV dose of BMN 673ts (tosylate salt) to male and female rats (n=12/sex/group):</p> <table border="1"> <thead> <tr> <th>Dose, mg/kg</th> <th colspan="2">0.015</th> <th colspan="2">0.1</th> <th colspan="2">1.0</th> <th colspan="2">0.1 IV</th> </tr> <tr> <th></th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> </tr> </thead> <tbody> <tr> <td>C_{max} (ng/mL)</td> <td>6</td> <td>5</td> <td>90</td> <td>88</td> <td>894</td> <td>1154</td> <td>312^a</td> <td>250^a</td> </tr> <tr> <td>AUC_{0-t} (ng·h/mL)</td> <td>47^b</td> <td>62^c</td> <td>490^d</td> <td>568^c</td> <td>4038^d</td> <td>6106^d</td> <td>752^c</td> <td>832^c</td> </tr> <tr> <td>AUC_{0-inf} (ng·h/mL)</td> <td>48</td> <td>62</td> <td>490</td> <td>569</td> <td>4039</td> <td>6105</td> <td>753</td> <td>833</td> </tr> <tr> <td>T_{1/2}</td> <td>25.6</td> <td>27.7</td> <td>37.9</td> <td>28.0</td> <td>36.8</td> <td>49.6</td> <td>21.6</td> <td>29.7</td> </tr> </tbody> </table>	Dose, mg/kg	0.015		0.1		1.0		0.1 IV			M	F	M	F	M	F	M	F	C _{max} (ng/mL)	6	5	90	88	894	1154	312 ^a	250 ^a	AUC _{0-t} (ng·h/mL)	47 ^b	62 ^c	490 ^d	568 ^c	4038 ^d	6106 ^d	752 ^c	832 ^c	AUC _{0-inf} (ng·h/mL)	48	62	490	569	4039	6105	753	833	T _{1/2}	25.6	27.7	37.9	28.0	36.8	49.6	21.6	29.7
Dose, mg/kg	0.015		0.1		1.0		0.1 IV																																																
	M	F	M	F	M	F	M	F																																															
C _{max} (ng/mL)	6	5	90	88	894	1154	312 ^a	250 ^a																																															
AUC _{0-t} (ng·h/mL)	47 ^b	62 ^c	490 ^d	568 ^c	4038 ^d	6106 ^d	752 ^c	832 ^c																																															
AUC _{0-inf} (ng·h/mL)	48	62	490	569	4039	6105	753	833																																															
T _{1/2}	25.6	27.7	37.9	28.0	36.8	49.6	21.6	29.7																																															

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Type of Study	Major Findings																																																																																
	<table border="1"> <tr> <td>(h)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>CL (mL/hr/kg)</td> <td>312</td> <td>241</td> <td>204</td> <td>176</td> <td>248</td> <td>164</td> <td>133</td> <td>120</td> <td></td> </tr> <tr> <td>V_{ss} (mL/kg)</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>700</td> <td>586</td> <td></td> </tr> <tr> <td>Bioavailability (%)</td> <td>42.6</td> <td>49.9</td> <td>65.1</td> <td>68.3</td> <td>53.7</td> <td>73.3</td> <td>NA</td> <td>NA</td> <td></td> </tr> </table> <p>a: C_{5min}, plasma concentration 5 min post administration; b: AUC₉₆; c: AUC₁₆₈; d: AUC₂₄₀</p>	(h)										CL (mL/hr/kg)	312	241	204	176	248	164	133	120		V _{ss} (mL/kg)	NA	NA	NA	NA	NA	NA	700	586		Bioavailability (%)	42.6	49.9	65.1	68.3	53.7	73.3	NA	NA																																									
(h)																																																																																	
CL (mL/hr/kg)	312	241	204	176	248	164	133	120																																																																									
V _{ss} (mL/kg)	NA	NA	NA	NA	NA	NA	700	586																																																																									
Bioavailability (%)	42.6	49.9	65.1	68.3	53.7	73.3	NA	NA																																																																									
Pharmacokinetics study in Beagle dogs following a single intravenous or oral gavage administration of BMN 673ts (Study# BMN673-10-073)	<p>Dog Plasma PK parameters of BMN 673fb (free base) following a single oral or IV dose of BMN 673ts (tosylate salt) to male and female dogs (n=3/sex/group):</p> <table border="1"> <thead> <tr> <th rowspan="2">Dose, mg/kg</th> <th colspan="2">0.0015</th> <th colspan="2">0.01</th> <th colspan="2">0.1</th> <th colspan="2">0.025 IV</th> </tr> <tr> <th>M</th> <th>F</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> </tr> </thead> <tbody> <tr> <td>C_{max} (ng/mL)</td> <td>0.18</td> <td>0.23</td> <td>3</td> <td>2</td> <td>55</td> <td>76</td> <td>20^a</td> <td>21^a</td> </tr> <tr> <td>AUC_{0-t} (ng·h/mL)</td> <td>9</td> <td>11</td> <td>65</td> <td>63</td> <td>584</td> <td>740</td> <td>285</td> <td>255</td> </tr> <tr> <td>AUC_{0-inf}^b (ng·h/mL)</td> <td>10</td> <td>14</td> <td>72</td> <td>69</td> <td>590</td> <td>746</td> <td>289</td> <td>260</td> </tr> <tr> <td>T_{1/2} (h)</td> <td>72.9</td> <td>89.3</td> <td>69.7</td> <td>65.2</td> <td>54.5</td> <td>58.0</td> <td>45.7</td> <td>51.3</td> </tr> <tr> <td>CL (mL/hr/kg)</td> <td>147</td> <td>127</td> <td>140</td> <td>147</td> <td>170</td> <td>135</td> <td>96</td> <td>97</td> </tr> <tr> <td>V_{ss} (mL/kg)</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>3543</td> <td>3835</td> </tr> <tr> <td>Bioavailability (%)</td> <td>59.6</td> <td>86.7</td> <td>62.4</td> <td>66.1</td> <td>51.1</td> <td>71.8</td> <td>NA</td> <td>NA</td> </tr> </tbody> </table> <p>a: C_{5min}, plasma concentration 5 min post administration; b: AUC₂₄₀</p>	Dose, mg/kg	0.0015		0.01		0.1		0.025 IV		M	F	M	F	M	F	M	F	C _{max} (ng/mL)	0.18	0.23	3	2	55	76	20 ^a	21 ^a	AUC _{0-t} (ng·h/mL)	9	11	65	63	584	740	285	255	AUC _{0-inf} ^b (ng·h/mL)	10	14	72	69	590	746	289	260	T _{1/2} (h)	72.9	89.3	69.7	65.2	54.5	58.0	45.7	51.3	CL (mL/hr/kg)	147	127	140	147	170	135	96	97	V _{ss} (mL/kg)	NA	NA	NA	NA	NA	NA	3543	3835	Bioavailability (%)	59.6	86.7	62.4	66.1	51.1	71.8	NA	NA
Dose, mg/kg	0.0015		0.01		0.1		0.025 IV																																																																										
	M	F	M	F	M	F	M	F																																																																									
C _{max} (ng/mL)	0.18	0.23	3	2	55	76	20 ^a	21 ^a																																																																									
AUC _{0-t} (ng·h/mL)	9	11	65	63	584	740	285	255																																																																									
AUC _{0-inf} ^b (ng·h/mL)	10	14	72	69	590	746	289	260																																																																									
T _{1/2} (h)	72.9	89.3	69.7	65.2	54.5	58.0	45.7	51.3																																																																									
CL (mL/hr/kg)	147	127	140	147	170	135	96	97																																																																									
V _{ss} (mL/kg)	NA	NA	NA	NA	NA	NA	3543	3835																																																																									
Bioavailability (%)	59.6	86.7	62.4	66.1	51.1	71.8	NA	NA																																																																									
Distribution																																																																																	
In vitro assessment of protein binding for MDV3800 in mouse, rat, dog, monkey, and human plasma (Study# MDV3800P005)	<p>Mean protein binding of talazoparib (% bound): Mouse: 95.3-95.8% Rat: 89.7-90% Dog: 62.8-64.1% Monkey: 66-68.7% Human: 73.3-74.5%</p>																																																																																
Absorption, distribution and excretion of ¹⁴ C-BMN 673ts following a single oral administration in rats (Study# BMN673-10-069)	<p>Rat</p> <ul style="list-style-type: none"> - Mean blood-to-plasma ratio = 0.572 (sex combined) - C_{max} in most tissues occurred by 1 h and 4 h post-dose in Sprague-Dawley (SD) or Long-Evans (LE) male rats, respectively. - Highest maximum concentrations detected in GI tract contents. - Highest tissue concentration in male SD rats were observed in liver, kidney medulla, kidney, kidney cortex and adrenal glands; these same tissues plus eye uveal tract, lymph nodes and skin (pigmented and nonpigmented) had high concentrations in LE rats. - Following a single oral administration in rats, radioactivity was detected in the brain choroid plexus up to 4 h post-dose in SD rats (up to 58% of blood levels) and in the first hour post-dose in LE rats (38% 																																																																																

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Type of Study	Major Findings
	of blood levels). Radioactivity detected in choroid plexus was 15% to 49% of that detected in tissues with highest concentrations 4 h post-dose in SD rats; and 7% to 25% of that detected in tissues with highest concentrations 1 h post-dose in LE rats.
Absorption and excretion of ¹⁴ C-BMN 673ts following a single oral administration to dogs (Study# BMN673-10-070)	Dog Following a single oral dose of 0.1 mg/kg: -Mean blood-to-plasma ratio = 0.931 (sex combined)
Metabolism	
Profiling and identification of metabolites in selected rat plasma, urine, and feces samples after a single dose oral administration of ¹⁴ C-BMN 673ts from Covance Study No. 8228660 (Study# BMN673-10-088)	Rat Following a single oral dose of 3 mg/kg [¹⁴ C]talazoparib to male and female SD rats (mean % of total parent and metabolites): -Plasma: 95.6% parent, 0.70% M1 (males only), 2.33% M2 -Feces: 64.9% parent, 1.96% M1, 1.12% M2 -Urine: 20.4% parent, 1.33% M1 (males only)
Profiling and identification of metabolites in selected dog plasma, urine, and feces samples after a single dose oral administration of ¹⁴ C-BMN 673ts from Covance Study No. 8228667 (Study# BMN673-10-089)	Dog Following a single oral dose of 3 mg/kg [¹⁴ C]talazoparib to male and female dogs (mean % of total parent and metabolites): -Plasma: 83.7% parent, 8.53% M2, 5.78% M6 -Feces: 35.5% parent, 0.43% M1, 10.5% M2, 2.47% M8 -Urine: 14.7% parent, ≤1.5% M1, M2, M4, M6, M8, M5, M7
Excretion	
Absorption, distribution and excretion of ¹⁴ C-BMN 673ts following a single oral administration in rats (Study# BMN673-10-069)	Rat Following a single oral dose of 3 mg/kg: - Fecal excretion was the major route of elimination, with ~72% in feces and ~23% in urine.
Absorption and excretion of ¹⁴ C-BMN 673ts following a single oral administration to dogs (Study# BMN673-10-070)	Dog - Following a single oral dose of 0.1 mg/kg, the mean recovery of radioactivity was ~94%. Approximately 87% of total radioactivity was recovered by 168 h post-dose. - Fecal excretion was the major route of elimination with, ~67% in feces and ~23% in urine.
TK data from general toxicology studies 13-Week oral study in rats (Study# 8279299)	Rat T _{1/2} : 21 to 52 h on Day 91 Accumulation: Yes, 3.8 to 5.0-fold for C _{max} ; 3.5 to 4.1-fold for AUC Dose proportionality: Approximately dose-proportional between 0.005 and 0.015 mg/kg/day on Days 1 and 91; and between 0.005 and 0.04 mg/kg/day on Day 91. Greater than dose-proportional between 0.005 and 0.05 mg/kg/day on Day 1.

Type of Study	Major Findings																																																				
		Day	Sex	Dose (mg/kg)	C _{max} (pg/mL)	AUC ₍₀₋₂₄₎ (pg·hr/mL)																																															
		1	M	0.005	523	6683																																															
				0.015	1923	23046																																															
				0.05	16033	131300																																															
			F	0.005	497	7274																																															
				0.015	1657	24631																																															
				0.05	16667	151365																																															
		91	M	0.005	1993	25512																																															
				0.015	8767	80262																																															
				0.04	23400	199480																																															
			F	0.005	2460	29832																																															
				0.015	8257	86608																																															
				0.04	35033	221983																																															
13-Week oral study in dogs (Study# 8279298)	<p>Dog T1/2: 61 to 82 h on Day 91 Accumulation: Yes, 2.1 to 4.4-fold for C_{max}; 2.6 to 4.2-fold for AUC Dose proportionality: Approximately dose-proportional, except for females on Day 1 where a greater than dose-proportional increase was observed.</p> <table border="1"> <thead> <tr> <th>Day</th> <th>Sex</th> <th>Dose (mg/kg)</th> <th>C_{max} (pg/mL)</th> <th>AUC₍₀₋₂₄₎ (pg·hr/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="6">1</td> <td rowspan="3">M</td> <td>0.0015</td> <td>102</td> <td>1467</td> </tr> <tr> <td>0.005</td> <td>402</td> <td>5840</td> </tr> <tr> <td>0.01</td> <td>820</td> <td>11690</td> </tr> <tr> <td rowspan="3">F</td> <td>0.0015</td> <td>75</td> <td>1358</td> </tr> <tr> <td>0.005</td> <td>624</td> <td>6863</td> </tr> <tr> <td>0.01</td> <td>1682</td> <td>19559</td> </tr> <tr> <td rowspan="6">91</td> <td rowspan="3">M</td> <td>0.0015</td> <td>278</td> <td>5556</td> </tr> <tr> <td>0.005</td> <td>1107</td> <td>19628</td> </tr> <tr> <td>0.01</td> <td>2011</td> <td>36190</td> </tr> <tr> <td rowspan="3">F</td> <td>0.0015</td> <td>323</td> <td>5746</td> </tr> <tr> <td>0.005</td> <td>1192</td> <td>23454</td> </tr> <tr> <td>0.01</td> <td>2896</td> <td>49888</td> </tr> </tbody> </table>						Day	Sex	Dose (mg/kg)	C _{max} (pg/mL)	AUC ₍₀₋₂₄₎ (pg·hr/mL)	1	M	0.0015	102	1467	0.005	402	5840	0.01	820	11690	F	0.0015	75	1358	0.005	624	6863	0.01	1682	19559	91	M	0.0015	278	5556	0.005	1107	19628	0.01	2011	36190	F	0.0015	323	5746	0.005	1192	23454	0.01	2896	49888
Day	Sex	Dose (mg/kg)	C _{max} (pg/mL)	AUC ₍₀₋₂₄₎ (pg·hr/mL)																																																	
1	M	0.0015	102	1467																																																	
		0.005	402	5840																																																	
		0.01	820	11690																																																	
	F	0.0015	75	1358																																																	
		0.005	624	6863																																																	
		0.01	1682	19559																																																	
91	M	0.0015	278	5556																																																	
		0.005	1107	19628																																																	
		0.01	2011	36190																																																	
	F	0.0015	323	5746																																																	
		0.005	1192	23454																																																	
		0.01	2896	49888																																																	
<p>TK data from reproductive toxicology studies Embryo-fetal development study in rats (Study# 20074799)</p>	<p>Rat (maternal values) T1/2: 4.9 to 8.5 h on DG17 Accumulation: Yes, for LD and MD, ~1.6 to 3.1-fold -Greater than dose proportional for 0.05 mg/kg dose -Greater than dose proportional for 0.15 mg/kg dose at GD6 but not GD17 (may be due to small sample size due to multiple deaths) Mean AUC₀₋₂₄ (GD 17): 0.015 mg/kg: 49.2 ng·h/mL 0.05 mg/kg: 201 ng·h/mL 0.15 mg/kg: 341 ng·h/mL</p>																																																				

LD: low dose; MD: mid dose; GD: gestation day

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: 13-week oral gavage toxicity and toxicokinetic study using once-daily administrations of BMN 673ts in rats with a 4-week recovery phase/8279299

Key Study Findings

- Five HD animals in main study and one TK animal were sacrificed in moribund conditions on Day 49; dose-limiting toxicity was due to hematology findings (up to severe decrease in red cell mass and white blood cells), which correlated with pale feet, eyes, and ears, hypoactivity, bone marrow hypocellularity and lymphoid depletion. One animal had elevated levels of AST and ALT, which correlated with single cell necrosis of hepatocytes.
- Major target organs were testis, epididymis, bone marrow, and lymphoid organs (lymph nodes and thymus) primarily at HD dose.

Conducting laboratory and location: (b) (4)

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 5, 15, 50/40* µg/kg/day, doses are expressed as the free base
*Rats at HD were not dosed on Day 50 to 63 due to up to severe reductions in red cell parameters, associated with pale eyes, ears and/or feet; On Day 64 they resumed dosing at a reduced dose of 40 µg/kg/day

Route of administration: Oral gavage

Formulation/Vehicle: Vehicle: 0.5% (w/v) carboxymethylcellulose (400 to 800 cps) in reverse osmosis water
Control article: (b) (4) SMCC (silicified microcrystalline cellulose, NF) (b) (4)

Species/Strain: Sprague Dawley rats

Number/Sex/Group: 18/sex/group

Age: 9 to 10 weeks old

Satellite groups/ unique design: 4-12/sex/group (TK)

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	LD female (tox: B60331 on Day 43), MD female (TK: B60377 on Day 1) and HD female (tox: B60386 on Day 43), most likely accidental. Deaths occurred after blood sampling without pre-existing clinical findings. HD males (tox: B60265, B60267, B60271, B60277; TK: B60279) and HD

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

	<p>female (tox: B60389): sacrificed in moribund conditions on Day 49</p> <ul style="list-style-type: none"> - Clinical signs: Reduced body weight between Day 42 and 49, pale ears, eyes or feet, hypoactive - Clinical pathology: marked to severe decrease in red cell mass and absolute reticulocyte count; mild to moderate decrease in white blood cells; mild to moderate high platelet counts (except female), glucose, urea nitrogen and triglycerides. Female had severe decrease in hematology parameters (i.e. hematocrit, -91%), and moderately high MCHC, mild to moderately low MCV, MCH and platelet count; mildly low sodium, potassium, and chloride levels. Animal B60267 had mildly high AST and ALT. - Histopathology: Similar microscopic findings as seen in animals at end of dosing; bone marrow hypocellularity, single cell necrosis of hepatocytes (in males B60267 and B60271)
Clinical Signs	HD: Hypoactivity (2/18M; 1/18F), pale ears (1/18M), eyes (2/18M; 2/18F) and/or feet (8/18M; 8/18F)
Body Weights	Percentage change in mean body weight: Males MD: up to -8.0% (Day 70 to 91) HD: up to -10.1% (Day 28 to 91)
Ophthalmoscopy	Unremarkable
Hematology	<p>HD: Decrease in RBC (up to -55%), hemoglobin (up to -43%), hematocrit (up to -43%), WBC (up to -56%), neutrophils (up to -57%), lymphocytes (up to -56%), monocytes (up to -84%), basophils (up to -80%), and large unstained cells (up to -75%). Increase in MCV, MCH up to 26%. This group had a dosing holiday (Day 50 to 63) and a dose reduction on Day 64.</p> <p>LD and MD: Changes in hematology parameters were generally consistent with what was observed at HD, albeit to a smaller magnitude and not statistically significant. Changes in RBC, HGB and HCT were statistically significant, but to a lesser magnitude ($\leq 5\%$).</p> <p>Hematology changes were reversible or partially reversible, except for decrease in large unstained cells.</p>
Coagulation	HD: Decrease in prothrombin time $\leq -10\%$.
Clinical Chemistry	HD: Decrease in total protein (up to -8%), globulin (up to -19%) and triglyceride (up to -26%) prior to dosing holiday (Day 42); Increase in glucose (up to 24%) and A/G ratio (up to 26%). Changes exhibited reversibility, except glucose remained increased in females (18%)
Urinalysis	Females: Reversible increase in urine volume: MD, 156%; HD, 224% Decrease in specific gravity: MD, -2%; HD -1.3%
Gross Pathology	<p><u>Early decedents:</u> HD: Lung, discolored (dark red or white) 2/4M, 1/2F; Pancreas, discolored (white) 3/4M; Pituitary, discolored (white) 4/4M;</p> <p><u>Schedule necropsy, end of dosing:</u> MD: Kidney, large 2/12M; Pancreas, discolored 1/12M; HD: Kidney, raised 1/12M; Pancreas, discolored (white) 2/9M, 2/11F; Testis, small 1/9M; Uterus, large 1/11F;</p>

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

	<u>Recovery:</u> LD: Kidney, large 1/6M MD: Kidney, large, abnormal shape 1/6F, Ureter, large 1/1F, Urinary bladder, calculus 1/6F and thickened 1/6F
Organ Weights	Decrease thymus in HD females; Increased spleen, decreased testis and epididymis in HD males. Change in testis and epididymis were non-reversible.
Histopathology Adequate battery: Yes	See below

LD: low dose; MD: mid dose; HD: high dose; M: males; F: females.

-: indicates reduction in parameters compared to control.

Doses ($\mu\text{g}/\text{kg}/\text{day}$)	Males				Females			
	0	5	15	50/40 ^a	0	5	15	50/40 ^a
n	12	12	12	9	12	12	12	11
Adrenal, Cortex								
Hypertrophy								
Minimal			1					
Vacuolation, increased								
Minimal	1	2	2					
Duodenum								
Necrosis, single cell, epithelial cells, increased								
Minimal				1				
Epididymis								
Cell debris, luminal								
Minimal				3				
Slight				4				
Reduced sperm, luminal								
Minimal				2				
Slight				4				
Moderate				2				
Vacuolation, ductal epithelium								
Minimal				2				
Slight				1				
Lung								
Infiltrate, macrophages, alveolus								
Minimal		1	1				2	
Infiltrate, mixed cells, alveolus								
Minimal		1		1				
Lymph Node, mandibular								
Infiltrate, mast cells								
Slight								1
Lymph Node, mesenteric								
Lymphocytes, decreased								
Minimal			2	9	1		4	6
Marrow, Femur								
Hypocellular								
Minimal				2				8
Slight				3				1

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Doses ($\mu\text{g}/\text{kg}/\text{day}$)	Males				Females			
	0	5	15	50/40 ^a	0	5	15	50/40 ^a
n	12	12	12	9	12	12	12	11
Increased myeloid/erythroid ratio				1				
Minimal				2				4
Infiltrate, mast cell								
Slight								1
Marrow, Sternum								
Hypocellular				2				5
Minimal				2				2
Slight								
Increased myeloid/erythroid ratio				1				
Minimal				2				3
Slight								
Infiltrate, mast cell								1
Moderate								
Muscle, Biceps Femoris								
Infiltrate, lymphocytes/macrophages								
Minimal			1					
Pancreas								
Atrophy, lobular				1	1	1		
Minimal								
Hyperplasia/fibrosis/pigment, islet								
Minimal		1						
Slight		1	1					
Spleen								
Hematopoiesis, extramedullary, increased				2				1
Minimal				4				
Slight								
Siderofibrosis								
Minimal			1					
Stomach, Nonglandular								
Hyperplasia/hyperkeratosis								
Minimal						1		
Thymus								
Lymphocytes, decreased				1				2
Minimal				1				2
Slight								
Tongue								
Inflammation, chronic								
Minimal							1	
Testis								
Degeneration/atrophy, seminiferous epithelium				4				
Minimal				3				
Slight								

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Doses ($\mu\text{g}/\text{kg}/\text{day}$)	Males				Females			
	0	5	15	50/40 ^a	0	5	15	50/40 ^a
n	12	12	12	9	12	12	12	11
Moderate				1				

a: Animals were dosed at 50 $\mu\text{g}/\text{kg}/\text{day}$ from Days 1 to 49 and at 40 $\mu\text{g}/\text{kg}/\text{day}$ from Days 64 to 91

Study title/ number: 13-week oral gavage toxicity and toxicokinetic study using once-daily administrations of BMN 673ts in dogs with a 4-week recovery phase/8279298

Key Study Findings

- The major target organs were male reproductive organs and bone marrow
- At 10 $\mu\text{g}/\text{kg}/\text{day}$, talazoparib caused cellular debris and aspermia in the epididymis; seminiferous tubule degeneration/atrophy in the testes associated with reduced organ weight; and reversible increase of myeloid/erythroid ratio in the bone marrow correlating with hematology changes.

Conducting laboratory and location: (b) (4)
(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 1.5, 5, 10 $\mu\text{g}/\text{kg}/\text{day}$, doses are expressed as the free base

Route of administration: Oral

Formulation/Vehicle: Vehicle: 0.5% (w/v) carboxymethylcellulose (400 to 800 cps) in reverse osmosis water
Control article: (b) (4) SMCC (b) (4) prepared in vehicle

Species/Strain: Beagle dog

Number/Sex/Group: Main: 4/sex/group; Recovery: 3/sex/group

Age: 9 months

Satellite groups/unique design: None

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No test-article related deaths. Control male (H09549): sacrificed in moribund conditions on Day 86 due to hypoactivity, body weight loss, reduced food intake, and low hematocrit. Clinical signs were associated with hypercellularity in bone marrow, extramedullary hematopoiesis in liver and spleen, and erythrophagocytosis and pigment in Kupffer cells of the liver. A cause of moribundity could not be determined.
Clinical Signs	Animals, including controls, had transient and infrequent emesis, fecal changes (discolored, few, liquid, mucoid or nonformed); and discharge

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

	from the eye for extended periods of time.
Body Weights	Unremarkable
Food consumption	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	<p>HD: Decreases in RBC (up to -33%), hemoglobin (up to -32%), hematocrit (up to -26%), starting on Day 15 for males and Day 22 for females; and basophils (up to -78%) on Days 43 and 92 of study. Increase in MCV, up to 10% (Day 92). On Days 8 to 22 of study, transient decreases in reticulocytes (up to -77%) in both sexes; and decreases in WBC, neutrophils and lymphocytes, ranging from -35% to -41% in males were noted. Transient decreases in platelets (up to -49%) at Day 15 for both sexes.</p> <p>LD and MD: Changes in hematology parameters were generally consistent with what was observed at HD, albeit to a smaller magnitude and not always statistically significant. Changes in RBC (up to -10%) for MD males, basophils (up to -56%) at LD/MD, WBC (-19%) for LD males, neutrophils (up to -27%) for LD/MD males were statistically significant.</p> <p>Hematology changes exhibited reversibility, except for decreased lymphocytes and increased MCV in HD males.</p>
Coagulation	Unremarkable
Clinical Chemistry	HD Females: Decrease in cholesterol (-22%) and triglycerides (-33%). Changes were not reversible but not significant.
Urinalysis	Unremarkable
Gross Pathology	<p><u>Schedule necropsy, end of dosing:</u> HD: Lung, discolored (tan or red) 2/4M; correlating with microscopic findings of slight chronic inflammation in lung (focal) or minimal congestion.</p> <p><u>Recovery:</u> LD: Epididymis, small 1/3M There were several tissues (cecum, colon, pituitary, stomach) that were discolored in single animals and without a dose-relationship (only present at one dose, usually low or mid doses).</p>
Organ Weights	Decreased testis weight at HD; correlating with degeneration/atrophy of organ.
Histopathology Adequate battery: Yes	<p><u>Schedule necropsy, end of dosing:</u> See table below</p> <p><u>Recovery:</u> LD: moderate granuloma in epididymis, 1/3M MD: Slight to minimal hypoplasia in testis, 2/3M HD: slight cell debris, luminal and slight reduced sperm, luminal in epididymis, 1/3M; slight degeneration/atrophy in seminiferous epithelium in testis, 1/3M</p>

LD: low dose; MD: mid dose; HD: high dose; M: males; F: females.

-: indicates reduction in parameters compared to control.

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Doses ($\mu\text{g}/\text{kg}/\text{day}$)	Males				Females			
	0	1.5	5	10	0	1.5	5	10
n	3	4	4	4	4	4	4	4
Epididymis								
Cell debris, luminal								
Minimal				1				
Slight				1				
Reduced sperm, luminal								
Minimal				1				
Slight				2				
Moderate				1				
Marrow, Femur								
Increased myeloid/erythroid ratio								
Slight				3				
Marrow, Sternum								
Increased myeloid/erythroid ratio								
Slight				3				1
Testis								
Hypoplasia, segmental								
Minimal	1	1	2	1				
Slight	1							
Degeneration/atrophy, seminiferous epithelium								
Slight				1				
Moderate				2				
Marked				1				

General toxicology; additional studies

Study title/ number: 28-Day oral gavage toxicity and toxicokinetic study using daily administrations of BMN 673ts in Sprague-Dawley rats with a 28-day recovery phase/ #8227533

In a GLP-compliant study, Sprague Dawley rats received doses of 0, 0.005, 0.015, or 0.05 mg/kg/day of test-article orally for 28 days followed by a 28-day recovery period. Test-article related clinical signs included stained haircoat in high dose group. BMN 673ts caused a reversible decrease of mean body weight (-5%), correlating with reduced food consumption in high dose group. Hematology analysis showed a marked decrease in reticulocytes at Day 8, which reversed by end of dosing period but caused a moderate to marked decrease in red cell mass by Day 29 at 0.05 mg/kg/day (Day 28 C_{max} = 19.5 ng/mL; $\text{AUC}_{0-24\text{h}}$ = 148 ng·h/mL). A decrease in white blood cells was noted at 0.05 mg/kg/day, most prominently affecting lymphocytes and neutrophils levels. These changes correlated with microscopic findings in bone marrow (up to slight hypocellularity); and lymph nodes, spleen, and thymus (up to moderate lymphocyte depletion, and reduced thymus organ weight). Test-article induced atrophy/degeneration of testes, associated with reduced testes weight; and sperm granulomas in the epididymis in HD males at end of dosing period. Granulomas were also noted in 2 males

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

at MD at end of dosing period, and in LD and MD males at end of recovery. Additionally, histological findings in glandular stomach and duodenum (apoptosis) and liver (hepatocyte necrosis) were noted at HD. Except for findings in male reproductive organs, all changes were reversible.

Study title/ number: 28-Day oral gavage toxicity and toxicokinetic study using daily administrations of BMN 673ts in dogs with a 29-day recovery phase/ #8227532

In a GLP-compliant study, Beagle dogs received oral doses via gavage of 0, 0.0005, 0.0015, 0.005 or 0.01 mg/kg/day of test-article for 28 days followed by a 29-day recovery period. At 0.005 mg/kg/day, a decrease in lymphocytes was noted. Decreases in red cell mass and white blood cell count were noted at 0.01 mg/kg/day, which correlated with microscopic findings in bone marrow. Hematology changes were reversible. Microscopically, reversible decreases in lymphocytes in GALT, lymph nodes, and splenic germinal centers; and reversible bone marrow hypocellularity were noted at ≥ 0.005 mg/kg/day. In dogs, adverse effects in male reproductive organs were not observed.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial reverse mutation assays using BMN 673 / AE01MH.502ICH.BTL

Key Study Findings:

- Talazoparib was not mutagenic under the conditions tested.

GLP compliance: Yes

Test system: Salmonella typhimurium strains TA 1535, TA 1537, TA 98, and TA 100 and Escherichia coli strain WP2 uvrA; up to 5000 $\mu\text{g}/\text{plate}$ +/- S9

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: In vitro mammalian chromosome aberration assay in human peripheral blood lymphocytes (HPBL) using BMN 673 / AE01MH.341ICH.BTL

Key Study Findings:

- Talazoparib induced increases in structural chromosome aberrations in human lymphocyte cultures in vitro, both in the presence and absence of metabolic activation under the conditions tested.

GLP compliance: Yes

Test system: Human peripheral lymphocyte; up to 380 $\mu\text{g}/\text{mL}$; +/- S9

Study is valid: Yes

Table 4: In Vitro Chromosomal Aberration Assay

Treatment	Cytotoxicity ^a (% of control)	Mean (%) Abnormal Cells	Mean (%) Polyploid Cells
Without metabolic activation (-S9) – 4 hr incubation			
DMSO, 1%	NA	0.0	0.0
Talazoparib, 50 µg/mL	26	14**	0.5
Talazoparib, 100 µg/mL	18	23**	0.0
Talazoparib, 200 µg/mL [†]	31	25**	0.0
Mitomycin-C, 0.6 µg/ml	31	44**	0.0
With metabolic activation (+S9) – 4 hr incubation			
DMSO, 1%	NA	0.5	0.0
Talazoparib, 50 µg/mL	4	18**	0.0
Talazoparib, 100 µg/mL	36	18**	0.0
Talazoparib, 225 µg/mL [†]	49	23**	0.0
Cyclophosphamide, 5 µg/ml	53	30**	0.0
Without metabolic activation (-S9) – 20 hr incubation			
DMSO, 1%	NA	1.5	0.0
Talazoparib, 0.5 µg/mL	10	18**	0.0
Talazoparib, 1.0 µg/mL	32	15**	0.0
Talazoparib, 2.5 µg/mL	45	26**	0.0
Mitomycin-C, 0.3 µg/ml	32	37**	0.5

** p < 0.01 (Fisher's Exact test compared to control values)

† = precipitate was observed

NA = Not applicable

a: Based on mitotic inhibition relative to DMSO. Cytotoxicity = [1-%mitotic index in treated/%mitotic index vehicle control]]X100

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Definitive micronucleus assay with BMN 673 following single oral doses to rats / AE01MH.125012ICH.BTL

Key Study Findings:

- Talazoparib was clastogenic under the conditions tested.

GLP compliance: Yes

Test system: Rat/Sprague-Dawley, bone marrow micronuclei; single oral dose of 0, 150, 300, 600 mg/kg; collection 24 hour (all doses) and 48 hour (0 and 600 mg/kg only) post-dose

Study is valid: Yes

Table 5: In Vivo Bone Marrow Micronucleus Analysis

Collection	Treatment	Sex (n=5/sex/group)	Number of MnPCE/10000 PCE scored
24h	Control	Males	13
		Females	20
	Talazoparib, 150 mg/kg	Males	206*
		Females	122*
	Talazoparib, 300 mg/kg	Males	222*
		Females	94*
	Talazoparib, 600 mg/kg	Males	178*
		Females	71*
Cyclophosphamide, 40 mg/kg	Males	434*	
	Females	198*	
48h	Control	Males	16
		Females	9
	Talazoparib, 600 mg/kg	Males	212*
		Females	112*

*p<0.05 (Kastenbaum-Bowman Tables)

MnPCE: micronucleated polychromatic erythrocytes; PCE: polychromatic erythrocytes

Control: vehicle; aqueous 0.5% (w/v) sodium carboxymethylcellulose (CMC; 400-800 cps)

5.5.3. Carcinogenicity

Not conducted and not required to support this NDA submission for a therapeutic intended to treat patients with advanced cancer.

5.5.4. Reproductive and Developmental Toxicology

Not conducted and not required to support this NDA submission for a therapeutic intended to treat patients with advanced cancer.

Embryo-Fetal Development

Study title/ number: An embryo-fetal development study of BMN 673 by oral gavage in rats/20074799

Key Study Findings

- Talazoparib caused mortality in dams at 0.15 mg/kg/day; doses \geq 0.015 mg/kg/day given to pregnant rats during period of organogenesis caused fetal death and resorptions.
- Skeletal (rib, skull, vertebra, sternebra) and visceral (eye, tail) malformations and variations occurred in live fetuses at 0.015 mg/kg/day
- NOAEL for maternal and developmental toxicity was not determined, < 0.015 mg/kg/day (C_{max} 3.93 ng/mL and AUC 49.2 ng·h/mL on GD 17)

Conducting laboratory and location:



Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

GLP compliance:

(b) (4)
Yes

Methods

Dose and frequency of dosing: 0, 0.015, 0.05, 0.15 mg/kg/day, once daily
Route of administration: Oral gavage
Formulation/Vehicle: Vehicle: 0.5% (w/v) carboxymethylcellulose (400 to 800 cps) in reverse osmosis water
Control article: Excipient, (b) (4) SMCC (b) (4) prepared in vehicle
Species/Strain: Rat/Sprague-Dawley
Number/Sex/Group: 25 females/group
Satellite groups: TK, 3-6 females/group
Study design: Pregnant female rats of approximately 75 days of age received 0, 0.015, 0.05, 0.15 mg/kg/day talazoparib on GD 6-17. Animals were euthanized on GD 21.

Deviation from study protocol affecting interpretation of results:

No

Observations and Results

Parameters	Major findings
Mortality	HD: 5/25 dams were found dead during GD 17 to 21; 3/25 dams were euthanized due to adverse clinical signs on GD 17 or 18. Animals presented red vaginal discharge, dehydration, hunched posture, cold to touch, hypoactivity, thin body condition due to reduced food consumption, partially closed and/or pale eyes, soft stools, and pale paws prior to death/sacrifice.
Clinical Signs	LD: 3/25 red vaginal discharge (GD 20), MD: 2/25 red vaginal discharge (GD 16), 3/25 slight to moderate dehydration, 2/25 hunched posture (GD 15) HD: 13/25 red vaginal discharge (GD 14), 18/25 slight to moderate dehydration, 19/25 hunched posture (GD 15), 2/25 cold to touch, 4/25 swollen soft, 3/25 thin, 7/25 pale skin, 3/25 eyes closed, 4/25 eyes pale
Body Weights	<u>Maternal</u> End of dosing, (body weight/body gain) LD: -10%/ -40% MD: -15%/ -67% HD: -27%/ -104% The gravid uterus weights and body weights without uterus were not reported. <u>Fetal (body weights)</u> LD: -27.5%M/-28.1%F
Food Consumption	From GD 6 to 18 LD: -6% MD: -14%

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

	HD: -37%
Necropsy findings Cesarean Section Data	Pregnancy occurred in all rats, except for one female in control and one in HD group LD: 5/25F with live fetuses; and 20/25F dead or resorbed MD/HD: Complete litter loss (dead or resorbed)
Necropsy findings Offspring	LD: -28% mean fetal weight See below (analysis was done in LD live fetuses, n=32 from 5 litters)

LD: low dose; MD: mid dose; HD: high dose; GD: gestational day

-: indicates reduction in parameters compared to control.

Table 6: Summary of Fetal Rat Malformation and Variations

Doses (mg/kg)	0	0.015	0.05	0.15
External (No. examined litter/fetus)	24/290	5/32	0/0	0/0
<i>Eye</i> Depressed Bulge	1/1	3*/6		
Visceral Malformation (No. examined litter/fetus)	24/290	5/32	0/0	0/0
<i>Eye</i> Small	1/1	2*/2		
<i>Tail</i> Tail – bent Tail - kinked		1/1 1/2		
Skeletal Malformations (No. examined litter/fetus)	24/290	5/32	0/0	0/0
<i>Rib</i> Rib - fused		1/1		
<i>Vertebrae</i> Vertebrae - cervical arch fused Cervical - hemivertebra	-	5***/9 1/1		
<i>Sternebrae</i> Sternebrae – split	-	3**/4		
Skeletal Variations (No. examined litter/fetus)	24/290	5/32	0/0	0/0
<i>Sternebrae</i> Sternebrae – incomplete ossification Sternebrae – isolated ossification site Sternebrae – misshapen	- - -	4***/6 1/1 2*/4		
<i>Skull</i> Zygomatic arch – misshapen	-	3**/4		
<i>Supernumerary rib</i> Cervical – short	-	2*/4		
<i>Vertebrae</i> Cervical arch – incomplete ossification Cervical arch – misshapen Lumbar centrum – bipartite ossification Thoracic centrum – unilateral ossification Thoracic centrum - unossified	- - - - -	5***/8 2*/3 1/1 1/1 1/1		

Significant finding, *p<0.05; **p<0.01; ***p<0.001

5.5.5. Other Toxicology Studies

Study title: Neutral red uptake phototoxicity assay of BMN673 in BALB/c 3T3 mouse fibroblasts/ Study# 20054208

Talazoparib was identified as phototoxic in a GLP BALB/c 3T3 mouse fibroblasts-NRU phototoxicity test, with an average IC₅₀ of 9.202 µg/mL (n=2) after ultraviolet radiation. Cell survival at the average IC₅₀ was at 90% and 80% in the two assays. Due to solubility, doses tested in this assay ranged from 0.6 to 31.9 µg/mL. Promethazine was used as a positive control to validate the assays.

Study title: A multiple dose phototoxicity study to determine the effects of oral gavage administration of PF-06944076 on eyes and skin in pigmented rats/ Study# 20116618

A GLP-compliant phototoxicity study was conducted in Long-Evans rats administered 0, 0.015 or 0.05 mg/kg talazoparib for 3 consecutive days, followed by a single exposure to UVR. Talazoparib did not cause any phototoxicity-related cutaneous or ocular reactions. Toxicokinetics showed systemic exposure in treated animals, with C_{max} and AUC values increasing in a dose-dependent manner and greater than dose proportional.

Study title: Mechanistic investigation of bone marrow suppression associated with talazoparib/ Study# 17LJ085

The objective of this assessment was to provide insight into the mechanism by which talazoparib may induced bone marrow toxicity. In vitro studies evaluated the effects of talazoparib alone or in combination with TMZ on cell viability and/or induction of caspase activation and DNA damage in human PBMC, human bone marrow CD34+ hematopoietic stem cells, or human, mouse or rat bone marrow mononuclear cells (BMMNCs). Results showed talazoparib had no lineage specific effects on cell viability in erythroid, myeloid, or megakaryocyte-specific lineages. In cross-species comparisons, talazoparib reduced cell viability in rat, mouse, and human bone marrow cells after a 4-day incubation, with IC₅₀ values of 3 nM for rat, 5 nM for mouse and 7 nM for human BMMNCs. A dose-dependent increase in caspase 3/7 activation was observed in hBMMNCs treated with talazoparib at concentration ≥ 333 nM, which was further potentiated in a synergistic fashion in the presence of TMZ. The addition of TMZ also induced caspase activation with lower concentrations of talazoparib.

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

X

X

Claudia P Miller
Primary Reviewer

Tiffany Ricks
Acting Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The proposed talazoparib dosing regimen for the proposed indication is 1 mg taken orally once daily (QD) with or without food. The Clinical Pharmacology section of the NDA is supported by the following studies and data analyses: single and repeat dose pharmacokinetics (PK) studies of talazoparib in cancer patients, a mass balance study, a food effect study, as well as dose-response (D-R) and exposure-response (E-R) analyses for safety and efficacy, population PK (PopPK) analyses to identify clinically important covariates on the talazoparib exposure, and potential QT/QTc prolongation assessment.

The overall efficacy and safety of the proposed talazoparib dosing regimen of 1 mg QD with dose modification steps in the event of adverse reactions to the lowest dose of 0.25 mg QD have been demonstrated in the EMBRACA trial and supported by the ABRAZO trial. The identified D-R and E-R relationships for efficacy and safety further support the proposed talazoparib dosing regimen. The PopPK analyses identified that moderate renal impairment and concomitant P-gp inhibitors increased talazoparib exposure to the extent that necessitates talazoparib dose adjustment.

