

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211651Orig1s000

OTHER REVIEW(S)



**U.S. FOOD & DRUG
ADMINISTRATION**

Consult Memorandum

Date: October 05, 2018

To: Suparna Wedam, M.D., Clinical Reviewer, CDER/OND/OHOP/DOP1
Fatima Rizvi, RPM, CDER/OND/OHOP/DOP1

Francisca E. Reyes Turcu -S
2018.10.05 07:47:55 -04'00'

From: Francisca Reyes Turcu, Ph.D., Scientific Reviewer, CDRH/OIR/DMGP/MPCB

Through: Soma Ghosh, Ph.D., Acting Branch Chief, CDRH/OIR/DMGP/MPCB
Yun-Fu Hu, Ph.D., Deputy Director, CDRH/OIR/DMGP
Reena Philip, Ph.D., Division Director, CDRH/OIR/DMGP

ICC#: ICC1800305

PMA#: P140020/S015 PMA supplement for BRACAnalysis CDx®

NDA#: NDA 211651

Drug Sponsor: Pfizer

Drug Name: TALZENNA (talazoparib)

1. BACKGROUND

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 most recently approved supplement to expand the indications for use (P140020/S0012) was approved on January 12, 2018 to identify patients with breast cancer with deleterious or suspected deleterious germline BRCA mutations who may be eligible for treatment with olaparib.

The current PMA supplement has been submitted for the BRACAnalysis CDx device to update the labeling for P140020 with the results of the Pfizer clinical study EMBRACA for use of talazoparib in breast cancer patients with germline deleterious or suspected deleterious mutations in BRCA1/BRCA2 genes (NDA 211651). CDER target action date for the NDA is October 15, 2018. For the proposed intended use expansion claim, there are no changes to the device reagents or to the device equipment for this submission. Although the device name will not undergo any changes, there will be labeling changes as a result of this supplement. This device is for prescription use only and has training and site restrictions.

2. INTENDED USE (IU)

BRACAnalysis CDx® is an *in vitro* diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in BRCA1 and BRCA2 are detected using multiplex PCR.

Results of the test are used as an aid in identifying patients who are or may become eligible for treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

Table 1: Companion diagnostic indications

www.fda.gov

Indication	Biomarker	Therapy
Breast Cancer	Deleterious or suspected deleterious mutations in <i>BRCA1</i> and <i>BRCA2</i> genes	Lynparza® (olaparib) Talzenna™ (talazoparib)
Ovarian Cancer	Deleterious or suspected deleterious mutations in <i>BRCA1</i> and <i>BRCA2</i> genes	Lynparza® (olaparib) Rubraca® (rucaparib)

Detection of deleterious or suspected deleterious germline BRCA variants by the BRACAnalysis CDx test in ovarian cancer patients is also associated with enhanced progression-free survival (PFS) from Zejula® (niraparib) or with Rubraca® (rucaparib) maintenance therapy. This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108.

3. INDICATION (Drug)