Recommendations

The proposed talazoparib dosing regimen of 1 mg QD is acceptable based on the efficacy and safety outcomes of the clinical trials with talazoparib and the D-R and E-R relationships for efficacy and for safety. From a Clinical Pharmacology standpoint, the NDA is approvable provided that the applicant and the FDA reach an agreement regarding labeling language. The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness for talazoparib is provided by a Phase 3 study (Study 673-301; EMBRACA). Supportive evidence of effectiveness is provided by a Phase 2 study (Study 673-201; ABRAZO) and the dose escalation and expansion study (Study PRP-001).
General dosing instructions	The proposed dosing regimen is 1 mg talazoparib once daily taken with or without food as food has no effect on the extent of talazoparib absorption.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Intrinsic Factors <ul style="list-style-type: none">Renal Impairment: The popPK analysis suggested that patients with moderate renal impairment (CLcr 30 - 59 mL/min) in the clinical studies had an average 37% decrease in talazoparib CL/F when compared to patients

	<p>with normal renal function (CLcr \geq90 mL/min). Dose reduction in patients with moderate renal impairment is recommended.</p> <p>Extrinsic Factors</p> <ul style="list-style-type: none"> Concomitant P-gp Inhibitors: Reduce Talzenna dose to 0.75 mg QD when coadministered with the P-gp inhibitors amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil. The popPK analysis suggested that coadministration with certain p-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil in the clinical trials resulted in an average 45% increase in talazoparib exposure and increased the rate of Talzenna dose reduction. Dose reduction in patients requiring concomitant administration of these P-gp inhibitors is recommended.
<p>Labeling</p>	<p>Intrinsic Factors:</p> <ul style="list-style-type: none"> Reduce the recommended dose of Talzenna (b) (4) in patients with moderate renal impairment (CLcr 30 - 59 mL/min). No dose adjustment is recommended for patients with mild renal impairment (CLcr 60 - 89 mL/min). Talzenna has not been studied in patients with severe renal impairment (CLcr <30 mL/min) or patients requiring hemodialysis. No dose adjustment is required for patients with mild hepatic impairment (total bilirubin \leq1 \times ULN and AST > ULN, or total bilirubin >1.0 to 1.5 \times ULN and any AST). Talzenna has not been studied in patients with moderate hepatic impairment (total bilirubin >1.5 to 3.0 \times upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin >3.0 \times ULN and any AST). <p>Extrinsic Factors:</p> <ul style="list-style-type: none"> In the clinical studies, co-administration with P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil resulted in an approximate 45% increase in talazoparib exposure and an increase in the rate of Talzenna dose reduction. If co-administration of Talzenna with these P-gp inhibitors cannot be avoided, reduce the Talzenna dose. When the

	<p>P-gp inhibitor is discontinued, increase the Talzenna dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the P-gp inhibitor.</p> <ul style="list-style-type: none"> • When co-administering Talzenna with P-gp inhibitors not listed above, monitoring patients for potential increased adverse reactions. • Co-administration with BCRP inhibitors may increase talazoparib exposure. If co-administration with a BCRP inhibitor cannot be avoided, monitoring patients for potential increased adverse reactions when co-administering.
<p>Bridge between the to-be-marketed and clinical trial formulations</p>	<p>Formulation DP Gen 2.0 administered in the form of 4 x 0.25 mg capsules was used in the pivotal Phase 3 study (EMBRACA), Phase 2 study (ABRAZO), the dose escalation study (PRP-001), and the food effect study. Formulation DP Gen 3.1 in 1 mg-strength capsules for the starting dose and 0.25 mg- strength capsules for dose reductions was used in the pivotal Phase 3 study (EMBRACA) and the Phase 2 study (ABRAZO). DP Gen 3.1 formulation and the proposed commercial drug product are identical except for the differences (b) (4) on the commercial capsules.</p> <p>Comparability of the 1-mg capsules from both formulations (1 mg DP Gen 2.0 vs 1 mg DP Gen 3.1) and the 0.25 mg capsule strength from both formulations is demonstrated via <i>in vitro</i> dissolution. However, comparability of the 1-mg strength capsule of DP Gen 3.1 versus 4 x 0.25-mg strength of DP Gen 2.0 is not supported by <i>in vitro</i> dissolution performance. However, the clinical comparability was established based on comparable trough concentrations observed in Studies ABRAZO and EMBRACA, not being a significant covariate in the PopPK analysis, as well as comparable efficacy and safety in studies ABRAZO and EMBRACA.</p>

Post-marketing Requirements and Commitments

The Applicant should conduct the following clinical pharmacology studies as post-marketing requirements (PMRs) and post-marketing commitments (PMCs). The PMR and PMC studies will be included in the Approval Letter with milestones agreed upon after negotiation with the Applicant.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
<input type="checkbox"/> PMC <input checked="" type="checkbox"/> PMR	Determination of an appropriate talazoparib dose for patients with severe renal impairment.	Talazoparib is largely eliminated via the renal route. In the clinical trials with talazoparib, patients with moderate renal impairment had an average of 37% increase in talazoparib exposure and dose reduction is recommended for this patient population. The effect of severe renal impairment on the exposure of talazoparib is unknown. The E-R relationship for safety suggests that higher talazoparib exposure was associated with a higher risk of Grade 3 or higher anemia and thrombocytopenia. This PMR study is to investigate the effect of severe renal impairment on talazoparib exposure to provide dose recommendation for this patient population.	The dedicated renal impairment Study MDV3800-01 is ongoing to evaluate the PK and safety of daily oral doses of 0.5 mg talazoparib in patients (n=24) with advanced solid tumors and normal or varying degrees of renal impairment.
<input type="checkbox"/> PMC <input checked="" type="checkbox"/> PMR	Determination of an appropriate talazoparib dose for patients with moderate and severe hepatic impairment.	The effect of moderate and severe hepatic impairment on the exposure of talazoparib is unknown as this patient population was not enrolled in the Talazoparib clinical trials. The E-R relationship for safety suggests that higher	The dedicated hepatic impairment Study MDV3800-02 is an ongoing to evaluate the PK and safety of daily oral doses of 0.5 mg talazoparib in patients (n=24) with advanced solid tumors and normal or varying degree of

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

		<p>talazoparib exposure was associated with a higher risk of Grade 3 adverse reactions and increased anemia and thrombocytopenia. Of note, although talazoparib is mainly eliminated via the renal route with 19.7% (13.6% unchanged) recovered in feces as evidenced in the mass balance study, the therapeutic window of talazoparib dose is narrow (between 0.9-1.0 mg QD) and modest impairment of hepatic clearance may lead to increased toxicity .</p>	<p>hepatic impairment.</p>
<p><input checked="" type="checkbox"/> PMC <input type="checkbox"/> PMR</p>	<p>Determination of an appropriate talazoparib dose for patients with concomitant use of a P-gp inducer.</p>	<p>Talazoparib is identified as a P-gp substrate in <i>in vitro</i> studies. Co-administering talazoparib with P-gp inducers may decrease talazoparib exposure and decrease its efficacy. Higher talazoparib exposure was associated with longer progression-free survival (PFS) in the analysis of exposure-response for efficacy. This PMC study will evaluate the effect of P-gp inducers on the exposure of talazoparib to inform if talazoparib dose adjustment is needed when co-</p>	<p>The drug-drug interaction study MDV3800-04 is an ongoing DDI study to evaluate the effects of multiple doses of rifampin (P-gp inducer) on the single dose PK of 0.5 mg or 1 mg talazoparib in patients with advanced solid tumors.</p>

		administering with P-gp inducers.	
--	--	-----------------------------------	--

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

After oral administration of 1 mg talazoparib once daily in cancer patients, the geometric mean [% coefficient of variation (CV%)] of area under the concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}) of talazoparib at steady-state was 208 (37%) (ng•hr/mL) and 16.4 (32%) ng/mL, respectively, in Study PRP-001. The pharmacokinetics (PK) of talazoparib is linear from 0.025 mg to 2 mg. The median accumulation ratio of talazoparib following repeated oral administration of 1 mg once daily was in the range of 2.3 to 5.2. Of note, majority of the clinical PK data reported in this review are those observed following the administration of talazoparib without regard to food.

Mechanism of Action

Talazoparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2, which play a role in DNA repair. *In vitro* studies with cancer cell lines that harbored defects in DNA repair genes, including BRCA 1 and 2, have shown that talazoparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, decreased cell proliferation, and apoptosis.

Absorption

The absolute bioavailability of talazoparib is unknown. Following oral administration of talazoparib, the median time to C_{max} (T_{max}) was generally between 1 to 2 hours after dosing.

Food Effect

Following a single oral dose of 0.5 mg of Talzenna with high-fat, high-calorie food (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), the mean C_{max} of talazoparib decreased by 46%, the median T_{max} was delayed from 1 to 4 hours with no change in the AUC_{inf}.

Distribution

The mean apparent volume of distribution of talazoparib is 420 L. *In vitro*, protein binding of talazoparib is 74% and is independent of talazoparib concentration.

Elimination

The mean terminal plasma half-life (±standard deviation, SD) of talazoparib is 90 (±58) hours, and the mean apparent oral clearance (inter-subject variability, CV%) is 6.45 L/h (31.1%) in cancer patients.

Metabolism

Talazoparib undergoes minimal hepatic metabolism. The identified metabolic pathways of talazoparib in humans include mono-oxidation, dehydrogenation, cysteine conjugation of mono-desfluoro-talazoparib, and glucuronide conjugation.

Excretion

Approximately 68.7% (54.6% unchanged) of the total administered radioactive dose [¹⁴C]talazoparib was recovered in the urine and 19.7% (13.6% unchanged) was recovered in the feces.

Drug-Drug Interaction Potential

Talazoparib is a substrate of the efflux transporters P-gp and BCRP.

Dose Selection Rationale and Dose- and Exposure-Response Relationships

In the dose escalation phase of Study PRP-001 (Part 1), 9 escalating doses of talazoparib ranging from 0.025 to 1.1 mg QD were evaluated to establish the maximum tolerated dose (MTD) and to determine the recommended Phase 2 dose (RP2D). At the dose level of 1.1 mg QD, 2 of 6 patients experienced a DLT, of whom 1 had Grade 4 thrombocytopenia and 1 had Grade 3 thrombocytopenia resulted in study drug discontinuation for 5 or more days in a cycle. Therefore, talazoparib 1 mg QD was selected as the RP2D and was used in the dose expansion phase of Study PRP-001 (Part 2). The E-R analysis for efficacy suggests that higher talazoparib exposure is associated with longer progression-free survival (PFS). The E-R analysis for safety indicates that higher talazoparib exposure is associated with a higher risk for Grade 3 or higher anemia and thrombocytopenia, and a trend for association between higher talazoparib exposure and Grade 3 or higher neutropenia. As these 3 safety endpoints correlate with talazoparib exposure levels, lowering the exposure by dosing interruption or dose reduction is expected to lead to a lower probability of having these events.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen of talazoparib is 1 mg QD orally with or without food.

Therapeutic Individualization

Renal Impairment: Talazoparib CL/F was decreased by 37.1% in patients with moderate renal impairment when compared to talazoparib CL/F in patients with normal renal function (CLcr ≥90 mL/min) based on a population PK analysis that included 490 patients, where 132 patients with mild renal impairment (CLcr <60-89 mL/min), 33 patients with moderate renal impairment and 1 patient with severe renal impairment (CrCl <30 mL/min). Based on the identified E-R for safety (Figure 1) as described in Section 2.1, a 37% decrease in talazoparib clearance is clinically meaningful. Therefore, a dosage adjustment from 1 mg QD to 0.75 mg QD is recommended in

patients with moderate renal impairment. The impact of severe renal impairment or hemodialysis on talazoparib CL/F is unknown. A clinical trial (Protocol C3441001) to assess talazoparib PK and safety in patients with varying degrees of renal impairment is ongoing.

P-gp inhibitors: Based on *in vitro* studies, talazoparib is a P-gp substrate. Co-administration of talazoparib with certain P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil in the clinical studies (PRP-001, PRP-002, ABRAZO and EMBRACA) increased talazoparib exposure by 44.7%, in conjunction with an increased rate of Talzenna dose reductions (41%). Considering the narrow therapeutic window of talazoparib and the E-R relationship for safety (Figure 1) as described in Section 2.1, a 45% increase in talazoparib exposure is clinically meaningful. If co-administration with these P-gp inhibitors cannot be avoided, reduce Talzenna dose from 1 mg QD to 0.75 mg QD.

Co-administration with P-gp inhibitors including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin in the clinical studies increased talazoparib exposure by 7.8% with 11% dose reduction. For these and other P-gp inhibitors, monitor patients for potential increased adverse reactions when coadministering with talazoparib and adjust the talazoparib dose based on tolerability.

BCRP inhibitors: Based on *in vitro* studies, talazoparib is a substrate of BCRP. Co-administration with BCRP inhibitors may increase talazoparib exposure. Monitoring patients for increased adverse reactions when co-administering BCRP inhibitors with talazoparib.

Outstanding Issues

The PK and potential increase in talazoparib exposure in patients with severe renal impairment as well as moderate and severe hepatic impairment have not been studied clinically. Dedicated clinical trials including renal impairment study (Study MDV3800-01) and hepatic impairment study (Study MDV3800-02) are currently ongoing. Results from these studies will inform Talzenna dosing recommendations in patients with severe renal impairment and patients with moderate or severe hepatic impairment.

Based on *in vitro* studies, talazoparib is a P-gp substrate; co-administration with P-gp inducers may decrease talazoparib exposures. A clinical trial is ongoing to assess the effect of rifampin as a P-gp inducer on the magnitude of decreased exposure of talazoparib.

Summary of Labeling Recommendations

Drug-Drug Interactions

Co-administration with P-gp inhibitors: The co-administration of talazoparib with P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil in a pooled analysis from clinical studies PRP-001, PRP-002, ABRAZO and EMBRACA increased talazoparib exposure by 44.7% with a rate of Talzenna[®] dose reduction of 41%. Considering the narrow therapeutic window of talazoparib and based on the E-R for safety and the dose-response

analysis, a 45% increase in talazoparib exposure is clinically meaningful. If co-administration with these P-gp inhibitors cannot be avoided, the Talzenna® dose is reduced from 1 mg QD to 0.75 mg QD. When the P-gp inhibitor is discontinued, the talazoparib dose is increased (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the P gp inhibitor. Moreover, co-administration with P gp inhibitors including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin in the clinical studies increased talazoparib exposure by 7.8% with a rate of dose reduction of 11%. For these and other P-gp inhibitors, patients are monitored for potential increased adverse reactions when co-administering with talazoparib and dose adjustments are based on tolerability.

Co-administration with P-gp inducers: The effect of P-gp inducers on PK of talazoparib has not been studied.

Co-administration with BCRP inhibitors: The effect of BCRP inhibitors on PK of talazoparib has not been studied. Co-administration with BCRP inhibitors may increase talazoparib exposure. Monitoring of patients for increased adverse reactions when co-administering BCRP inhibitors with talazoparib is recommended.

Organ Impairment

Patients with Renal Impairment: Talazoparib CL/F was decreased by 14.4% in patients with mild renal impairment (CLcr 60 - 89 mL/min, n=132) and 37.1% in patients with moderate renal impairment (CLcr 30 - 59 mL/min, n=33), when compared to patients with normal renal function (CLcr \geq 90 mL/min, n=324). The PK of talazoparib have not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or in patients requiring hemodialysis.

Patients with Hepatic Impairment: Mild hepatic impairment (total bilirubin \leq 1.0 \times ULN and AST > ULN, or total bilirubin >1.0 to 1.5 \times ULN and any AST) had no effect on the PK of talazoparib. The PK of talazoparib have not been studied in patients with moderate (total bilirubin >1.5 to 3.0 \times ULN and any AST) or severe hepatic impairment (total bilirubin >3.0 \times ULN and any AST).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of general pharmacology and PK characteristics of talazoparib are shown in Table 7.

Table 7. Summary of General Pharmacology and Pharmacokinetic Characteristics of Talazoparib

Pharmacology	
Mechanism of Action	<ul style="list-style-type: none">Inhibits poly ADP ribose polymerase (PARP) enzyme activity; IC50 values for PARP1 and PARP2 of 0.7 nM and

	<p>0.3 nM, respectively.</p> <ul style="list-style-type: none"> Traps PARP on DNA, preventing alternative methods of DNA repair.
Active Moieties	Unchanged talazoparib is the active moiety.
QT Prolongation	<p>The IC50 for hERG inhibition is >100 µM (38000 ng/mL) and is approximately >6996-fold above the observed unbound human clinical exposure at 1 mg daily human dose based on mean unbound steady state Cmax of 5.46 ng/mL.</p> <p>No large mean QTc prolongation effect (i.e., >20 ms) was detected for the proposed therapeutic dosing regimen of talazoparib (1 mg QD) in the dedicated QT Study MDV3800-14. Based on central tendency analysis, the largest upper bound of the 2-sided 90% CI was 11.5 ms with the corresponding mean of 6.9 ms for the change from baseline in QTcF (ΔQTcF), which occurred at 1-hour post-dose on Day 22. There was no placebo or positive control in the study. There was no statistically significant exposure-response relationship between ΔQTcF and talazoparib concentrations.</p>
General Information	
Bioanalysis	<p>High-performance liquid chromatography tandem mass spectrometry (LC-MS/MS) was used for the quantitative determination of talazoparib (validation report C3449004). The lower limit of quantitation (LLOQ) for talazoparib in human plasma was initially at 5.00 pg/mL, with linearity demonstrated up to 5,000 pg/mL, which was later raised to better represent the concentrations of the clinical samples to LLOQ at 25.0 pg/mL up to ULOQ at 25,000 pg/mL. Accuracy (%RE) and precision (%CV) of the quality controls (QCs) for the runs used in measuring talazoparin were ≤15%, which are acceptable based on the current Bioanalytical Method Validation Draft FDA Guidance for Industry</p>
Healthy vs. Patients	<p>The PK of talazoparib are comparable between cancer patients and healthy subjects. The geometric mean CL/F after administration of a single 0.5 mg talazoparib dose to healthy subjects in Study 673-103 was 7.99 L/hr and 8.19 L/hr in the fasted and fed conditions, respectively. This value was generally in a comparable range with that observed in patients following a single 1 mg dose of talazoparib (5.12 to 7.71 L/hr). In addition, the t½ of talazoparib in healthy subjects ranged from 81.3 to 208 hours (Study 673-103), which is within the mean range observed across studies conducted in patients receiving a single dose of talazoparib (52.9 to 229 hours).</p>

Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	After oral administration of 1 mg talazoparib QD in patients in study PRP-001, the geometric mean [% coefficient of variation (CV%)] of AUC and C _{max} of talazoparib at steady-state was 208 (37%) ng.hr/mL and 16.4 (32%) ng/mL, respectively.		
Maximally Tolerated Dose or Exposure	The maximum tolerated dose (MTD) of talazoparib is 1 mg QD.		
Dose Proportionality	Dose proportional exposure over the dose range of 0.025 mg to 2 mg.		
Accumulation	The median accumulation ratio of talazoparib following repeated oral administration of 1 mg once daily was in the range of 2.3 to 5.2.		
Variability	After oral administration of 1 mg talazoparib QD in patients, the inter-subject variability (CV%) of steady-state AUC _{0-tau} was 37% and of C _{max} was 32%.		
Absorption			
Bioavailability	The absolute bioavailability of talazoparib was not determined. Based on the results of the mass balance study, approximately 68.7% (54.6% unchanged) of the total administered radioactive dose [¹⁴ C]talazoparib was recovered in urine and 19.7% (13.6% unchanged) was recovered in feces; therefore, the bioavailability of talazoparib is estimated to be at least 55% .		
T_{max}	After oral administration of 1 mg talazoparib QD in patients, the median time to C _{max} (T _{max}) was generally between 1 to 2 hours after dosing.		
Food effect ^a (Fed/fasted)	AUC_{0-∞}	C_{max}	T_{max}
	Geometric Mean Ratio [90% CI] 97.62 (92.48 - 103.05)	Geometric Mean Ratio [90% CI] 53.88 (48.12 - 60.34)	Effect on time to reach C _{max} increased by a median of 2.6 hours
^a After a high-fat meal consisting of approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively)			
Distribution			
Volume of Distribution	The mean apparent volume of distribution (V _{ss} /F) of talazoparib is 420 L.		
Plasma Protein Binding	<i>In vitro</i> , protein binding of talazoparib is 74% and is independent of talazoparib concentration.		
As Substrate of Transporters	<ul style="list-style-type: none"> Substrate of p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Talazoparib is not a substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1 and MATE2-K, and BSEP. 		
Elimination			

Terminal Elimination Half-Life	The mean terminal plasma half-life (\pm standard deviation) of talazoparib is 90 (\pm 58) hours.
Effective Elimination Half-Life	The effective $t_{1/2}$ is similar to the terminal elimination $t_{1/2}$.
Metabolism	
Fraction Metabolized (% dose)	Talazoparib undergoes minimal hepatic metabolism (<10%).
Primary Metabolic Pathway(s)	The identified metabolic pathways of talazoparib in humans include mono-oxidation, dehydrogenation, cysteine conjugation of mono-desfluoro-talazoparib, and glucuronide conjugation.
Excretion	
Primary Excretion Pathways (% dose) \pmSD	<ul style="list-style-type: none"> Feces: 19.7% (13.6% unchanged talazoparib). Urine: 68.7% (54.6% unchanged talazoparib).
Interaction liability (Drug as Perpetrator)	
Inhibition/Induction of Metabolism	<ul style="list-style-type: none"> Talazoparib is minimally metabolized by metabolic pathways; therefore, inhibition or induction of metabolism unlikely affects talazoparib exposure. Talazoparib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Talazoparib is not an inhibitor of UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 Talazoparib is not an inducer CYP1A2, CYP2B6, or CYP3A4.
Inhibition/Induction of Transporter Systems	<ul style="list-style-type: none"> Talazoparib is not an inhibitor of transporters including P-gp, BCRP, organic anion transporting polypeptide [OATP]1B1, OATP1B3, organic cationic transporter [OCT]1, OCT2, organic anion transporter [OAT]1, OAT3, bile salt export pump [BSEP], multidrug and toxin extrusion [MATE]1, and MATE2-K.

* PK parameters are presented as geometric mean (%CV) or median (minimum, maximum) unless otherwise noted.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Dose-response (D-R) and exposure-response (E-R) relationships for efficacy provide supportive evidence of effectiveness for the proposed talazoparib dosing regimen, 1 mg QD. The D-R relationship, as evidenced from the dose escalation phase (Part 1) of Study PRP-001, suggests that 1 mg QD is correlated with the highest objective response rate (ORR) as summarized in Table 8. Of note, the results from D-R analyses for ORR from Study PRP-001 should be interpreted with caution due to the limited number of patients treated at each dose level.

Table 8. Summary of Efficacy Outcomes in Study PRP-001

Study PRP-001	Dosing Regimen	Number of Breast Cancer Patients	Number of Breast Cancer Patients with Objective Response (ORR%)	Number of Patients (All Tumor Types)	Number of All Tumor Types Patients with Objective Response (ORR%)
Dose Escalation	0.025 mg QD	0	0	3	0 (0%)
	0.05 mg QD	0	0	3	0 (0%)
	0.1 mg QD	0	0	3	1 (33%)
	0.2 mg QD	0	0	2	1 (50%)
	0.4 mg QD	0	0	3	0 (0%)
	0.6 mg QD	1	0 (0%)	6	2 (33%)
	0.9 mg QD	2	1 (50%)	6	4 (66%)
	1 mg QD	2	1 (50%)	5	3 (60%)
	1.1 mg QD	3	0 (0%)	6	0 (0%)
Dose Expansion	1 mg QD	12	6 (50%)	67	13 (20%)

Source: prepared by the reviewer.

In addition, the relationship between talazoparib exposure and efficacy endpoints was evaluated. A positive E-R relationship was identified between talazoparib exposure (average daily exposure; Cav_{g,t}) and PFS.

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

The proposed dosing regimen of 1 mg talazoparib QD is appropriate for the indicated patient population. In the dose escalation phase (Part 1) of Study PRP-001, 9 escalating doses of talazoparib ranging from 0.025 to 1.1 mg QD were evaluated in Part 1 of Study PRP-001. At the higher dose level, 1.1 mg QD, 2 of 6 patients experienced a DLT, of whom 1 had Grade 4 thrombocytopenia and 1 had Grade 3 thrombocytopenia that resulted in study drug discontinuation for 5 or more days in a cycle as summarized in Table 9 below. Therefore, talazoparib 1.0 mg QD was considered the MTD and selected as the RP2D.

Table 9. Summary of Safety Outcomes Used to Determine Dose Escalation and Maximum Tolerated Dose of Talazoparib (Study PRP-001)

Dosing Regimen	Number of Patients	Number of Patients with Cycle 1 DLTs
0.025 mg QD	3	0
0.05 mg QD	3	0
0.1 mg QD	3	0
0.2 mg QD	3	0
0.4 mg QD	3	0
0.6 mg QD	6	0
0.9 mg QD	6	1
1 mg QD	6	0
1.1 mg QD	6	2

Source: prepared by the reviewer.

In addition, the relationships between talazoparib exposure and safety endpoints were evaluated. Higher talazoparib exposure (Cavg,t) was associated with a higher risk of Grade 3 or higher anemia and thrombocytopenia. A trend of association between higher talazoparib exposure and Grade 3 or higher neutropenia was observed, therefore, based on the aforementioned factors, and taking into consideration of the narrow therapeutic window of talazoparib, a higher than the MTD starting dose is not recommended for safety reasons. As these 3 safety endpoints correlate with talazoparib exposure levels as shown in Figure 1 below, lowering the exposure by dosing interruption or dose reduction will lead to a lower probability of having these events.

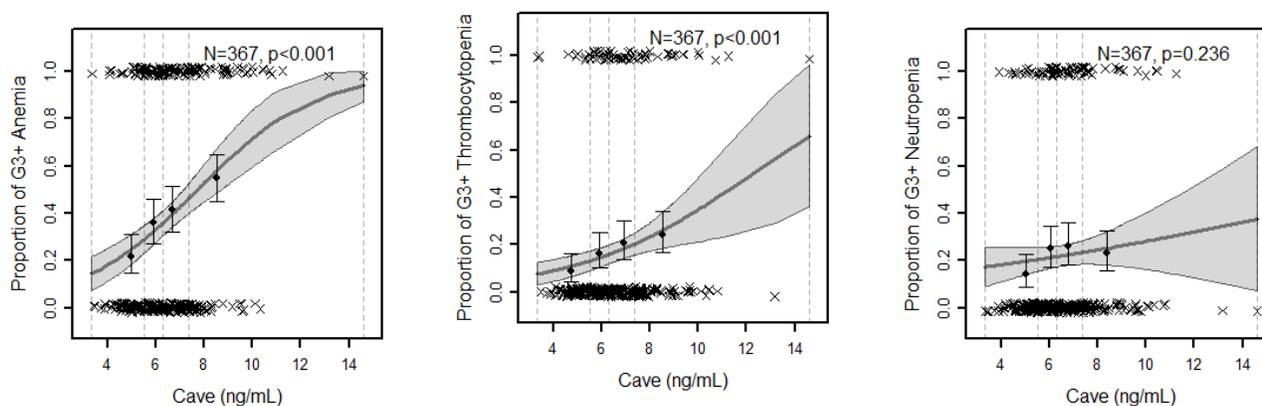


Figure 1. Exposure-Response for Safety Analysis for Anemia, Thrombocytopenia, and Neutropenia

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

Renal Impairment

The talazoparib dose is reduced from 1 mg QD to 0.75 mg QD for patients with moderate renal impairment. No dose adjustments are recommended for patients with mild renal impairment or mild hepatic impairment, based on factors such as age, sex, weight, or race (White, Asian, Black, or others).

Talazoparib CL/F was decreased by 14.4% in patients with mild renal impairment and 37.1% in patients with moderate renal impairment, based on the PopPK analysis, when compared to patients with normal renal function as shown in Figure 2 below. The PK of talazoparib have not been studied in patients with severe renal impairment or in patients requiring hemodialysis. A dedicated PMR clinical trial (renal impairment Study MDV3800-01) is intended to inform dosing recommendations in patients with severe renal impairment.

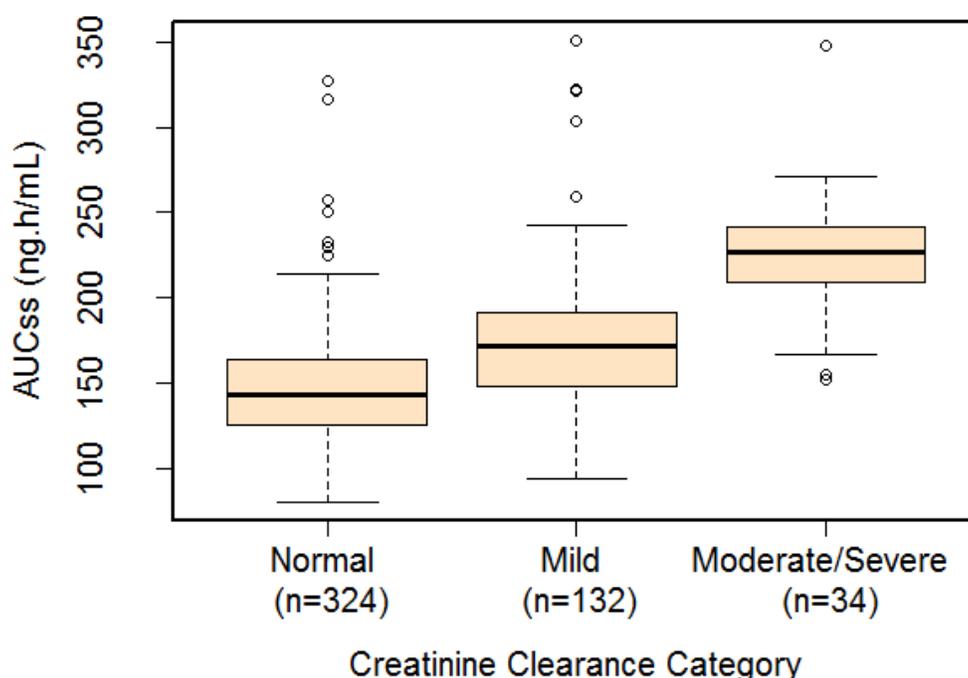


Figure 2. The Effect of Renal Impairment on Talazoparib Exposure.

Source: Prepared by the reviewer.

Hepatic Impairment

Mild hepatic impairment had no effect on the PK of talazoparib based on the PopPK analysis. The PK of talazoparib have not been studied in patients with moderate or severe hepatic impairment. A dedicated ongoing clinical trial (hepatic impairment Study MDV3800-02) is intended to inform dosing recommendations in patients with moderate or severe hepatic impairment.

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

Food-Drug Interactions

Talazoparib capsules can be taken with or without food. Food intake decreased the rate but not the extent of talazoparib absorption. In the food-effect Study 673-103, following a single oral dose of 0.5 mg talazoparib with a high-fat meal consisting of approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively, the mean C_{max} of talazoparib was decreased by approximately 46%, whereas the AUC_{0-inf} was not affected relative to the administration of a single dose of talazoparib following an overnight fast. Consistent with the findings from Study 673-103, the PopPK analysis indicated that food decreased the absorption rate (K_a) but had no impact on the extent of the absorption (F₁). Furthermore, the efficacy and safety of talazoparib were established in the pivotal Phase 3 study, 673-301, where talazoparib capsules were administered without regard to food intake.

Drug-Drug Interactions

Effects of Other Drugs on Talazoparib

P-gp Inhibitors:

In the PopPK analysis, the Applicant divided P-gp inhibitors into 2 groups: “potent” and “moderate/weak” P-gp inhibitors based on the magnitude of the effect of a P-gp inhibitor on the exposure (AUC) of *in vivo* P-gp substrates. According to the University of Washington Drug Interaction Database (<https://www.druginteractioninfo.org/>), the Applicant found the co-administration of the following P-gp inhibitors “amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valsopodar, and verapamil” lead to an AUC fold-increase ≥ 2 in the *in vivo* P-gp substrates; and coadministration of the following P-gp inhibitors “atorvastatin, azithromycin, conivaptan, diltiazem, diosmin, eliglustat, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinesis extract” lead to an AUC fold-increase less than 2 but greater than 1.4 for *in vivo* P-gp substrates.

In the PopPK dataset (n=490), 21 patients were on the following P-gp inhibitors: amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil. The effect of these P-gp inhibitors on talazoparib exposure was statistically significant, and their coadministration with talazoparib increased talazoparib exposure by 44.7% and was associated with a higher dose reduction rate in the clinical studies. In contrary, 35 patients were on concomitant “moderate/weak” P-gp inhibitors including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin and the effect of these P-gp inhibitors on talazoparib exposure is minimum (increased by 7.8%), with a rate of dose reduction of 11%.

When all P-gp inhibitors were used as a single covariate on the relative bioavailability in the PopPK analysis, the talazoparib exposure increased by 19.6% which does not warrant a dose adjustment. Given that differential effect on talazoparib exposure was observed with different

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

P-gp inhibitors and talazoparib has narrow therapeutic window, analysis by pooling all concomitant P-gp inhibitors may underestimated the effect of certain P-gp inhibitors; therefore, perform grouping analysis based on magnitude of effect is justifiable. Based on the group analysis results, if coadministration with the P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil cannot be avoided, it is recommended to reduce the Talzenna dose from 1 mg QD to 0.75 mg QD. When the P-gp inhibitor is discontinued, it is recommended to increase the talazoparib dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the P gp inhibitor.

For co-administration with P-gp inhibitors including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin in the clinical studies which increased talazoparib exposure by 7.8% with a rate of dose reduction of 11%, it is recommended to monitor patients for potential increased adverse reactions when co-administering with talazoparib and adjust dose based on tolerability.

P-gp Inducers:

The effect of P-gp inducers on PK of talazoparib has not been studied. The applicant is conducting a clinical trial to evaluate the effect of rifampin on the PK of talazoparib (DDI Protocol C3441004) to inform dosing recommendations for the coadministration with P-gp inducers.

BCRP Inhibitors:

Talazoparib is a P-gp and BCRP substrate, based on *in vitro* studies. The efflux ratio in BCRP-transfected cell monolayer was slightly above 2 relative to that of P-gp (>50), indicating that the effect of BCRP on talazoparib exposure is less than the effect of P-gp. However, the experiments are conducted in different cell lines and the results cannot be directly compared (P-gp in MDCK cells transfected with MDR1 and BCRP in Caco-2 cells). Available data of concomitant administration of BCRP inhibitors was limited to 3 patients in talazoparib clinical studies. Moreover, the lack of selective and specific *in vivo* BCRP inhibitors renders a DDI study infeasible. Based on these factors, it is recommended that monitor patients for increased adverse reactions when a BCRP inhibitor is coadministered with talazoparib.

Acid-Reducing Agents:

Talazoparib *in vitro* solubility at the highest dose strength is 1 mg talazoparib in 250 mL of aqueous media at different pH levels. Co-administration of acid-reducing agents including PPI, H₂RA, or other acid reducing agents has no effect on the absorption of talazoparib. This conclusion is based on the PopPK analysis of the clinical data which indicates that co-administration of acid-reducing agents in 190 patients including proton pump inhibitors (PPI, n=158), Histamine 2 receptor antagonists (H₂RA, n=20), or other acid reducing agents (n=48) had no significant impact on the absorption of talazoparib.

Effects of Talazoparib on Other Drugs

- **Metabolic Enzyme Substrates:** Talazoparib did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2D6, 2C19, or 3A4/5 at clinically relevant concentrations (Table 10). Talazoparib is not an inhibitor of UGT1A1, 1A4, 1A6, 1A9, 2B7, and 2B15 (Table 11). Furthermore, talazoparib is not an inducer of CYP1A2, CYP2B6, or CYP3A4 (Table 12).

Table 10. IC₅₀ Values for Talazoparib Inhibition of CYP Activities in Human Liver Microsomes

CYP Enzyme	Substrate	Talazoparib IC ₅₀ (μM)
CYP1A2	Phenacetin	> 10
CYP2B6	Efavirenz	> 10
CYP2C8	Amodiaquine	> 10
CYP2C9	Diclofenac	> 10
CYP2C19	S-Mephenytoin	> 10
CYP2D6	Dextromethorphan	> 10
CYP3A4/5	Midazolam	> 10
CYP3A4/5	Testosterone	> 10

Source: BioMarin BMN673-14-004 Final Study Report, Table 3, Page 28.

Table 11. IC₅₀ Values for Talazoparib Inhibition of UGT Activities in Human Liver Microsomes

UGT Enzyme	Substrate	Talazoparib IC ₅₀ (μM)
1A2	β-Estradiol-3-Glucuronyl Transferase	> 10
1A4	Trifluoperazine- <i>N</i> -Glucuronyl Transferase	> 10
1A6	5-Hydroxytryptophol- <i>O</i> -Glucuronyl Transferase	> 10
1A9	Propofol- <i>O</i> -Glucuronyl Transferase	> 10
2B7	Zidovudine-5'-Glucuronyl Transferase	> 10
2B15	S-Oxazepam-Glucuronyl Transferase	> 10

Source: PF-06944076 Final Study Report, Table 6, Page 16.

Table 12. Talazoparib Induction of Mean mRNA and Activity Levels of CYP Enzymes

Talazoparib (μ M)	CYP1A2		CYP2B6		CYP3A4/5	
	mRNA	Activity	mRNA	Activity	mRNA	Activity
0.003	0.91	1.05	0.89	0.91	0.94	1.02
0.01	0.73	0.9	0.69	0.84	0.59	0.96
0.03	0.93	1.03	0.9	1.09	1.13	1.06
0.1	0.79	0.95	0.75	0.99	0.56	0.99
0.3	0.77	0.99	0.6	0.96	0.71	0.99
1	0.88	0.85	0.54	0.92	0.63	1.05
3	1.01	0.92	0.61	0.99	0.82	1.18
10	0.7	0.83	0.53	0.94	0.79	0.98
Known positive inducer ^a	31.6	5.57	5.26	10.3	5.34	3.26

^a Omeprazole 50 μ M for CYP1A2, phenobarbital 750 μ M for CYP2B6, rifampin 20 μ M for CYP3A4/5
^b Mean fold change relative to vehicle control from three human hepatocyte lots

Source: BioMarin BMN673-14-003 Final Study Report, Figures 8, 10, 13, 15, 18, 20, pages 43-65

Transporter Substrates: Talazoparib is not an inhibitor of transporters including P-gp, BCRP, organic anion transporting polypeptide [OATP]1B1, OATP1B3, organic cationic transporter [OCT]1, OCT2, organic anion transporter [OAT]1, OAT3, bile salt export pump [BSEP], multidrug and toxin extrusion [MATE]1, and MATE2-K (Table 13 and Table 14).

Table 13. In Vitro Data for the Inhibition of OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2-K, and BSEP Mediated Transport by Talazoparib and Reference Inhibitor

Transporter	Reference Inhibitor	% Inhibition by Talazoparib	% Inhibition by Reference Inhibitor
OAT1	100 µM probenecid	3.62 ± 6.71	82.8 ± 0.954
OAT3	100 µM probenecid	-1.65 ± 12.3	96.3 ± 7.50
OCT1	100 µM quinidine	-7.88 ± 2.90	45.7 ± 4.17
OCT2	100 µM quinidine	1.86 ± 11.1	67.2 ± 2.86
OATP1B1	100 µM rifampicin	4.84 ± 14.7	99.6 ± 0.305
OATP1B3	100 µM rifampicin	6.43 ± 6.93	98.2 ± 1.56
MATE1	10 µM cimetidine	-14.3 ± 9.45	85.0 ± 1.14
MATE2K	10 µM cimetidine	31.8 ± 9.68	71.4 ± 2.59
BSEP	300 µM rifampicin	2.73 ± 5.12	96.8 ± 0.344
<p>Probe substrate for each transporter was 10 µM MPP+ (OCT1), 10 µM metformin (OCT2, MATE1 and MATE2-K), 2 µM p-aminohippurate (OAT1), 10 µM p-aminohippurate (OAT3), 2 µM estradiol-17β-D-glucuronide (OATP1B1), 10 µM CCK-8 (OATP1B3), and 300 µM rifampicin (BSEP) .</p> <p>Source: BioMarin Study BMN673-13-070 Final Study Report, Tables 4, 6, Page 20, and 21.</p>			

Table 14. In Vitro Data for the Inhibition of BCRP and P-gp Mediated Transport by BMN 673ts and Reference Inhibition

Test Conditions	Efflux ratio (Papp B->A)/(Papp A->B)	Inhibition (%)
BCRP - 1.0 µM Talazoparib	5.34 ± 0.0757	2.73 ± 1.70
BCRP - 100 µM chrysin (reference) ^a	1.18 ± 0.0193	84.8 ± 1.61
P-gp - 1.0 µM Talazoparib	42.4 ± 0.293	2.29 ± 0.692
P-gp - 100 µM verapamil (reference) ^a	1.45 ± 0.0369	90.5 ± 0.778

Probe substrate for each transporter was 0.1 µM digoxin (P-gp) and 0.025 µM genistein (BCRP).
^a 100 µM chrysin and 100 µM verapamil are reference inhibitors for BCRP, and P-gp, respectively.

Source: BioMarin Study BMN673-13-070 Final Study Report, Table 5, Page 21.

X

X

Amal Ayyoub
 Primary Reviewer

Hong Zhao
 Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 15: Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
EMBRACA (C3441009)	NCT01945775	Phase 3, open-label, randomized study to compare talazoparib versus physician's choice therapy (PCT) with HER2-negative locally advanced or MBC and gBRCAm	Talazoparib 1mg orally daily vs PCT (capecitabine, vinorelbine, gemcitabine, or eribulin)	PFS assessed by blinded independent radiology facility (IRF)	Until disease progression/death or unacceptable toxicity	431	Patients with HER2- negative MBC and gBRCAm. Patients must have received prior anthracycline and taxane therapy.	145 centers in 16 countries
<i>Studies to Support Safety</i>								
ABRAZO (C3441008)	NCT02034916	Phase 2, 2-stage, 2-cohort study in patients with gBRCAm, locally advanced or MBC	Talazoparib 1mg orally daily	ORR assessed by blinded independent radiology facility (IRF)	Until disease progression/death or unacceptable toxicity	84	<u>Cohort 1:</u> Patients with a documented CR or PR to a prior platinum-containing regimen for metastatic disease <u>Cohort 2:</u> Patients who received more than 2 prior cytotoxic chemotherapy regimens for metastatic disease and no prior platinum therapy for metastatic disease.	34 centers in 5 countries
C3441007	NCT01286987	First-in-human, single-arm, study of talazoparib in patients with advanced or recurrent solid tumors	Talazoparib 0.025-1.1mg orally daily	Part 1: Maximum tolerated dose (MTD)	Until disease progression/death or unacceptable toxicity	77 received 1 mg daily	Patients with advanced or recurrent solid tumors	6 centers in 2 countries

7.2. Review Strategy

Dr. Suparna Wedam conducted the clinical review and Dr. Stella Karuri conducted the statistical review. The clinical and statistical review was primarily based on results from the EMBRACA Study.

The clinical and statistical review included the following:

1. Literature review of gBRCAm metastatic breast cancer.
2. Research of the FDA data base for regulatory history of the talazoparib IND 108,708 and review of meeting minutes conducted during drug development.
3. Review of applicant submitted CSR, protocol, protocol amendments, and selected datasets for the EMBRACA Study.
4. Review of selected case report forms (CRFs) for the EMBRACA Study.
5. Review of selected patient narratives for serious adverse events and deaths in the EMBRACA Study.
6. Review of the Clinical Outcomes Assessment (COA) data submitted for the EMBRACA study.
7. Review of response to clinical and biostatistical queries sent to applicant.
8. Review of consultation reports from the Office of Scientific Investigations.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. EMBRACA

Trial Design

The EMBRACA study (NCT01945775) was a phase 3, open-label, randomized, multi-center trial of talazoparib versus physician's choice of therapy (PCT: capecitabine, vinorelbine, gemcitabine or eribulin) designed to assess the efficacy and safety of single agent talazoparib in patients with gBRCAm who received no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic breast cancer. Patients were required to have documentation of a deleterious, suspected deleterious or pathogenic germline BRCA1 or BRCA2 mutation from Myriad Genetics or another laboratory approved by the applicant. Patients were randomized at 145 centers across 16 countries, including the United States.

Patients with first-line locally advanced or MBC with no prior adjuvant chemotherapy could only be enrolled if they would otherwise receive 1 of the 4 protocol-specified PCT. PCT was

determined prior to randomization for each individual patient.

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

- Talazoparib capsule 1mg orally QD continuous dosing

OR a physician's choice of one of the following chemotherapy regimens:

- Oral capecitabine 1250 mg/m² twice daily for 14 days, repeated every 21 days
- Intravenous (IV) eribulin mesylate 1.4 mg/m² (equivalent to 1.23 mg/m²) on Day 1 and Day 8, repeated every 21 days
- IV gemcitabine 1250mg/m² on Day 1 and Day 8, repeated every 21 days
- IV vinorelbine 30 mg/m² on Day 1 and Day 8, repeated every 21 days

Reviewer Comment: The selected doses appear appropriate. The talazoparib dosage is the dose selected from the phase 1 study. The doses for capecitabine and eribulin are the FDA-approved doses for advanced/metastatic breast cancer. Gemcitabine is FDA approved at the selected dose in combination with paclitaxel for MBC; however, single agent gemcitabine at the selected dose is listed as a treatment option in the NCCN Breast Cancer guidelines. Vinorelbine is not FDA-approved for use in breast cancer; however, single agent vinorelbine at the dose selected is often used in clinical practice and is listed as a treatment option in the NCCN Breast Cancer guidelines. During an End of Phase 2 (EOP2) Meeting (April 12, 2013), the choice of control arm agents for this phase 3 study was discussed and agreed by the agency.

Patients continued treatment until radiological disease progression as determined by the Independent Radiology Facility (IRF) also called blinded independent central review or BICR, occurrence of unacceptable toxicity, subject or physician decision to stop treatment or until the study is terminated by the Sponsor.

Baseline radiological tumor assessments were performed no more than 28 days before the start of treatment. Tumor assessments were performed by CT or MRI. All patients also had nuclear medicine whole body bone scans within 12 weeks before randomization. After randomization, CT/MRI was performed at the end of every 6 weeks (± 7 days) for the first 30 weeks and then every 9 weeks (± 7 days) thereafter, up to objective disease progression. If bone metastases were seen at baseline, bone scans were repeated every 12 weeks (± 7 days) until radiographic disease progression as determined by the IRF or initiation of a new antineoplastic therapy and as clinically indicated. In patients without baseline bone lesions, bone scans were repeated only as clinically indicated. Tumor assessments were allowed as clinically indicated anytime during the study, and at the time of clinical suspicion of disease progression.

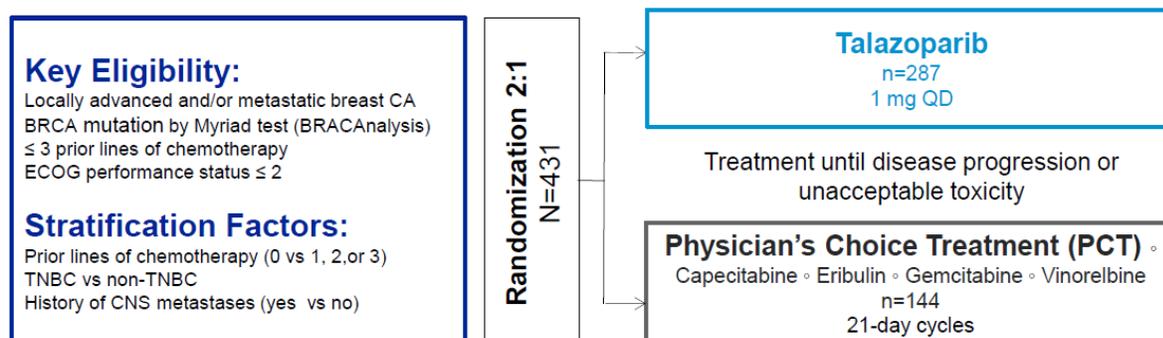
Randomization was stratified by:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0 vs. 1, 2, or 3)

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

- Triple negative (estrogen-receptor negative, progesterone-receptor negative, HER2-negative) vs. non-triple negative breast cancer based on most recent biopsy
- History of central nervous system (CNS) metastases vs. no CNS metastases

Figure 3: EMBRACA Study Design



Source: Talazoparib Applicant Orientation Meeting slide deck

Key Eligibility Criteria:

Inclusion Criteria:

- Histologically or cytologically confirmed carcinoma of the breast
- Locally advanced breast cancer that is not amenable to curative radiation or surgical cure and/or metastatic disease appropriate for systemic single cytotoxic chemotherapy
- Documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation
- No more than 3 prior chemotherapy-inclusive regimens for locally advanced and/or metastatic disease (no limit on prior hormonal therapies or targeted anticancer therapies such as mechanistic target of rapamycin [mTOR] or CDK4/6 inhibitors, immuno-oncology agents, tyrosine kinase inhibitors, or monoclonal antibodies against CTL4 or VEGF)
- Prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated
- 18 years of age or older
- Measurable or non-measurable, evaluable disease by RECIST v.1.1
- ECOG performance status ≤ 2
- Adequate organ function as defined below:
 - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN); if liver function abnormalities are due to hepatic metastasis, then AST and ALT ≤ 5 × ULN
 - Total serum bilirubin ≤ 1.5 × ULN (≤ 3 × ULN for Gilbert's syndrome)
 - Calculated creatinine clearance ≥ 30 mL/min by local laboratory or Cockcroft-Gault formula
 - Hemoglobin ≥ 9.0 g/dL with last transfusion at least 14 days before randomization

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

- Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$
- Platelet count $\geq 100,000/\text{mm}^3$
- Able to take oral medications
- Willing and able to provide written, signed informed consent after the nature of the study has been explained, and prior to any research-related procedures
- A female of childbearing potential must not be pregnant and must agree to avoid pregnancy during the study by using a highly effective birth control method from the time of the first dose of study drug through 45 days after the last dose of study drug
- Male subjects must use a condom when having sex with a pregnant woman and when having sex with a woman of childbearing potential from the time of the first dose of study drug through 105 days after the last dose of study drug. Contraception should be considered for a non-pregnant female partner of childbearing potential
- Male and female subjects must agree not to donate sperm or eggs, respectively, from the first dose of study drug through 105 days and 45 days after the last dose of study drug, respectively
- Willing and able to comply with all study procedures

Exclusion Criteria:

- First-line locally advanced and/or metastatic breast cancer with no prior adjuvant chemotherapy unless the Investigator determines that one of the 4 cytotoxic chemotherapy agents in the control arm would be otherwise offered to the subject
- Prior treatment with a PARP inhibitor (not including iniparib)
- Not a candidate for treatment with at least 1 of the treatments of protocol-specific physician's choice (ie, capecitabine, eribulin, gemcitabine, vinorelbine)
- Subjects who had objective disease progression while receiving platinum chemotherapy administered for locally advanced or metastatic disease; subjects who received low-dose platinum therapy administered in combination with radiation therapy are not excluded
- Subjects who have received platinum in the adjuvant or neoadjuvant setting are eligible; however, subjects may not have relapsed within 6 months of the last dose of prior platinum therapy
- Cytotoxic chemotherapy within 14 days before randomization
- Radiation or anti-hormonal therapy or other targeted anticancer therapy within 14 days before randomization
- Has not recovered from the acute toxicities of previous therapy, except treatment related alopecia or laboratory abnormalities otherwise meeting the inclusion requirements stated in the inclusion criteria
- HER2 positive breast cancer
- Active inflammatory breast cancer
- CNS metastases
 - Exception: Adequately treated brain metastases documented by baseline CT or MRI scan that has not progressed since previous scans and that does not require corticosteroids (except prednisone ≤ 5 mg/day or equivalent) for management of

- CNS symptoms. A repeat CT or MRI following the identification of CNS metastases (obtained at least 2 weeks after definitive therapy) must document adequately treated brain metastases
- Subjects with leptomeningeal carcinomatosis are not permitted
 - Prior malignancy except for any of the following:
 - Prior BRCA-associated cancer as long as there is no current evidence of the prior cancer
 - Carcinoma in situ or non-melanoma skin cancer
 - A cancer diagnosed and definitively treated ≥ 5 years before randomization with no subsequent evidence of recurrence
 - Known to be human immunodeficiency virus positive
 - Known active hepatitis C virus, or known active hepatitis B virus
 - Use of any IP or investigational medical device within 14 days before randomization
 - Major surgery within 14 days before randomization
 - Myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (New York Heart Association [NYHA] > class II), unstable angina, or unstable cardiac arrhythmia requiring medication
 - Female subjects who are breastfeeding at Screening or planning to become pregnant at any time during study participation through 45 days after the last dose of study drug; male subjects planning to impregnate a partner at any time during study participation through 105 days after the last dose of study drug
 - Concurrent disease or condition that would interfere with study participation or safety, such as any of the following:
 - Active, clinically significant infection either grade > 2 by National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) v4.03 or requiring the use of parenteral anti-microbial agents within 14 days before randomization
 - Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders
 - Non-healing wound, ulcer, or bone fracture, not including a pathological bone fracture caused by a pre-existent pathological bone lesion
 - Known hypersensitivity to any of the components of talazoparib

Reviewer Comment: Amendment 1 to the protocol waived the requirement for prior anthracycline/taxane if use was medically contraindicated; and allowed patients to be enrolled for first line treatment of advanced/metastatic breast cancer (without prior adjuvant chemotherapy) if the Investigator determined that one of the 4 cytotoxic chemotherapy agents in the control arm would be otherwise offered to the subject. Prior therapy with hormonal therapy was not required for patients with HR-positive disease.

Dose modifications:

Chemotherapy:

Reference was made to the local package inserts for information on dosing and management of

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

toxicity of capecitabine, vinorelbine, gemcitabine, and eribulin.

Talazoparib:

Daily dosing of talazoparib can be interrupted for recovery from toxicity for up to 28 days. For interruptions longer than 28 days, treatment at the same or a reduced dose can be considered based on a discussion between the Sponsor or designee and Investigator if evidence of response or clinical benefit to talazoparib is noted.

Dose Modifications Based on Hematologic or Nonhematologic Toxicities are shown in the following table:

Toxicity	Recommended Dose Modification
Liver test abnormalities	Refer to the liver safety test monitoring and assessment rules in Section 9.4.7.3 . Dose interruption and/or dose reduction may be required for Grade 2 AST or ALT values, depending on the liver test values at Screening.

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Toxicity	Recommended Dose Modification
Grade 1 or 2 toxicity (other than liver test abnormalities)	No requirement for dose interruption or dose reduction. If the toxicity persists at Grade 2 (for ≥ 7 days), a dose reduction to the next lower dose level (eg, from 1.0 mg/day to 0.75 mg/day) may be implemented at the discretion of the Investigator.
Grade 3 nonhematologic toxicity (other than liver test abnormalities)	Daily dosing must be held for Grade 3 AEs considered related to talazoparib. Supportive care should be implemented as appropriate (eg, anti-emetics, anti-diarrheal agents). Talazoparib dosing may resume at the next lower dose level (eg, from 1.0 mg/day to 0.75 mg/day, 0.75 mg/day to 0.5 mg/day to 0.25 mg/day) when toxicity resolves to Grade 1 or returns to baseline.
Grade 3 hematologic toxicity	Daily dosing must be held for Grade 3 laboratory abnormalities known to be associated with talazoparib per the current IB. Supportive care should be implemented as appropriate (eg, growth factor support, blood products). Talazoparib dosing may resume at the next lower dose level when toxicity resolves to Grade 1 or would meet the eligibility criteria (Section 9.3).
Grade 4 nonhematologic toxicity (other than liver test abnormalities)	Daily dosing must be held for Grade 4 AEs (regardless of relationship to talazoparib). Supportive care should be implemented as appropriate (eg, anti-emetics, anti-diarrheal agents). Talazoparib may resume at a lower dose level (1-2 dose level decrease) when toxicity resolves to Grade 1 or returns to baseline.
Grade 4 hematologic toxicity	Daily dosing must be held for Grade 4 laboratory abnormalities (regardless of relationship to talazoparib). Supportive care should be implemented as appropriate (eg, growth factor support, blood products). Talazoparib may resume but must be at a lower dose level when toxicity resolves to Grade 1 or would meet the eligibility criteria (Section 9.3); this should be a 1-2 dose level decrease per Investigator discretion.

Source: EMRACA protocol page 127

Dose Modifications for Talazoparib:

	Dose Level
Initial dose level	1.0 mg/day
First dose level reduction	0.75 mg/day
Second dose level reduction	0.5 mg/day
Third dose level reduction	0.25 mg/day

Source: EMRACA protocol page 128

Dose modification guidelines were also provided for temporary and permanent discontinuation

in the setting of suspected drug induced liver injury (DILI) in either treatment arm.

Concomitant Medications:

Supportive medications may be provided prophylactically or therapeutically at the Investigator's discretion, with the exception that granulocyte-colony stimulating factor (G-CSF) is only allowed in the rescue setting. Bisphosphonates and the monoclonal antibody denosumab permitted for treatment, or prophylaxis, of bone metastases as per local standards of care.

Guidelines for concomitant use of talazoparib with inhibitors or inducers of P-glycoprotein (P-gp) or inhibitors of breast cancer resistance protein (BCRP) are as follows

- Use of strong P-gp inhibitors, P-gp inducers, or BCRP inhibitors should be avoided
- Caution should be used for coadministration of other P-gp inhibitors, P-gp inducers, or BCRP inhibitors

External beam radiotherapy was allowed, following consultation with the medical monitor.

Subjects were not allowed to receive any other systemic anticancer therapies while on study prior to radiographic disease progression as determined by the IRF.

A subject could be referred for surgery of a metastatic lesion(s), when considered to be in the best interest of the subject. The subject could continue study if the subject was receiving clinical benefit from the study drug per Investigator discretion. If the target lesions were removed, the subject was to be excluded from the measurable disease population.

Discontinuation rules:

- Serious or intolerable AE or clinically significant laboratory abnormality
- Subject requires medication or medical procedure prohibited by the protocol
- Subject does not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or does not meet entry criteria
- Subject is lost to follow-up
- Subject becomes pregnant
- Subjects may be removed from study if considered by the Investigator or Sponsor to be in the best interest of the subject

Study Endpoints:

The primary endpoint of the EMBRACA study was progression-free survival (PFS) as assessed by IRF. PFS was defined as time from randomization until the date of radiologic progressive disease per RECIST v.1.1 with modifications as determined by the central IRF or death from any cause, whichever comes first. Modifications included criteria regarding progression by bone metastasis for patients enrolled with bone only lesions. Another modification was a requirement for progression by imaging (omitting progression by digital photography or physical examination for superficial lesions). Modifications to RECIST 1.1 used for assessment are shown in Table 16.

Table 16: Modifications to RECIST 1.1 criteria

Original element of RECIST 1.1	Modifications	Rationale
(Bone scans) can be used to confirm the presence or disappearance of bone lesions... the finding of a new lesion should be unequivocal... (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions).	Progression based on new bone scan lesions should be confirmed using CT or MRI whenever possible. If bone lesions are confirmed on later CT or MRI scan, progression should be assigned to the visit in which new lesion(s) were first seen on bone scan (in a manner similar to other equivocal new lesions). In the absence of structural confirmation (CT/MRI), the pattern of lesions on the bone scan must clearly indicate metastasis, usually with at least 2 new lesions present.	The population consists of metastatic subjects who have had prior treatment and includes enrollment of subjects whose disease is limited to bone metastases. Caution must be used when determining progression based on new bone scan lesions, particularly since a flare reaction can cause a lesion appear new that was previously too subtle to be seen.
Progressive Disease of Non-target lesions: Unequivocal progression of existing non-target lesions.	Worsening of bone metastasis seen on bone scan alone, in the best judgment of the reader, must be such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.	Modification has been established because of the difficulty in interpreting the significance of changes in bone metastases in the possible presence of the flare phenomenon.
"Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more	Documentation of superficial lesions by photography and physical examination will not be included in the response assessment.	Due to the superiority of anatomical imaging in assessing tumor burden, physical examination will not be considered for documentation of progression (or response) within the context of the central review. For similar reasons and compounded by the operational difficulty in obtaining consistent data, photographs will also not be
Original element of RECIST 1.1	Modifications	Rationale
objective and may also be reviewed at the end of the study."		included in the review.

Source: EMRACA Independent Efficacy Review Charter, pp 27-28

Secondary efficacy endpoints include overall response rate (ORR) and overall survival (OS). ORR was determined by the IRF and defined as the proportion of patients with a partial or complete response as defined by RECIST v.1.1 with modifications in the ITT with measurable disease population. Confirmation of response by subsequent tumor assessment (at least 4 weeks) was not required. OS was defined as the time from randomization to death due to any cause.

Exploratory endpoints included:

- Quality of life assessment using EORTC QLQ-C30 and EORTC QLQ-BR23
- Duration of response (DOR)

Reviewer Comment: RECIST CR, PR and SD were not adjudicated by IRF; confirmed ORR by IRF was therefore not available. Following an IR dated 05/23/2018, the sponsor provided data on confirmed investigator assessed ORR (confirmation at least 4 weeks following initial CR/PR response).

Diagnostic Assay:

All patients were required to have documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation from Myriad Genetics or other laboratory approved by the Sponsor; for data obtained regarding a BRCA1/2 mutation from a non-Myriad laboratory, the pathology report was submitted to and approved by the Sponsor and a blood sample was sent to Myriad for analysis before randomization.

Reviewer Comment: The applicant chose Myriad Genetics as a partner in developing a companion diagnostic for BRCA1 and BRCA2 testing for use with talazoparib treatment. Further discussion regarding the companion diagnostic is included in Section 4.4.

Safety analyses:

On-study safety assessments for the EMBRACA study are shown in Table 17.

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Table 17: Schedule of Safety Assessments

Study Visit or Cycle	Screening/ Baseline ^a		Cycles 1 and 2 ^b			Cycles ≥ 3 ^b			Every 6 Weeks	Every 9 Weeks	Unsch ^d	End of Trt ^e	LT FU ^f
	Day -28 to -1	Day -7 to -1	Day 1	Day 8	Day 15	Day 1	Day 8 ^c	Day 15 ^c	Wks 6, 12, 18, 24, 30	Wks 39+	Varies	30 days postdose(-3 to +10)	q60 days; q90 days
Window (Days)	na	na		± 3	± 3		± 3	± 3	± 7	± 7	na	-3 to +10	± 7; ± 14
Informed consent ^g	X												
Medical history ^h	X												
Vital signs ⁱ	X	X	X	X	X	X					[X]	X	
Physical examination ^j	X	X	X			X					[X]	X	
ECOG performance status	X		X			X						X	
Tumor assessment ^k	X								X	X	[X]	X	
Tumor markers ^l	[X]								[X]	[X]		[X]	
Brain CT or MRI ^m	X								[X]	[X]	[X]		
Bone scan ⁿ	X								q12 wks	q12 wks	[X]		
PK blood sampling ^o			X			X					[X]		
Clinical laboratory tests ^p													
Hematology	X	X	X	X	X	X	[X]	[X]			[X]	X	
Serum chemistry	X	X	X			X					[X]	X	
Coagulation/urinalysis		X											
Creatinine clearance	X												
Serum pregnancy test ^q	X		[X]			[X]					[X]	[X]	
Urine pregnancy test ^r			X			X					[X]	X	
Quality of life ^s		X	X			X						X	
Adverse events ^t	X	X	X	X	X	X	[X]	[X]			X	X	
12 lead ECG ^u		X									[X]	X	
Concomitant medications ^v	X	X	X	X	X	X	[X]	[X]			X	X	
Patient contact: LT FU													X
Talazoparib treatment ^w						Once –daily dosing							
Chemotherapy treatment ^w			X	[X]	[X]	X	[X]	[X]					
BRCA1/2 mutations ^x	X												
Germline BRCA assay ^y	X												
Genomic analysis ^z	X											[X]	
Tumor tissue collection ^{aa}	X												

Multi-disciplinary Review and Evaluation NDA 211651 TALZENNA (Talazoparib)

Study Visit or Cycle	Screening/ Baseline ^a		Cycles 1 and 2 ^b			Cycles ≥ 3 ^b			Every 6 Weeks	Every 9 Weeks	Unsch ^d	End of Trt ^e	LT FU ^f
	Day -28 to -1	Day -7 to -1	Day 1	Day 8	Day 15	Day 1	Day 8 ^g	Day 15 ^g	Wks 6, 12, 18, 24, 30	Wks 39+	Varies	30 days postdose(-3 to +10)	q60 days; q90 days
Window (Days)	na	na		± 3	± 3		± 3	± 3	± 7	± 7	na	-3 to +10	± 7; ± 14
Optional tumor biopsy ^{bb}		[X]										[X]	

Source: 673-301 protocol (Appendix 16.1.1)

[X]Optional

Note: All assessments were performed before dosing except as indicated.

AE=adverse event; aPTT=activated partial thromboplastin time; BRCA=breast cancer susceptibility gene; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30/QLQ-BR23=European Organization for Research and Treatment of Cancer Quality of Life Cancer Questionnaire/Breast Cancer Module; FFPE=Formalin fixed paraffin-embedded; INR=international normalized ratio; LT FU=long-term follow-up; MRI=magnetic resonance imaging; na=not applicable; PK=pharmacokinetic(s); PT=prothrombin time; q=every; SAE=serious adverse event; Trt=treatment; Unsch=unscheduled; Wks=weeks.

a. Screening occurred within 28 days and baseline within 7 days before randomization. Screening and baseline procedures could be performed on the same day within 7 days before randomization. Physical examination, vital signs, and clinical laboratory assessments did not need to be repeated at baseline if screening was within 7 days before randomization. First dose of study drug occurred within 5 days of randomization.

b. The first day of treatment in Cycle 1 was considered study Day 1. Each cycle was 21 days long.

c. Could be omitted in Cycles ≥3 if no significant toxicities were reported. Patients receiving talazoparib or capecitabine were not required to take study drug at the clinic if the visit was optional.

d. Anytime necessary to assess or follow up AEs, to perform scans, at patient or investigator request. Imaging could be performed for patients who were symptomatic or for determination of radiographic disease progression. PK assessments were obtained as appropriate for patients assigned to talazoparib.

e. Could occur 27 to 40 days after the last dose of study drug. Tumor assessments were required if not performed in the previous 28 days.

f. Follow-up for survival, cause of death, and additional cancer treatment every 60 days (± 7 days) after last dose for 1 year, every 90 days (± 14 days) thereafter, or when requested by the Sponsor.

g. Required before any protocol specified procedures or assessments were performed. Consent for BRCA1/2 testing only could be obtained at any time (including prior to screening).

h. Includes full cancer history, prior treatments, and demographics.

i. Systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature at scheduled time points; weight at screening, baseline, predose on Day 1 of each cycle, and end of treatment; height at screening only.

j. Complete exam at screening and baseline; subsequent examinations were at the discretion of the investigator based on the patient's clinical condition.

k. CT (preferred), MRI, or X-ray. CT/MRI scans performed before signed informed consent and within the 28-day screening period could be used for screening if completed per study specific requirements. Tumor assessments occurred as clinically indicated anytime during the study and at the time of clinical suspicion of disease progression. Clinical disease progression was verified by radiographic imaging as determined by independent central review. Tumor assessments continued for patients who discontinued study drug for reasons other than radiographic disease progression or initiation of a new antineoplastic therapy. Postbaseline assessments were to be performed using the same technique used at screening/baseline.

l. Optional tumor marker assessments (CA 15.3, CA 27.29) were not repeated if normal at baseline.

m. Newly diagnosed CNS metastases at screening/baseline made a patient ineligible until such time as it could be adequately treated, at which point the patient could be rescanned. Postbaseline assessments were to be performed using the same technique used at screening/baseline. If adequately treated metastatic disease to the brain was

present at screening/baseline, an MRI/CT scan was performed during the study as clinically indicated.

n. Bone scan obtained up to 12 weeks before randomization could be used as screening/baseline assessment. If metastatic bone disease was present at screening/baseline, a bone scan was performed every 12 weeks and as clinically indicated. Postbaseline assessments were to be performed using the same technique used at screening/baseline.

o. Blood was collected on Day 1 of Cycles 1 through 4 for patients randomly assigned to talazoparib. Predose samples were collected ≤60 minutes before dosing and whether or not the patient had eaten within 2 hours before dosing was recorded. Postdose samples were collected ≥30 minutes after dosing and at least 2 hours apart. If a dose was skipped on Day 1 of Cycles 1 through 4, the PK samples were collected on the day the patient resumed talazoparib.

p. Hematology: weekly blood counts for the first 2 Cycles; for Cycle 3 and thereafter, blood counts were obtained on Day 1 of each cycle and Day 8 or Day 15. Not required on Days 8 or 15 if performed at a local laboratory and provided to the investigator for evaluation 24 hours before dosing. Hematology assessments could be performed within 72 hours before dosing and were to be evaluated for abnormalities before dosing. Serum chemistry could be performed within 72 hours prior to dosing.

Coagulation: aPTT and PT/INR were assessed only at baseline. Urinalysis: microscopy required if dipstick results for blood and leukocyte esterase were positive. Calculated creatinine clearance used local laboratory results or was calculated by Cockcroft-Gault formula.

q. For women of child-bearing potential only. Local urine or serum (as per local regulations/practice) pregnancy test performed at Day 1 of each cycle; if a urine pregnancy test was positive, study drug must be interrupted and a serum pregnancy test performed.

r. EORTC QLQ-C30/EORTC QLQ-BR23 questionnaire.

s. AEs were recorded after the first dose of study drug until 30 days after the last dose of study drug or before initiation of a new antineoplastic therapy, whichever occurred first. SAEs associated with protocol-imposed interventions were recorded after written informed consent and before initiation of study drug. SAEs assessed as related to study drug after the end of treatment visit were recorded. AEs and pregnancies ongoing at the end of treatment were followed up until resolution or until considered stable by the investigator. Patients who did not visit the clinic on Days 8 or 15 of Cycle ≥3 were assessed for AEs by phone.

t. Performed at end of treatment if clinically indicated

u. Recorded all concomitant medications or therapies, including herbal supplements, taken from 28 days before randomization to 30 days after the last dose. Patients who did not visit the clinic on Days 8 or 15 of cycle ≥3 were contacted for evaluation by phone.

v. Administered once daily by mouth in repeated 21-day cycles. Administered at the clinic on selected clinic visit days.

w. Physician's choice chemotherapy administered as described in Section 9.4.1.2.

x. Documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation could be provided for enrollment based on a prior analysis if the pathology laboratory was preapproved by the Sponsor.

y. A blood sample was collected at any time during screening/baseline for patients with prior documentation of BRCA carrier status. For patients without prior documentation, a blood sample was collected as early as possible during the screening period.

z. Blood sample for disease-related research, including but not limited to genomic analysis. Collected any time during screening/baseline and at radiographic disease progression (+ 35 days).

aa. Archival FFPE tumor tissue slides; tumor blocks could be submitted with Sponsor approval. Randomization could occur without tumor tissue samples.

bb. Performed only if consent was provided. Collected anytime during screening/baseline and at radiographic disease progression (+ 35 days) or at the time of study drug discontinuation.

Source: EMBRACA CSR pages 38-40

Statistical Analysis Plan

Sample Size Consideration

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

The study was sized to detect a PFS hazard ratio (HR) of 0.67 with 90% power using a log-rank test with alpha (two-sided) equal to 0.05. Assuming an exponential distribution, the targeted HR corresponded to an increase in median PFS of 2.3 months (6.9 months versus 4.6 months). Up to 429 patients were to be randomized at a ratio of 2:1 to the talazoparib and PCT arms and a total of 288 PFS events were needed for the PFS analysis.

The study was also powered for OS. At a two-sided 0.05 significance level, approximately 321 death events would have 80% power to detect a HR of 0.72. Under an exponential model assumption, this corresponded to an increase in median OS from 20 months in the PCT arm to 27.8 months in the talazoparib arm.

Analysis Populations

Intent-to-treat population (ITT): The efficacy population was defined as the ITT population consisting of all randomized patients. Patients were to be grouped per the treatment assigned at randomization.

ITT with measurable disease population: The ITT with measurable disease analysis population was defined as all patients in the ITT population who have at least 1 target lesion identified at baseline.

Safety population: The safety population was defined as all randomized patients who receive at least 1 dose or partial dose of study drug (talazoparib or PCT). Unless otherwise specified, all safety analyses used the safety population per the actual treatment received (not the treatment assigned).

Patient reported outcome (PRO) evaluable population: The PRO-Evaluable population was defined as all patients who have completed the PRO questionnaire at baseline and at least one visit post baseline.

Efficacy Analysis Methods

The primary analysis was event driven and was timed to occur with 288 PFS events (by IRF) in the ITT population. The primary method of analysis was a stratified log-rank test, with stratification factors equal to the IVRS/IWRS stratification factors:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0 vs 1, 2, or 3)
- Triple-negative (estrogen-receptor negative, progesterone-receptor negative, human epidermal growth factor receptor 2 [HER2]-negative) vs non triple-negative receptor status based on most recent biopsy
- History of central nervous system (CNS) metastasis vs no CNS metastasis

The hazard ratio with a two-sided 95% confidence interval was to be derived from a stratified Cox proportional hazards model with the same three stratification factors used in the stratified

log-rank test.

The censoring rules used in the primary PFS analysis are shown in Table 18.

Table 18: Censoring rules for PFS Analysis

Censoring Categories	Date of Censoring
Patients who did not have baseline or post baseline tumor assessments and did not die on or before the data cutoff date	Randomization date
Patients who did not have radiographic progression as determined by IRF and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before the data cutoff date
Patients who did not have radiographic progression as determined by IRF on or before initiation of a new antineoplastic therapy and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before initiation of a new antineoplastic therapy and on or before the data cutoff date
Patients who had 2 or more consecutive missed scheduled tumor assessments immediately prior to disease progression	Date of the last adequate tumor assessment without evidence of disease progression before the 2 missed tumor assessments and on or before the data cutoff date
Patients who had the first radiographic progression as determined by IRF after the date of study drug discontinuation + 30 days and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before the date of study drug discontinuation + 30 days and on or before the data cutoff date

Source: EMBRACA SAP version 4

If PFS results reached statistical significance, formal hypothesis tests for OS would be performed via a stratified log-rank test with stratification factors equal to the randomization stratification factors.

Interim Analyses

No interim analysis was planned for PFS. One interim analysis of OS was to be performed at the time of the PFS analysis at a 0.0001 significance level using Haybittle-Peto boundary if PFS is statistically significant, with approximately 160 deaths. At the interim OS analysis, OS data would be summarized descriptively with the HR and its 95% CI and no formal hypothesis testing was to be performed. The final analysis of OS would be conducted with the occurrence of approximately 321 death events at a 2-sided 0.0499 significance level.

Reviewer’s comments: No other multiplicity adjustments were planned for other secondary endpoints apart from OS. The Haybittle-Peto boundaries are more conservative than the O’Brien Fleming type boundaries.

Date of initial study protocol was July 17, 2013. The applicant submitted 1 protocol amendment and 4 administrative letters to the EMBRACA study. Key changes from the amendment are

summarized below:

Amendment 1 (December 14, 2015; Amendment 1 was finalized after 184 patients had been randomized):

- Change the Sponsor from BioMarin Pharmaceuticals, Inc. to Medivation, Inc. and update all contact information accordingly
- Increases allowed number of prior cytotoxic regimens from 2 to 3
- Adjusts the prior platinum use restrictions to permit enrollment if a subject had at least 6 months (previously 12 months) of stable disease following the last dose of platinum in the neoadjuvant/adjuvant setting; in addition, only subjects who had a documented disease progression to prior platinum therapy administered in the locally advanced/metastatic setting are excluded
- Waive the requirement for prior anthracycline/taxane if use was medically contraindicated
- Allow de novo stage IV disease if the treatment plan involves a protocol-specified physician's choice agent
- Allow an ECOG performance status score of 2
- Add liver safety monitoring guidelines for both treatment arms
- Update the dose modification guidelines taking into consideration the type of toxicity
- Update randomization stratum for number of prior cytotoxic regimens for advanced breast cancer from zero versus 1 or 2 to zero versus 1, 2, or 3 for consistency with updated inclusion criterion
- Clarify that the most recent biopsy data will be used to determine whether the patient had triple negative breast cancer or hormone receptor positive breast cancer for stratification purposes
- The protocol was revised to permit flexibility in the estimated sample size. No change was made to the underlying statistical assumptions (the estimated Hazard Ratio for median PFS remains 0.67; control arm and experimental arm estimates for median progression-free survival (PFS) remain 20 and 30 weeks; the required number of PFS events remains 288)
- Remove the specific methodologies to be used for the interim overall survival (OS) analysis; clarifies that the multiplicity adjustment procedure and the timing/conduct of the OS analyses to be described in the Statistical Analysis Plan

SAP Amendments

There were four versions of the SAP; the initial version of the SAP is dated February 28, 2013. The agency provided feedback to this SAP in a meeting on December 4th, 2013 (IND108708). Details of the major changes to the four versions of the SAP are given below:

1. Version 1 dated February 28, 2013: The primary endpoint was PFS (IRF assessed) and the secondary endpoints were OS and ORR. Imaging was to be performed every 8 weeks until 48 weeks, then every 12 weeks thereafter. Three-hundred seventy patients were

to be randomized 2:1 into the two arms (Physician's choice: eribulin, gemcitabine, vinorelbine, capecitabine, ixabepilone). The target number of PFS events for primary efficacy analysis was 256 and the target PFS HR was 0.67. No target HR for OS was specified. No multiplicity adjustments were defined for OS and ORR.

2. Version 2 dated November 7, 2016: The primary endpoint was PFS (IRF assessed) and the secondary endpoints were OS and ORR. Imaging was to be performed every 6 weeks from the date of randomization for the first 30 weeks, and every 9 weeks thereafter. Up to 429 patients were to be randomized 2:1 (talazoparib:PCT) with PCT therapies: capecitabine, eribulin, gemcitabine, or vinorelbine. The target number of PFS events for primary efficacy analysis was 288 and the target PFS HR was 0.67. Testing the secondary endpoints would not be performed if the PFS results were not significant. Following a win on PFS, ORR would be tested with a stratified Cochran-Mantel-Haenszel test at a 0.01 significance level. An interim OS analysis would also be performed with alpha at 0.0001, followed by a final OS analysis with the occurrence of 321 deaths. If ORR results were not significant then the interim and final analyses for OS would be performed with interim and overall alpha at 0.0001 and 0.04 respectively. If OS results were significant then ORR would be tested using a stratified Cochran-Mantel-Haenszel test at a 0.01 significance level.
3. Version 3 dated July 1, 2017: The PRO population was defined as given in the final version. The analysis plan for primary and key secondary endpoints would proceed as outlined in Version 2.
4. Version 4 dated September 1, 2017: This is the final analysis plan. Multiplicity adjustments for ORR were removed to allow for an alpha of 0.0499 for the final OS analysis.

Reviewer's comments: There were no major changes to the primary efficacy endpoints and analysis prior to data cut-off that would compromise the integrity of the trial.

8.1.2. Study Results

Compliance with Good Clinical Practices

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

Financial Disclosure

Talazoparib (and each of its' ongoing clinical trials) was sold to Medivation Inc., with the

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

transaction closing on October 5, 2015. Subsequently, Medivation Inc. was acquired by Pfizer on September 28, 2016 (with Medivation becoming a subsidiary of Pfizer from Q4-2016 to the time of this NDA submission). The financial disclosures provided are for both Pfizer, inclusive of the 1 year under Medivation, and BioMarin.

All investigators were assessed for each of the two financial disclosure sponsors for equity interest, significant payments of other sorts, other compensation by the sponsor and propriety interest. Financial disclosure information is provided for covered studies C3441008 (ABRAZO), C3441009 (EMBRACA), and C3441007 (phase 1 FIH study).

There was no financial information to disclose in 2,266 of the 2,341 clinical investigators (96.8%) who participated in the covered studies. Due Diligence activities were required for 53 of 2,341 (2.3%) clinical investigators. 22 of the 2,341 clinical investigators listed in the study report had financial information to disclose, which represents 0.9% of the total number of all clinical investigators (this included 16 unique clinical investigators that reached at least one disclosure threshold).

Twelve of the investigators from the EMBRACA study had financial information to disclose and are summarized in Table 19.

Table 19: Summary of Financial Disclosures for the EMBRACA study

Clinical Site Number	Investigator Name (PI or SI)	EMBRACA Patient Enrollment at Site	Disclosure
(b) (6)	(b) (6)	3	Research and Development: \$333,796.50
		3	Research and Development: \$198,458.00
		8	Speaker Honorarium: \$42,035.00
		4	Speaker Honorarium: \$27,250.00
		1	Speaker Honorarium: \$26,432.00
		3	Speaker Honorarium: \$25,800.00
		6	Speaker Honorarium and Consultant: \$34,910.01
		3	Speaker Honorarium and Consultant: \$67,183.75
		1	Speaker Honorarium: \$25,643.00
		3	Speaker Honorarium and Consultant: \$34,817.03
		5	Speaker Honorarium: \$31,575.00
		6	Speaker Honorarium: \$35,979.75

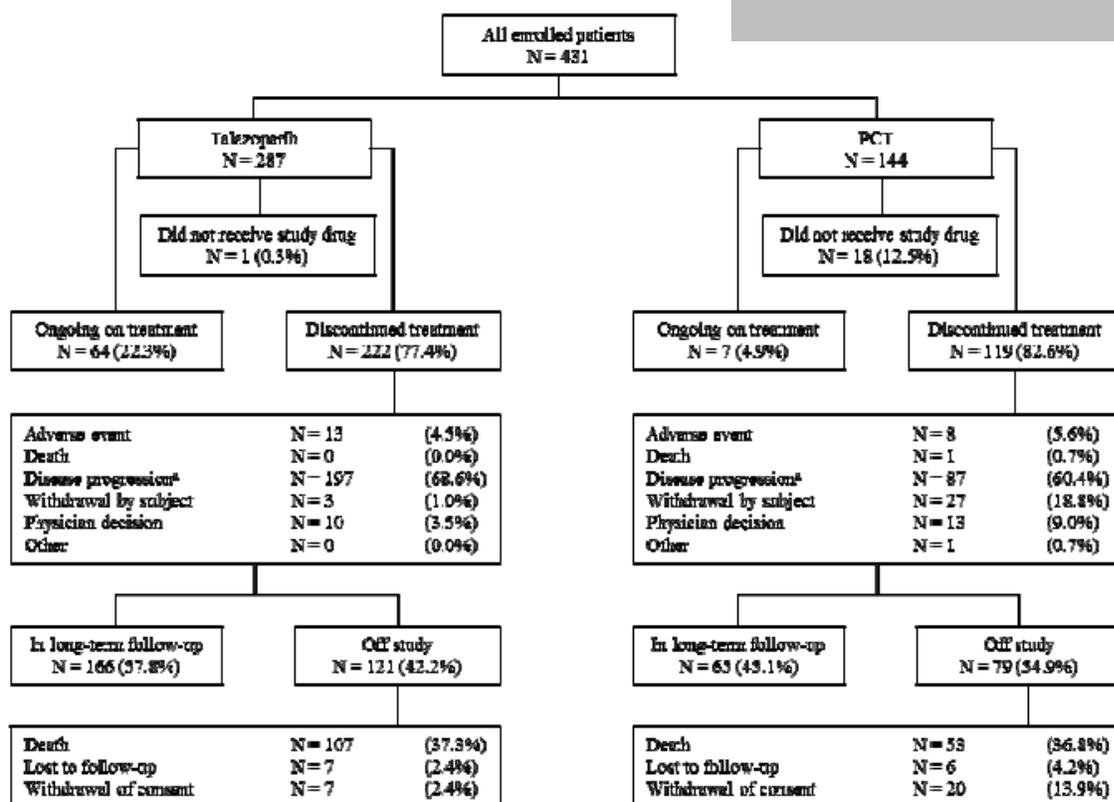
Source: NDA 211651, Section 1.3.4 Financial Disclosures PI: Principle Investigator; SI: Sub-Investigator.

Reviewer Comment: Sites with investigators that had significant disclosable interests enrolled approximately 10.7% (N=46) of the total number of patients in the EMBARCA study. Each individual site enrolled between 0.2-1.9% of the population which is small and unlikely to affect the results of the study.

Patient Disposition

Between October 2013 and April 2017, 995 patients were screened for the EMBRACA study and 431 patients were randomized. Of the 431 patients enrolled, 287 patients were randomized to the talazoparib arm and 144 patients were randomized to the PCT arm. Nineteen (19) patients (1 in the talazoparib arm and 18 in the PCT arm) were randomized but not treated. Sixty-four patients (22.3%) in the talazoparib arm and 7 patients (4.9%) in the PCT arm remained on study drug treatment as of the September 15, 2017 data cutoff date. Patient disposition is shown in Figure 4.

Figure 4: Patient Disposition



Source: Table 14.1.2.1

ITT=intent-to-treat; PCT=physician's choice treatment.

a. Disease progression was by local investigator assessment.

Source: EMBRACA CSR, page 79

Protocol Violations/Deviations

A formal acknowledgment by the study team was made that deviations were reviewed and GCP compliance was maintained. Protocol deviations were classified as "deviation" or "major deviation" according to protocol deviation specification document. As of the data cutoff date (September 15, 2017), 91 patients (21.1%) had major protocol deviations, with 65 patients (22.6%) in the talazoparib arm and 26 patients (18.1%) in the PCT arm. Major protocol deviations from the EMBRACA study are shown in Table 20.

The following were considered major deviations:

- Patients who were enrolled into the study even though they did not meet eligibility criteria
- Patients who developed withdrawal criteria during the study but were not withdrawn
- Patients who received an incorrect dose

- Patients who received an excluded concomitant treatment during the study
- Patients who were not consented prior to undergoing a protocol-specific procedure that is NOT considered standard of care

Table 20: Major protocol deviations in EMBRACA study

Protocol Deviation Category	Talazoparib N=287 N (%)	PCT N=144 N (%)
Any major protocol deviation	65 (23)	26 (18)
Study drug not discontinued or modified per protocol	24 (8)	1 (0.7)
Incorrect stratification	19 (7)	8 (6)
Imaging assessment not performed	10 (3)	9 (6)
Exclusion criteria met	8 (3)	3 (2)
Inclusion criteria not met	7 (2)	3 (2)
Dosing error	4 (1)	1 (0.7)
ICF not signed before study procedures conducted	1 (0.3)	2 (1)
Imaging not submitted to imaging vendor	1 (0.3)	0
Imaging performed out of window	1 (0.3)	0
Study drug not dispensed per IRT	1 (0.3)	0
Study drug not reduced or modified per protocol	1 (0.3)	0
Other ^a	0	1 (0.7)

PCT=Physician's choice treatment; Source: Modified from EMBRACA CSR Table 6; Table 16.2.2; advv.jmp

^aPatient (b) (6) had an approximate 4-month interruption (April 7, 2016-August 15, 2016) in eribulin dosing to receive and recover from radiotherapy (May 16, 2016-July 8, 2016).

Reviewer Comment: The protocol deviations in each category were well balanced between the two arms except for “Study drug not discontinued or modified per protocol”, which had a much higher rate in the talazoparib treatment arm. The applicant states this difference may be in part due to the protocol providing different dose modification instructions for talazoparib and PCTs. Detailed instructions for dose modifications for patients in the talazoparib arm were provided in in the EMBRACA protocol. Dose modifications for PCTs were to be handled according to the relevant package insert and institutional practice, and therefore no specific guidance was provided regarding dose modification for the PCT arm.

Incorrect stratification was the most common major protocol deviation, occurring in a total of 27 patients on study. The most common stratification error was secondary to incorrect counting of prior therapy (sites were not initially provided with a list of drugs considered to be “cytotoxic” therapy). In addition, the initial randomization form did not use the phrase “for locally advanced/metastatic disease;” therefore, many sites included drugs used in the neoadjuvant/adjuvant setting when they counted cytotoxic drugs. Further, the initial protocol did not clarify that the most recent biopsy data should be used for determination of TNBC or hormone receptor positive breast cancer status for stratification purposes, and sites variably used initial and most recent data; this was clarified in the December 2015 protocol

amendment. A total of 20 patients (4.6%) did not meet at least 1 inclusion or exclusion criterion. The most common eligibility criteria deviation was exclusion criterion 11 (ie, excluded inadequately treated CNS metastases) in 3 patients (0.7%). The natures of these deviations are unlikely to have affected the efficacy results.

Baseline Demographic Characteristics

The baseline demographics and disease characteristics for patients enrolled on the EMBRACA study are shown in Table 21 and Table 22.

Table 21: EMBRACA Baseline Demographics

	Talazoparib N=287	PCT N=144
Sex		
Female	283 (99%)	141 (98%)
Male	4 (1%)	3 (2%)
Age		
Mean (SD)	47.5 (11.6)	49.4 (12.1)
Median (Min-Max)	45 (27 - 84)	50 (24 - 88)
<50 years	182 (63%)	67 (47%)
50 to <65 years	78 (27%)	67 (47%)
>=65 years	27 (9%)	10 (7%)
Race		
White	192 (67%)	108 (75%)
Black or African American	12 (4%)	1 (1%)
Asian	31 (11%)	16 (11%)
Other	5 (2%)	1 (1%)
Not reported	47 (16%)	18 (13%)
Ethnic Group		
Hispanic or Latino	31 (11%)	15 (10%)
Not Hispanic or Latino	210 (73%)	111 (77%)
Not reported	46 (16%)	18 (13%)
ECOG		
0	153 (53%)	84 (58%)
1	127 (44%)	57 (40%)
2	6 (2%)	2 (1%)
Unknown	1 (<1%)	1 (1%)
Geographic Region		
Europe	134 (47%)	56 (39%)
North America	99 (35%)	57 (40%)
Rest of the World	54 (19%)	31 (22%)

PCT=Physician's choice treatment; Source: EMBRACA adsl.xpt

Reviewer Comment: Baseline demographics were similar for both treatment arms except for the following which differed by >5%: patients aged <50 years, patients aged 50 to <65 years Race, and Geographic Region. It is unlikely that these differences affected the efficacy results.

Patients in the EMBRACA study had a lower median age when compared to the median age of patients with MBC overall. This is not surprising since MBC patients with gBRCA mutation tend to be younger. Most of the patients were White, and the remainder was predominantly Asian or not reported. As in many clinical trials, Blacks were under represented. Most of the patients were female as would be expected; in addition, 7 male patients were enrolled on to study. Most patients had an ECOG PS of 0 in both treatment arms.

Table 22: EMBRACA Baseline Disease Characteristics

	Talazoparib N=287 (%)	PCT N=144 (%)
BRCA Status		
BRCA1 positive	133 (47)	63 (44)
BRCA2 positive	154 (54)	81 (56)
HER2 Status		
Negative	287 (100)	144 (100)
ER Status		
Positive	151 (53)	80 (56)
Negative	136 (47)	64 (44)
PR Status		
Positive	104 (36)	66 (46)
Negative	181 (63)	77 (53)
Unknown	2 (<1)	1 (<1)
ER and PR Status		
ER+ and PR+	98 (34)	62 (43)
ER- and PR+	6 (2)	4 (3)
ER+ and PR-	51 (18)	17 (12)
ER- and PR-	130 (45)	60 (42)
ER unknown or PR unknown	2 (<1)	1 (<1)
Primary tumor location at baseline		
Bone only metastatic disease	25 (9)	16 (11)
Other	262 (91)	128 (89)
History of CNS Metastasis (eCRF)		
Yes	43 (15)	20 (14)
No	244 (85)	124 (86)
Prior Hormonal therapy		
Yes	161 (56)	77 (53)
No	126 (44)	67 (47)
Prior Neo/Adjuvant therapy		
Yes	238 (83)	121 (84)

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

No	49 (17)	23 (16)
Prior Anthracycline Treatment		
Yes	243 (85)	115 (80)
No	44 (15)	29 (20)
Prior Taxane Treatment		
Yes	262 (91)	130 (90)
No	25 (9)	14 (10)
Prior Taxane or Anthracycline Treatment		
Yes	280 (98)	139 (97)
No	7 (2)	5 (3)
Prior Platinum for Advanced Disease		
Yes	24 (8)	16 (11)
No	263 (92)	128 (89)
Received Prior Platinum as Neo/Adjuvant Treatment		
Yes	24 (8)	15 (10)
No	263 (92)	129 (90)
Prior cytotoxic chemo for advanced disease(eCRF)		
Yes	176 (61)	90 (63)
No	111 (39)	54 (38)
Prior Radiotherapy		
Yes	223 (78)	107 (74)
No	64 (22)	37 (26)

PCT=Physician's choice treatment; Source: EMBRACA adsl.xpt

Reviewer Comment: Baseline disease characteristics were similar between the two arms. The only factor that differed by >5% was the number of patients with PR positive/negative disease. Fifteen percent of patients in the talazoparib arm and 14% of patients in the PCT arm had a history of CNS metastases.

Patients were required to have received treatment with an anthracycline and/or a taxane (unless contraindicated) in the neoadjuvant, adjuvant, and/or metastatic treatment setting. First-line treatment for advanced or metastatic disease with no prior adjuvant chemotherapy was allowed if the investigator determined that 1 of the 4 chemotherapy choices in the control arm would be an appropriate treatment option for the patient. Ninety-one percent (91%) of patients in the TALZENNA arm had received prior taxane therapy, and 85% had received prior anthracycline therapy in any setting. There were a similarly small percentage of patients (2% of patients in the talazoparib arm and 3% in the PCT arm) in both treatment arms that had not received prior taxane or anthracycline therapy.

Data of stratification factors were collected in both the interactive voice and web response system (IVRS/IWRS) and CRF. The discordance and concordance between CRF and IVRS/IWRS in

the stratification factors are shown in Table 23.

Table 23: Concordance and Discordance of Stratification Data between eCRF and IVRS/IWRS in EMBRACA

	Concordance/Discordance	Talazoparib N=287 N (%)	PCT N=144 N (%)
CNS Metastasis	Concordance	284 (99)	143 (99.3)
	Discordance	3 (1)	1 (0.7)
Prior Chemotherapy Regimens for Metastatic Disease	Concordance	267 (93)	134 (93)
	Discordance	20 (7)	10 (7)
Triple negative breast cancer	Concordance	284 (99)	140 (97.2)
	Discordance	3 (1)	4 (2.8)

Source: EMBRACA adsl.xpt

Reviewer Comment: There were no notable differences between arms with respect to the IVRS/IWRS and the CRF based stratification data. Following the intent-to-treat rule, the primary efficacy analysis used IVRS/IWRS based stratification data. To evaluate the robustness of the results, a sensitivity analysis using CRF-based stratification data was performed and results are shown in the section of efficacy results.

Subsequent therapies after progression on Study are shown in Table 24.

Table 24: Subsequent neoplastic treatment received in >1% of talazoparib arm

Antineoplastic treatment	Talazoparib (N=287) N (%)	PCT (N=144) N (%)
Carboplatin	82 (29)	38 (26)
Capecitabine	59 (21)	14 (10)
Gemcitabine	48 (17)	23 (16)
Eribulin	32 (11)	17 (12)
Paclitaxel	25 (9)	10 (7)
Cisplatin	23 (8)	9 (6)
Cyclophosphamide	19 (7)	8 (6)
Letrozole	18 (6)	6 (4)
Palbociclib	18 (6)	11 (8)
Fulvestrant	16 (6)	12 (8)
Methotrexate	15 (5)	2 (1)
Doxorubicin	11 (4)	5 (4)
Investigational drug	11 (4)	7 (5)
Paclitaxel albumin	11 (4)	6 (4)
Exemestane	10 (4)	7 (5)
Fluorouracil	10 (4)	2 (1)
Everolimus	9 (3)	5 (4)
Vinorelbine	9 (3)	5 (4)
Vinorelbine tartrate	9 (3)	3 (2)
Eribulin mesilate	8 (3)	1 (1)
Bevacizumab	7 (2)	2 (1)
Gemcitabine hydrochloride	6 (2)	3 (2)
Docetaxel	5 (2)	4 (3)
Pembrolizumab	5 (2)	4 (3)
Epirubicin	4 (1)	0
Trastuzumab	4 (1)	1 (1)

Source: EMBRACA adcm.xpt

Reviewer Comment: Carboplatin was the most common subsequent therapy in both arms. Although not shown in the above table, 20 patients (14%) in the PCT arm (compared to 2 patients in the talazoparib arm) went on to receive treatment with the PARP inhibitor olaparib. The choice of subsequent therapies could affect the final OS results for this study.

Treatment Compliance and Concomitant Medications

Treatment Compliance

Patients were instructed to bring all used and unused oral study drug containers to each study visit. Compliance with oral therapy dosing (talazoparib and capecitabine) was assessed by reconciliation of the used and unused study drug at least once per cycle. Since PCT may have been dispensed by an external pharmacy, some sites did not assess patient compliance by study drug reconciliation as outlined in the protocol, but instead used the study's patient diary to verify compliance with oral study drug.

Concomitant Medications

Use of immunostimulants (e.g., growth factor support such as filgrastim) was required for 25 patients (8.7%) in the talazoparib arm and 22 patients (17.5%) in the PCT arm. In the talazoparib arm, 73 patients (25.5%) received an antianemic preparation (most of which appeared to be vitamin or mineral supplements) during the study, compared with 18 patients (14.3%) in the PCT arm. In the talazoparib treatment arm, 109 patients (38.1%) received RBC transfusions during the study compared with 7 patients (5.6%) in the PCT arm. Nine (9) patients (3.1%) in the talazoparib arm received a platelet transfusion during the study, compared with no patients in the PCT arm.

Use of antidiarrheals, intestinal anti-inflammatory/anti-infective agents was higher in the PCT arm, primarily in those patients who received capecitabine (29.1%), compared to those patients who received talazoparib (10.5%). Use of antiemetics was also higher in the PCT arm (45.2% compared to 27.6% in the talazoparib arm), as was use of systemic corticosteroids (43.7% in the PCT arm compared to 23.1% in the talazoparib arm); this was likely due to the use of corticosteroids as premedication for the control arm drugs. Use of dermatologic agents (emollients and protectives; other dermatological preparations) were higher in the PCT arm, primarily in those patients who received capecitabine (14.5% and 7.3%, respectively), compared to those patients who received talazoparib (1.7% and 1.0%, respectively).

Reviewer Comment: Use of concomitant medications varied between the two arms as would be expected based on the adverse event profile and need for premedication. Patients in the talazoparib arm received more antianemic preparations (such as iron supplements, etc), RBC transfusions and platelet transfusions compared to PCT; whereas, patients in the PCT arm received more growth factor support, antidiarrheals, anti-infective agents, antiemetics, systemic corticosteroids and dermatologic agents compared to the talazoparib arm.

Data Quality and Integrity

The data is located at the following link: \\CDSESUB1\evsprod\NDA211651\0001.

There were no significant issues with the quality or integrity of the data submitted by the applicant. The agency sent the applicant the following information requests (IR) which resulted in further datasets and data summaries:

1. IR sent on May 23rd, 2018 – Requesting the applicant provide details of confirmed investigator assessed ORR,

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

2. IR sent on June 28th, 2018 – Requesting SAS code and clarification datasets/variables for EMBRACA that were used to create the primary efficacy dataset ADEFF.XPT,
3. IR sent on July 2nd, 2018 – Requesting that the applicant submit additional summaries for the PRO data,
4. IR sent on July 3rd, 2018 – Following response to (4), the agency sent a follow-up request that the Applicant submit stand-alone SAS code to derive investigator and BIRC assessed tumor responses from the SDTM tables.

Data, code and summaries from the above requests are in the folder:

\\CDSESUB1\evsprod\NDA211651

Efficacy Results – Primary Endpoint

As shown Table 25, the estimated medians for IRF assessed PFS in the talazoparib and PCT arms were 8.6 months (95% CI: 7.2 – 9.3 months) and 5.6 months (95% CI: 4.2 – 6.7 months), respectively. The estimated hazard ratio was 0.54 (95% CI: 0.41 - 0.71). The results are statistically significant with a p-value less than 0.0001.

Table 25: PFS-IRF Results

	Talazoparib (N=287)	PCT (N=144)	All (N=431)
Events	186 (65%)	83 (58%)	269 (62%)
Median (95% CI), in months	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)	
p-value ¹	< 0.0001		
HR (95% CI) ²	0.54 (0.41, 0.71)		
¹ p-value from a stratified log-rank test stratified by IVRS/IWRS factors: number of prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease (0 vs 1, 2, or 3); TNBC (yes vs no); and history of central nervous system (CNS) metastases (yes vs no) ² HR estimated from Cox-PH model with strata equal to IVRS/IWRS stratification factors; treatment included as covariate, HR < 1 favors talazoparib			

Source: EMBRACA CSR Table 15 and adeff.xpt

Table 26 gives the proportions of PFS-IRF events. Approximately 62% of patients were assessed as having an IRF assessed event. There was higher censoring on the PCT arm (42% versus 35%). The proportion of patients censored at the last assessment prior to beginning new antineoplastic treatment in the PCT arm was approximately double that of the talazoparib arm (20.1% compared to 9.8%). The proportion of patients censored at randomization in the talazoparib versus PCT arm was 0.4% versus 13.2%.

Table 26: PFS-IRF Event and Censoring Summary

Event/Censoring description	Talazoparib (N=287)		PCT (N=144)	
	N	(%)	N	(%)
PFS Events (Total)	186	(64.8)	83	(57.6)
Radiographic PD	157	(54.7)	68	(47.2)
Deaths	29	(10.1)	15	(10.4)
Censored (Total)	101	(35.2)	61	(42.4)
Censored on date of the last adequate tumor assessment	71	(24.7)	12	(8.3)
Censored on date of the last adequate tumor assessment on or before initiation of a new antineoplastic therapy	28	(9.8)	29	(20.1)
Censored on date of the last adequate tumor assessment on or before the date of study drug discontinuation + 30 days	1	(0.4)	1	(0.7)
Censored at randomization Date	1	(0.4)	19	(13.2)

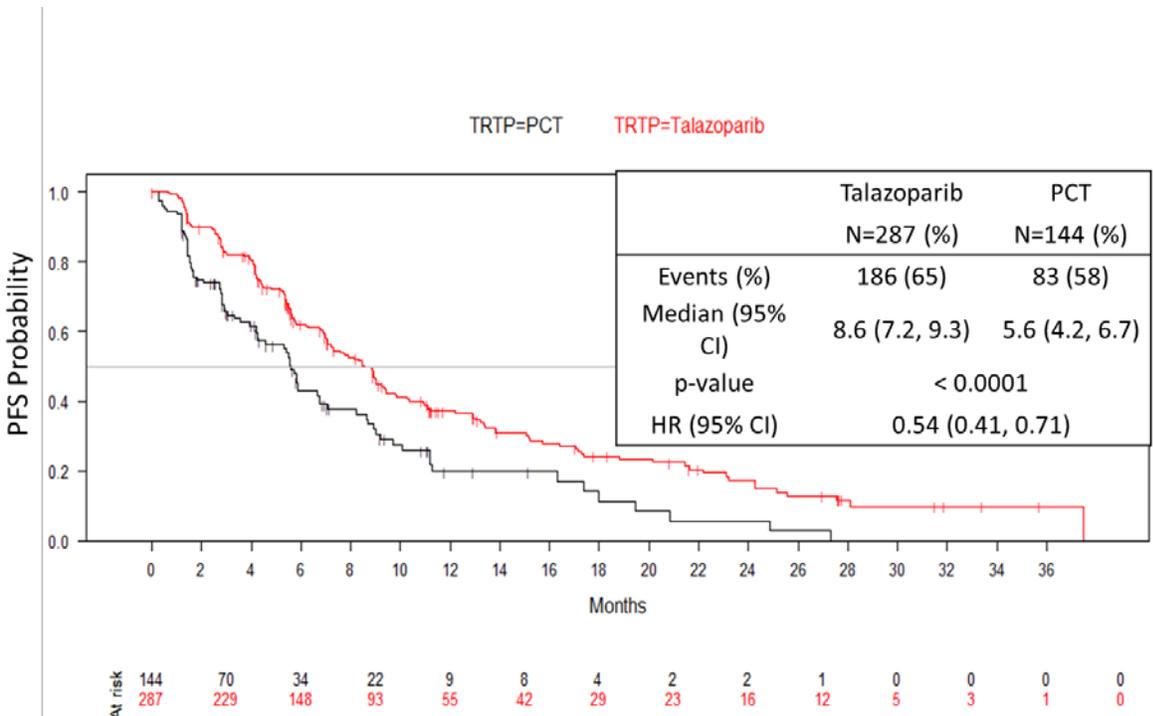
Source: EMBRACA adeff.xpt

Reviewer’s comments: *As EMBRACA was an open-label trial, censoring at baseline in the PCT arm was likely to be higher, since patients randomized to the control arm in an open-label might choose not to continue in the study (18 patients randomized to the PCT arm did not receive treatment). We performed a sensitivity analysis to assess the impact of baseline censoring. Details of this analysis and the results are given in the section on sensitivity analyses.*

The majority of the patients who were censored due to the initiation of a new antineoplastic treatment prior to PD had investigator assessed PD before starting new treatment. Of the 28 patients in the talazoparib arm who were censored due to the initiation of a new antineoplastic treatment prior to PD, 24 patients (8.4% of patients in the talazoparib arm) were deemed to have progressed via investigators’ assessments. Similarly, of the 29 patients in the PCT arm who were censored due to the initiation of a new antineoplastic treatment prior to PD, 16 patients (11% of patients in the PCT arm) were deemed to have progressed via investigators’ assessments. The discrepancy in the proportion of patients in the treatment arms who were censored due to the initiation of neoplastic treatment might be due to investigator bias; investigators were more likely to start new treatment prior to radiographic progression in the PCT arm than in the talazoparib arm. We therefore performed a sensitivity analysis to assess the impact of this bias by assuming that censored patients in the talazoparib arm (censored due to initiation of new antineoplastic therapy) progressed at their next tumor assessment. This analysis put the talazoparib arm at a disadvantage. The results are discussed in the section on sensitivity analysis.

Figure 5 shows the Kaplan-Meier curves of IRF-assessed PFS.

Figure 5: Kaplan-Meier Plots of IRF-assessed PFS (DCO: September 15th, 2017)



[Source: ADEFF.XPT]

Investigator-assessed PFS

Table 27 gives investigator-assessed PFS results (PFS-Inv). The PFS probabilities, estimated by the Kaplan-Meier method, are given in Figure 6. The estimated medians for PFS-Inv in the talazoparib and PCT arms were 7 months and 4.4 months, respectively. The estimated stratified hazard ratio was 0.54 (95% CI: 0.42 – 0.69). The estimated unstratified HR was 0.56 (95% CI: 0.44 – 0.71). The early discordance rate (EDR), which is the proportion of time the investigator calls progression earlier than the IRF (as a proportion of all investigator-assessed PD calls), had a positive differential of 6% between the talazoparib arm and the PCT arm. The late discrepancy rate (LDR), which is the proportion of time the investigator calls progression later than IRF (as a proportion of all discrepancies) had a negative differential of -9%.

Table 27: Investigator-assessed PFS Results

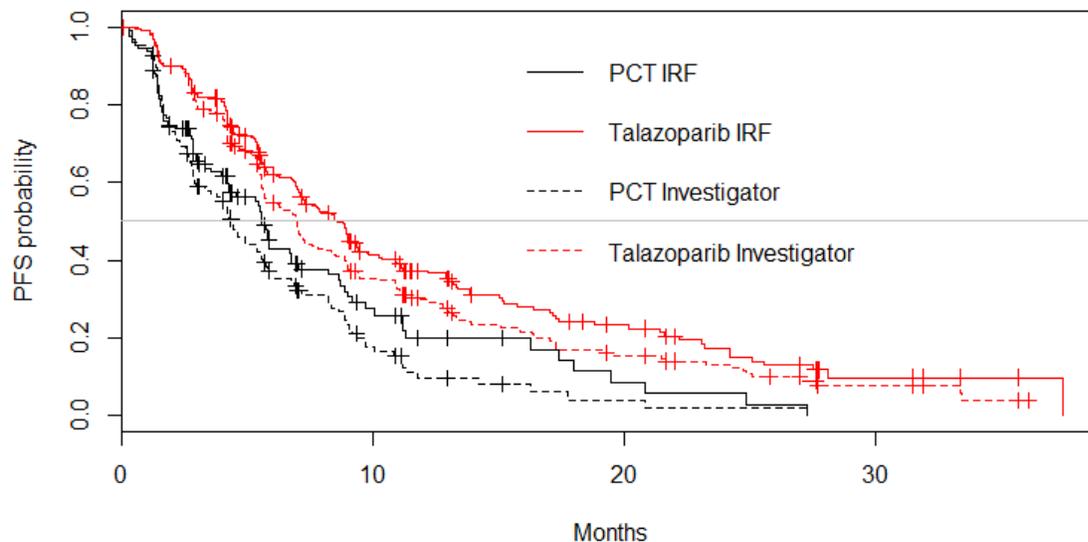
	Talazoparib (N=287)	PCT (N=144)	All (N=431)
Events (%)	217 (76%)	102 (70%)	319 (74%)
Median (95% CI), in months	7.0 (5.7, 7.6)	4.4 (2.9, 5.6)	
HR (95% CI) ¹	0.54 (0.42, 0.69)		
			Differential
EDR	32%	26%	6%
LDR	38%	45%	-9%
¹ HR estimated from Cox-PH model with strata equal to IVRS/IWRS stratification factors: number of prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease (0 vs 1, 2, or 3); TNBC (yes vs no); and history of central nervous system (CNS) metastases (yes vs no); treatment included as covariate, HR < 1 favors talazoparib EDR=Early discrepancy rate, LDR=Late discrepancy rate			

Source: EMBRACA adefx.xpt

Reviewer’s Note: The estimated positive EDR and negative LDR differentials do not suggest investigator bias in favor of talazoparib. The derived EDR and LDR rates in the CSR ignore censoring, however in our calculation, censoring was considered as Table 27.

Figure 6 shows the Kaplan-Meier curves of progression-free survival based on investigator and IRF assessments. PFS probabilities from the two methods of assessments diverge three months after randomization.

Figure 6: Kaplan-Meier Plots of investigator and IRF-assessed PFS



Source: EMBRACA adefeff.xpt, adttee.xpt

Reviewer Comment: *Though curves per investigator did not overlap with those per IRF, the magnitudes of improvement in PFS by talazoparib compared to PCT are similar in the two analyses.*

Subgroup Analyses

Exploratory analyses of IRF-assessed PFS was performed in the following subgroups: the stratification factors, age, region, race, hormone receptor status, prior hormone treatment, prior platinum treatment, prior taxane and anthracycline treatment. The estimated median PFS, HR and 95% confidence interval for the HR are given in Table 28. In groups with at least 30 patients, the talazoparib arm had longer PFS compared to the PCT arm. In addition, the estimated hazard ratios had values less than one, favoring talazoparib over PCT.

Table 28: PFS-IRF subgroup analyses

Subgroup		Tala	PCT	Tala	PCT	Tala	PCT	HR (95% CI)
		N		Events		Median ¹ (months)		
Triple negative BC	No	157	84	86	43	9.4	6.7	0.49 (0.33, 0.71)
	Yes	130	60	100	40	5.8	2.9	0.62 (0.43, 0.9)
Number of prior cytotoxic tmt for metastatic/advanced disease	0	111	54	69	23	9.8	8.7	0.6 (0.37, 0.97)
	1	107	54	69	34	8.1	5.6	0.57 (0.38, 0.87)
	2	57	28	41	20	5.8	5.3	0.7 (0.41, 1.19)
	3+	12	8	7	6	6.3	4.2	0.57 (0.19, 1.73)
History of CNS mets	No	244	124	154	68	8.9	5.9	0.61 (0.46, 0.82)
	Yes	43	20	32	15	5.7	1.6	0.41 (0.22, 0.79)
Age group	50 to <65	78	67	45	39	9.8	5.9	0.53 (0.34, 0.82)
	<50	182	67	128	39	7.6	4.2	0.57 (0.39, 0.81)
	>=65	27	10	13	5	12.9	8.2	0.39 (0.13, 1.15)
Region	Europe	134	56	78	33	8.8	4.2	0.6 (0.4, 0.9)
	North America	99	57	67	32	9.0	5.8	0.53 (0.34, 0.81)
	Rest of the World	54	31	41	18	5.6	5.5	0.68 (0.38, 1.19)
Race	Asian	31	16	26	8	5.6	5.4	0.68 (0.3, 1.55)
	Black	12	1	9	0	7.3	NE	NE
	Not reported	47	18	32	12	7.0	4.2	0.66 (0.34, 1.29)
	Other	5	1	2	1	10.3	1.4	0.22 (0.01, 3.59)
	White	192	108	117	62	9.0	5.8	0.55 (0.4, 0.75)
ER/PR status	ER or PR unknown	2	1	2	0	4.4	NE	NE
	ER+ and PR+	98	62	56	32	8.9	6.7	0.52

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

								(0.33, 0.82)
	ER+ and PR-	51	17	23	9	12.2	5.9	0.24 (0.1, 0.56)
	ER- and PR+	6	4	5	2	1.4	9.1	4.68 (0.53, 41.46)
	ER- and PR-	130	60	100	40	5.8	2.9	0.62 (0.43, 0.9)
BRCA status by central testing								
	BRCA1	123	60	93	35	6.9	3.5	0.68 (0.46, 1.00)
	BRCA2	147	78	78	47	9.8	5.7	0.48 (0.33, 0.69)
Prior hormone tmt	No	126	67	92	42	5.8	3.5	0.67 (0.47, 0.97)
	Yes	161	77	94	41	9.8	6.7	0.5 (0.34, 0.73)
Prior plat tmt for advanced disease	No	263	128	173	73	8.9	5.8	0.58 (0.44, 0.77)
	Yes	24	16	13	10	5.6	4.3	0.69 (0.29, 1.62)
Prior Taxane tmt	No	25	14	14	8	7.7	3.3	0.57 (0.23, 1.39)
	Yes	262	130	172	75	8.9	5.7	0.6 (0.46, 0.79)
HR+ & no prior hormone tmt	No	272	130	180	78	8.5	5.5	0.58 (0.44, 0.76)
	Yes	15	14	6	5	9.0	5.9	0.65 (0.2, 2.17)
Prior taxane or anthracycline tmt	No	7	5	1	3	NE	3.9	0.15 (0.02, 1.47)
	Yes	280	139	185	80	8.5	5.6	0.61 (0.46, 0.79)
CNS mets at baseline	No	254	129	162	72	8.9	5.8	0.62 (0.47, 0.82)
	Yes	33	15	24	11	5.6	1.5	0.25 (0.11, 0.58)

¹ Median estimated from Kaplan-Meier probabilities

² HR estimated from unstratified Cox-PH model with treatment group as covariate

Abbreviations: Tala=talazoparib; BC=Breast cancer; mets=metastases; tmt=treatment; NE=not estimable

Source: EMBRACA adsl.xpt, adefl.xpt

Reviewer's Comments: There were no multiplicity adjustments for subgroup analyses. These analyses are considered exploratory or hypothesis-generating and no formal inference may be drawn. No apparent outliers were observed from the subgroup analyses. The applicant

reported stratified hazard ratios estimated using the Cox-PH model, we report the unstratified hazard ratios.

All subgroups appear to benefit from talazoparib treatment, except for ER-/PR+ subgroup; however, this is a very small group with only 10 patients and a large confidence interval.

In an Information Response dated 9/4/2018, the Applicant provided further information regarding responses in the 48 patients (33 vs 15 patients in the talazoparib and PCT arms, respectively), identified as having CNS mets at baseline. Best Intracranial ORR for patients with CNS mets at baseline was 18% (4CRs, 2PRs) for the talazoparib arm and 20% (3 CRs) in the PCT arm. Nine out of 33 (27.3%) patients in the talazoparib arm had disease progression event due to intracranial lesion progression or a new intracranial lesion compared to five out of 15 (33.3%) patients in the PCT arm disease progression event due to intracranial lesion progression or a new intracranial lesion.

Sensitivity Analyses

The sensitivity analyses performed by the Applicant to assess the robustness of the primary efficacy results include the following analyses:

1. Analysis to assess the impact of clinical progression (as assessed by the investigator) – Patients who were assessed to have clinically progressed prior to radiographic progression as assessed by IRF, were considered as events in this analysis with the event date equal to the date of clinical progression.
2. Analysis to assess the impact of treatment discontinuation for any reason – Patients who discontinued treatment prior to radiographic progression were considered as PD events in this analysis with the event date equal to the date of treatment discontinuation.
3. Analysis to assess the impact of on-study radiotherapy – Patients who started radiotherapy prior to radiographic progression were considered as PD events with the event date equal to the date that radiotherapy was started.
4. Analysis to assess the impact of antineoplastic treatment – Patients who started a new antineoplastic treatment prior to radiographic progression were considered as PD events with the event date equal to the date that the treatment was started.
5. An unstratified analysis.

The agency performed the following sensitivity analyses:

1. Analysis to assess the impact of censoring at baseline – This analysis assumed that patients on the PCT arm who were censored at randomization were progression-free

and used the OS information.

2. Analysis to assess the impact of an imbalance in censoring due to start of antineoplastic therapy – Patient in the talazoparib arm who started a new antineoplastic therapy prior to radiographic progression were assumed to have had a PD event at their next assessment. This analysis put the talazoparib arm at a disadvantage.
3. The IRF-based adjudicated PD status and PD date were derived from the IRF database. Following an information request, the Applicant derived the PD status from the IRF raw tumor burden information (including measurements on target lesions, non-target lesions and bone lesions identified by the 2 individual readers) per the modified RECIST v1.1 using a SAS program. A sensitivity analysis was performed using this derived PD status.
4. Analysis using CRF stratification factors – There was some discordance between IVRS/IWRS and CRF stratification factors. A sensitivity analysis was performed where stratification factors from CRF were used.

Results of the sensitivity analyses are summarized Table 29.

Table 29: PFS-IRF Sensitivity Analyses

Sensitivity analyses	Talazoparib Median PFS (months)	PCT Median PFS (months)	HR (95% CI) ¹	
Impact of clinical progression by investigator	8.5	5.6	0.52	(0.4, 0.68)
Impact of treatment discontinuation for any reason	6.8	2.8	0.39	(0.31, 0.5)
Impact of on-study radiotherapy	8.6	5.8	0.58	(0.44, 0.77)
Impact of post baseline antineoplastic therapies	7.1	3.9	0.46	(0.36, 0.59)
Unstratified analysis	8.6	5.6	0.59	(0.45, 0.77)
FDA Analysis				
Analysis to assess the impact of censoring at baseline	8.6	5.6	0.54	(0.42, 0.72)
Analysis to assess the impact of an imbalance in censoring due to start of antineoplastic therapy (a)	7.7	5.6	0.62	(0.48, 0.81)
Analysis using PD status derived from raw tumor assessments	8.6	5.5	0.54	(0.41, 0.71)

Analysis using CRF stratification factors	8.6	5.6	0.55	(0.42, 0.72)
¹ HR estimated from Cox-PH model with strata equal to IVRS/IWRS stratification factors: number of prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease (0 vs 1, 2, or 3); TNBC (yes vs no); and history of central nervous system (CNS) metastases (yes vs no); treatment included as covariate, HR < 1 favors talazoparib				

Source: EMBRACA adeff.xpt

Reviewer’s Comments: *The estimated hazard ratios from the analyses listed above are less than one and have upper confidence bounds less than one. Results from these sensitivity analyses support the findings from the primary efficacy analysis of longer progression free survival in the talazoparib arm.*

Efficacy Results – Secondary and other relevant endpoints

OS Analysis

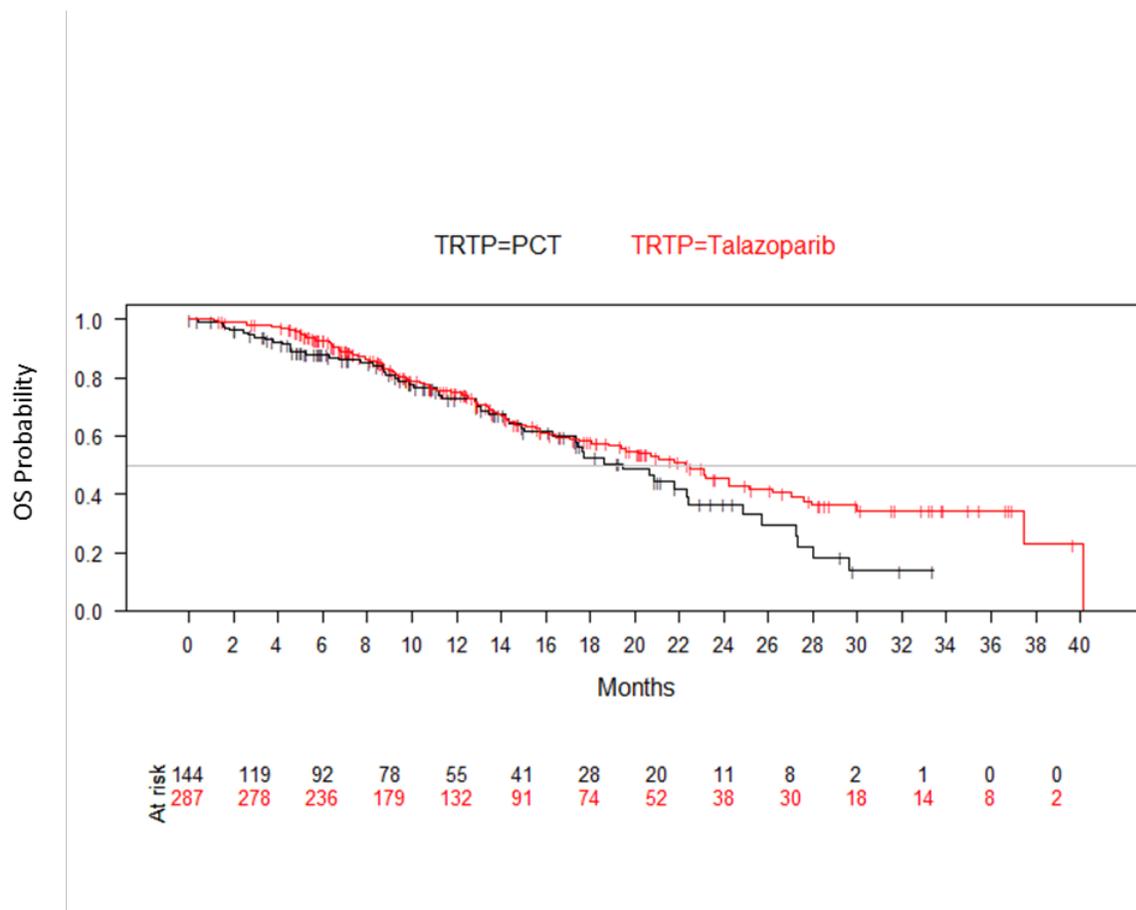
At data cut off, there were 163 (37.8%) deaths, approximately 51% of the required number of deaths for the final OS analysis. The results of the OS analysis are given in Table 30; plots of the Kaplan-Meier survival probabilities are given in Figure 7. The estimated median survival were 22.3 months and 19.5 months in the talazoparib and PCT arms, respectively. The median follow-up times estimated using the reverse Kaplan-Meier method in the talazoparib and PCT arm were 14.8 months and 13.7 months, respectively. The results from the stratified log-rank test were not statistically significant (HR: 0.76 (95% CI: 0.55, 1.06), p-value=0.1053). The final analysis is timed to occur with 321 deaths.

Table 30: OS Efficacy Results

	Talazoparib N=287	PCT N=144
Events (%)	108 (37.6%)	55 (38.2%)
Median (95% CI) ¹ Months	22.3 (18.1, 26.2)	19.5 (16.3, 22.4)
HR (95% CI) ²	0.76 (0.55, 1.06)	
p-value (log-rank test) ³	0.1053	
¹ Median estimated from Kaplan-Meier probabilities ² HR estimated from Cox-PH model with strata equal to IVRS/IWRS stratification factors; HR < 1 favors talazoparib ³ p-value from a stratified log-rank test stratified by IVRS/IWRS stratification factors		

Source: EMBRACA adttee.xpt

Figure 7: Kaplan-Meier plot of overall survival (DCO September 15th, 2017)



Source: EMBRACA adttee.xpt

Reviewer's comments: Results from the interim OS analysis did not cross the pre-specified boundary corresponding to the statistical significance level of 0.0001. The final analysis is timed to occur with 321 deaths.

Investigator Assessed ORR

The pre-specified efficacy population for ORR analysis was all randomized patients with measurable disease at baseline. Table 31 gives the best overall response (investigator-assessed) using RECIST v 1.1. Responses were confirmed by a second response at least 4 weeks after the initial response with no evidence of progression between confirmation visits. Response rates were 50.2% and 18.4% in the talazoparib and PCT arms, respectively. The estimated median duration of response (DOR) on the talazoparib arm was 6.4 months and 3.9 months in the PCT arm.

Table 31: ORR results

Response	Talazoparib N ¹ =219 (%)	PCT N ¹ =114 (%)
Complete response	12 (5.48)	0 (0)
Partial response	98 (44.75)	21 (18.42)
Stable disease	69 (31.51)	45 (39.47)
Progressed	36 (16.44)	29 (25.44)
Non-evaluable	4 (1.83)	19 (16.67)
Responses (ORR%)	110 (50.23)	21 (18.42)
ORR 95% CI ²	(43.41, 57.04)	(11.78, 26.77)
Median DOR (95% CI) ³ , in months	6.4 (5.4, 9.5)	3.9 (3.0, 7.6)

¹Patients with measurable disease
²Confidence intervals obtained using the exact method
³Median DOR for confirmed responses, estimates obtained using the Kaplan-Meier method

Source: EMBRACA adresp.xpt, invdorc.xpt submitted following IR request dated July, 3rd, 2018

Reviewer's comments: Per SAP, no multiplicity adjustments were planned for other secondary endpoints apart from OS, therefore, ORR analysis is considered exploratory. IRF assessed response rates were not available as only progression events were adjudicated by the independent review.

Dose/Dose Response

Not applicable to this NDA.

Durability of Response

These issues are addressed throughout the efficacy review given that the primary endpoint (PFS) of the trial is a time to event endpoint.

Persistence of Effect

These issues are addressed throughout the efficacy review given that the primary endpoint of the trial is a time to event endpoint.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Two PRO instruments were used in this application, the EORTC-QLQ-C30 questionnaire and the EORTC-QLQ-BR23 questionnaire.

Data collected with these instruments were reviewed but their results were not considered as part of the efficacy analysis. PRO results were, however, considered important for the review of safety and tolerability. This review is in the section on Clinical Outcome Assessment (COA), Analyses Informing Safety/Tolerability (Section 8.2.6) and in the Appendix for additional COA analyses (Appendix 19.5).

Additional Analyses Conducted on the Individual Trial

No other additional efficacy analysis was conducted.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

This section is not applicable. In NDA211651, efficacy was assessed based on data from a single clinical trial (EMBRACA) reviewed above.

Primary Endpoints

This section is not applicable. In NDA211651, efficacy was assessed based on data from a single clinical trial (EMBRACA) reviewed above.

Secondary and Other Endpoints

This section is not applicable. In NDA211651, efficacy was assessed based on data from a single clinical trial (EMBRACA) reviewed above.

Subpopulations

This section is not applicable. In NDA211651, efficacy was assessed based on data from a single clinical trial (EMBRACA) reviewed above.

Additional Efficacy Considerations

This section is not applicable. In NDA211651, efficacy was assessed based on data from a single clinical trial (EMBRACA) reviewed above.

8.1.4. Integrated Assessment of Effectiveness

The efficacy of talazoparib in BRCA-mutated HER2-negative breast cancer patients is supported by the single randomized trial, EMBRACA. The primary endpoint of IRF-assessed PFS was prolonged in patients treated with talazoparib (estimated median PFS of 8.6 months) compared to PCT (estimated median PFS of 5.6 months), and the estimated HR of 0.54 was statistically significant (95% CI: 0.41 – 0.71, p-value < 0.0001). IRF-assessed PFS was analyzed in the following subgroups: stratification factors (number of prior lines of chemotherapy, triple negative status, history of CNS metastases), age, region, race, hormone receptor status, prior

hormone treatment and prior platinum treatment. The estimated hazard ratios for these subgroups showed no evidence of a PFS detriment from talazoparib. These subgroup analyses are considered exploratory and results from small subgroups are more subject to random variation.

Investigator assessed PFS supports the results from the primary efficacy analysis. Overall survival results are immature; 51% of the planned number of deaths had occurred at the clinical data cutoff date, and the final analysis of OS is timed to occur with 321 deaths. The estimated investigator-assessed ORR in the talazoparib arm was higher (50.2% versus 18.4%) among patients with measurable disease at baseline and the median duration of response was longer (6.4 months versus 3.9 months).

8.2. Review of Safety

8.2.1. Safety Review Approach

The focus of the safety review for this application is the 286 patients treated with talazoparib 1mg/day in the phase 3 EMBRACA Study. The data cutoff for the original submission was September 15, 2017, and January 31, 2018, for the Safety Update. Supportive safety data was obtained from 83 patients treated with talazoparib in the phase 2 ABRAZO study, 77 patients treated with talazoparib 1mg/day in the phase 1 dose-escalation study (Study PRP-001 [C3441007]), 37 patients from the cardiac repolarization study and an additional 11 patients in the extension study for a total of 494 patients (treated with talazoparib at 1mg/day).

Adverse events of special interest (AESIs) identified by the applicant for talazoparib include hepatic disorders and myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and are further discussed in Section 8.2.4. Additional AESIs associated with other PARP inhibitors include new malignancies and pneumonitis and are also discussed in Section 8.2.4.

8.2.2. Review of the Safety Database

Overall Exposure

The safety of talazoparib has been assessed in 11 Sponsor-initiated clinical studies (7 completed, 4 ongoing) outlines in Table 32. This includes studies in various solid tumors, hematologic malignancies and healthy volunteers at doses ranging from 0.1-2 mg/day.

Table 32: Talazoparib exposure in Sponsor-initiated studies

Study Number	Indication	Number exposed to 1mg/day	# Patients or Subjects Treated Overall	Study Status
<i>Studies in Patients with Solid Tumors</i>				
673-301 (EMBRACA)	Phase 3, gBRCA mutated locally advanced or metastatic breast cancer	286	434 (126 treated with PCT)	Completed
673-201 (ABRAZO)	Phase 2, gBRCA mutated locally advanced or metastatic breast cancer	83	83	Completed
PRP-001 (C3441007)	Phase 1, first in human dose escalation study in advanced solid tumors	77	110 (33 at other doses)	Completed
MDV3800-14 (C3441005)	Phase 1, cardiac repolarization study in patients with advanced solid tumors	37	37	Completed
MDV3800-13 (C3441010)	Single arm, open label extension study	46*	80 (37 at other doses)	Ongoing
MDV3800-01 (C3441001)	Phase 1, PK study in pts with advanced solid tumors with renal impairment	0	NA	Ongoing
MDV3800-02 (C3441002)	Phase 1, PK study in pts with advanced solid tumors with hepatic impairment	0	NA	Ongoing
MDV3800-03 (C3441003)	Phase 1, ¹⁴ C-labeled talazoparib in patients with advanced solid tumors	6	6	Completed
MDV3800-04 (C3441004)	Phase 1, PK study with rifampin and itraconazole in advanced solid tumors	0	NA	Ongoing
<i>Studies in Patients with Hematological Malignancies or Healthy Volunteers</i>				
673-103 (C3441023)	Food effect study in healthy male volunteers	0	18	Completed
PRP-002 (C3441022)	Phase 1, patients with advanced hematological malignancies	0	33	Completed

PCT=physician's choice therapy; NA=not available for these ongoing studies

Source: EMBRACA Integrated Summary of Safety page 21

*Six (6) patients who started Study PRP-001 and 29 patients who started Study MDV3800-14 at talazoparib 1 mg/day and continued in the extension study (MDV3800-13) were counted only once. The group of patients who received talazoparib 1 mg/day (highlighted gray in the above table) is referred to as the "Talazoparib 1 mg/day Population" (N=494).

Relevant characteristics of the safety population:

A total of 412 patients out of 431 randomized patients received at least 1 dose of study drug on the EMBRACA study. One patient randomized to talazoparib and 18 patients randomized to PCT did not receive treatment. The most frequently selected PCT was capecitabine (55 patients [44%]), followed by eribulin (50 patients [40%]), gemcitabine (12 patients [10%]), and vinorelbine (9 patients [7%]). Baseline demographic and disease characteristics for the full analysis set were generally well balanced between treatment arms as seen in Table 21 and Table 22.

Adequacy of the safety database:

As of the September 15, 2017, safety data is available from 494 patients with solid tumors in Phase 1-3 studies who received talazoparib 1 mg/day, 70 patients with solid tumors in Phase 1

studies who received talazoparib at starting doses other than 1 mg/day, and 18 healthy volunteers from Sponsor-initiated clinical studies (total of 582 patients). This includes the 286 patients that received talazoparib in the pivotal phase 3 EMBRACA study.

At the time of the Safety Update, data on an additional 8 additional patients treated with talazoparib 1mg/day was available (total 502 patients).

8.2.3. 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

Adequate definitions for adverse events (AEs) and serious adverse events (SAEs) were provided. AE data were coded using MedDRA version 20.0, and AEs and laboratory parameters were graded for severity using the CTCAE version 4.03. Treatment-emergent AEs (TEAEs) were defined as any AEs that newly developed or worsened in severity following initiation of study drug.

All SAEs were reported regardless of causality. The safety reporting period for SAEs began from the time of the signing of the main ICF through 30 days after the last dose of study drug (permanent discontinuation of talazoparib or PCT), or prior to initiation of a new antineoplastic therapy, whichever occurred first.

A safety overview of key adverse events in the EMBRACA Study is shown Table 33.

Table 33: Overview of Safety in EMBRACA

	Talazoparib N=286 (%)	PCT N=126 (%)
Grade 1-4 TEAEs	282 (99)	123 (98)
Grade 3-4 TEAEs	193 (68)	80 (64)
Serious TEAEs (SAEs)	91 (32)	37 (29)
Deaths due to TEAEs within 30 days	6 (2)	4 (3)
Treatment discontinuation due to TEAEs	13 (5)	7 (6)
Dose reduction due to TEAEs	51 (18)	29 (23)
Dose interruption due to TEAEs	185 (65)	63 (50)
Dose modification* (reduction and/or interruption) due to TEAEs	190 (66)	75 (60)

PCT=Physician's choice treatment; Source: EMBRACA adae.xpt and adsl.xpt datasets

** Dose modifications are defined as a dose reduction or dosing interruption. Dose reductions are defined as any reduction of planned dosage. Dosing interruptions for talazoparib are defined as doses skipped due to AE but*

resumed per investigator judgement.

Routine Clinical Tests

The schedule of assessments for the EMBRACA Study, as outlined in the protocol, is shown in Section 8.1.1, Table 17. The figure depicts the frequency of laboratory testing, vital signs, physical exam, and adverse event monitoring. Hematology parameters were monitored weekly during Cycles 1 and 2, due to the high prevalence of hematologic adverse events with talazoparib. After two cycles, monitoring could be extended to every 3 weeks, but if any events of hematological toxicities occur, monitoring was to be increased as appropriate.

8.2.4. Safety Results

Deaths

All deaths on the EMBRACA study are summarized in Table 34. A total of 15 deaths occurred within 30 days of last study treatment and 10 of these deaths were associated with an AE: 6 patients (2.1%) in the talazoparib arm and 4 patients (3.2%) in the PCT arm. The AEs associated with death in the talazoparib arm were general physical health deterioration (2 patients); and cerebral hemorrhage, liver disorder, neurological symptom, and VOD (1 patient each). There was one death associated with an AE in each treatment arm that was considered related to treatment: VOD on the talazoparib arm and sepsis on the PCT arm.

Table 34: Deaths on EMBRACA study (data cutoff 9/15/2017)

	Talazoparib N=286 (%)	PCT N=126 (%)
Total number of deaths	108 (38)	53 (42)
Deaths (<30 days after last treatment dose)	10 (4)	5 (4)
Disease progression	7 (2)	4 (3)
Cerebral hemorrhage	1 (<1)	0
VOD*	1 (<1)	0
Worsening neurological symptoms	1 (<1)	0
Sepsis*	0	1 (1)
Deaths (>30 days after last treatment dose)	98 (34)	48 (38)
Disease progression	89 (31)	47 (37)
Unknown cause of death	2	0
Cardiopulmonary failure	2	0
Cardiac and respiratory arrest	1 (<1)	0
Attempted suicide with medicine	1 (<1)	0
Cardiac decompensation	1 (<1)	0
Cerebral ischemia	1 (<1)	0
Circulatory-Respiratory Failure	1 (<1)	0
Unknown	0	1 (1)

PCT=Physician's choice treatment; Source: EMBRACA adsl.xpt and adae.xpt datasets

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

**Treatment related death*
VOD=veno-occlusive liver disease.

Narratives for the 15 deaths that occurred within 30 days of last study treatment are provided below:

1. Patient (b) (6): 45 y.o. Hispanic female with MBC (liver, bone, and lymph nodes) previously treated with adjuvant fluorouracil, epirubicin, and cyclophosphamide and radiotherapy at left chest wall started treatment with talazoparib on (b) (6). The study drug was interrupted on (b) (6) due to a Grade 3 thrombocytopenia, and never resumed due to progressive disease in the liver. On (b) (6), 24 days after stopping the study drug, the patient died due to progressive disease. No autopsy was performed, and the investigator considered that the death was related to the disease under investigation.

Reviewer Comment: This assessment appears reasonable.

2. Patient (b) (6): 37 y.o. Black female with MBC (lung, adrenal gland, lymph nodes, liver and skin) previously treated with neoadjuvant doxorubicin/cyclophosphamide/paclitaxel, mastectomy, chest wall radiotherapy and adjuvant capecitabine started treatment with talazoparib on (b) (6). On (b) (6), approximately 3 months after the start of the study drug, the patient was hospitalized with Grade 3 malignant pleural effusion, Grade 4 anemia and Grade 4 neutropenia. The study drug was permanently discontinued due to disease progression, with the last dose taken on (b) (6). On (b) (6), the patient received post study systemic anti-cancer treatment with ixabepilone and cisplatin. On (b) (6), approximately 20 days after the last dose of the study drug, the patient died due to progressive disease. No autopsy was performed, and the investigator considered that the death was not related to study drug.

Reviewer Comment: This assessment appears reasonable.

3. Patient (b) (6): 41 y.o. female with MBC (hilar, lung, mediastinum, and left lymph node) previously treated with mastectomy, adjuvant docetaxel/cyclophosphamide; carboplatin, radiotherapy and anastrozole in recurrent setting started treatment with talazoparib on (b) (6). On (b) (6), approximately 6 months after the start of study drug, the patient experienced symptomatic progressive brain disease and study drug was permanently discontinued. The patient received post study anti-cancer treatment with cytarabine on (b) (6). On (b) (6), 19 days after the last dose of study drug, the patient died due to disease progression. Autopsy was not performed. This death was not considered to be due to study drug.

Reviewer Comment: This assessment appears reasonable.

4. Patient (b) (6): 57 y.o. female with MBC (liver and peritoneum) previously treated with mastectomy, adjuvant epirubicin/cyclophosphamide/paclitaxel, radiotherapy and letrozole; paclitaxel albumin and exemestane/everolimus in recurrent setting started treatment with talazoparib on (b) (6). On (b) (6), the patient was withdrawn from the study due to clinical progression. On (b) (6), approximately 12 days after the last dose of the study drug, the patient was hospitalized and received chemotherapy treatment with carboplatin and paclitaxel albumin. On (b) (6) 23 days after the last dose of study drug, the patient died due to disease progression. Autopsy was not performed. This death was not considered to be due to study drug.

Reviewer Comment: This assessment appears reasonable.

5. Patient (b) (6): 45 y.o. Asian female with MBC (right parasternal metastases, bilateral pleural effusions, mediastinum, skin lesions) previously treated with mastectomy, adjuvant epirubicin/cyclophosphamide/fluorouracil/paclitaxel, radiotherapy and anastrozole; and exemestane/everolimus in recurrent setting started treatment with talazoparib on (b) (6). On (b) (6), approximately 5 months after the start of the study drug, the patient experienced Grade 3 transient ischemic attack and was hospitalized. On (b) (6) an MRI of the spine revealed extensive leptomeningeal disease in the cord, conus, and filum consistent with progressive disease and study treatment was permanently discontinued on (b) (6). The patient received post study systemic treatment of capecitabine (b) (6). On (b) (6), 16 days after the last dose the study drug the patient died due to disease progression. Autopsy was not performed. This death was not felt to be due to study drug.

Reviewer Comment: This assessment appears reasonable.

6. Patient (b) (6): 76 y.o. female with MBC (multiple lesions in the right breast and liver) previously treated with mastectomy, adjuvant doxorubicin/cyclophosphamide/paclitaxel, radiotherapy and tamoxifen started treatment with talazoparib on (b) (6). Study drug was permanently discontinued due to clinical progression (felt to be from hepatic metastases) with the last dose of study drug taken on (b) (6). On (b) (6), approximately 1 month after the stop of the study drug, the patient died due to progressive disease (liver metastases). Hepatic enzymes increased were the only symptom of the disease progression. An autopsy was not performed. Both the Investigator and the Applicant considered that the events as unrelated to study drug. The fatal progression of the underlying malignancy is considered the most likely cause.

Reviewer Comment: This assessment appears reasonable.

7. Patient (b) (6): 65 y.o. female with MBC (lung and brain) previously treated with bilateral breast conserving surgery, adjuvant

fluorouracil/epirubicin/cyclophosphamide/paclitaxel, mastectomy; letrozole, paclitaxel, bevacizumab, tamoxifen, capecitabine, radiotherapy in the recurrent setting started treatment with talazoparib on [REDACTED] (b) (6). On [REDACTED] (b) (6), approximately 1 month after the start of the study drug, the patient was hospitalized with Grade 4 cerebral hemorrhage. The patient had a platelet count of $118 \times 10^3/\text{mm}^3$ on the same day. It was reported that she had subarachnoid and intra-parenchymal hematoma with cerebral metastases consistent with disease progression. The study drug was permanently discontinued in response to the event of cerebral hemorrhage, with last dose taken on [REDACTED] (b) (6). On [REDACTED] (b) (6), the patient died as a result of the cerebral hemorrhage. Autopsy was not performed. Both the Investigator and Applicant assessed cerebral hemorrhage as not related to the study drug.

Reviewer Comment: This assessment appears reasonable.

8. Patient [REDACTED] (b) (6): 34 y.o. patient with MBC (liver and bone) started treatment with talazoparib [REDACTED] (b) (6). The patient developed asymptomatic Grade 2 ALT and AST increase with normal bilirubin followed 3 weeks later by Grade 3 liver test abnormalities (ALT and AST with normal bilirubin) while receiving talazoparib at 0.75 mg/day, approximately 6 months after initiating treatment and 1 month after the dose was increased from 0.5 mg/day. Talazoparib dosing was discontinued 10 days later due to Grade 4 thrombocytopenia. Ten days after talazoparib dosing was discontinued, the patient was admitted to a health care facility with acute hepatic failure attributed to veno-occlusive liver disease (VOD) of the liver by the investigator. Concomitant medications at the time included naloxone/tilidine and metamizole. On [REDACTED] (b) (6), 16 days after the last dose of the study drug, the patient died due to Grade 5 suspected VOD of the liver. Clinical symptoms of VOD (such as hepatomegaly and right upper quadrant pain) were not noted. Autopsy was not performed. The cause of death was also reported as disease progression.

A magnetic resonance image (MRI) with contrast performed 3 days before the patient died showed ascites, bilateral pleural effusions, and no clear evidence of liver metastases. The investigator assessed the events of thrombocytopenia and VOD as related to talazoparib. The Applicant assessed the acute hepatic failure as possibly related to talazoparib, noting that the assessment is confounded by the patient's progressive metastatic disease (notable for new onset malignant ascites and bilateral pleural effusions), possible sepsis (as suggested by an elevated procalcitonin), and possible disseminated intravascular coagulation or thrombotic thrombocytopenic purpura (as suggested by progressive thrombocytopenia with no decrease in WBCs and hemoglobin, and reduced fibrinogen and antithrombin III). Based on the information provided, the Applicant considered VOD an unlikely etiology, a consideration supported by 2 hepatologist consultants to the Applicant who reviewed the case.

Reviewer Comment: Although it cannot be certain, it is likely this patient died due to progression of disease and likely did not have VOD.

9. Patient (b) (6): 40 y.o. Asian female with MBC (liver, lymph nodes and bone) previously treated with doxorubicin/cyclophosphamide and radiotherapy started treatment with talazoparib on (b) (6). On (b) (6), 7 days after the start of the study drug, the patient experienced Grade 3 metastases to meninges and was hospitalized on the same day. The study drug was temporarily stopped on (b) (6) and restarted on (b) (6). On (b) (6), the patient underwent a whole spine MRI scan which revealed leptomeningeal metastases involving the posterior fossa and spinal canal, with involvement of the nerve roots of the cauda equina. Multiple osseous metastases were seen within the spine with no evidence of cord compression. Study drug was temporarily stopped on (b) (6) while patient received radiotherapy and was resumed on (b) (6). On (b) (6), a subsequent brain MRI revealed marked progression of the posterior fossa leptomeningeal disease. The patient was subsequently referred to radio oncology for palliative radiotherapy and the study drug was permanently discontinued as a result of the event with the last dose of study drug taken on (b) (6). On (b) (6), the patient died at home due to worsening neurological symptoms. Autopsy was not performed. Both the Investigator and Applicant assessed Neurological symptom as not related to the study drug.

Reviewer Comment: This assessment appears reasonable.

10. Patient (b) (6): 34 y.o. female with MBC (mediastinum, liver, lymph nodes, adrenal gland, and brain) previously treated with neoadjuvant doxorubicin/cyclophosphamide/docetaxel/cisplatin, mastectomy, and radiotherapy started treatment with talazoparib on (b) (6). On (b) (6), 8 days after the last dose of the study drug, the patient was hospitalized as a result of Grade 3 dyspnea and pleural cavity fluid removal was performed. On (b) (6), 14 days after the last dose of study drug, the patient was hospitalized due to a second episode of Grade 3 dyspnea. The patient underwent another pleural cavity fluid removal. On (b) (6), approximately 18 days after the last dose of the study drug, the patient died due to progressive disease. An autopsy was not performed. Both the Investigator and Applicant assessed this death as not related to the study drug.

Reviewer Comment: This assessment appears reasonable.

11. Patient (b) (6): 42 y.o. female with MBC (breast and bone) previously treated with adjuvant docetaxel/doxorubicin started treatment with capecitabine on (b) (6). On (b) (6), the patient was hospitalized for Grade 3 mucosal inflammation and Grade 4 encephalopathy. On (b) (6), the patient was diagnosed with Grade 4 sepsis from neutropenia secondary to the study drug and died on (b) (6). An autopsy was not performed. The Investigator assessed mucosal inflammation, sepsis, and encephalopathy as related to the study drug. The Applicant assessed the events as related to the study drug.

Reviewer Comment: This assessment appears reasonable based on the temporal relationship of events.

12. Patient (b) (6): 42 y.o. female with MBC (liver, breast, lymph nodes and bone) previously treated with paclitaxel albumin and atezolizumab started treatment with capecitabine on (b) (6). On (b) (6), the patient was hospitalized for Grade 3 nervous system disorder. Brain computerized tomogram (CT) on (b) (6), was normal and did not show any brain metastases. On (b) (6), the event of nervous system disorder worsened, and the patient died on the same day during hospitalization due to disseminated malignant neoplasm of breast cancer. An autopsy was not performed. The Investigator and Applicant considered that there was not a reasonable possibility that the event Nervous System Disorder was related to the study drug.

Reviewer Comment: This assessment appears reasonable.

13. Patient (b) (6): 45 y.o. female with MBC (lymph nodes and a left pleural effusion) previously treated with mastectomy and adjuvant fluorouracil/epirubicin/cyclophosphamide/docetaxel started treatment with capecitabine on (b) (6). The study drug was permanently discontinued due to symptomatic progression (new bone lesion) with the last dose taken on (b) (6). The patient's post study systemic anti-cancer therapies included olaparib and carboplatin. On (b) (6), approximately 29 days after the last dose of the study drug, the patient died due to the disease progression. No autopsy was performed. The Investigator and Applicant considered there was not a reasonable possibility that the event was related to study drug.

Reviewer Comment: This assessment appears reasonable.

14. Patient (b) (6): 35 y.o. female with MBC (right cerebellum) previously treated with carboplatin and paclitaxel albumin and radiotherapy started treatment with capecitabine on (b) (6). The study drug was permanently discontinued in response to general physical health deterioration with last dose taken on (b) (6). On (b) (6), cytological findings of cerebrospinal fluid were consistent with carcinoma. On (b) (6), 19 days after the last dose of the study drug the patient died due to progressive disease. No autopsy was performed. The Investigator and applicant assessed the general physical health deterioration as not related to the study drug.

Reviewer Comment: This assessment appears reasonable.

15. Patient (b) (6): 43 y.o. female with MBC (liver, lymph nodes, right axilla, and skin) previously treated with adjuvant epirubicin/paclitaxel/cyclophosphamide, breast

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

conserving surgery, radiotherapy; capecitabine in recurrent setting started treatment with eribulin on [REDACTED] (b) (6). On [REDACTED] (b) (6), the patient received her last dose of eribulin which was discontinued due to disease progression. On [REDACTED] (b) (6), general physical health deterioration worsened, and the patient died on the same date due to progressive disease. The fatal outcome was reported as a result of progressive metastatic triple negative breast cancer (pulmonary, hepatic and cutaneous metastases). An autopsy was not performed.

Reviewer Comment: This assessment appears reasonable.

In the Talazoparib 1mg/day safety population, there were 24 deaths that occurred within 30 days after the last dose of study drug (this includes the 10 deaths already outlined above). The cause of death for the 24 patients includes:

- Disease progression (13)
- Cerebral hemorrhage (1)
- Dyspnea (1)
- Lung infection (1)
- Metastases to lung (1)
- Respiratory failure (1)
- Suspected VOD of liver (1)
- Worsening neurologic symptoms (1)
- Not stated (4)

The event of VOD (outlined above, patient [REDACTED] (b) (6)) in the EMBRACA study was the only death associated with an AE considered related to study drug by the investigator.

Deaths in Safety Update (data cutoff 1/31/2018):

A total of 143 patients (50.0%) died in the talazoparib arm of the EMBRACA study at the time of the safety update. This is an increase of 12.2% (35 patients) from the initial submission. In the PCT arm, there was an increase 6.3% (8 patients) in deaths since the initial submission. Progressive disease was the cause of death for 130 patients in the talazoparib arm (increase of 34 patients since the initial submission) and 58 in the PCT arm (increase of 7 patients since the initial submission). The numbers of patients who died within 30 days of the first dose of study drug and within 30 days of the last dose of study drug were unchanged from the initial submission. In the Study 673-301 Safety Population and Talazoparib 1 mg/day Population, the incidences of AEs associated with death were unchanged from the initial submission.

In the Talazoparib 1 mg/day Population, since the initial submission, 2 new deaths (one due to each ovarian cancer and failure to thrive) occurred within 30 days after the last dose of study drug (24 patients in the initial submission and 26 patients in the Safety Update). In the Talazoparib 1 mg/day Population, AEs associated with death within 30 days after the last dose of study drug were reported for 20 patients in the initial submission and 23 patients in the

SU (increase in 1 patient each for ovarian cancer, cerebrovascular accident, and fatigue). The AE of fatigue associated with death was updated as follows by the clinical study site subsequent to the data snapshot for the SU analyses: the severity of the AE of Grade 5 fatigue was updated to Grade 3 fatigue, and a Grade 5 event of failure to thrive was added.

Serious Adverse Events

Table 35: SAEs that occurred in >1 patient in either treatment arm of EMBRACA

Serious AE	Talazoparib N=286 (%)	Chemotherapy N=126 (%)
Patients with SAE	91 (32)	37 (29)
Anemia	17 (6)	0
Pyrexia	7 (2)	2 (2)
Vomiting	5 (2)	2 (2)
Back pain	5 (2)	1 (1)
Pleural effusion	4 (1)	7 (6)
Dyspnea	4 (1)	0
Headache	4 (1)	0
Platelet count decreased	4 (1)	0
Neutropenia	3 (1)	4 (3)
Abdominal pain	3 (1)	2 (2)
Pneumonia	3 (1)	2 (2)
Metastases to central nervous system	3 (1)	0
Pulmonary embolism	3 (1)	0
General physical health deterioration	2 (1)	2 (2)
Nausea	2 (1)	1 (1)
Bone pain	2 (1)	0
Cytomegalovirus infection	2 (1)	0
Diplopia	2 (1)	0
Non-cardiac chest pain	2 (1)	0
Pain in extremity	2 (1)	0
Pericardial effusion	2 (1)	0
Respiratory tract infection	2 (1)	0
Seizure	2 (1)	0
Thrombocytopenia	2 (1)	0
Deep vein thrombosis	1 (<1)	2 (2)
Neutrophil count decreased	1 (<1)	2 (2)
Diarrhea	0	3 (2)
Abdominal pain upper	0	2 (2)
Dehydration	0	2 (2)

Source: EMBRACA adae.xpt dataset

Reviewer Comment: The overall incidence of SAEs was similar in the two treatment arms for EMBRACA. Anemia was the most common SAE (5.9%) in the talazoparib treatment arm and

no cases in the chemotherapy arm. The SAEs seen with talazoparib treatment are similar to the known safety profile of PARP inhibitors. These mainly include hematologic events that can be managed by dose interruption and/or reduction, as well as supportive care therapies.

There was only a slight increase in the number of SAEs with the Safety Update (96 patients in the talazoparib arm and 39 patients in the PCT arm with ≥ 1 SAE).

Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuation:

13 patients (4.5%) in the talazoparib arm and 7 patients (5.6%) in the PCT arm had an AE that was the primary reason for permanent study drug discontinuation as shown in Table 36:

Table 36: AE leading to permanent discontinuation in >1 patient in talazoparib arm

Preferred Term	Talazoparib N=286	Chemotherapy N=126
Anemia	2	0
Accidental overdose	1	0
Cerebral hemorrhage	1	0
Dyspnea	1	0
Glioblastoma multiforme	1	0
Headache	1	0
Metastases to meninges	1	0
Neutropenia	1	1
Obstructive airways disease	1	0
Thrombocytopenia	1	0
Transient ischemic attack	1	0
Vomiting	1	0
Fatigue	0	1
General health deterioration	0	1
Mucosal inflammation	0	1
Peripheral edema	0	1
Rash	0	1
Generalized rash	0	1

Source: EMBRACA CSR Table 14.3.2.4.2; adae.xpt

In the Talazoparib 1 mg/day Population, 3.6% of patients had an AE associated with permanent study drug discontinuation. Anemia was the primary reason for permanent study drug discontinuation in 3 patients (0.6%) and all other AEs associated with permanent study drug discontinuation occurred in 1 patient each.

Dose Reduction:

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

In the EMBRACA study, a total of 52% of patients in the talazoparib arm and 36% of patients in the PCT arm were reported to have AEs associated with dose reduction. In the talazoparib arm, the most frequently reported (>5%) AEs associated with dose reductions were anemia (32%), neutropenia (15%), and thrombocytopenia (6%). The most frequently reported (>5%) AEs associated with dose reductions in the PCT arm included palmar-plantar erythrodysesthesia syndrome (10%, all among patients taking capecitabine), neutropenia (6%), diarrhea (6%, all among patients taking capecitabine), and neutrophil count decreased (6%).

Other AEs associated with dose reduction were generally similar across the different PCTs.

Dose Modification:

In the EMBRACA study, 66.4% of patients in the talazoparib arm and 59.5% of patients in the PCT arm had an AE associated with dose modification. AEs associated with dose modification reported at a $\geq 5\%$ higher incidence in the talazoparib arm compared with the PCT arm were anemia, neutropenia, and thrombocytopenia. The AEs associated with dose modification reported at a $\geq 5\%$ higher incidence in the PCT arm compared with the talazoparib arm were decreased neutrophil count, nausea, diarrhea, and palmar-plantar erythrodysesthesia syndrome.

In the Talazoparib 1 mg/day Population, AEs associated with dose modification, defined as any dose reduction or dosing interruption, were reported for 62.3% of patients. The most common AEs ($\geq 5\%$ of patients in the Talazoparib 1 mg/day Population) associated with dose modification were anemia, neutropenia, thrombocytopenia, and decreased platelet count.

Significant Adverse Events

MDS and AML

MDS

There were two cases of pancytopenia reported in the talazoparib 1mg/day safety database. Both cases occurred on the talazoparib treatment arm of the EMBRACA study. The Applicant states that upon medical review of the available data, neither case of pancytopenia was consistent with the clinical presentation and course of MDS. Both cases are discussed below:

Patient (b) (6): 48 y.o. female with MBC (liver, bone, and a periportal lymph node) diagnosed with infiltrating ductal carcinoma of the breast (b) (6) and developed metastatic disease (b) (6). Patient was previously treated with neoadjuvant veliparib/carboplatin/paclitaxel and doxorubicin/cyclophosphamide followed by mastectomy and axillary lymph node dissection and adjuvant carboplatin and radiotherapy started treatment with talazoparib (b) (6). On (b) (6), the patient was discontinued from the study due to progressive disease in the liver and lymph nodes. On (b) (6), the patient had Grade 3 anemia and neutropenia. On (b) (6), the patient had complaints of uncontrolled back, bilateral hip and lower extremity pain and had Grade 2 platelet count decreased. She underwent a transfusion of 2 units of packed red blood cells (PRBCs). On (b) (6), after transfusion with PRBC, hydration and antibiotics,

the patient was assessed as stable and discharged home.

On [REDACTED] (b) (6), approximately 51 days after the start of the study drug and 31 days since the last dose of study drug, the patient was hospitalized for further evaluation of Grade 4 pancytopenia and a bone marrow aspiration was performed under CT fluoroscopic guidance. On [REDACTED] (b) (6), results of bone marrow core biopsy showed metastatic carcinoma consistent with breast primary. Results from cytogenetic analysis: "Cytogenetic analysis was performed to rule out myelodysplastic syndrome. The analysis showed that a single culture from the bone core specimen failed to grow. Despite culture and harvest attempts, no metaphases were available for analysis. It was noted the specimen had a low cell yield which likely contributed to the lack of culture growth. Myelodysplastic syndrome was not ruled out; however, it was reported that additional studies would not be performed."

On [REDACTED] (b) (6), approximately 2 months after the last dose of the study drug, the patient died due to progressive disease. Autopsy was not performed. No other details were reported.

Reviewer Comment: Agree that pancytopenia in this case is likely due to metastatic breast cancer.

Patient [REDACTED] (b) (6): 53 y.o. female with MBC (liver) diagnosed with infiltrating ductal carcinoma of the breast [REDACTED] (b) (6) and developed metastatic disease [REDACTED] (b) (6). Patient was previously treated with mastectomy, adjuvant fluorouracil/epirubicin/cyclophosphamide, radiotherapy and adjuvant letrozole started treatment with talazoparib [REDACTED] (b) (6).

On [REDACTED] (b) (6), approximately 4 months after the start of the study drug, the patient experienced Grade 1 pancytopenia. On [REDACTED] (b) (6), Grade 1 worsened to Grade 2 pancytopenia and patient received 2 units of whole blood on [REDACTED] (b) (6). On [REDACTED] (b) (6), the patient's condition improved to Grade 1 pancytopenia. The study drug was interrupted from [REDACTED] (b) (6), in response to Grade 2 anemia, and resumed on [REDACTED] (b) (6). On [REDACTED] (b) (6), Grade 1 pancytopenia was considered resolved without sequelae. On [REDACTED] (b) (6), the patient started to receive the study drug at a reduced dose of 0.75 mg. On [REDACTED] (b) (6), approximately 10 months after the start of the study drug, the patient experienced a serious adverse event of Grade 2 anemia and was hospitalized for blood transfusion. On [REDACTED] (b) (6), the serious adverse event of anemia resolved, and the patient was discharged from the hospital on the same day. Patient had best response of PR and remained on treatment as of the [REDACTED] (b) (6), data lock date.

Reviewer Comment: Agree that the clinical narrative does not support a diagnosis of MDS.

AML

There were no cases of AML on the talazoparib treatment arm of EMBRACA or in the Talazoparib 1mg/day safety database in the original submission.

Across the entire talazoparib development program, there was one case of leukemia reported

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

for a patient in Study MDV3800-13 who received a starting dose of talazoparib at 0.5 mg/day Patient (b) (6): This patient had salivary gland cancer with metastases to the lung and was initially enrolled in Study MDV3800-01 (study of talazoparib in patients with impaired renal function) prior to the extension study when the dose of talazoparib was escalated to 0.75 mg/day. The total duration of talazoparib treatment was approximately 4 months. The initial blood smear results were abnormal with 6% blasts and minimal cytoplasm; the investigator confirmed the diagnosis of leukemia. While the investigator could not rule out a possible relationship with talazoparib, previous chemotherapies taken by the patient, specifically cyclophosphamide, are known to be associated with second primary malignancies, such as lymphomas and leukemias. Results from bone marrow biopsy and flow cytometry showed abnormal findings compatible with AML, and a diagnosis of AML originating from MDS was established.

There was one event of acute promyelocytic leukemia in the PCT arm of the EMBRACA study.

The following case of AML was reported in a patient treated on the talazoparib arm of EMBRACA in the Safety Update:

Patient (b) (6): 58-year-old White female with MBC (lung and brain) previously treated with neoadjuvant doxorubicin/docetaxel/cyclophosphamide, bilateral mastectomy, paclitaxel albumin/carboplatin, radiotherapy to the left chest wall, lung mass excision, craniectomy for brain mets, brain radiotherapy started treatment with talazoparib (b) (6) (b) (6)

On (b) (6) the patient was noted to have grade 3 thrombocytopenia. The patient was feeling fatigued and on (b) (6), the study drug was temporarily interrupted due to the event of thrombocytopenia. On (b) (6), a bone marrow biopsy revealed 50% hypercellular marrow with 19% to 20% myeloblasts and decreased megakaryopoiesis with hypolobated forms. Iron stores were present. No increase in reticulin fibrosis was noted and no metastatic malignancy was identified. Flow cytometry showed atypical left-shifted myeloid maturation with 19% CD34+ myeloblasts. Antibody results were positive for CD34 and CD117 with 20% myeloblasts. Cytogenetic results are still pending. Based upon biopsies results, the patient was diagnosed with a serious adverse event of AML with an onset date of (b) (6) (b) (6) approximately 24 months after the start of the study drug. The study drug was never resumed and was permanently discontinued due to the event of AML with the last dose taken on (b) (6). The treatment with chemotherapy decitabine and venetoclax was planned for (b) (6); however, the patient decided not to pursue chemotherapy and died on (b) (6) (b) (6) due to AML.

The Investigator considered there was a reasonable possibility that AML was related to the study drug. The Sponsor considered that the patient's prior systemic anticancer treatment that included 6 cycles of neoadjuvant cyclophosphamide, docetaxel, doxorubicin, and 6 cycles of carboplatin and paclitaxel albumin for her advanced disease and prior radiation therapy provide an alternative etiology for AML.

Reviewer Comment: Agree that there is a reasonable possibility that the AML was related to talazoparib treatment. However, other confounding factors do include the prior treatment with cytotoxic chemotherapy.

Hepatotoxicity

In the talazoparib arm of EMBRACA, 9.1% of patients had at least 1 hepatotoxicity related AE, versus 19.8% of patients in the PCT arm. Within the PCT arm, hepatotoxicity-related AEs were reported for 12.7% of patients taking capecitabine, 20.0% of patients taking eribulin, 41.7% of patients taking gemcitabine, and 33.3% of patients taking vinorelbine.

No patients in the Talazoparib 1 mg/day Safety Population (including the EMBRACA study) met the criteria for Hy's law.

Pneumonitis/ILD

There were no cases of pneumonitis in the EMBRACA study.

In the Talazoparib 1 mg/day Safety Population, pneumonitis was reported in 1 patient (0.2%) who was treated in Study 673-201. For this patient (Patient (b) (6)), the AE of grade 1 pneumonitis was first reported on Day 43 and was considered related to study drug by the investigator. Concurrently, the patient had a dosing interruption of talazoparib due to grade 3 pneumonia, which was not considered related to study drug by the investigator. Study drug was resumed after resolution of pneumonia, and the AE of pneumonitis resolved by Day 85. The patient continued to receive a total of over 9 months of treatment with talazoparib.

No AEs of pneumonitis were reported for patients treated at starting talazoparib doses other than 1 mg/day.

New malignancies

In the Talazoparib 1 mg/day Population, 7 AEs of second primary malignancies were reported for 6 patients (squamous cell carcinoma of skin [2 patients], and basal cell carcinoma, glioblastoma multiforme, intraductal proliferative breast lesion, neoplasm skin, and ovarian neoplasm [1 patient each]). Of these events, 3 were reported for 3 patients in the talazoparib arm of EMBRACA compared with 2 SAEs of second primary malignancies reported for 1 patient in the PCT arm of EMBRACA (malignant melanoma and second primary malignancy). None of the events were considered related to study drug by the investigator.

Treatment Emergent Adverse Events

Table 37: TEAEs that occurred in $\geq 10\%$ of patient in either treatment arm of EMBRACA

Preferred Terms (PTs)	Talazoparib N=286 (%)			Chemotherapy N=126 (%)		
	Grade 1-4	Grade 3	Grade 4	Grade 1- 4	Grade 3	Grade 4
Blood and lymphatic system disorders						
Anemia	150 (52)	109 (38)	2 (1)	23 (18)	5 (4)	1 (1)
Leukopenia	23 (8)	8 (3)	1 (<1)	12 (10)	5 (4)	2 (2)
Neutropenia	76 (27)	43 (15)	8 (3)	37 (29)	17 (14)	14 (11)
Thrombocytopenia	46 (16)	18 (6)	5 (2)	7 (6)	2 (2)	0
Gastrointestinal disorders						
Abdominal pain	32 (11)	2 (1)	0	20 (16)	2 (2)	0
Constipation	63 (22)	1 (<1)	0	27 (21)	0	0
Diarrhea	63 (22)	2 (1)	0	33 (26)	7 (6)	0
Dyspepsia	28 (10)	0	0	9 (7)	0	0
Nausea	139 (49)	1 (<1)	0	59 (47)	2 (2)	0
Vomiting	71 (25)	7 (2)	0	29 (23)	2 (2)	0
General disorders and administration site conditions						
Asthenia	42 (15)	5 (2)	0	12 (10)	2 (2)	0
Fatigue	144 (50)	5 (2)	0	54 (43)	4 (3)	0
Pyrexia	30 (11)	1 (<1)	0	21 (17)	0	0
Infections and infestations						
Upper respiratory tract infection	37 (13)	0	0	13 (10)	0	0
Urinary tract infection	28 (10)	1	0	3 (2)	0	0
Viral upper respiratory tract infection	30 (11)	2 (1)	0	8 (6)	0	0
Investigations						
Neutrophil count decreased	28 (10)	11 (4)	1 (<1)	18 (14)	8 (6)	5 (4)
Platelet count decreased	35 (12)	14 (5)	5 (2)	3 (2)	0	0
Weight decreased	22 (8)	0	0	15 (12)	1 (1)	0
Metabolism and nutrition disorders						
Decreased appetite	61 (21)	1 (<1)	0	28 (22)	1 (1)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	49 (17)	1 (<1)	0	15 (12)	0	0
Back pain	60 (21)	7 (2)	0	20 (16)	2 (2)	0
Myalgia	21 (7)	0	0	13 (10)	0	0
Pain in extremity	40 (14)	2 (1)	0	14 (11)	0	0
Nervous system disorders						
Dizziness	48 (17)	1 (<1)	0	13 (10)	2 (2)	0
Dysgeusia	29 (10)	0	0	11 (9)	0	0
Headache	93 (33)	5 (2)	0	28 (22)	1 (1)	0
Psychiatric disorders						
Insomnia	35 (12)	0	0	10 (8)	0	0
Respiratory, thoracic and mediastinal disorders						

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talzoparib)

Cough	56 (20)	2 (1)	0	20 (16)	0	0
Dyspnea	50 (18)	7 (2)	0	19 (15)	3 (2)	0
Skin and subcutaneous tissue disorders						
Alopecia	72 (25)	0	0	35 (28)	0	0

Source: EMBRACA adae.xpt dataset

Reviewer Comment: TEAEs that differ by >5% between the two arms and that are higher in the talzoparib treatment arm include: anemia, thrombocytopenia, fatigue, dizziness, and headache. This corresponds to the known toxicity profile for PARP inhibitors. TEAEs that differ by >5% between the two arms and that are higher in the PCT treatment arm include: abdominal pain and pyrexia.

Laboratory Findings

Table 38 Laboratory Abnormalities in ≥25% of Patients in EMBRACA

Parameter	Talzoparib N ^a =286 (%)			Chemotherapy N ^a =126 (%)		
	Grades 1-4	Grade 3	Grade 4	Grades 1-4	Grade 3	Grade 4
Decrease in hemoglobin	90	39	0	77	6	0
Decrease in platelets	55	11	4	29	2	0
Decrease in neutrophils	68	17	3	70	21	17
Decrease in lymphocytes	76	17	0.7	53	8	0.8
Decrease in leukocytes	84	14	0.3	73	22	2
Increase in glucose ^b	54	2	0	51	2	0
Increase in aspartate aminotransferase	37	2	0	48	3	0
Increase in alkaline phosphatase	36	2	0	34	2	0
Increase in alanine aminotransferase	33	1	0	37	2	0
Decrease in calcium	28	1	0	16	0	0

Source: EMBRACA adlb.xpt dataset

Abbreviation: N=number of patients.

- This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
- This number represents non-fasting glucose.

Reviewer Comment: Laboratory abnormalities that differ by >5% and higher in the talazoparib arm include: decrease in hemoglobin, decrease in platelets, decrease in lymphocytes, decrease in leukocytes, and decrease in calcium. Most of these laboratory abnormalities are expected with the known hematologic toxicity seen with talazoparib.

Vital Signs

No clinically relevant trends in vital signs were evident during the study.

Electrocardiograms (ECGs)

Electrocardiograms were only performed at screening and if clinically indicated in the EMBRACA study.

QT

In Study MDV3800-14 (A Phase 1, Open-Label Study to Assess the Effects of Talazoparib on Cardiac Repolarization in Patients With Advanced Solid Tumors), using a central vendor to assess QTc parameters, it was determined that no patients had a post baseline absolute mean maximum QTcF or QTcB >500 msec or an increase from time-matched baseline for QTcF or QTcB values >60 msec. Exposure response analyses using matched PK-ECG data indicated that talazoparib did not have a concentration-dependent effect on heart rate, QTcF, or QTcB at the recommended dose of 1 mg/day.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Adverse events of special interest to talazoparib (MDS/AML and hepatotoxicity) were discussed in Section 8.2.4.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Two PRO instruments were used in this application, the EORTC-QLQ-C30 questionnaire and the EORTC-QLQ-BR23 questionnaire.

The EORTC QLC-C30 questionnaire is a standardized instrument for measuring health status consisting of 30 items and 5 domains: physical, role, emotional, cognitive, and social function. The EORTC-QLQ-BR23 is a breast cancer specific questionnaire which supplements the EORTC-QLQ-C30 questionnaire. The EORTC-QLQ-BR23 consists of 23 questions that focus on treatment-related symptoms as well as patients concerns such as feelings of decreased attractiveness and femininity.

According to the assessment schedule in the protocol, patients were to complete the PRO assessments at baseline and every treatment cycle (3 weeks) till disease progression and at the end of treatment visit. The completion rate of answering at least 50% of questions within each domain of QLQ-C30 was above or around 70% in assessments up to week 43.

The results of analyses of PRO data collected through the EORTC-QLQ-C30 and the EORTC-QLQ-BR23 questionnaires are discussed in detail in the COA appendix (Appendix 19.5).

Reviewer's Comments: Without control of the type 1 error rate, PRO endpoints were considered as exploratory endpoints, to be analyzed and interpreted with no formal statistical testing. In addition, EMBRACA was an open label study with varied treatment schedules and administration in the control arm. PRO results are not likely to offer unbiased and conclusive evidence of patients' quality of life. The applicant however proposed (b) (4) (b) (4) in Section 14 of the draft label. Given the limitations discussed above, we suggest not including (b) (4) in Section 14 of the product label.

8.2.7. Safety Analyses by Demographic Subgroups

TEAEs in different age subgroups in the talazoparib treatment arm are shown in Table 39.

Table 39: TEAEs >10% in any age subgroup on the talazoparib arm

Preferred Term	Talazoparib (Age≤50) N=187 (%)			Talazoparib (Age 50-64) N=70 (%)			Talazoparib (Age>64) N=29 (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Blood and lymphatic system disorders									
Anemia	96 (51)	64 (34)	2 (1)	38 (54)	34 (49)	0	16 (55)	11 (38)	0
Leukopenia	19 (10)	8 (4)	1 (1)	4 (6)	0	0	0	0	0
Neutropenia	55 (29)	33 (18)	6 (3)	18 (26)	7 (10)	2 (3)	3 (10)	3 (10)	0
Thrombocytopenia	34 (18)	14 (8)	5 (3)	9 (13)	3 (4)	0	3 (10)	1 (3)	0
Gastrointestinal disorders									
Abdominal pain	21 (11)	2 (1)	0	7 (10)	0	0	4 (14)	0	0
Abdominal pain upper	18 (10)	0	0	4 (6)	0	0	2 (7)	0	0
Constipation	40 (21)	1 (1)	0	16 (23)	0	0	7 (24)	0	0
Diarrhea	36 (19)	1 (1)	0	19 (27)	1 (1)	0	8 (28)	0	0
Dyspepsia	16 (9)	0	0	8 (11)	0	0	4 (14)	0	0
Nausea	97 (52)	1 (1)	0	29 (41)	0	0	13 (45)	0	0
Stomatitis	11 (6)	0	0	9 (13)	0	0	4 (14)	0	0
Vomiting	45 (24)	5 (3)	0	19 (27)	1 (1)	0	7 (24)	1 (3)	0
General disorders and administration site conditions									

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Asthenia	28 (15)	4 (2)	0	10 (14)	0	0	4 (14)	1 (3)	0
Fatigue	91 (49)	2 (1)	0	36 (51)	3 (4)	0	17 (59)	0	0
Influenza like illness	10 (5)	0	0	0	0	0	6 (21)	0	0
Non-cardiac chest pain	11 (6)	2 (1)	0	0	0	0	3 (10)	0	0
Edema peripheral	0	0	0	8 (11)	0	0	5 (17)	1 (3)	0
Pyrexia	19 (10)	0	0	9 (13)	1 (1)	0	2 (7)	0	0
Infections and infestations									
Bronchitis	0	0	0	0	0	0	4 (14)	0	0
Influenza	0	0	0	0	0	0	4 (14)	1 (3)	0
Pneumonia	0	0	0	0	0	0	3 (10)	3 (10)	0
Upper respiratory tract infection	24 (13)	0	0	10 (14)	0	0	3 (10)	0	0
Urinary tract infection	18 (10)	0	0	6 (9)	1 (1)	0	4 (14)	0	0
Viral upper respiratory tract infection	18 (10)	0	0	8 (11)	2 (3)	0	4 (14)	0	0
Investigations									
Neutrophil count decreased	15 (8)	7 (4)	0	9 (13)	4 (6)	0	4 (14)	0	1 (3)
Platelet count decreased	20 (11)	10 (5)	1 (1)	10 (14)	3 (4)	1 (1)	5 (17)	1 (3)	3 (10)
Weight decreased	11 (6)	0	0	9 (13)	0	0	2 (7)	0	0
White blood cell count decreased	13 (7)	6 (3)	0	10 (14)	4 (6)	0	4 (14)	0	0
Metabolism and nutrition disorders									
Decreased appetite	32 (17)	0	0	20 (29)	1 (1)	0	9 (31)	0	0
Musculoskeletal and connective tissue disorders (SOC)									
Arthralgia	26 (14)	1 (1)	0	16 (23)	0	0	7 (24)	0	0
Back pain	37 (20)	5 (3)	0	13 (19)	2 (3)	0	10 (35)	0	0
Muscle spasms	0	0	0	0	0	0	3 (10)	0	0
Musculoskeletal chest pain	18 (10)	0 (0)	0 (0)	7 (10)	1 (1)	0	2 (7)	0	0
Musculoskeletal pain	15 (8)	1 (1)	0	7 (10)	1 (1)	0	4 (14)	0	0
Myalgia	14 (8)	0 (0)	0 (0)	7 (10)	0	0	0	0	0
Neck pain	0	0	0	8 (11)	0	0	0	0	0
Pain in extremity	22 (12)	2 (1)	0	11 (16)	0	0	7 (24)	0	0
Nervous system disorders									
Dizziness	30 (16)	1 (1)	0	12 (17)	0	0	6 (21)	0	0
Dysgeusia	14 (8)	0	0	10 (14)	0	0	5 (17)	0	0
Headache	74 (40)	4 (2)	0	12 (17)	0	0	7 (24)	1 (3)	0
Neuropathy peripheral	0	0	0	7 (10)	0	0	5 (17)	0	0
Psychiatric disorders									

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Depression	11 (6)	0	0	8 (11)	0	0	2 (7)	0	0
Insomnia	22 (12)	0	0	11 (16)	0	0	2 (7)	0	0
Respiratory, thoracic and mediastinal disorders									
Cough	36 (19)	2 (1)	0	13 (19)	0	0	7 (24)	0	0
Dyspnea	31 (17)	2 (1)	0	12 (17)	3 (4)	0	7 (24)	2 (7)	0
Oropharyngeal pain	19 (10)	0	0	4 (6)	0	0	2 (7)	0	0
Productive cough	0	0	0	0	0	0	3 (10)	0	0
Skin and subcutaneous tissue disorders									
Alopecia	39 (21)	0	0	19 (27)	0	0	14 (48)	0	0
Rash	14 (8)	0	0	8 (11)	0	0	5 (17)	0	0
Vascular disorders									
Hot flush	15 (8)	0	0	7 (10)	0	0	0	0	0

Source: EMBRACA adae.xpt

Reviewer Comment: *In general, the most common adverse events noted with talazoparib therapy are similar across age groups. With only 29 (10%) patients in the age >64 years subgroup, it is difficult to make any conclusions regarding varying toxicity between the subgroups.*

8.2.8. Specific Safety Studies/Clinical Trials

Not Applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See Pharmacology/Toxicology Review.

Human Reproduction and Pregnancy

No clinical data on exposure during pregnancy are available. Based on its mechanism of action, talazoparib may cause fetal harm when administered to a pregnant woman.

Talazoparib caused fetal malformations, structural variations, and death in an embryofetal development study in rats.

Pediatrics and Assessment of Effects on Growth

The safety and efficacy of talazoparib have not been established in pediatric patients. The applicant submitted a request for waiver of pediatric studies at the time of NDA submission on April 6, 2018. The PerRC met on September 12, 2018, and agreed to grant a full waiver, as requested.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

One patient in the EMBRACA Study accidentally self-administered thirty 1-mg capsules of talazoparib on Day 1. She underwent prompt gastric decontamination with gastric lavage and administration of orally activated charcoal within approximately 15 minutes after ingesting study drug. The patient remained asymptomatic throughout a 10-day hospitalization period. Hematology and chemistry laboratory test results were normal 3 hours after study drug administration and during her stay in the hospital. PK analysis showed that study drug exposure was 10-fold higher than expected after a 1 mg dose.

There is no specific treatment in the event of talazoparib overdose.

Drug Abuse Potential

There is no evidence that talazoparib is habit forming or could lead to dependence.

Withdrawal and/or Rebound

No studies have been conducted on talazoparib withdrawal or rebound.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable. Talazoparib is not approved in any market.

Expectations on Safety in the Postmarket Setting

Not applicable.

8.2.11. Integrated Assessment of Safety

The primary safety analysis for talazoparib for the treatment of patients with gBRCA, Her2-negative metastatic breast cancer came from the EMBRACA study with 286 patients treated with talazoparib. Supportive evidence came from an additional 208 patients treated with talazoparib at 1mg/day resulting in the Talazoparib 1mg/day Safety Population (494 patients total). Data for a total of 582 patients treated with talazoparib at various dose levels was submitted with the initial NDA.

The key AEs with talazoparib and other PARP inhibitors include MDS/AML, pneumonitis, and new primary malignancies. There was one case of AML in the talazoparib treatment arm of EMBRACA and a total of two cases across the talazoparib safety database in patients with solid tumors. There were no cases of pneumonitis in the EMBRACA study. There was one case of grade 1 pneumonitis in the Talazoparib 1 mg/day Safety Population. Seven AEs of second primary malignancies were reported for 6 patients in the Talazoparib 1 mg/day Population, including 3 reported for 3 patients in the talazoparib arm of EMBRACA. None of the events were considered related to study drug by the investigator. MDS/AML and myelosuppression have been included in the “Warnings and Precautions” section of the label so that clinicians can monitor patients appropriately.

The safety profile of talazoparib for the treatment of patients with gBRCA, HER2-negative metastatic breast cancer is generally tolerable, with adverse reactions manageable with talazoparib dose reduction, temporary treatment discontinuation, and/or standard medical care. Common adverse reactions ($\geq 20\%$) noted with talazoparib are similar to those previously noted in patients treated with other PARP inhibitors and include fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, decreased appetite. More patients treated with talazoparib required antianemic treatments, blood transfusions and platelet transfusions compared to the PCT treatment arm. Whereas, more patients in the PCT arm received antidiarrheals, intestinal anti-inflammatory/anti-infective agents, antiemetics (including systemic steroids) and dermatologic agents compared to the talazoparib treatment arm. Discontinuation due to anemia, neutropenia, and thrombocytopenia occurred, respectively, in 0.7%, 0.3%, and 0.3% of patients treated with talazoparib.

MDS/AML and myelosuppression have been included in the “Warnings and Precautions” section of the label so that clinicians can monitor patients appropriately.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

No statistical issues impacting the primary efficacy analyses were identified. The study met its primary endpoint of PFS. The results appeared consistent across sensitivity analyses, and no apparent outliers were observed in subgroup analyses.

8.4. Conclusions and Recommendations

The review team recommends regular approval for olaparib for the following indication:

- TALZENNA is a poly- (ADP -ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2 negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA (1).

The recommendation is based upon review of the results from EMBRACA, an open-label trial randomizing 431 patients (2:1) with gBRCAm HER2-negative locally advanced or metastatic breast cancer to receive talazoparib (1 mg) or PCT (capecitabine, eribulin, gemcitabine, or vinorelbine). All patients were required to have a known deleterious or suspected deleterious gBRCA mutation and must have received no more than 3 prior cytotoxic chemotherapy regimens for metastatic or locally advanced disease. Patients were required to have received treatment with an anthracycline and/or a taxane (unless contraindicated) in the neoadjuvant, adjuvant, and/or metastatic treatment setting. First-line treatment for advanced or metastatic disease with no prior adjuvant chemotherapy was allowed if the investigator determined that 1 of the 4 chemotherapy choices in the control arm would be an appropriate treatment option for the patient. Prior treatment with hormonal therapy was not required for patients with HR-positive disease. The trial demonstrated a statistically significant and clinically meaningful improvement in IRF assessed PFS for patients randomized to talazoparib (estimated median PFS 8.6 months) versus PCT (estimated median PFS 5.6 months), with a hazard ratio of 0.54 (95% CI: 0.41, 0.71; $p < 0.0001$). Subgroup and sensitivity analyses all support the primary efficacy endpoint results. OS analysis was not mature at the time of the PFS analysis.

The safety profile of the talazoparib was adequately assessed in the submitted database. Talazoparib was generally tolerable with adverse reactions manageable with dose reduction, temporary treatment discontinuation, and/or standard medical care. The key AESIs with talazoparib and other PARP inhibitors include MDS/AML, pneumonitis, and new primary malignancies. There was one case of AML in the talazoparib treatment arm of EMBRACA and a total of two cases across the talazoparib safety database in patients with solid tumors. There were no cases of pneumonitis in the EMBRACA study. Three primary new malignancies were reported in 3 patients in the talazoparib arm of EMBRACA. None of the events were considered related to study drug by the investigator. MDS/AML and myelosuppression have been included in the "Warnings and Precautions" section of the label so that clinicians can monitor patients appropriately. Adverse reactions (incidence $\geq 20\%$) include fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, decreased appetite. The safety profile is acceptable for this patient population with a serious and life-threatening

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

disease. All disciplines agreed that talazoparib had a favorable risk-benefit profile and did not identify any outstanding issues that precluded approval.

X

X

Stella Karuri
Primary Statistical Reviewer

Lijun Zhang
Statistical Team Leader

X

X

Suparna Wedam
Primary Clinical Reviewer

Laleh Amiri-Kordestani
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No ODAC was convened for this application.

10 Pediatrics

As is described in section 8.4 of product labeling, the safety and efficacy of talazoparib have not been established in pediatric patients. The applicant submitted a request for waiver of pediatric studies at the time of NDA submission on April 6, 2018. The PeRC met on September 12, 2018 and agreed to grant a full waiver, as requested.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

The table below summarizes significant changes to the proposed prescribing information made by FDA. This labeling was under negotiation at the time of this review. See the final approved prescribing information for TALZENNA accompanying the NDA 211651 approval letter for more information.

Summary of Significant Labeling Changes		
Section	Proposed Labeling	Approved Labeling
HIGHLIGHTS		
Indications and Usage	<i>See the revisions to the FPI Indications and Usage (1) below.</i>	<i>See the revisions to the FPI Indications and Usage (1) below.</i>
Adverse Reactions	Most common (\geq (b) (4) %) adverse reactions of any grade were fatigue, anemia, nausea, neutropenia, thrombocytopenia, and headache. (6) ...	FDA revised the incidence rate to \geq 20% and added common ARs for thrombocytopenia, vomiting, alopecia, diarrhea, and decreased appetite. FDA added "Most common laboratory abnormalities (\geq 25%) were: Decreases in hemoglobin, platelets, neutrophils, lymphocytes, leukocytes, and calcium. Increases in glucose, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. (6.1)"
Drug Interactions	<ul style="list-style-type: none"> (b) (4) P-gp Inhibitors: Reduce dose. (2.3, 7.1) (b) (4) (b) (4) BCRP Inhibitors: (b) (4) (7.1) 	FDA revised to: <ul style="list-style-type: none"> P-gp Inhibitors: Reduce TALZENNA dose for certain P-gp inhibitors, and monitor for potential increased adverse reactions as appropriate. (2.5, 7.1, 12.3) BCRP Inhibitors: Monitor for potential increased adverse reactions. (7.1) FDA removed (b) (4) (b) (4) for P-gp and BCRP inhibitors.
FULL PRESCRIBING INFORMATION		
1. Indications and	TALZENNA is indicated for	FDA revised to:

<p>Usage</p>	<p>the treatment of adult patients with germline breast cancer susceptibility gene (BRCA)-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TRADENAME [see Dosage and Administration (2.1)].</p>	<p>“TALZENNA is indicated for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA) mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA approved companion diagnostic for TALZENNA [see Dosage and Administration (2.1)].”</p>
<p>2. Dosage and Administration</p>	<p>2.3 Dose Modifications for Adverse Reactions</p> <p>...</p>	<p>FDA revised this subsection to add a third dose reduction level (0.25 mg once daily), “Treatment with TALZENNA should be discontinued if more than three dose reductions are required.”, and to remove non-actionable information consistent with FDA labeling guidance.</p> <p>FDA created numbered subsections for the dose modification for renal impairment (2.4) and Use with P-glycoprotein (P-gp) inhibitors (2.5).</p>
<p>5. Warnings and Precautions</p>	<p>5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia</p> <p>Leukemia Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received (b) (4)</p> <p>(b) (4)</p> <p>(b) (4). Overall, MDS/AML has been reported in (b) (4)</p>	<p>FDA moved this subsection from 5.2 to 5.1 to reflect the clinical importance and severity of MDS/AML, revised this section to add an additional MDS/AML case, and added discontinuation criteria as follows:</p> <p>“Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received TALZENNA. Overall, MDS/AML has been reported in 2 out of 584 (0.3%) solid tumor patients treated with TALZENNA in clinical studies. The duration of TALZENNA treatment in these two patients prior to developing MDS/AML was 4 months and 24 months, respectively.</p>

	<p>(b) (4) solid tumor patients treated with talazoparib in clinical studies. (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) If MDS/AML is confirmed, talazoparib should be discontinued.</p>	<p>Both patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.</p> <p>Do not start TALZENNA until patients have adequately recovered from hematological toxicity caused by previous chemotherapy. Monitor complete blood counts for cytopenias at baseline and monthly thereafter. For prolonged hematological toxicities, interrupt TALZENNA and monitor blood counts weekly until recovery. If the levels have not recovered after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue TALZENNA.”</p>
	<p>5.2 Myelosuppression ...</p>	<p>FDA revised this subsection to add the incidence of Grade ≥3 anemia, neutropenia, and thrombocytopenia; and the required monitoring of complete blood counts.</p>
	<p>5.3 Embryo-Fetal Toxicity ...</p>	<p>FDA revised this subsection to add that the embryo-fetal toxicity associated with TALZENNA is related to both animal data and the mechanism of action, added the specific toxicities observed with talazoparib exposure in animals, and the occurrence of these at exposures less than (0.24 times the AUC) the recommended human dose of 1 mg daily.</p> <p>FDA also added advice to males with female partners of reproductive potential to use effective contraception based on TALZENNA genetic toxicity and animal</p>

		reproductive studies.
6. Adverse Reactions	6.1 Clinical Trial Experience ...	<p>FDA revised this subsection and the results from the proposed (b) (4) patients using a pooled safety analysis including the EMBRACA registration study, (b) (4) (b) (4) (b) (4) (b) (4) to base the results for labeling on the EMBRACA trial (n=412).</p> <p>FDA revised the Adverse Reactions (ARs) table (Table 3) to apply an incidence of $\geq 20\%$ (b) (4) (b) (4)</p> <p>FDA revised the Laboratory Abnormalities table (Table 4) to add decreases in neutrophils, increase in glucose, increase in AST, increase in ALT, increase in alkaline phosphatase, and decrease in calcium based on the FDA safety review. <i>See 8.2.4. Safety Results, Laboratory Findings for more information.</i></p>
7. Drug Interactions	7.1 Effect of Other Drugs on TALZENNA ...	<p>FDA revised this section to add: “Coadministration with P-gp inhibitors may increase talazoparib exposure.” ... “When coadministering TALZENNA with P-gp inhibitors not listed above, monitor patients for potential increased adverse reactions [see</p>

		<p><i>Dosage and Administration (2.5), Clinical Pharmacology (12.3)].”</i></p> <p>...</p> <p>“Coadministration with BCRP inhibitors may increase talazoparib exposure. If coadministration cannot be avoided, monitor patients for potential increased adverse reactions when coadministering [see <i>Clinical Pharmacology (12.3)].”</i></p> <p>FDA revised the proposed interacting product list to include products studied and applicable to patients being treated for this indication.</p> <p><i>See 19.4.2. Sponsor’s Population Pharmacokinetics and E-R Analysis for more information.</i></p>
8. Use in Specific Populations	8.1 Pregnancy ...	<p>FDA revised the Risk Summary in this subsection to include fetal malformations observed in pregnant rats (i.e., structural skeletal variations and embryo-fetal death) at 0.24 times (b) (4) compared to the recommended dose of 1 mg daily.</p>
	8.3 Females and Males of Reproductive Potential	<p>Based on the FDA Pharmacology/Toxicology review, FDA added the following: <u>Infertility</u> <i>Males</i> Based on animal studies, TALZENNA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].</p>
	8.5 Geriatric Use	<p>FDA revised this section to reflect the exposure of TALZENNA in 494 patients and to clarify that 5 patients over ≥ 85 years of age had been treated.</p>
12. Clinical Pharmacology	12.1 Mechanism of Action ...	<p>This subsection was revised to remove undefined terms (b) (4), to reflect the established mechanism of action, and to remove any potential</p>

		<p>unsupported information that could suggest a therapeutic advantage or be misleading in accordance with current FDA guidance.</p>
	<p>12.3 Pharmacokinetics ...</p>	<p>FDA revised this subsection to better reflect the recommend format in current FDA guidance.</p> <p>FDA added the following: <i>Effect of Other Drugs on Talazoparib</i> Effect of P-gp inhibitors: Coadministration with P gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil in clinical studies increased talazoparib exposure by 45% [see <i>Dosage and Administration (2.5), Drug Interactions (7.1)</i>].</p> <p>Coadministration with P gp inhibitors including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin in clinical studies increased talazoparib exposure by 8% [see <i>Dosage and Administration (2.5), Drug Interactions (7)</i>].</p>
<p>14. Clinical Studies</p>	<p>14.1 EMBRACA Study (NCT01945775) ...</p>	<p>FDA added the following to the study description: “First-line treatment for advanced or metastatic disease with no prior adjuvant chemotherapy was allowed if the investigator determined that 1 of the 4 chemotherapy choices in the control arm would be an appropriate treatment option for the patient.”</p> <p>FDA added the following to the demographic and baseline disease characteristics: “Fifteen percent (15%) of patients in the TALZENNA arm and 14% of patients in the chemotherapy arm had a history of CNS metastases.”</p>

		<p>FDA removed (b) (4)</p> <p>(b) (4)</p> <p>FDA revised (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) to “Consistent PFS results were observed across patient subgroups defined by study stratification factors (line of therapy, TNBC status, and history of CNS metastases).” and removed the proposed (b) (4)</p> <p>(b) (4)</p> <p>FDA removed (b) (4) from the Efficacy Results table (Table 5) and added the following statement to the textual description of results, “The overall survival (OS) data were not mature at the time of the final PFS analysis (38% of patients had died).”</p> <p>FDA retained ORR in Table 5, but revised the ORR and Duration of Response to reflect the FDA Statistical Analysis results. FDA also removed (b) (4)</p> <p>(b) (4)</p> <p>FDA removed claims (b) (4)</p> <p>(b) (4)</p>
--	--	--

11.2. Patient Labeling

A Patient Package Insert (PPI) is included with the TALZENNA labeling. A brief summary of the significant changes made during FDA review of the TALZENNA PPI are as follows:

- Revised the order of the “most important information I should know about TALZENNA” to reflect the reordering of the Warnings and Precautions section in the Full Prescribing Information (FPI).
- Revised the “What is TALZENNA” section to reflect the revisions to the Indications and Usage section in the FPI.
- Added “have kidney problems” to the “Before taking TALZENNA, tell your healthcare provider about all your medical conditions...” section.
- Added “and may cause loss of pregnancy (miscarriage)” and pregnancy testing statements to the pregnancy information in the PPI to be consistent with the Embryo-Fetal toxicity information in the FPI.
- Added loss of appetite, diarrhea, vomiting, and hair loss to the list of most common adverse reactions to reflect revisions to the FPI.
- Added a statement regarding male fertility consistent with revisions to the FPI.

See the FDA OPDP/DMPP Review filed under this NDA for complete details.

William Pierce

X

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS were required for talazoparib based on the review of this NDA.

13 Postmarketing Requirements and Commitment

Postmarketing Requirements:

PMR 3476-1: Determine the appropriate dosing recommendations in patients with moderate and severe hepatic impairment by using the results from clinical trial C3441002 entitled, “A Phase 1 Open-Label Pharmacokinetics and Safety Study of Talazoparib (MDV3800) in Patients With Advanced Solid Tumors and Normal or Varying Degrees of Hepatic Impairment”. Submit datasets with the final report.

Rationale: In the clinical trials with talazoparib, patients with moderate or severe hepatic impairment were not enrolled. Based on the exposure-response for safety, higher talazoparib exposure was associated with a higher risk of Grade 3 adverse reactions and increased anemia and thrombocytopenia. The effect of moderate and severe hepatic impairment on the exposure of talazoparib is unknown and dose adjustment may be needed.

PMR 3476-2: Determine the appropriate dosing recommendations in patients with severe renal impairment by using the results from clinical trial C3441001 entitled, “A Phase 1 Open-Label Pharmacokinetics and Safety Study of Talazoparib (MDV3800) in Patients with Advanced Solid Tumors and Normal or Varying Degrees of Renal Impairment”. Submit datasets with the final report.

Rationale: Talazoparib is largely eliminated via the renal route. In the clinical trials with talazoparib, patients with moderate renal impairment had an average of 37% increase in talazoparib exposure and dose reduction is recommended for patients with moderate renal impairment. The effect of severe renal impairment on the exposure of talazoparib is unknown. Based on the exposure-response relationship for safety, higher talazoparib exposure was associated with a higher risk of Grade 3 or higher anemia and thrombocytopenia. This PMR study is to investigate the effect of severe renal impairment on talazoparib exposure to provide dose recommendation for patients with severe renal impairment.

Postmarketing Commitments:

PMC 3476-3: Submit the final overall survival analysis with datasets and final report from EMBRACA clinical trial entitled, “A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of BMN 673 versus Physician’s Choice in Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer, Who Have Received No More than 2 Prior Chemotherapy Regimens for Metastatic Disease”

Rationale: The final OS results of EMBRACA will be important to further understand the clinical meaningfulness of talazoparib in HER2 negative metastatic breast cancer patients.

PMC 3476-4: Submit the final report and datasets from the clinical trial (Protocol C3441004)

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

entitled, “A Phase 1 Open-Label, Two-Arm, Drug-Drug Interaction Study to Evaluate the Effect of Rifampin on the Pharmacokinetics of Talazoparib in Patients with Advanced Solid Tumors” to determine appropriate dosing recommendations with co-administering talazoparib with P-gp inducers.

Rationale: Talazoparib is identified as a P-gp substrate in the in vitro study. Coadministering talazoparib with P-gp inducers may decrease talazoparib exposure and decrease its efficacy. Higher talazoparib exposure was associated with longer progression-free survival (PFS) in the exposure-response for efficacy analysis. This PMC study will evaluate the effect of P-gp inducers on the exposure of talazoparib to inform if talazoparib dose adjustment is needed when coadministering with P-gp inducers.

14 Division Director (DHOT)

John K Leighton

X

15 Division Director (OCP)

Nam Atiqur Rahman

X

16 Division Director (OB)

Rajeshwari Sridhara

X

17 Division Director (Clinical)

Julia Beaver

X

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of talazoparib was also assessed by Drs. Amiri-Kordestani and Wedam, and I concur with their recommendations to approve this drug. My signature below represents an approval recommendation for the clinical portion of this application under the OCE. My signature below also represents the approval decision of this application under CDER.

Gideon Blumenthal

X

19 Appendices

19.1. References

American Cancer Society Facts and Figures. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf>

Bayraktar S, Gutierrez-Barrera AM, Lin H, Elsayegh N, Tasbas T, Litton JK et al. Outcome of metastatic breast cancer in selected women with or without deleterious BRCA mutations. Clin Exp Metastasis 2013;30:631–42.

Goodwin PJ, Phillips KA, West DW, et al. Breast cancer prognosis in BRCA1 and BRCA2 mutation carriers: An international perspective breast cancer family registry population-based cohort study. J Clin Oncol 2012;30:19-26.

Murai J, Huang SY, Renaud A, et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther 2014; 13(2):433-43.

National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Breast cancer; Version 2 2018.

Rennert G, Bisland-Naggan S, Barnett-Griness O, Bar-Joseph N, Zhang S, Hedy S. Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. N Engl J Med 2007;357:115-23.

Turner NC, Telli ML, Rugo HS, et al. Final results of a phase 2 study of talazoparib (TALA) following platinum or multiple cytotoxic regimens in advanced breast cancer patients (pts) with germline BRCA1/2 mutations (ABRAZO). J Clin Oncol 2017; 15(Suppl):Abstr 1007.

19.2. Financial Disclosure

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

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 1713		
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): 12		
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: <u>12</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>37</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages].

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Pharmacometrics Review

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

Does exposure-response (E-R) analysis support the proposed starting dose of talazoparib?

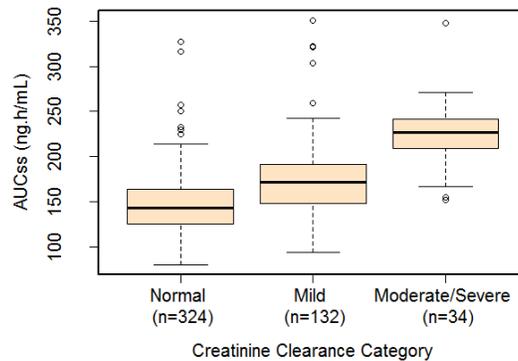
Yes. Positive E-R relationship was identified between talazoparib exposure (average daily exposure) and PFS. A lower starting dose may risk loss of efficacy. Positive E-R relationships were identified between talazoparib exposure and the probability of Grade 3 and above anemia and thrombopenia. The proposed starting dose of 1 mg QD is the maximum tolerated dose

identified in phase 1 study. Therefore, a higher starting dose is not recommended for safety reasons.

Does population pharmacokinetics (PPK) analysis and E-R analysis support the proposed dose adjustment (from 1.0 mg to 0.75 mg) in patients with moderate renal impairment (RI)?

Yes. Based on PPK analysis, baseline creatinine clearance was a significant covariate talazoparib exposure. When RI was evaluated as a categorical covariate, talazoparib apparent clearance (CL/F) was decreased by 14.4% and 37.1% in patients with mild and moderate RI, respectively (Figure 8). The magnitude of exposure increase is high considering significant association between talazoparib with anemia and thrombocytopenia. Therefore, the proposed dose adjustment appears reasonable.

Figure 8. The Effect of Renal Impairment on Talazoparib Exposure



Source: Reviewer's analysis.

19.4.2. Sponsor's Population Pharmacokinetics and E-R Analysis

PPK Analysis

Objectives

- To describe the population PK of talazoparib in patients with advanced cancer based on pooled data from Studies PRP-001, PRP-002, 673-201, and 673-301.
- To identify significant covariates that affect talazoparib PK.
- To evaluate the PK comparability of 4 x 0.25 mg capsules and 1 mg capsules as 1 mg dose.
- To provide post hoc CL/F estimates which will be used to generate individual patient's exposure metrics to be used in exposure-response analysis for selected efficacy and safety endpoints.

Data, Software, Methods

All patients treated with talazoparib and with available talazoparib plasma concentrations (from at least 1 postdose visit with actual collection date and time) were included in the nonlinear mixed effects modeling (NONMEM) PPK data file. Study design features are summarized in Table 3. PPK analyses were performed with NONMEM Version 7.3. First order conditional

estimation method with interaction (FOCEI) was implemented. Base model was a 2-compartment model with first order absorption and a lag time for absorption. Potential covariates were selected based on availability and the integrity of information (e.g. demographics and laboratory test), the mechanistic rationale, literature research, and visual inspection on the plots of empirical Bayes estimates (EBEs) of the interpatient random effects versus covariates (Table 40). Potential covariates were tested for significance in a stepwise manner using stepwise covariate modeling (SCM) with statistical criteria of $p=0.05$ for forward inclusion step and $p=0.001$ for backward elimination step. Model selection was based on change in the objective function value, visual inspection of diagnostic plots, precision of the parameter estimates, as well as decreases in both interpatient variability and residual variability. Model validation was conducted by visual predictive check (VPC), prediction and variance-corrected VPC, and standardized VPC (SVPC) in the overall population and stratified by significant covariates.

Table 40: Covariates Included in the PPK Analysis (and the Final model).

Covariate	Range	PK Para.	Covariate	Range	PK Para.
Age	49 (18-88) years	<u>CL/F</u>	<i>H2RA:PPI:otherARA:none</i>	20:158:48:264	Ka, F1
Race	41:449 (Asian:non Asian)	<u>CL/F</u>	<i>Strong Pgp inhibitor</i>	21:434 (Y/None)	Ka, <u>F1</u>
Baseline CrCL	105 (26-362) mL/min	CL/F	<i>Moderate/Weak Pgp inhibitor</i>	35:434 (Y/None)	Ka, F1
Body weight	67 (36-162) kg	<u>V2/F</u>	<i>Form (1:0.25:0.05:mix)*</i>	270:255:3:45	<u>Ka</u> , F1
<i>BCRP inhibitor</i>	3:487 (Y/N)	Ka, F1	<i>Food (fasted:fed:unknown)*</i>	312:301:355	<u>Ka</u> , F1
<i>P-gp inducer</i>	1:489 (Y/N)	Ka, F1			

*Time-varying covariates are highlighted in Italics. CrCL = Creatinine clearance; CL/F = apparent clearance; V2 = apparent volume of distribution of central compartment; Ka = Absorption rate constant; F1 = Bioavailability; * number of patients with record in each category*

Source: summarized from Population PK report, Table 4 and 5

Results

PK data from patients who were treated at dose levels that were lower than the therapeutic range (0.25-1 mg) or at very high dose level (30 mg), duplicate PK samples, PK samples assayed beyond stability, pre-treatment samples were excluded from PPK analysis. The percentage of post-dose BLQ data among all of the PK observations was low (1.89%) and were excluded from the analysis. The final included a total of 6207 PK observations from 490 patients.

A linear 2-compartment model with first-order absorption and a lag time for absorption was used to describe talazoparib PK. Age, race, and BCCL were included as covariates on CL/F, BWT was included as covariate on V2/F, Food and FORM were included as covariates on Ka, and PGPINH1 was included as covariate on F1. The estimated PK parameter values and associated statistics are shown in Table 41.

Table 41. Summary of Population Pharmacokinetic Parameters

Parameter	Estimate	SE	RSE %	Shrinkage (%)
CL/F (L/hr)	6.37	0.125	1.96	23.84
V ₂ /F (L)	162	6.43	3.97	89.36
Q/F (L/hr)	6.24	0.85	13.62	51.01

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

V ₃ /F (L)	223	18.3	8.21	53.19
k _a (1/hr)	1.22	0.209	17.13	15.78
Lag (hr)	0.243	0.00139	0.57	--
F ₁ (fixed)	1	--	--	--
Age effect on CL/F	-0.00124	0.00178	-143.55	--
RACEN effect on CL/F	0.237	0.0584	24.64	--
BCCL effect on CL/F	0.289	0.059	20.42	--
BWT effect on V ₂ /F	1.21	0.128	10.58	--
FOOD1 effect on K _a	-0.496	0.116	-23.39	--
FOOD2 effect on K _a	-0.451	0.174	-38.58	--
FORM2 effect on K _a	0.576	0.301	52.26	--
FORM3 effect on K _a	3.96	3.54	89.39	--
FORM4 effect on K _a	1.36	0.808	59.41	--
PGPINH1 effect on F ₁	0.447	0.202	45.19	--
CL/F ω ² (%CV)	0.0725 (26.93%)	0.00977	13.48	--
V ₂ /F ω ² (%CV)	0.00243 (4.93%)	0.0183	753.09	--
Q/F ω ² (%CV)	3.17 (178.04%)	0.236	7.45	--
V ₃ /F ω ² (%CV)	0.903 (95.03%)	0.271	30.01	--
ka ω ² (%CV)	2.72 (164.92%)	0.258	9.49	--
Thetarized Sigma (log additive)	0.611	0.0173	2.83	7.22

The population estimates are reported for a cancer patient from non-Asian RACE with a baseline creatinine clearance of 104.6 mL/min at age of 49 years old, with a baseline body weight of 67.0 kg, taking a 1 mg dosage of 1 x 1 mg capsule under fasting condition and without taking a strong P-gp inhibitor.

BCCL=baseline creatinine clearance; BWT=baseline body weight; FOOD1=fed condition; FOOD2=unknown; FORM2=0.25 mg capsule formulation; FORM3=0.05 mg capsule formulation; FORM4=mixture of 0.05 mg and 0.25 mg capsules formulation; PGPINH1=strong P-gp inhibitor; RACEN=Asian vs. Non-Asian race.

Source: Population PK report, Table 1

Co-administration of strong P-gp inhibitors increased the relative bioavailability of talazoparib by 44.7% when compared to talazoparib administered alone. Baseline creatinine clearance was a significant covariate on CL/F. When renal impairment was evaluated as a categorical covariate, talazoparib CL/F was decreased by 14.4% and 37.1% in patients with mild and moderate renal impairment, respectively. Insufficient data is available in patients with severe renal impairment.

Food intake and formulation strengths (1 mg, 0.25 mg, 0.05 mg, or a mixture of 0.25 and 0.05 mg) are significant covariates on the rate of absorption but had no effect on the extent of the absorption. Formulation strength effect was evaluated because in vitro comparability was not demonstrated between the 0.25 mg and 1 mg strengths from different generations of formulation. Simulation suggested bioequivalence after a single dose or at steady state in patients taking the 1 x 1 mg capsule or 4 x 0.25 mg capsules as starting dose.

Age (18-88 years) and race (Asian versus non-Asian) were significant covariates on CL/F. Baseline body weight (35.7-162 kg) was a statistically significant covariate on V₂/F. These effects were not considered clinically significant in the studied range.

Other covariates in this analysis, including co-administration of acid-reducing agents including PPI, H2RA, or other acid reducing agents, sex (437 female and 53 male), and mild hepatic

impairment (118 mild hepatic impairment versus 372 normal hepatic function), did not show significant impact on overall exposure (AUC_{0-∞}) of talazoparib. Insufficient data was available in patients with moderate or severe hepatic impairment.

Reviewer's Comments:

- In the Final model, parameters were generally well estimated with the majority of relative standard error less than 30%. Shrinkage was acceptable on clearance. The following alternative models were evaluated upon inspection of sponsor's dataset and Final model:*
 - The effect of age on clearance was not estimated with good precision. Covariate model on V₂/F may be overparameterized as suggested by large uncertainty in the estimate of intersubject variability. Removing age or ω^2 on V₂/F from the Final model does not significantly change OFV.*
 - The addition of study effect (Study 002 in patients with hematological malignancies) on the intercompartment clearance significantly reduced OFV and intersubject variability.*
 - Capping baseline creatinine clearance with more physiologically relevant upper bound values (e.g. 150 or 200 mL/min) reduced OFV but did not have significant impact on parameter estimates or conclusions regarding the effect of renal function on drug exposure.*
 - The 1 mg strength was used only in Phase 2 and Phase 3 studies with 1 pre-dose sample and up to 2 post-dose PK samples on each PK sampling day. Despite of an effort to separate PK sampling time within each individual, majority of PK samples were collected within 30 min around either 0.5 hour or 2.5 hours post-dose. Therefore, available data may not be adequate to fully characterize the absorption phase of the 1 mg capsule, and the effect of formulation strength on bioavailability may not be identified at the same time. Reviewer evaluated alternative models in which the effect of formulation strengths was placed on bioavailability or on both bioavailability and absorption rate constant. Alternative models suggested that the bioavailability of the 0.25 mg strength may be up to 9% higher than that of the 1 mg strength. However, these alternative models did not outperformed sponsor's Final model based on an inspection of OFV and other diagnostic measures. Alternative models also suggested that the overall exposure at steady state would be generally comparable between the two formulation strengths.*

Individual post hoc estimates of PK parameters and predicted exposure are highly correlated between the Final model and the alternative models evaluated by the reviewer. Diagnostic plots of sponsor's model showed reasonable fit. VPC plots showed good agreement in the observed and simulated data. Sponsor's model can be used to simulate exposure metrics in exposure-response analyses.
- Reviewer agree with sponsor's conclusions that moderate renal impairment and concomitant use with a strong P-gp inhibitor are the only significant covariate that have clinically relevant impact on talazoparib exposure, based on PPK analysis.*
 - In post hoc analysis based on the Final model, the predicted steady state exposure is 34.9% higher exposure in patients with moderate or severe RI than in patients with normal renal function. When RI was evaluated as a categorical covariate, talazoparib*

clearance was decreased by 14.4% and 37.1% in patients with mild and moderate RI, respectively.

- *A strong P-gp inhibitor in this study refers to any one of the following drugs: amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil.*

Exposure-Response (E-R) Analysis

Objectives

- To characterize the relationship between talazoparib exposure and PFS for Studies 673-201 and 673-301 separately;
- To characterize the relationship between talazoparib exposure and selected safety endpoints including Grade 3 and higher anemia, neutropenia, and thrombocytopenia using pooled data from Studies 673-201 and 673-301;
- To identify potential prognostic factors for selected efficacy and safety endpoints.

Reviewer's Comments: E-R analysis for PFS in Study 673-201 was not included in this review.

Data, Software, and Methods

All patients in the talazoparib arm in the original dataset were included in the E-R analysis unless the patients had missing covariates; missing covariates were not imputed. Missing data were not imputed in this analysis.

The Cox proportional hazard model was used to quantify the effects of talazoparib exposure and other baseline covariates on efficacy and safety endpoints. Time-varying average talazoparib concentration values, $C_{avg,t}$ on the original scale or log transformed, were used in the E-R analysis for safety and efficacy. $C_{avg,t}$ was calculated by dividing the average daily dose up to the time each endpoint occurred in the study by the post hoc estimate of CL/F. Other tested covariates in the univariate analyses were pre-selected and included the demographic, baseline disease status, baseline laboratory test values, prior therapy, and formulation strength. Likelihood ratio tests were used to examine the statistical significance of each covariate. Covariates associated with a p-value of 0.05 or less were simultaneously included in the multivariate analysis using the Cox proportional model. Talazoparib exposure measure $C_{avg,t}$ was retained in each step of multivariate analyses. Insignificant covariates were removed in each step until all the covariates included (other than the exposure metrics) were all significant (p-value: 0.05). If the exposure metrics were significant, this model was considered as final model; otherwise, the exposure metrics were to be removed and another stepwise multivariate analysis was to be performed until all the covariates included were significant

Results

PFS data from a total of 412 patients, 286 in talazoparib arm and 126 in physician's choice arm were available from this study. Only patients from talazoparib arm with PK parameter (n=275) were used in the ER analysis. Univariate analysis suggested that $C_{avg,t}$, and $\text{Log}(C_{avg,t})$, disease free interval, baseline lactate dehydrogenase, age, baseline, tumor size, baseline aspartate

aminotransferase, baseline alanine aminotransferase, baseline, absolute neutrophil count, baseline lymphocyte count, visceral disease status, prior hormone therapy, triple negative status, BRCA1 status, history of central nervous system metastases, and prior chemotherapy were significantly associated with PFS. Selection among highly correlated covariates was determined by p-value. For example, $C_{avg,t}$ had a lower p-value for significance than $\log(C_{avg,t})$ and was used in multivariate analysis. The final model is presented in Table 42.

Table 42. Multivariate Analysis of Cox Proportional Hazard Model for PFS in Study 301

Variable	Coefficient	Hazard Ratio (95% CI)	p-value
$C_{avg,t}$ (ng/mL)	-0.1262	0.8814 (0.8153-0.9529)	0.0015
BLDH (U/L)	0.0005	1.0005 (1.0002-1.0008)	0.0005
DFI (DFI >12 months vs DFI ≤12 months)	-0.4437	0.6417 (0.4764-0.8643)	0.0035
Visceral (visceral vs non-visceral)	0.4856	1.6251 (1.1471-2.3021)	0.0063

BLDH=baseline lactate dehydrogenase; DFI=disease free interval; Visceral=visceral disease status.

Source: E-R analysis report, Table 18

379 patients who received talazoparib and had PK parameters in studies 673-201 and 673-301 were included in the E-R analysis for anemia, thrombocytopenia, or neutropenia. Univariate analysis suggested that $C_{avg,t}$, $\log(C_{avg,t})$, REGION, ECOG status, baseline absolute neutrophil count, prior radiotherapy and baseline hemoglobin (BHGB) were significantly associated with anemia; $C_{avg,t}$, REGION, ECOG status, baseline albumin, baseline alkaline phosphatase, baseline lactate dehydrogenase (LDH), baseline lymphocyte count, prior radiotherapy, prior platinum therapy, prior chemotherapy, and BHGB were significantly associated with thrombocytopenia; and baseline body weight, LDH, baseline lymphocyte count, baseline absolute neutrophil count, and BHGB were significantly associated with neutropenia. The final models for anemia and thrombocytopenia are presented in Table 43. There was a numerical trend where higher talazoparib exposure is associated with higher probability of neutropenia as indicated by the hazard ratio of 2.218 (p-value: 0.06).

Table 43. Final Model for Anemia and Thrombocytopenia.

	Variable	Coefficient	Hazard Ratio (95% CI)	p-value
Anemia	$C_{avg,t}$ (ng/mL)	0.2586	1.2951 (1.1819, 1.4192)	3.03 E-08
	BHGB (g/L)	-0.0364	0.9642 (0.9505, 0.9782)	6.26 E-07
Thrombocytopenia	$C_{avg,t}$ (ng/mL)	0.1502	1.1621 (1.0074, 1.3406)	0.0394
	REGION 2 vs 1	-1.4538	0.2337 (0.1005, 0.5435)	0.0007
	REGION 3 vs 1	-1.8304	0.1604 (0.0426, 0.6041)	0.0068
	PR_PLATINUM	0.9236	2.5183 (1.4855, 4.2691)	0.0006
	BHGB (g/L)	-0.0705	0.9320 (0.9134, 0.9509)	6.91 E-12
	REGION 2:STDAY_TH	0.0174	1.0175 (1.0032, 1.0321)	0.0167
	REGION 3:STDAY_TH	0.0198	1.0200 (1.0044, 1.0360)	0.0121

$C_{avg,t}$ =time-varying talazoparib concentration; BHGB=baseline hemoglobin; PR_PLATINUM=prior platinum therapy; REGION 1=North America, 2=Europe, 3=Rest of World; REGION 2:STDAY_TH and REGION 3:STDAY_TH: interaction term between REGION and time.

Source: E-R analysis report, Table 28 and Table 35

Formulation strength was not associated with PFS or selected safety endpoints.

Reviewer's Comments:

Sponsor's E-R analyses were based on interval censoring. The final event dates in the E-R dataset were pooled across all patients and used to define evaluation intervals for each individual. Reviewer can repeat sponsor's analyses.

Because disease progression was not evaluated in most of the event end dates in these intervals, reviewer conducted exploratory analysis in which a patient's actual disease progression evaluation dates were used to define interval and the average daily exposure during the interval was used as the exposure metrics. Reviewer's analysis also suggests a positive E-R relationship between PFS and talazoparib exposure with a hazard ratio of 0.88 (95% CI: 0.81,0.97) in univariate analysis and similar value in multivariate analysis. Formulation strength was not associated with PFS in reviewer's analysis.

Reviewer conducted traditional E-R analysis for safety in which only the time to first event (or end of study) for each individual was used the analysis. The average daily exposure up to the time of evaluation was used as the exposure metrics. Reviewer's analysis suggested positive E-R relationships between the average daily exposure up to the time of evaluation and all three selected safety endpoints. The hazard ratios (95% CI) based on univariate analysis were 1.46 (1.35, 1.58), 1.48 (1.35, 1.63), and 1.56 (1.38, 1.77) for anemia, thrombocytopenia, and neutropenia, respectively. These relationships remained positive in multivariate analysis. When the post hoc estimate of steady state daily exposure was used as the exposure metrics, E-R relationship remained statistically significant for anemia and thrombocytopenia in both univariate and multivariate analysis. Formulation strength was not associated with these safety endpoints in reviewer's analysis.

Reviewer agrees with sponsor's conclusions on a positive E-R relationship for PFS, anemia, and thrombocytopenia, on the positive trend for neutropenia, and on a lack of association between formulation strength and PFS or the selected safety endpoints.

19.4.3. Appendix

Table 44. Summary of Studies Included in the Population PK Analysis

Protocol Number	Protocol Design	Population	Dose/Regimen	PK Sampling Schedule
PRP-001	Phase 1, open-label, dose escalation study	<p>Patients with advanced or recurrent solid tumors.</p> <p>Part 2 includes patients with BRCA associated cancers (breast, ovarian, prostate & pancreatic cancer), SCLC & Ewing sarcoma.</p>	<p>Part 1: Increasing doses of talazoparib, starting at 0.025 mg QD. Daily doses were 0.025, 0.05, 0.1, 0.2, 0.4, 0.6, 0.9, 1.0, and 1.1 mg QD.</p> <ul style="list-style-type: none"> • Cycle 1: Single dose on Day 1, then daily on Days 8-35, followed by 7 days off-treatment. • Cycles 2, 3 & ≥4: talazoparib daily on Days 1 to 28 of 28-day cycles. 	<p>Part 1: dense PK on C1D1 and C1D35, ≤2 hours predose, 15, 30, 45, 60 minutes and 2, 3, 4, 5, 6, 8, and 10 hours post-dose; predose on multiple other days.</p> <p>Part 2: dense PK on C1D1 and C2D1, ≤2 hours predose, 30 and 60 minutes, and 2, 3, and 4 hours after dosing; predose on multiple other days</p>

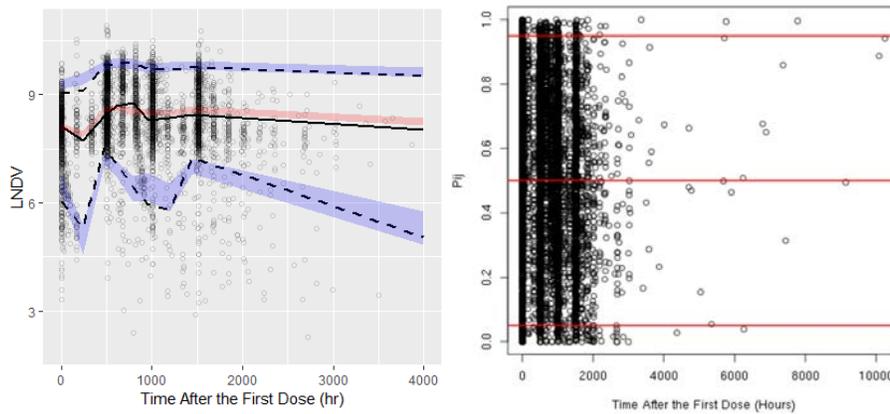
Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

			Part 2: talazoparib 1 mg QD in 28 day cycles	
PRP-002	Phase 1, open-label study	Patients with advanced hematological malignancies; Patients with AML, MDS, CLL or MCL who failed, declined or not eligible for standard therapy.	Part 1: Patients received increasing doses of talazoparib. Daily doses were 0.1, 0.2, 0.3, 0.45, 0.9, 1.35 and 2 mg QD in 21 day cycles.	C1D1 and C2D1: ≤ 2 hours predose, 15 and 30 minutes, and 1, 2, 3, 4, 6, 8, 10 hours post-dose; predose on multiple other days
673-201	Phase 2, 2-stage, 2-cohort study	Patients with locally advanced or metastatic breast cancer with a germline BRCA1 or BRCA2 mutation.	Talazoparib 1.0 mg administered orally daily for 21 days in repeated 21-day cycles.	Sparse sampling on Day 1 of treatment cycles 1 through 4: one pre-dose sample ≤ 60 minutes prior to dosing, and 2 post-dose samples collected ≥ 30 minutes after dosing (≥ 2 hours apart). Within individual subjects, efforts should be made to collect PK samples at different times relative to dosing across the study days with PK assessments.
673-301	Phase 3, open-label, randomized, parallel, 2-arm, multi-center study	Patients with germline BRCA mutations who had received no more than 3 prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic breast cancer.	Talazoparib 1.0 mg administered orally daily for 21 days in repeated 21-day cycles.	

AML=acute myeloid leukemia; BRCA=breast cancer gene; CLL=chronic lymphocytic leukemia; MCL=mantle cell lymphoma; MDS=myelodysplastic syndrome; SCLC= small cell lung cancer.

Source: Population PK report, Table 1, and individual study protocols

Figure 9. Prediction- and Variance-Corrected VPC Plots (Left) and Standardized Visual Predictive Check (Right) for the Final Model



Source: Reviewer's analysis and Population PK report, Figure 15

19.5. Additional Clinical Outcome Assessment Analyses

Overview

EMBRACA is a randomized open-label Phase 3 study of talazoparib versus physician's choice in germline BRCA-mutated HER2 negative patients with locally advanced and/or metastatic breast cancer. Two patient reported outcomes (PRO) instruments were used in the EMBRACA trial, the

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talzoparib)

EORTC QLQ-C30 questionnaire and the EORTC-QLQ-BR23 questionnaire. PRO endpoints were exploratory, with no formal statistical testing and no control of type I error rate prespecified.

Study Design/Methods

Trial design and frequency administration

Refer to the main review for a description of the trial design.

According to the assessment schedule in the protocol, patients were to complete the PRO assessments at baseline and every treatment cycle (3 weeks) till disease progression and at the end of treatment visit.

PRO Instruments

EORTC-QLQ-C30

The EORTC-QLQ-C30 instrument consists of thirty questions which include five multi-item functional subscales (physical, role, emotional, cognitive, and social), three multi-item symptom subscales (fatigue, pain, nausea/vomiting), a two-item global QoL subscale, and five single items which assess common cancer symptoms (See Table 45). The questionnaire can be obtained from the following link: <http://groups.eortc.be/qol/eortc-qlq-c30>.

Table 45: EORTC-QLQ-C30 Subscales and Items

	Label	Items (Questions) Included	Possible Raw Scores of Response for Items
Global Health Status / QOL	QL2	29, 30	1-7
Functional Subscales			
Physical functioning	PF2	1-5	1-4
Role functioning	RF2	6, 7	1-4
Emotional functioning	EF	21-24	1-4
Cognitive functioning	CF	20, 25	1-4
Social functioning	SF	26, 27	1-4
Symptom Subscales/Items			
Fatigue	FA	10, 12, 18	1-4
Nausea and vomiting	NV	14, 15	1-4
Pain	PA	9, 19	1-4
Dyspnea	DY	8	1-4
Insomnia	SL	11	1-4
Appetite loss	AP	13	1-4
Constipation	CO	16	1-4
Diarrhea	DI	17	1-4
Financial difficulties	FI	28	1-4

Source: SAP Version 4

EORTC QLQ-BR23

The EORTC-QLQ-BR23 is a breast cancer specific questionnaire which supplements the EORTC-QLQ-C30 questionnaire. The EORTC-QLQ-BR23 consists of 23 questions that focus on treatment-related symptoms as well as patients concerns such as feelings of decreased attractiveness and femininity (See Table 46). The questionnaire can be obtained from the following link:

http://groups.eortc.be/qol/sites/default/files/img/slider/specimen_br23_english.pdf.

Table 46: EORTC-QLQ-BR23 Subscales and items

	Label	Items (Questions) Included	Possible Raw Scores of Response for Items
Functional Subscales/Items			
Body image	BRBI	39-42	1-4
Sexual functioning	BRSEF	44, 45	1-4
Sexual enjoyment	BRSEE	46	1-4

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Future perspective	BRFU	43	1-4
Symptom Subscales/Items			
Systemic therapy side effects	BRST	31-34, 36-38	1-4
Breast symptoms	BRBS	50-53	1-4
Arm symptoms	BRAS	47-49	1-4
Upset by hair loss	BRHL	35	1-4

Source: SAP Version 4

Reviewer Comments: *EORTC QLQ-BR-23 is not fit-for-purpose for the context of this drug development program as it lacks clinical relevance since the item content more related to post-surgical changes (e.g., body image, sexual function, symptoms related to upper extremity dysfunction and localized symptoms). We are concerned that these symptoms are less likely to be responsive to the positive or negative effects of systemic treatment in this metastatic disease setting.*

Scoring of PRO Instruments

Except for items 29 and 30 in the EORTC-QLQ-C30, which form the Global Health Status/QOL subscale, all other items have four possible scores for responses (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). For most items, the response “very much” indicates a poorer quality of life (e.g., “Do you have any trouble taking a long walk?”). However, for QLQ-BR23 Module items 44, 45, and 46 regarding sexual activity, the response “very much” indicates better quality of life. The Global Health Status (GHS) composed of items 29 and 30 (“How would you rate your overall health/quality of life during the past week?”) have 7 possible scores for responses, ranging from 1 = very poor to 7 = excellent.

Raw scores for the symptom, functional, and global health status/QOL subscales were calculated by taking the mean score of the items composing the subscale. If less than half of the items were non-missing, the subscale was missing at that time point for the patient. Missing scores were not imputed. A linear transformation was used to transform the total raw score for a subscale to values in the [0, 100] range. Following the transformation, higher scores in the functional subscales/items represent a “better” level of functioning, while higher scores in the symptom subscales/items represent a “worse” level of symptoms.

Statistical Analysis Plan

Patient reported outcomes were exploratory endpoints of the EMBRACA study. There was no specific hypothesis testing plan, nor were there type I error adjustments for multiple comparisons.

The PRO analysis population consisted of patients with one baseline and one post-baseline PRO response with the analysis by the randomized treatment allocation.

The pre-specified PRO analyses included use of summary statistics per treatment group, per visit for each of the 15 subscales of EORTC-QLQ-C30, as well as for each of the 8 subscales of the EORTC-QLQ-BR23. Random effects models were to be used to model the Global Health Status/QOL subscale of the EORTC-QLQ-C30 and the breast symptoms subscale of the EORTC-QLQ-BR23 with treatment as a fixed covariate.

The Global Health Status/QOL from the EORTC-QLQ-C30 and the breast symptoms scale from EORTC-QLQ-BR23 were to be analyzed using time-to-event methods such as Kaplan-Meier probabilities and the Cox proportional hazards model. These methods would help compare time to deterioration between the two arms, with deterioration defined as:

- Global Health Status/QOL - Time from randomization to the first observation with at least a 10 point decrease and no subsequent observations with less than 10 point decrease from baseline.
- Breast symptom scale - Time from randomization to the first observation with at least a 10 point increase and no subsequent observations with less than 10 point increase from baseline.

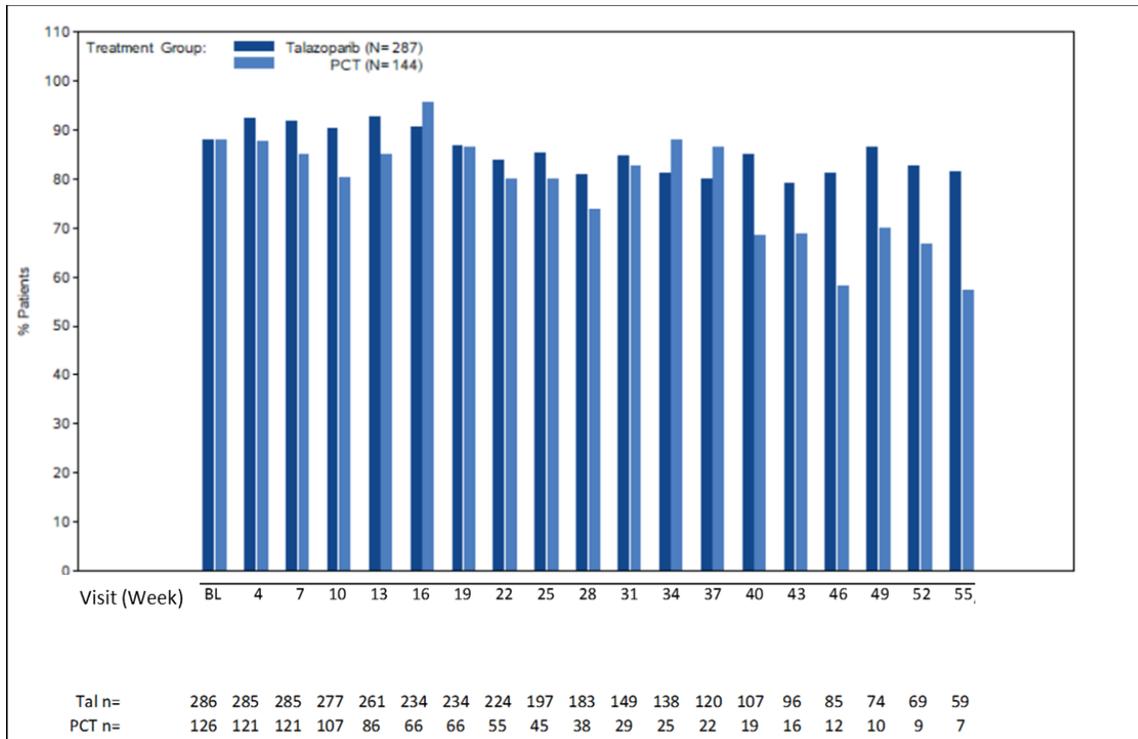
Reviewer Comments: *The time-to-deterioration analysis is considered as exploratory analysis. The definition of deterioration, as well as the 10 point cut-off used, are subjective and have not been validated in this patient population.*

PRO Results

EORTC-QLQ-C30 Results

Figure 10 shows the completion rate defined as the proportion of completed forms, forms with all subscales having less than half of items missing. The denominator is equal to the number of patients on treatment at the assessment. There was around or above 70% compliance in the first 15 assessments (up to and including Week 43). There was no evidence that overall completion rates were dissimilar between the treatment arms.

Figure 10: EORTC-QLQ-C30 Completion*, denominator is number of patients eligible (on-going treatment)



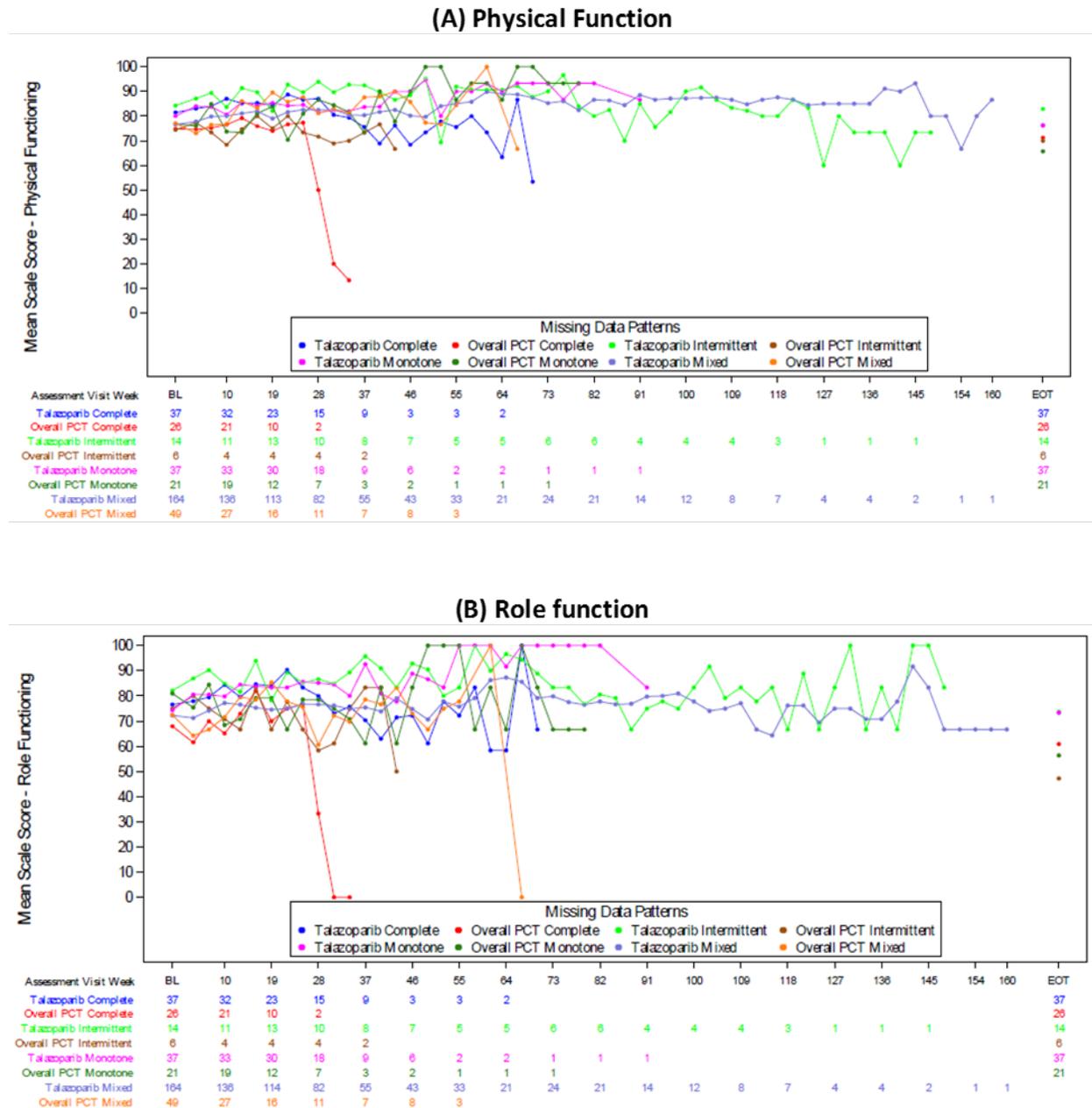
* Complete if all subscales had less than 50% missing items,
 Source: CSR, ADQOL.XPT, Response to IR dated April 30, 2018

Figure 11 gives the means of the physical function scores and the role function scores, grouped by missing data pattern. Patterns are defined as complete, intermittent missing, monotone missing, and mixed following the classification rules below:

- Complete: PRO assessments at all time points including EOT (end of treatment)
- Monotone Missing: PRO assessments at Baseline and EOT; and only one continuous period of missing PRO assessment between baseline and EOT
- Of the remaining:
 - Intermittent Missing: If PRO assessment at EOT present
 - Mixed: IF PRO assessment at EOT absent

Note: Patients with missing baseline were removed; patients who have PRO assessment at EOT and EOT reason is non-PD were removed.

Figure 11: Mean score for EORTC-QLQ-C30 domain scores (Physical and Role function) by visit and by type of missing data patterns

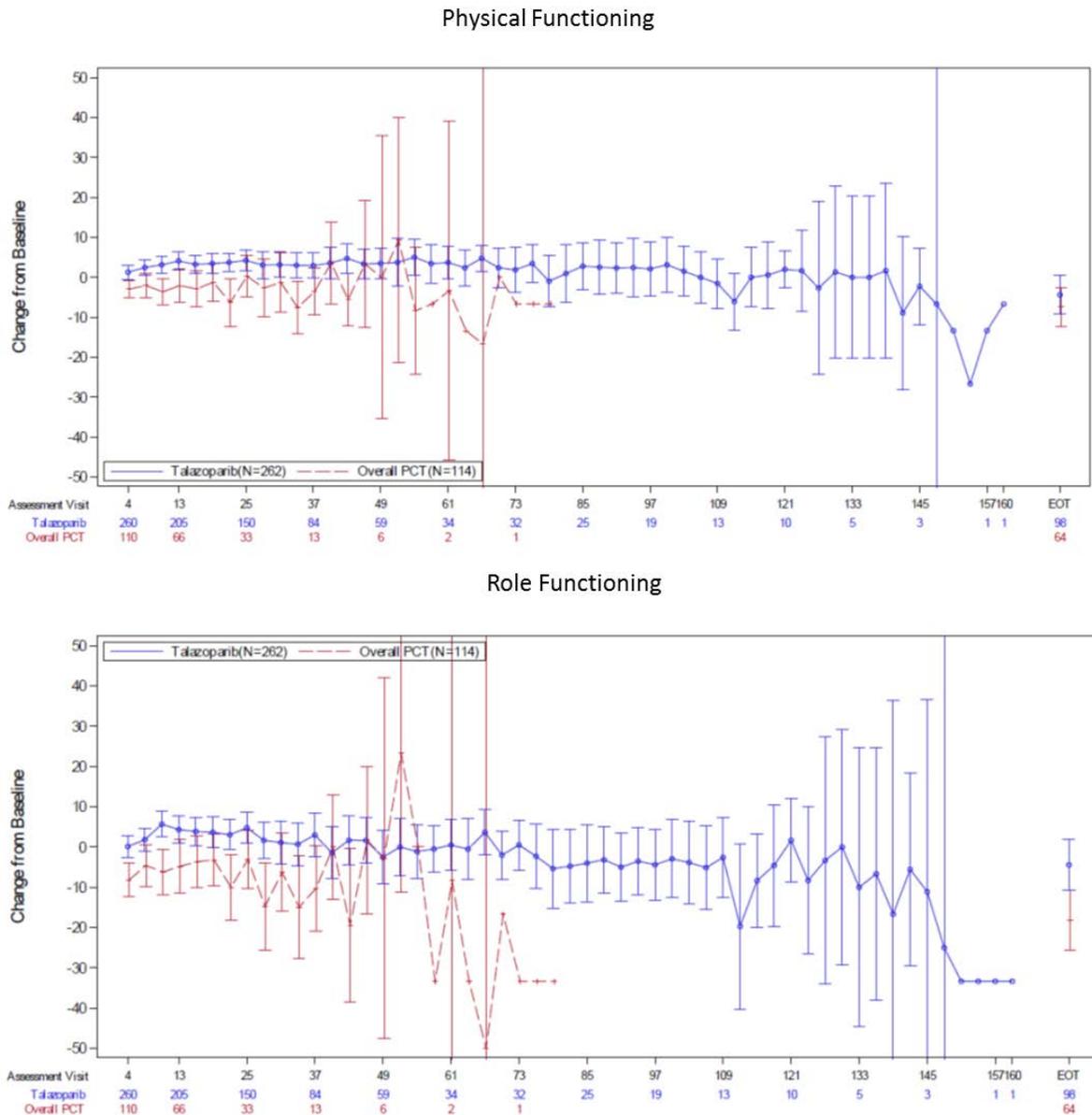


Source: IR response dated July, 12, 2018

Reviewer's comments: *There is no evidence that the treatment influences missingness or that missingness has an effect on either the physical function or role function score. The percentage of missing is higher in the PCT arm because fewer patients were randomized to this arm (2:1 randomization ratio) and 18 patients discontinued the trial right after randomization.*

Figure 12 show the mean of change from baseline per visit for the Physical and Role function subscale. The talazoparib arm has relatively stable mean of change from baseline score within the first year, following randomization.

Figure 12: Changes from baseline scores for EORTC-QLQ-C30 Physical function and Role function score, higher values indicate better outcomes.



Source: ADQOL.XPT, Response to IR, April 30th, 2018

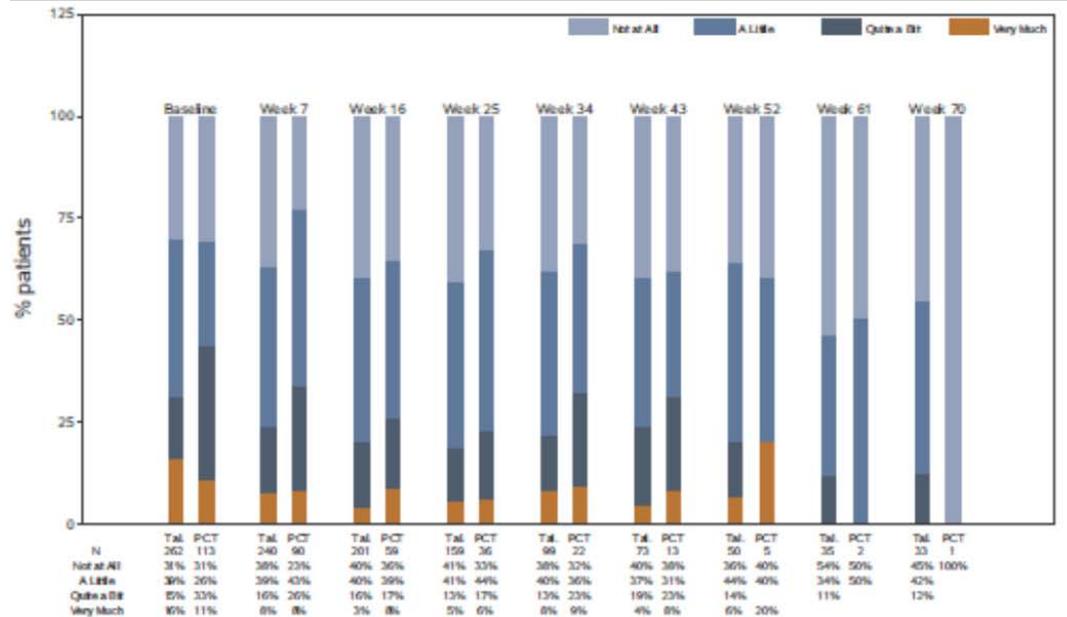
Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Reviewer's comments: These analyses are considered exploratory analyses. EMBRACA was an open label trial, PRO outcomes are therefore likely to be biased. There is also relatively low information on PCT arm after Week 37 for meaningful inference.

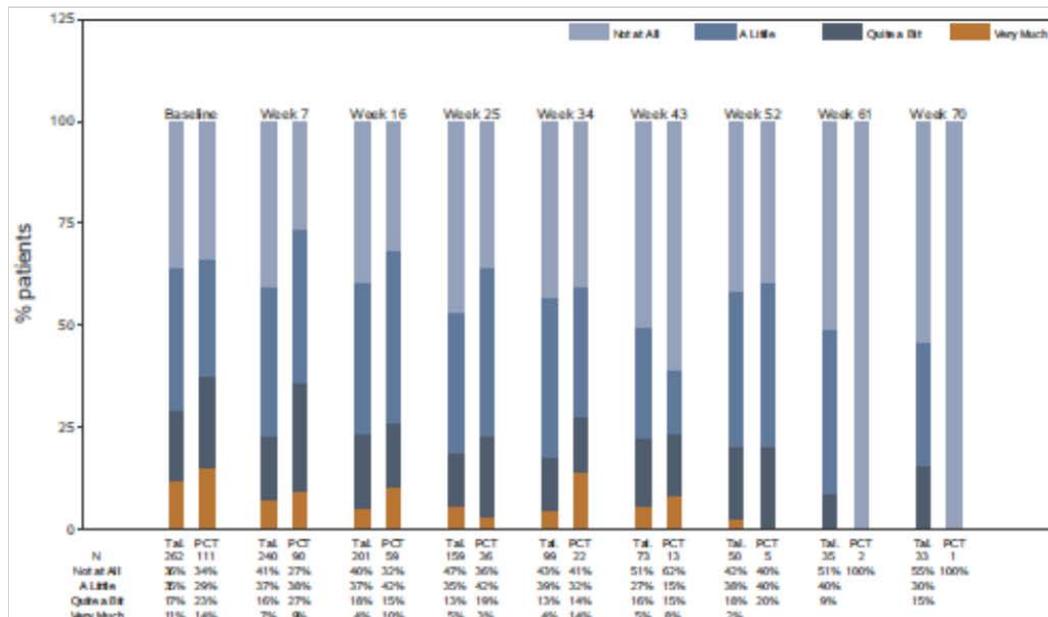
Figure 13 gives the distribution of raw scores per assessment visit for EORTC-QLQ-C30 physical and role function items (Item 1-7).

Figure 13: Distribution of raw scores by visit for EORTC-QLQ-C30 physical and role function items

Item 1: Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase

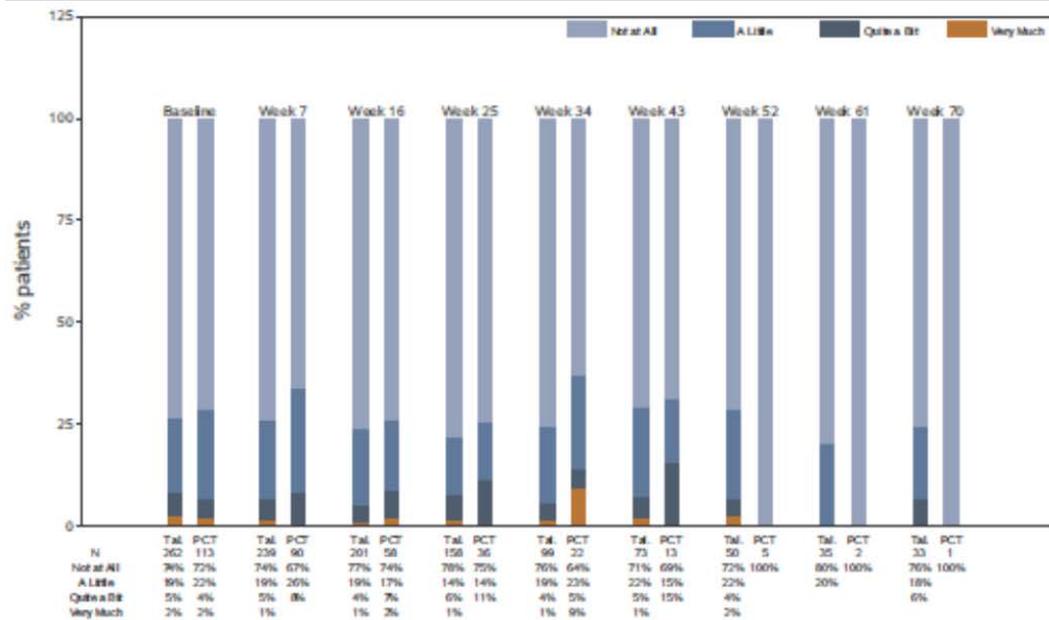


Item 2: Do you have any trouble taking a long walk

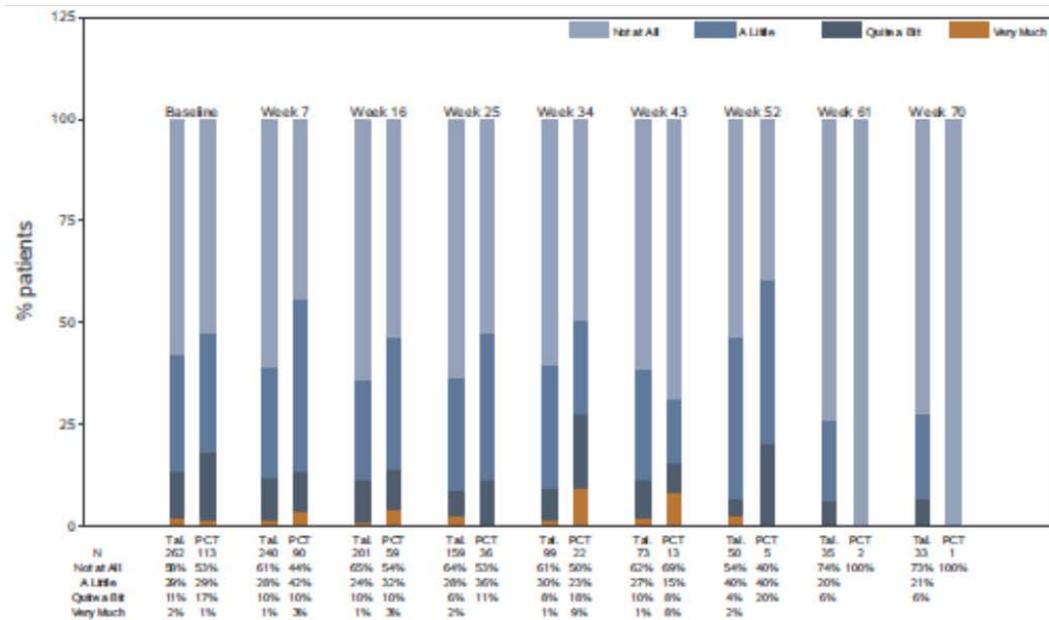


Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

Item 3: Do you have any trouble taking a short walk outside of the house

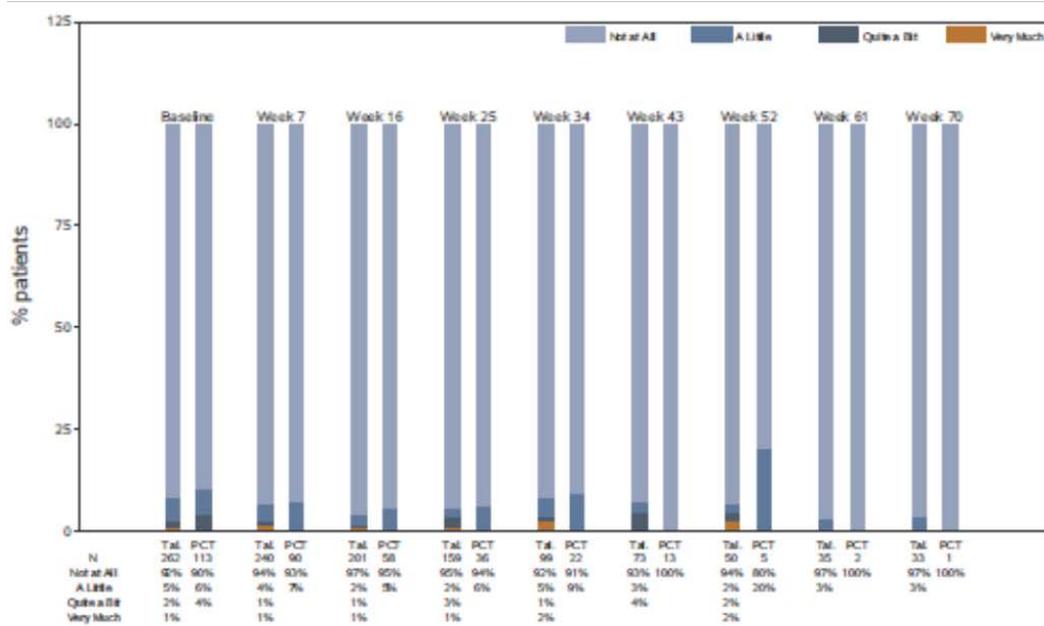


Item 4: Do you need to stay in bed or a chair during the day

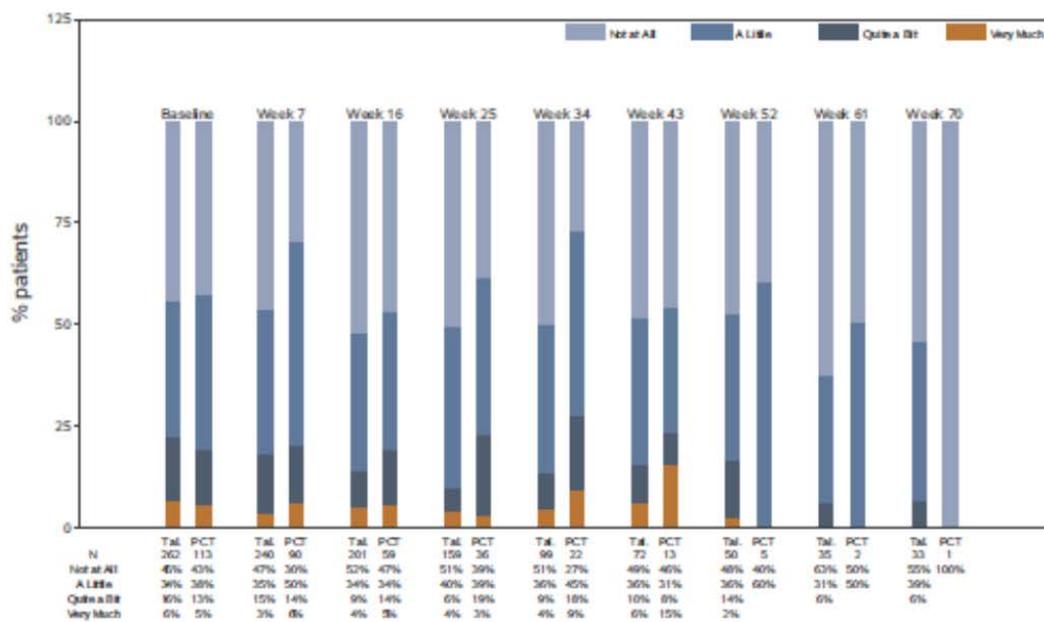


Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

Item 5: Do you need help with eating, dressing, washing yourself or using the toilet

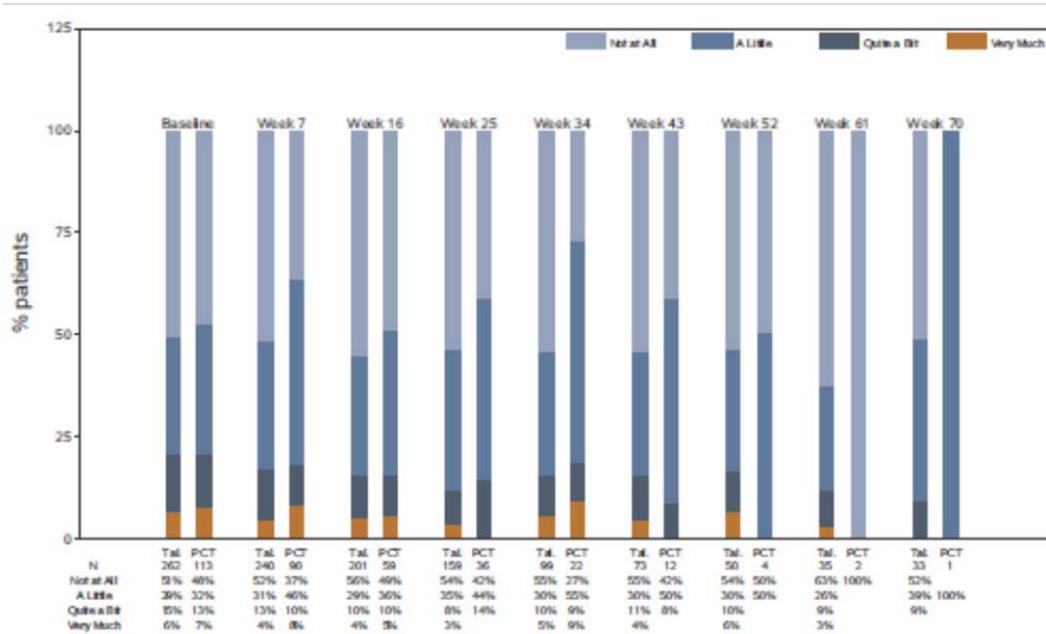


Item 6: Were you limited in doing either your work or other daily activities



Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Item 7: Were you limited in pursuing your hobbies or other leisure time activities



Source: IR response dated July, 12, 2018

The review team also identified several symptom items in EORTC QLQ-C30 and BR-23 for further descriptive exploratory analysis on tolerability. These items included the following:

EORTC QLQ-C30

- Pain (items 9 and 19)
- Fatigue (items 10, 12, and 18)
- Appetite loss (item 13)
- Nausea (item 14)
- Vomiting (item 15)
- Constipation (item 16)
- Diarrhea (item 17)

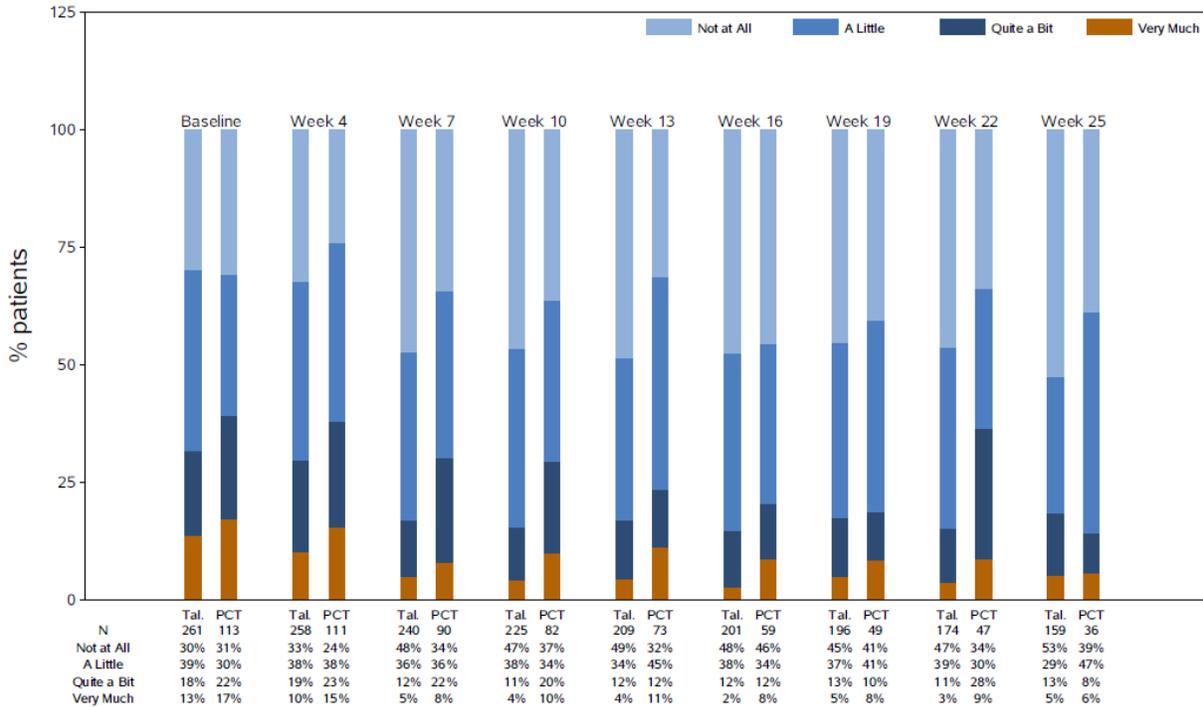
EORTC QLQ BR-23

- Alopecia (items 34 and 35)
- Headache (item 38)

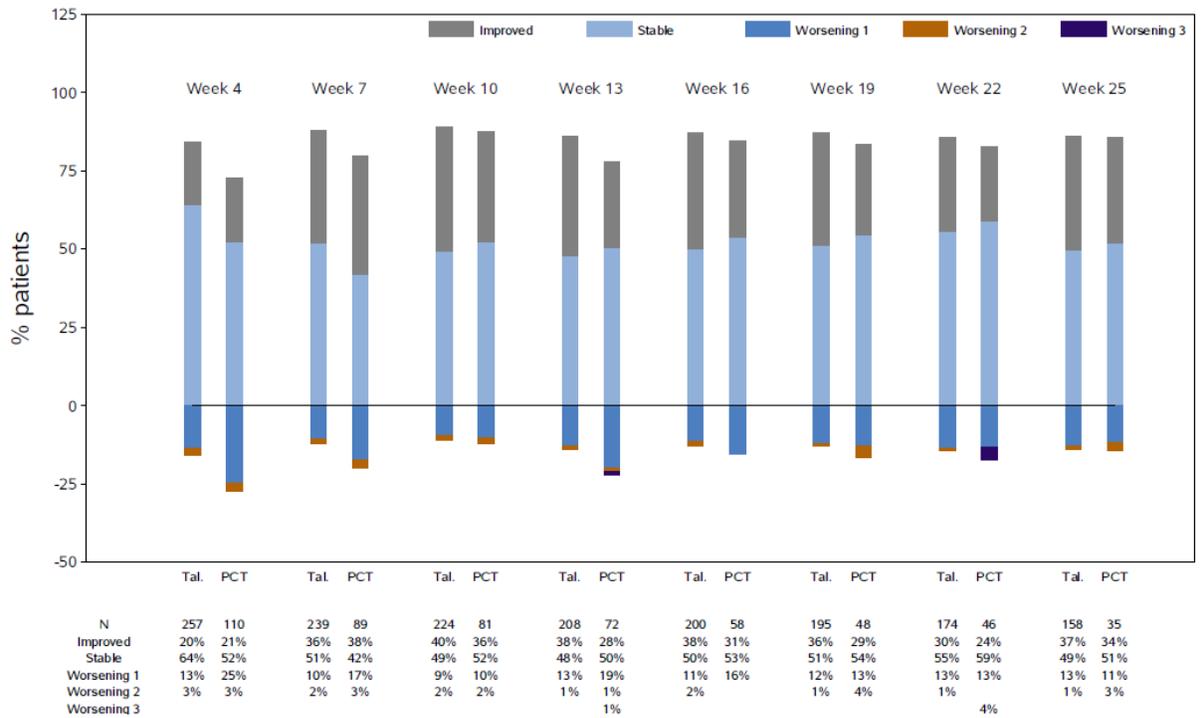
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC QLQ-C30 Item 9: Have you had pain

Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of score categories by visit (first 6 months) - (PRO-Evaluable Population)
 9: Have you had pain



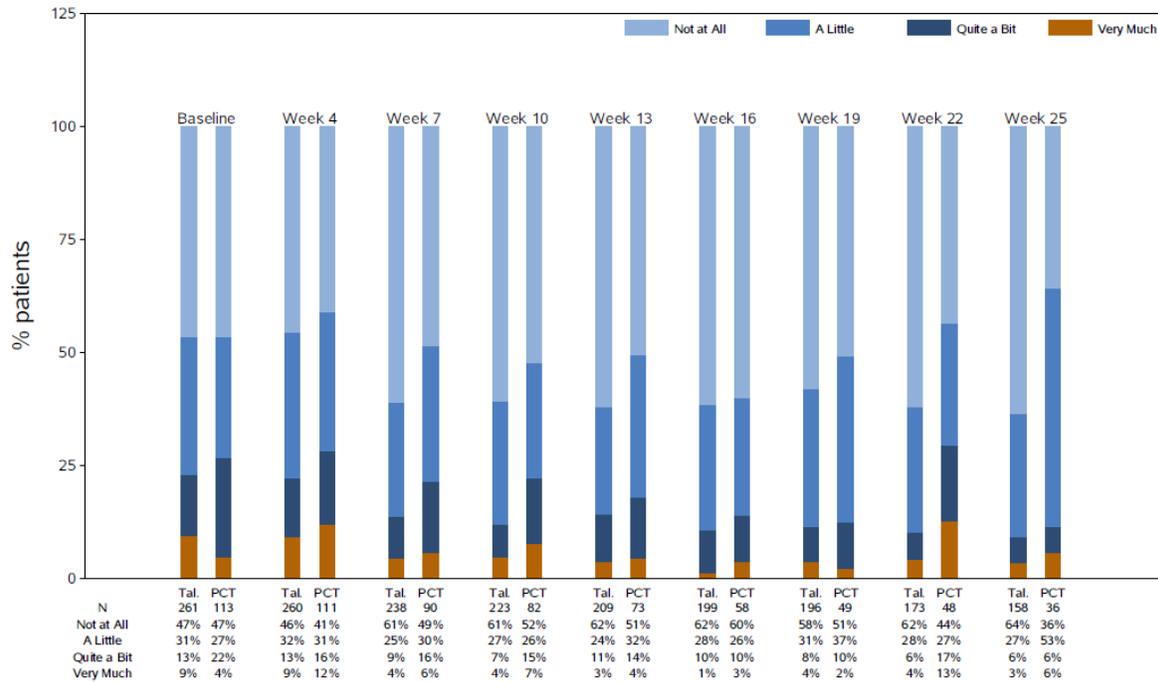
Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 9: Have you had pain



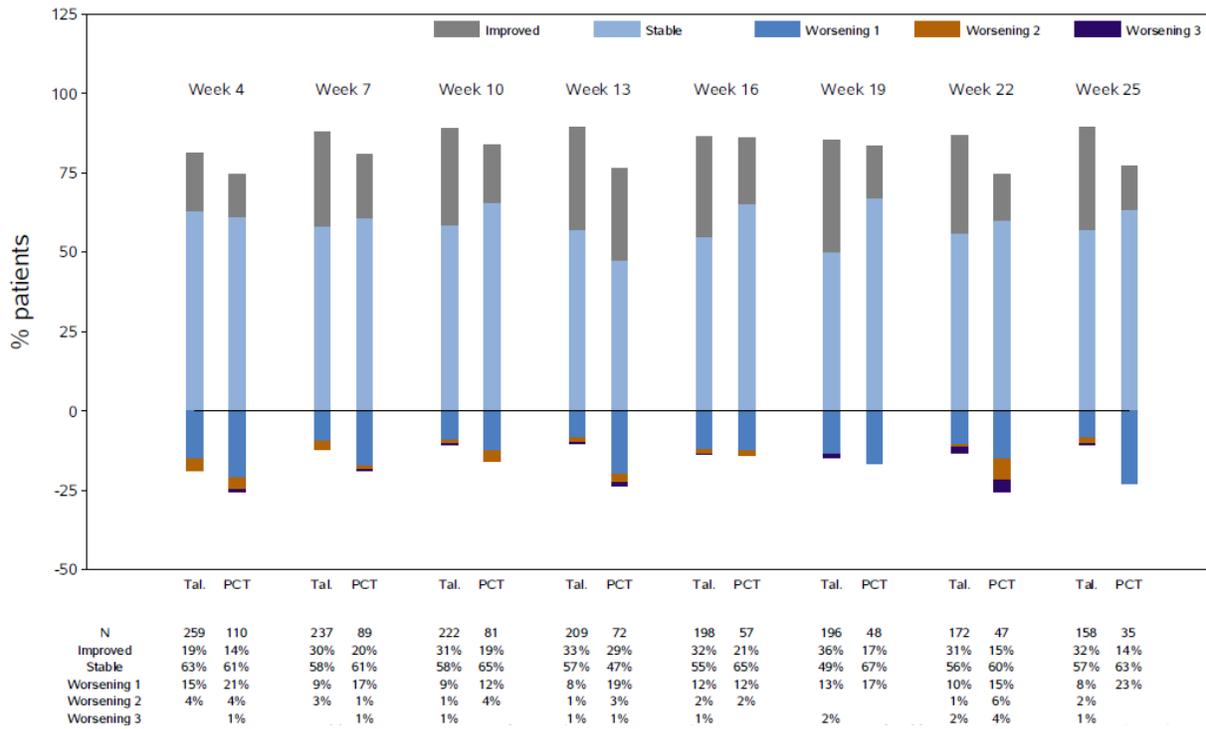
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC QLQ-C30 Item 19: Did pain interfere with your daily activities

Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of score categories by visit (first 6 months) - (PRO-Evaluable Population)
 19: Did pain interfere with your daily activities



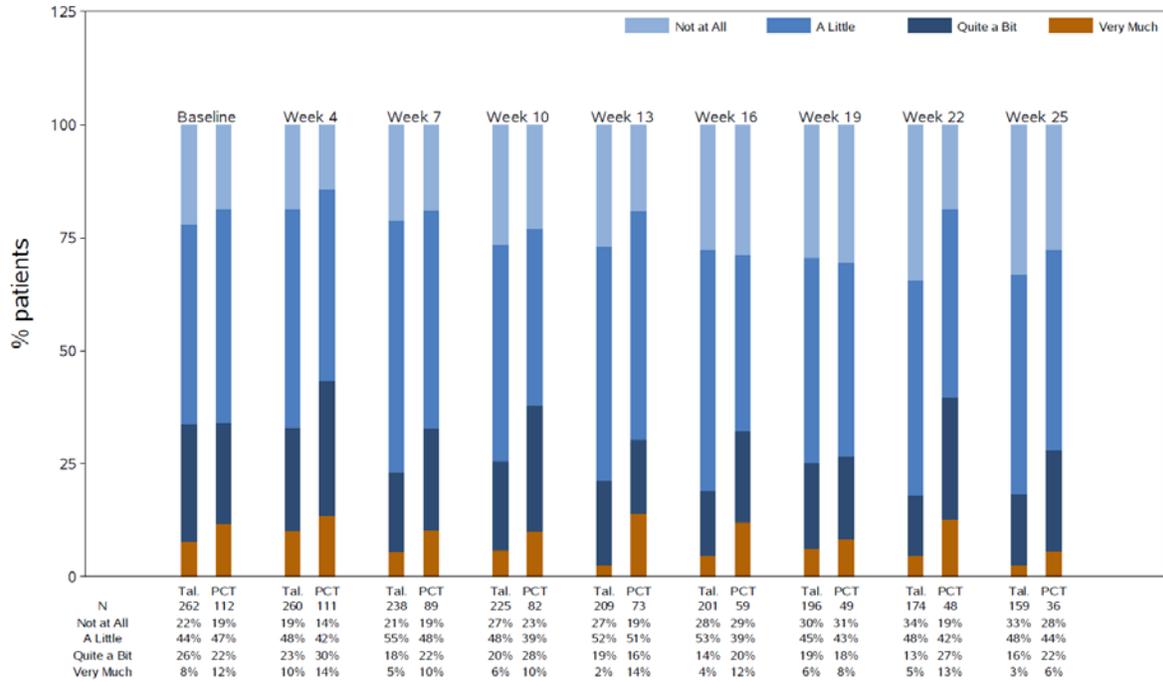
Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 19: Did pain interfere with your daily activities



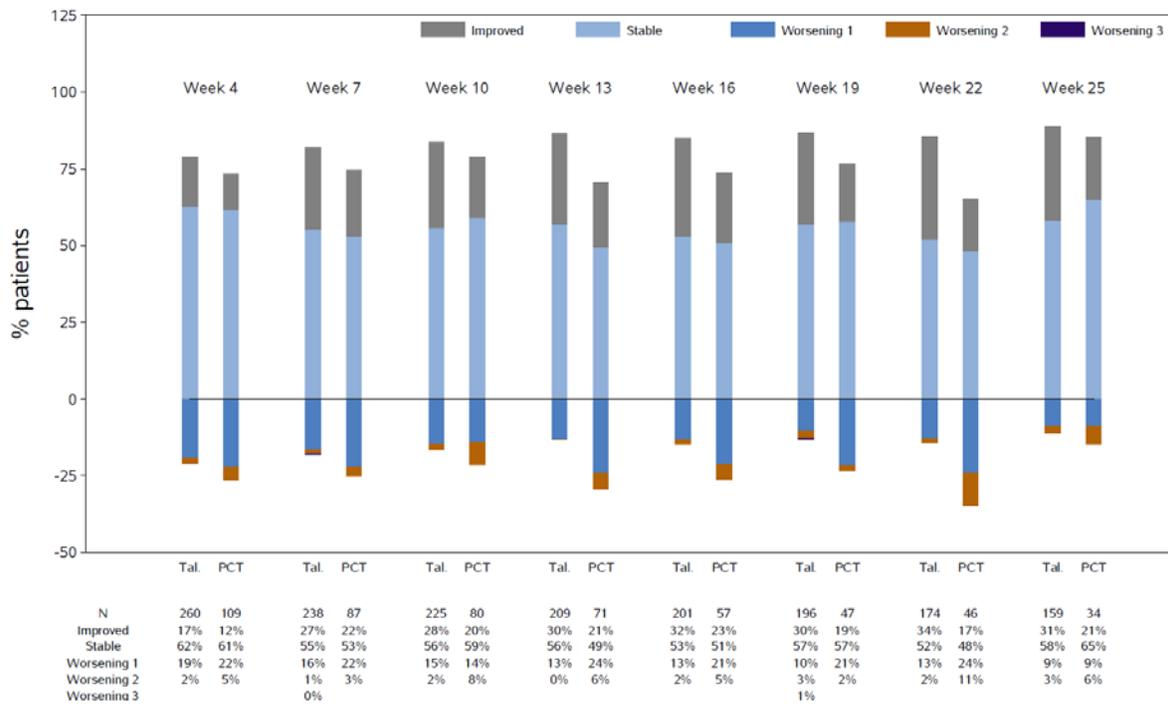
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC QLQ-C30 Item 10: Did you need to rest

Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of score categories by visit (first 6 months) - (PRO-Evaluable Population)
 10: Did you need to rest



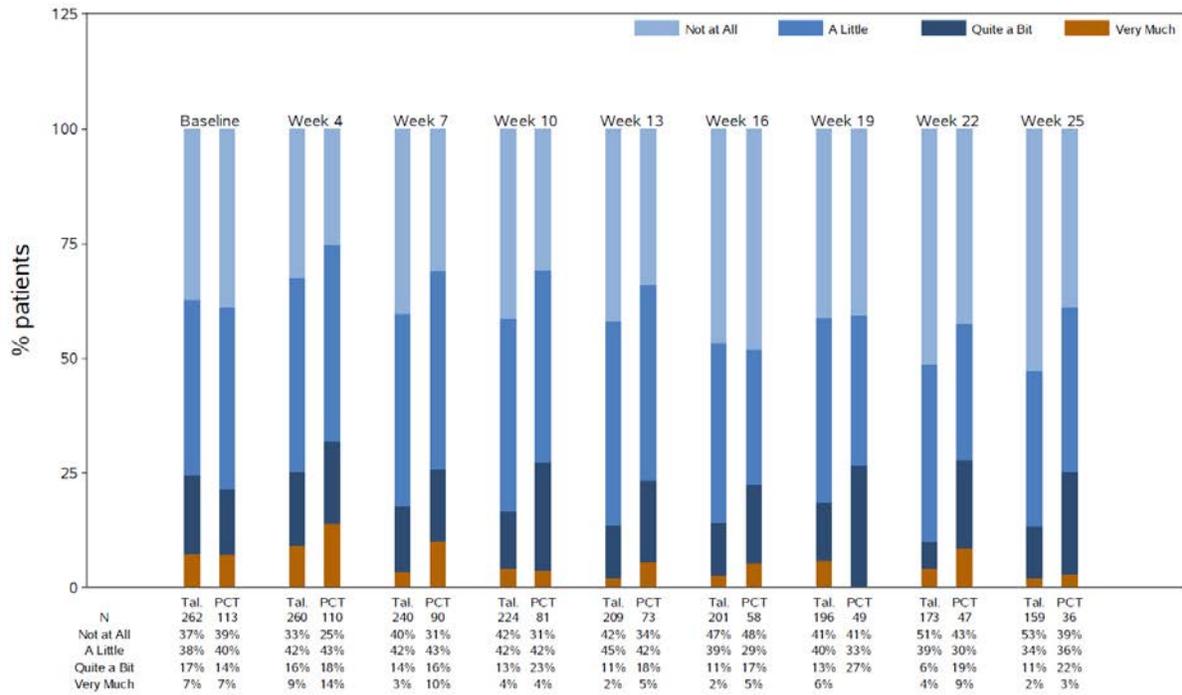
Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 10: Did you need to rest



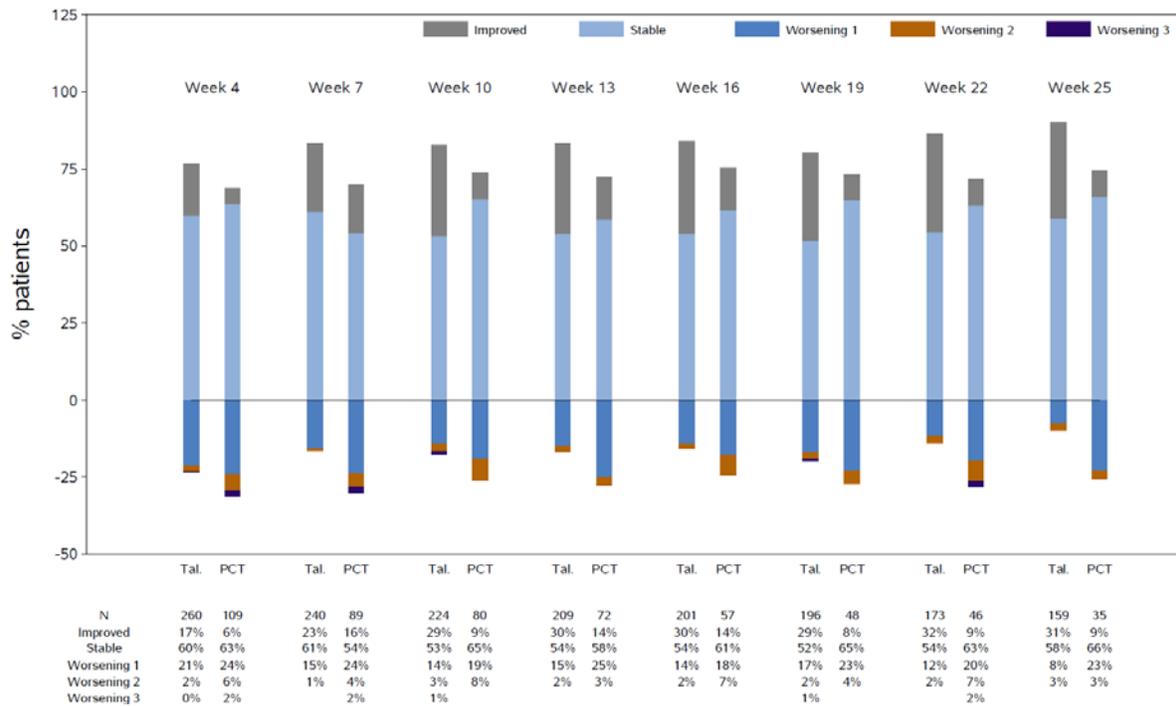
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC QLQ-C30 Item 12: Have you felt weak

12: Have you felt weak



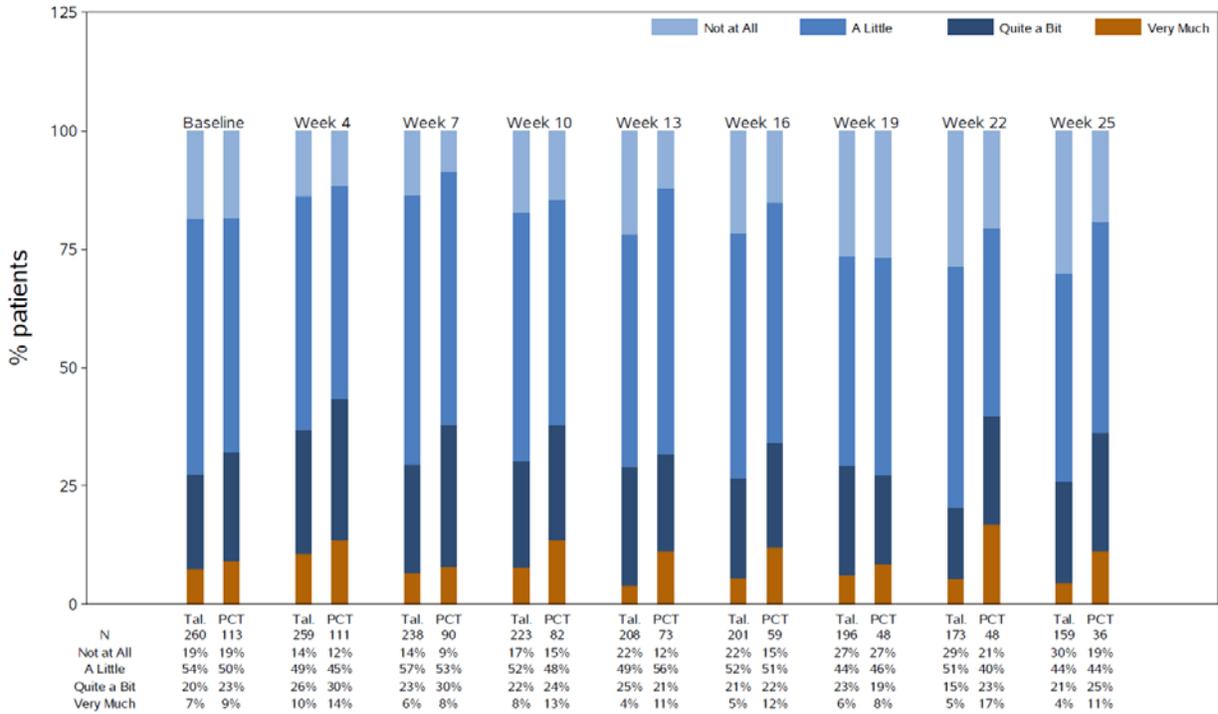
Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 12: Have you felt weak



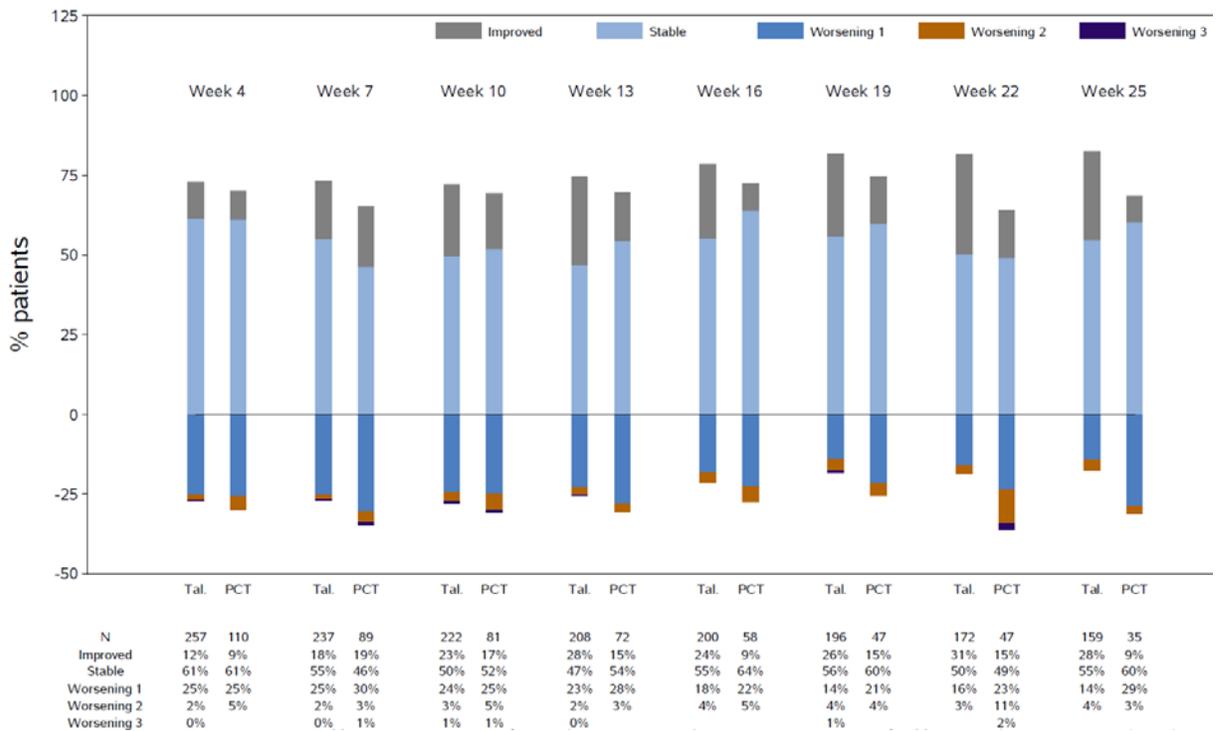
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC QLQ-C30 Item 18: Were you tired

Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of score categories by visit (first 6 months) - (PRO-Evaluable Population)
 18: Were you tired



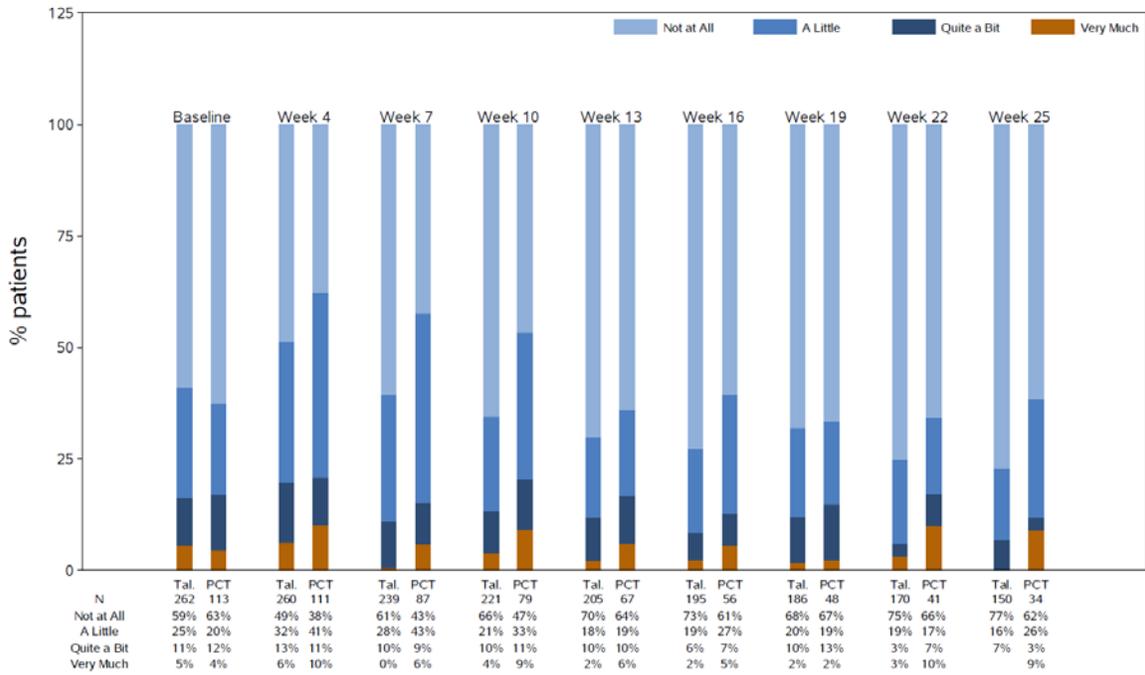
Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 18: Were you tired



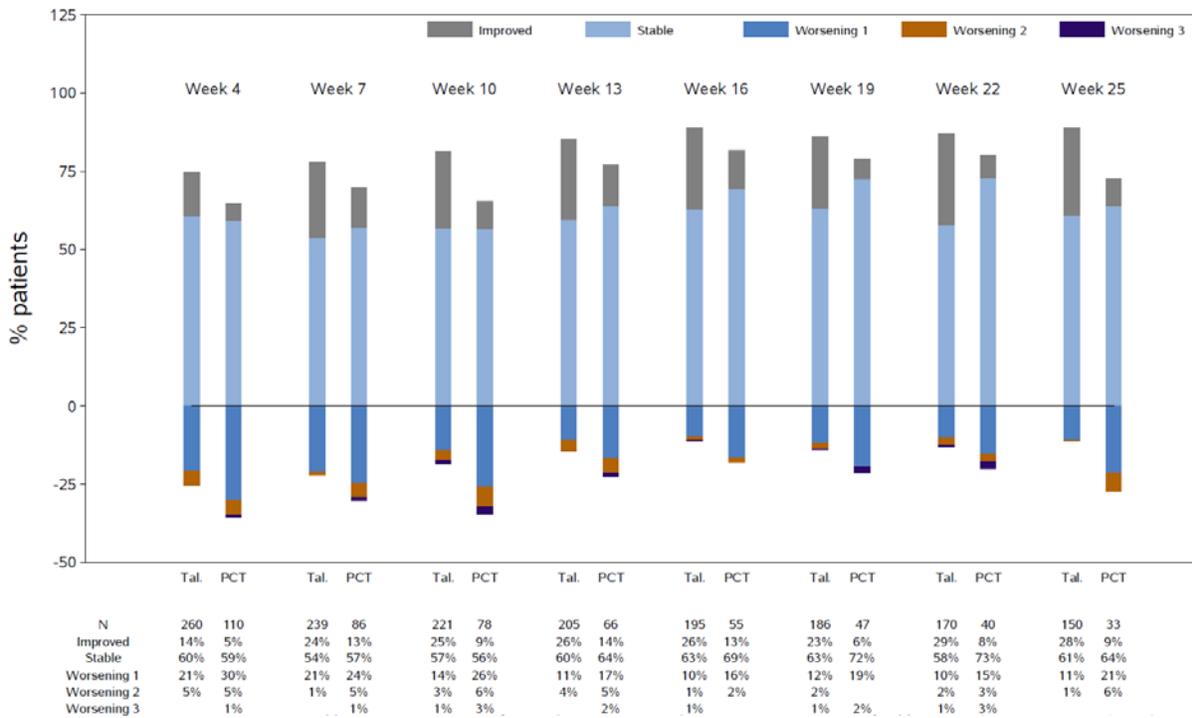
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC QLQ-C30 Item 13: Have you lacked appetite

Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of score categories by visit (first 6 months) - (PRO-Evaluable Population)
 13: Have you lacked appetite

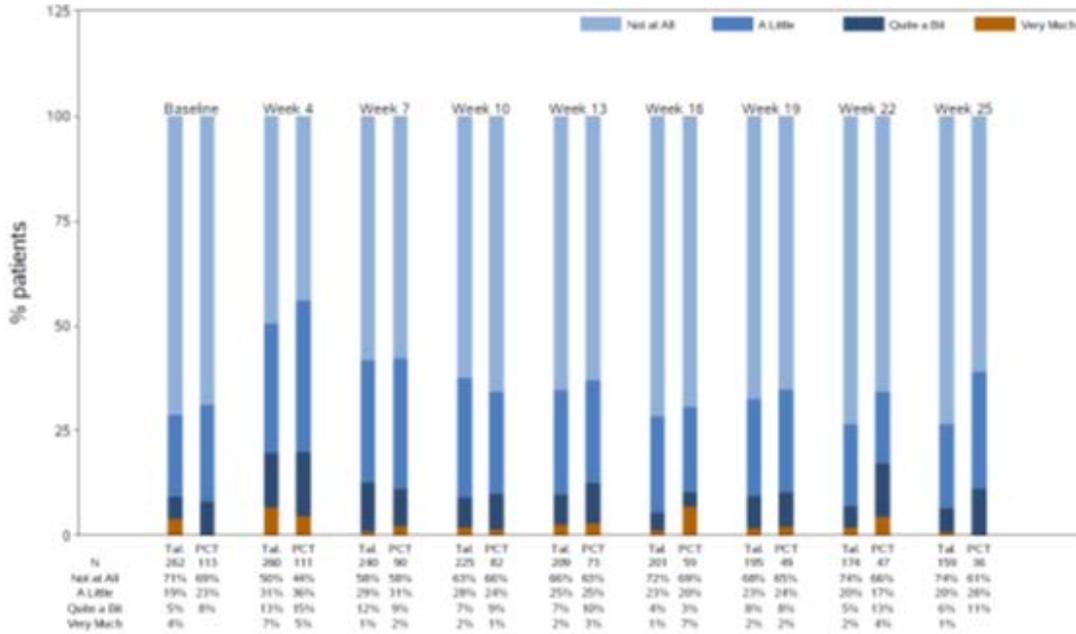


Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 13: Have you lacked appetite

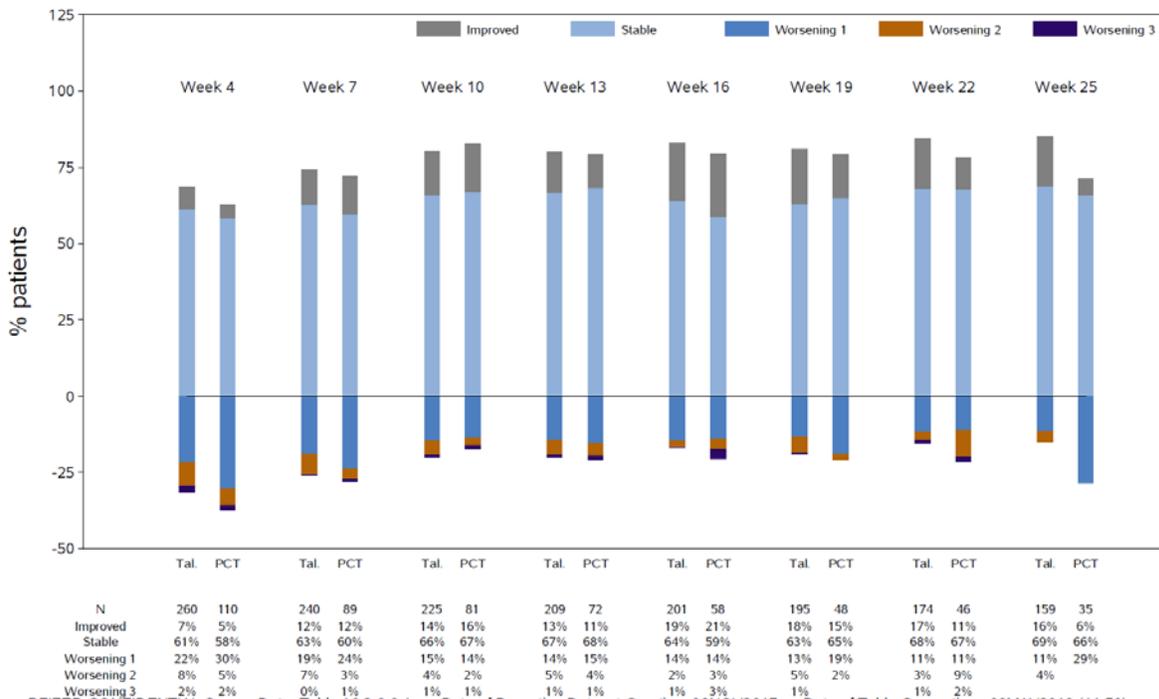


EORTC QLQ-C30 Item 14: Have you felt nauseated

Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of score categories by visit (first 6 months) - (PRO-Evaluable Population)
 14: Have you felt nauseated



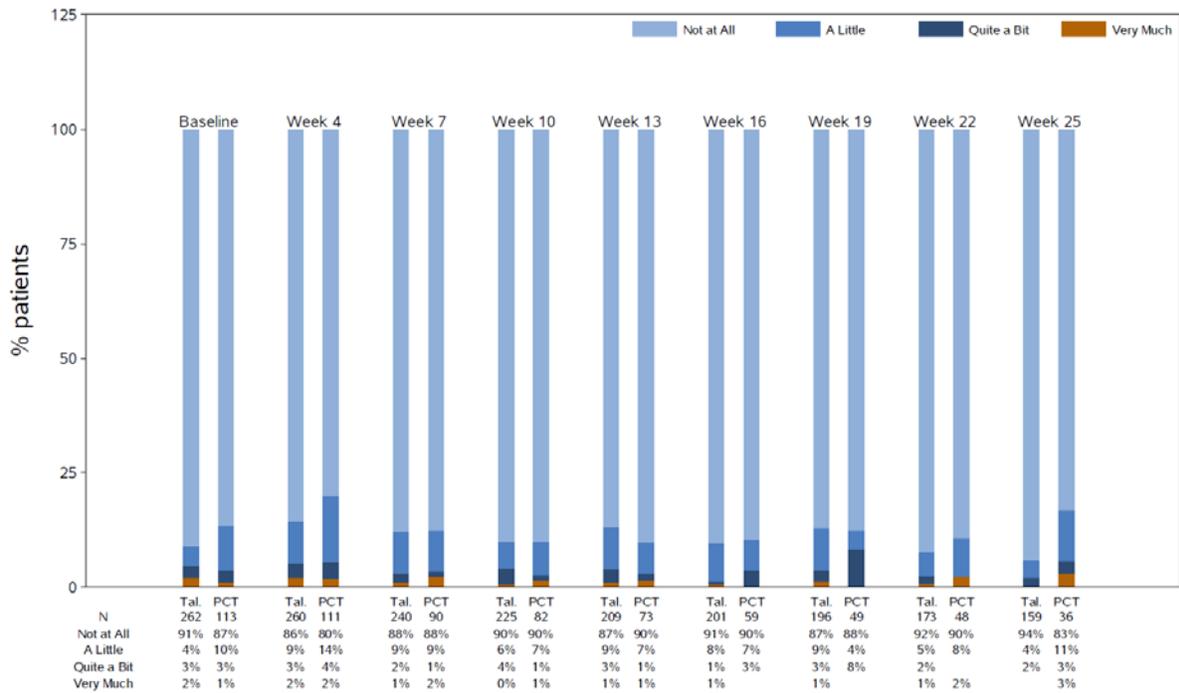
Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 14: Have you felt nauseated



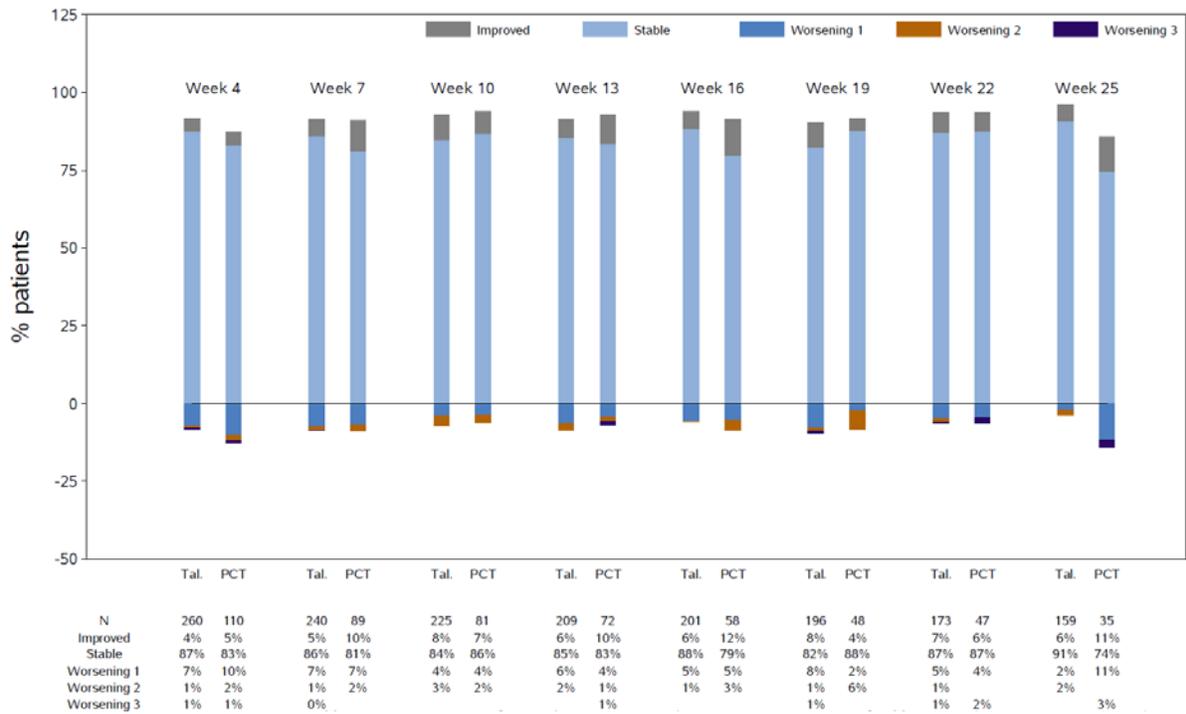
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC QLQ-C30 Item 15: Have you vomited

Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of score categories by visit (first 6 months) - (PRO-Evaluable Population)
 15: Have you vomited



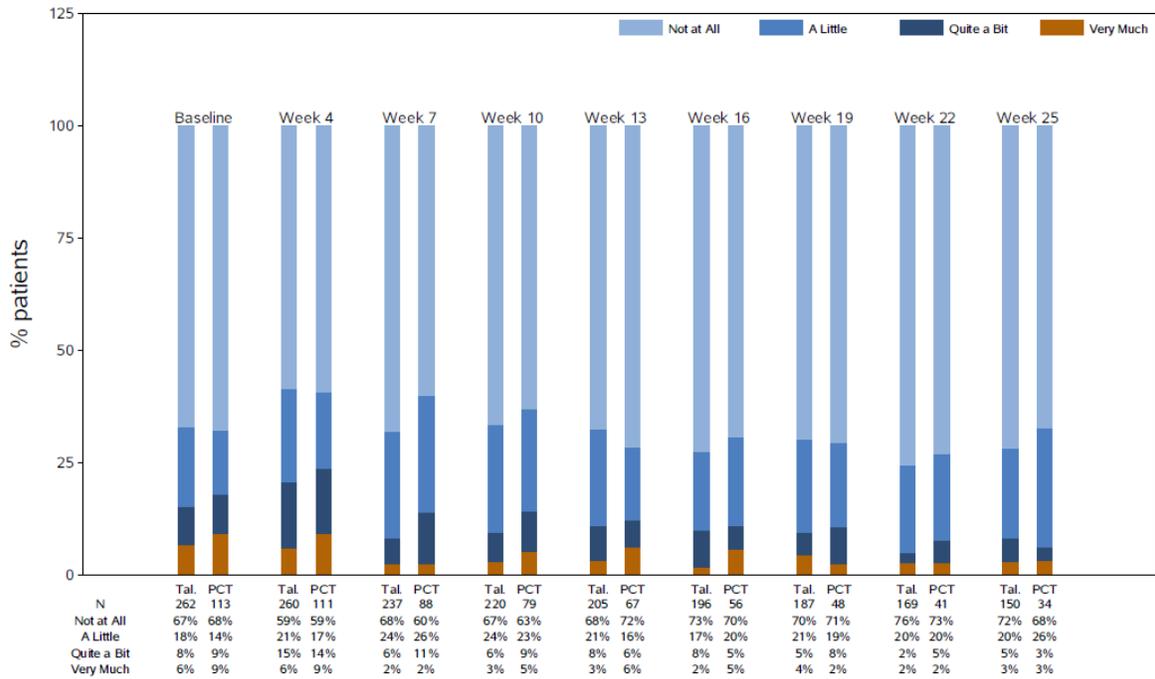
Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 15: Have you vomited



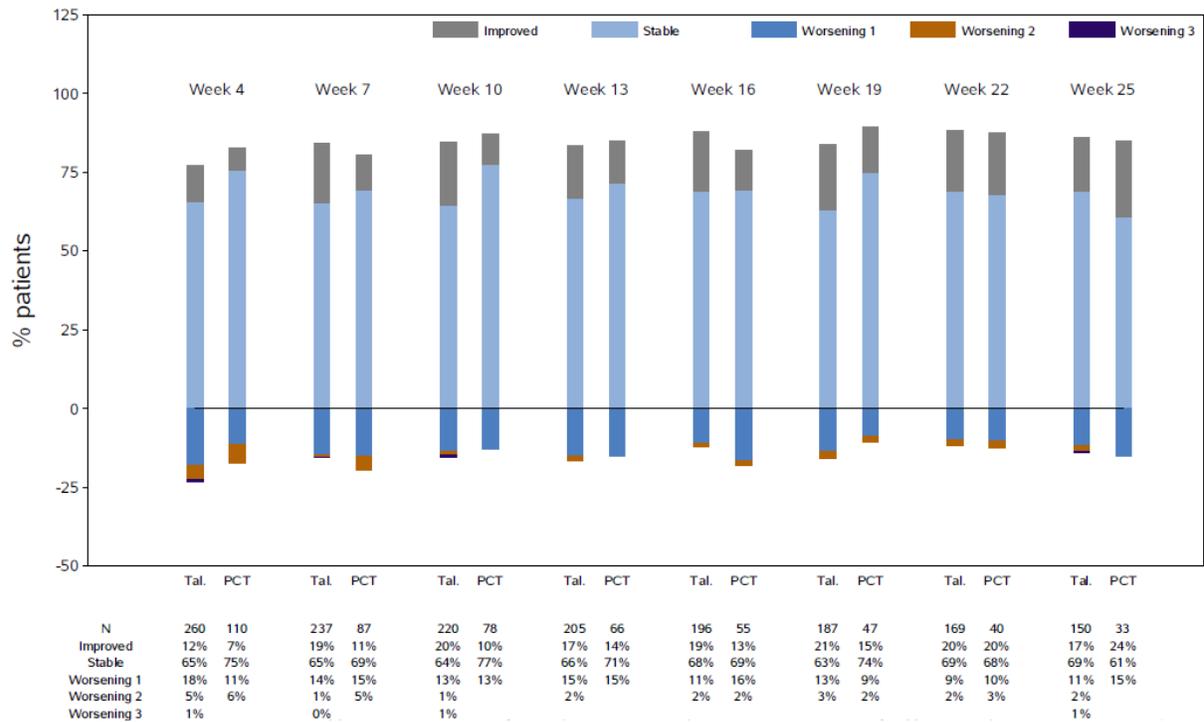
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC QLQ-C30 Item 16: Have you been constipated

Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of score categories by visit (first 6 months) - (PRO-Evaluable Population)
 16: Have you been constipated



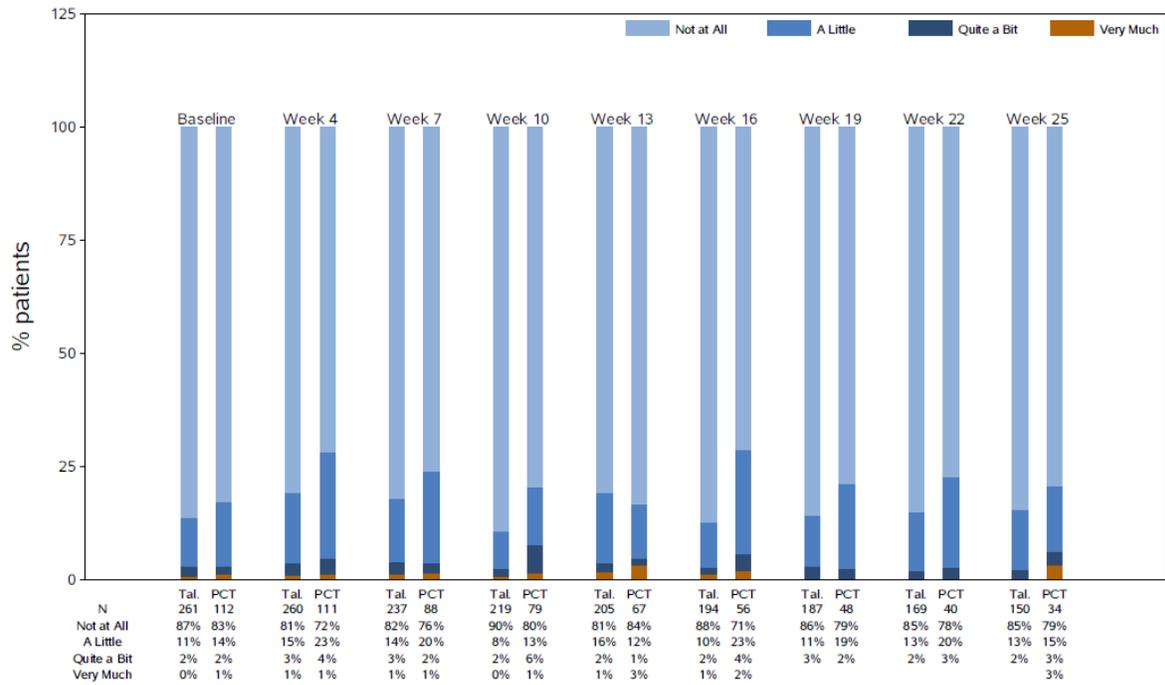
Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 16: Have you been constipated



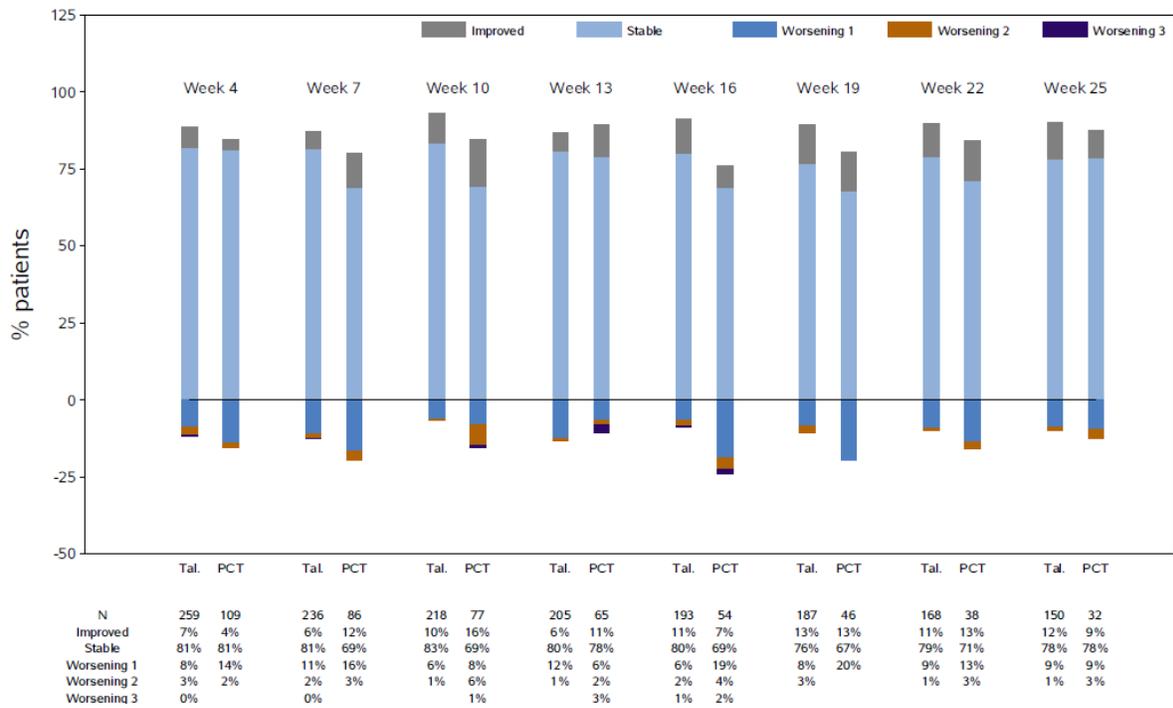
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC QLQ-C30 Item 17: Have you had diarrhea

Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of score categories by visit (first 6 months) - (PRO-Evaluable Population)
 17: Have you had diarrhea



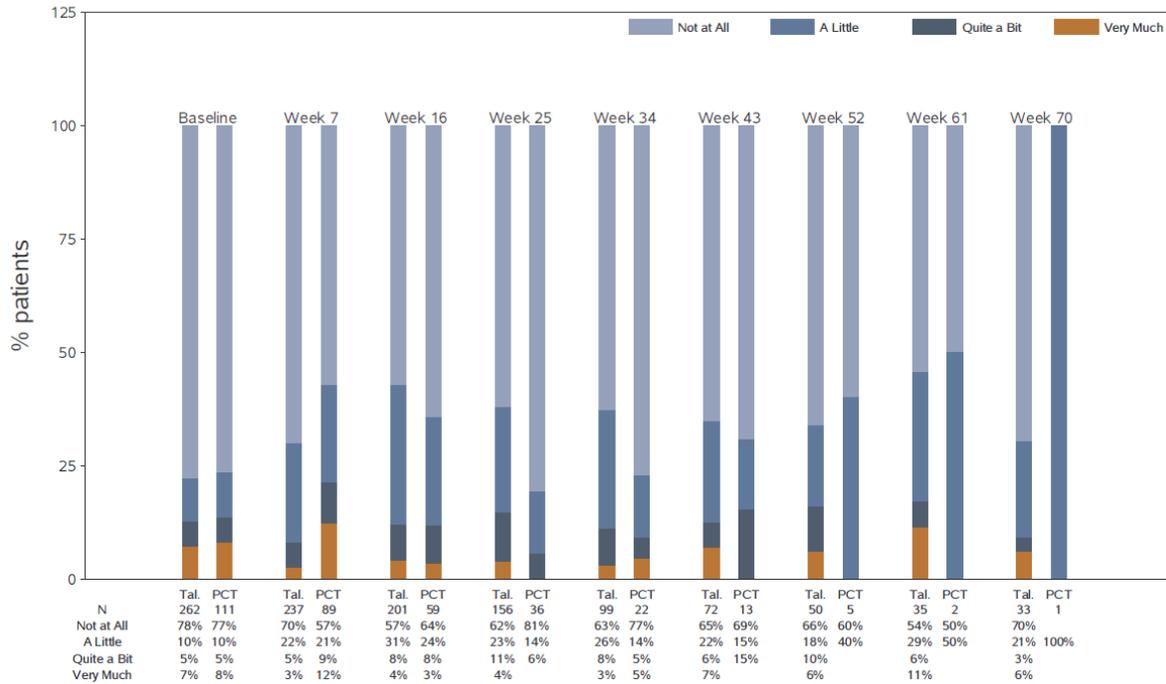
Bar chart of EORTC QLQ-C30 Item level analysis - Distribution of Change from Baseline score categories by visit (first 6 months) - (PRO-Evaluable Population)
 17: Have you had diarrhea



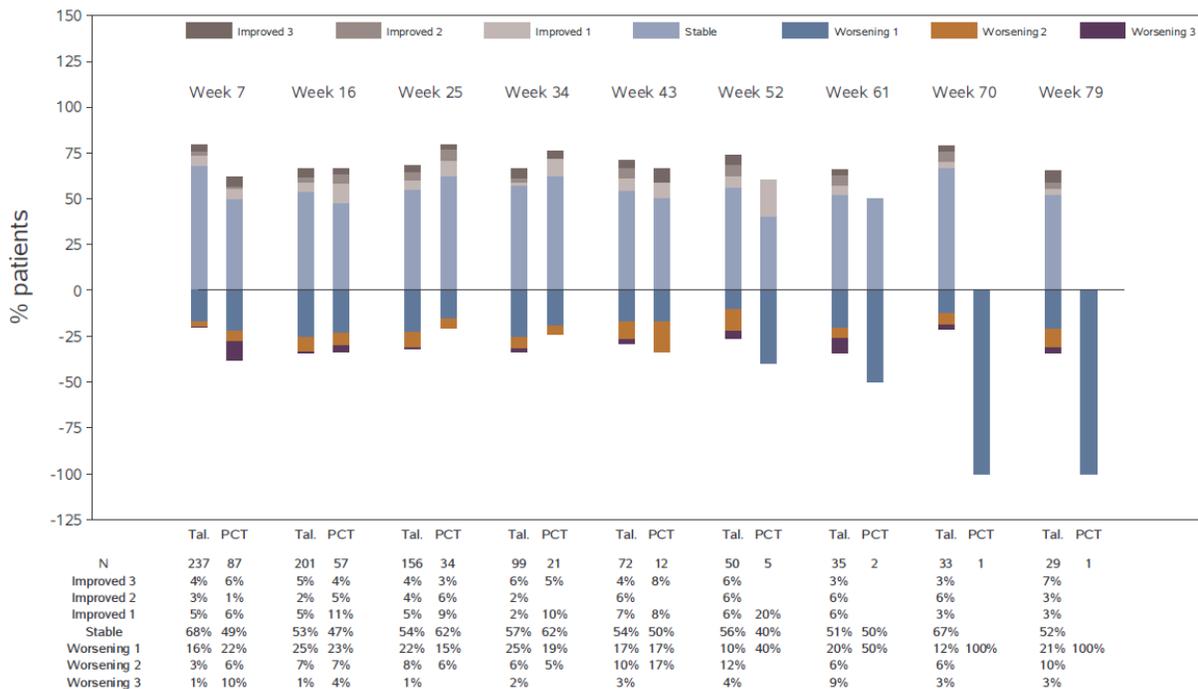
Multi-disciplinary Review and Evaluation NDA 211651
 TALZENNA (Talazoparib)

EORTC-QLQ-BR23 Item 34: Have you lost any hair

Bar chart of EORTC QLQ-BR23 Item level analysis - Distribution of score categories by visit - (PRO-Evaluable Population)
 34: Have you Lost Any Hair



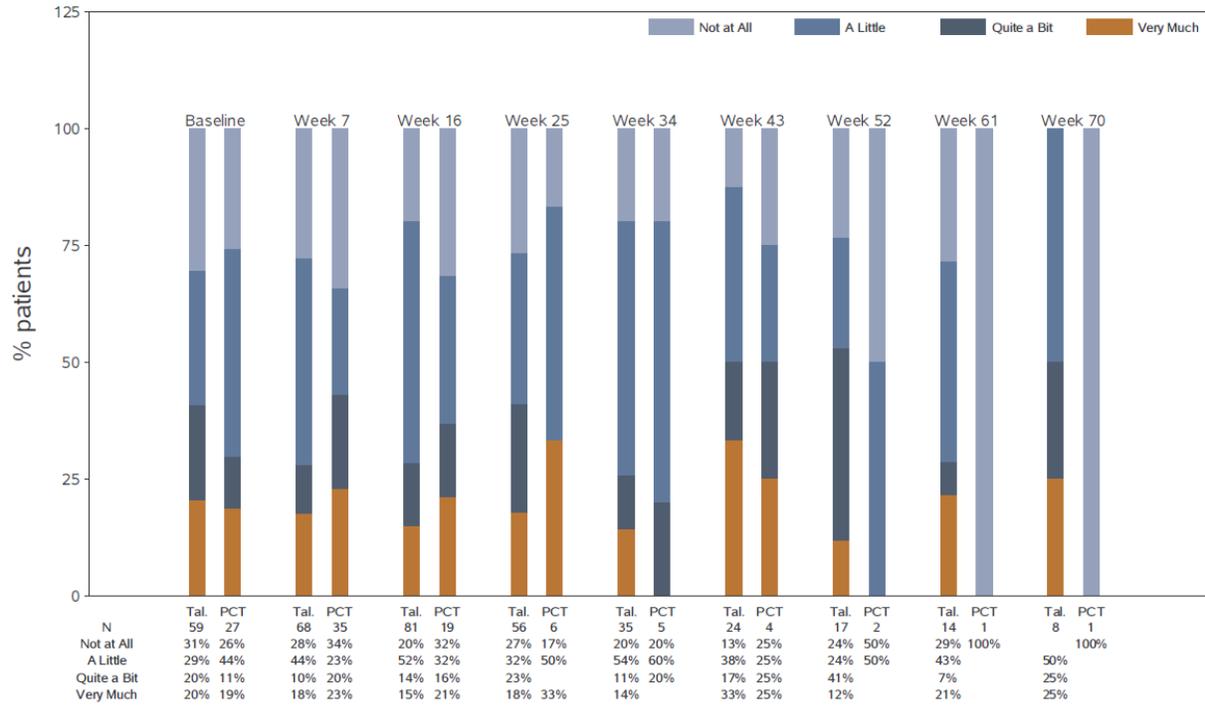
Bar chart of EORTC QLQ-BR23 Item level analysis - Distribution of Change from Baseline original score categories by visit - (PRO-Evaluable Population)
 34: Have you Lost Any Hair



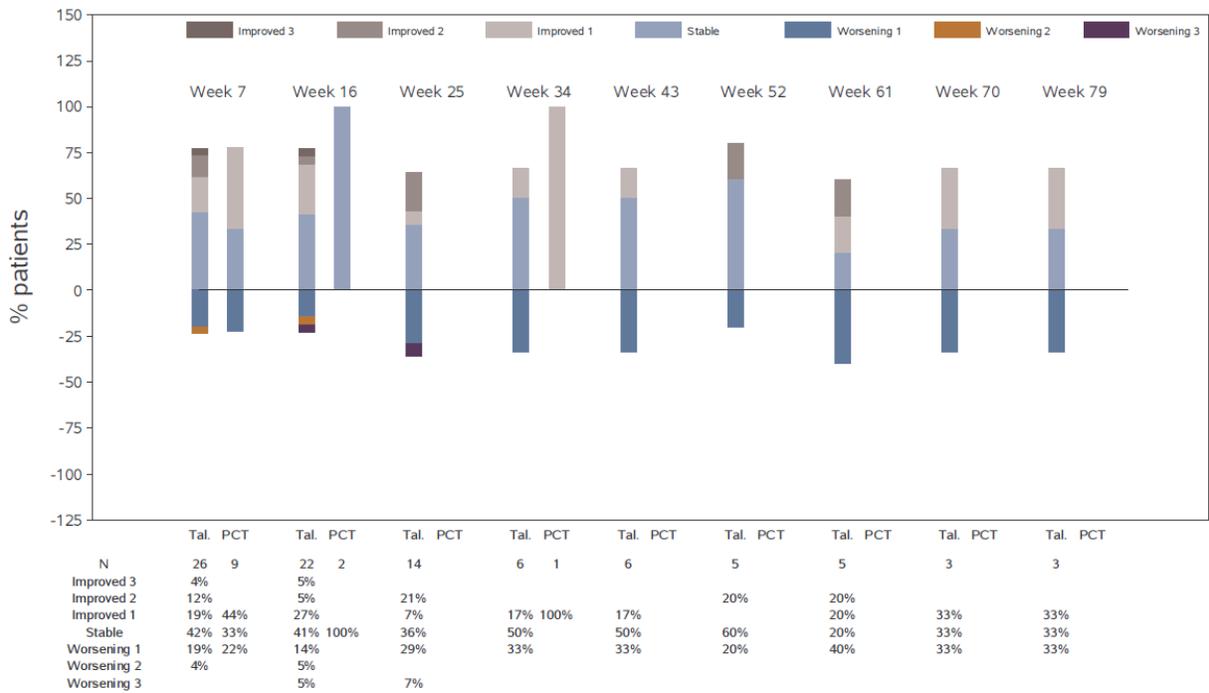
EORTC-QLQ-BR23 Item 35: Were you upset by the loss of your hair

Multi-disciplinary Review and Evaluation NDA 211651 TALZENNA (Talazoparib)

Bar chart of EORTC QLQ-BR23 Item level analysis - Distribution of score categories by visit - (PRO-Evaluable Population)
35: Were you upset by the loss of your hair



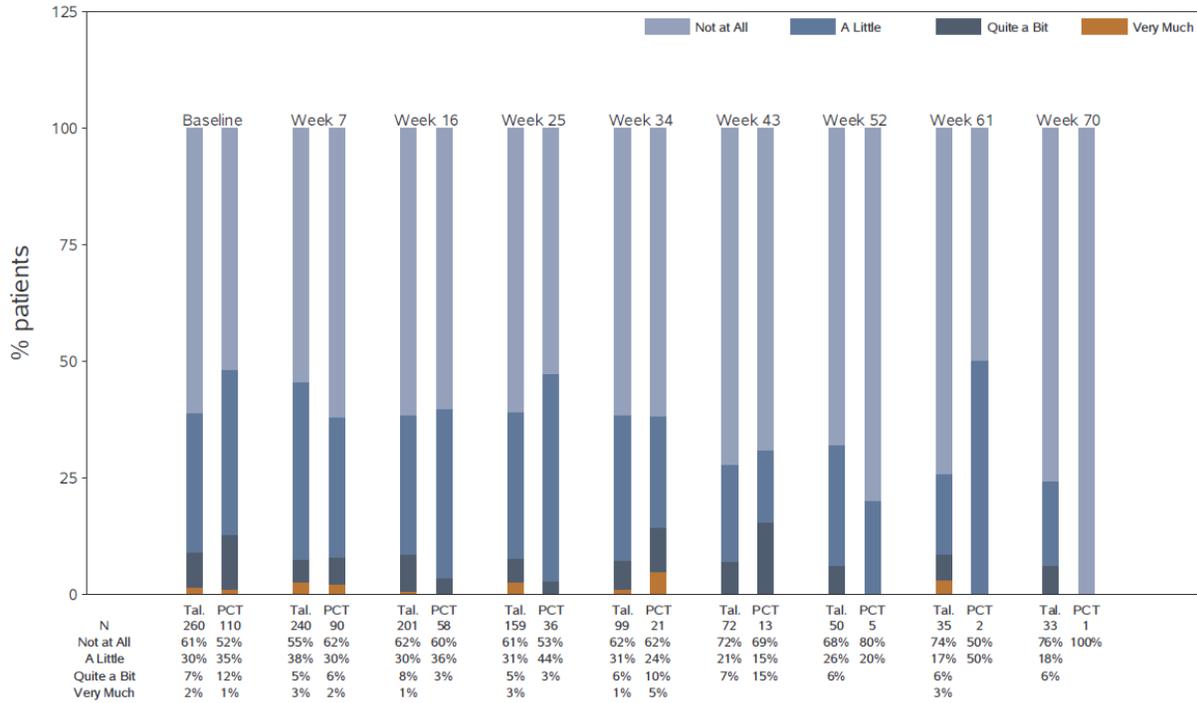
Bar chart of EORTC QLQ-BR23 Item level analysis - Distribution of Change from Baseline original score categories by visit - (PRO-Evaluable Population)
35: Were you upset by the loss of your hair



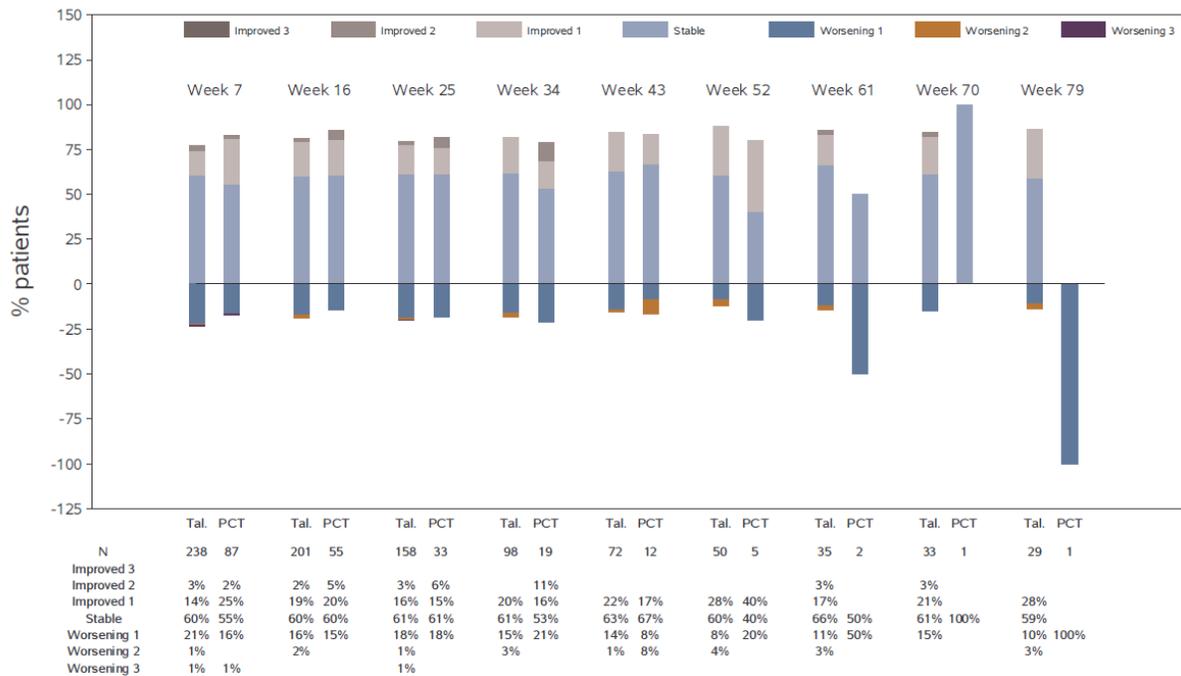
EORTC-QLQ-BR23 Item 38: Did you have headaches

Multi-disciplinary Review and Evaluation NDA 211651 TALZENNA (Talazoparib)

Bar chart of EORTC QLQ-BR23 Item level analysis - Distribution of score categories by visit - (PRO-Evaluable Population)
38: Did you Have Headaches



Bar chart of EORTC QLQ-BR23 Item level analysis - Distribution of Change from Baseline original score categories by visit - (PRO-Evaluable Population)
38: Did you Have Headaches



Source: IR responses dated April 30, 2018 and July, 12, 2018

Multi-disciplinary Review and Evaluation NDA 211651
TALZENNA (Talazoparib)

Reviewer's comments: *At the item level, there is no evidence of a trend of raw score and the change of raw score in the talazoparib arm. Results in the PCT arm should be interpreted with caution due to the small sample size in later assessments.*

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FATIMA M RIZVI
10/15/2018

CLAUDIA P MILLER
10/15/2018

TIFFANY RICKS
10/15/2018

HALEH SABER on behalf of JOHN K LEIGHTON
10/15/2018

AMAL AYYOUB
10/15/2018

PENGFEI SONG on behalf of HONG ZHAO
10/15/2018

NAN ZHENG
10/15/2018

JINGYU YU
10/15/2018

BRIAN P BOOTH on behalf of NAM ATIQR RAHMAN
10/15/2018

LIJUN ZHANG on behalf of STELLA W KARURI
10/15/2018

LIJUN ZHANG
10/15/2018

WILLIAM F PIERCE
10/15/2018

SUPARNA B WEDAM
10/15/2018

LALEH AMIRI KORDESTANI
10/15/2018

RAJESHWARI SRIDHARA
10/15/2018

JULIA A BEAVER
10/15/2018

GIDEON M BLUMENTHAL
10/15/2018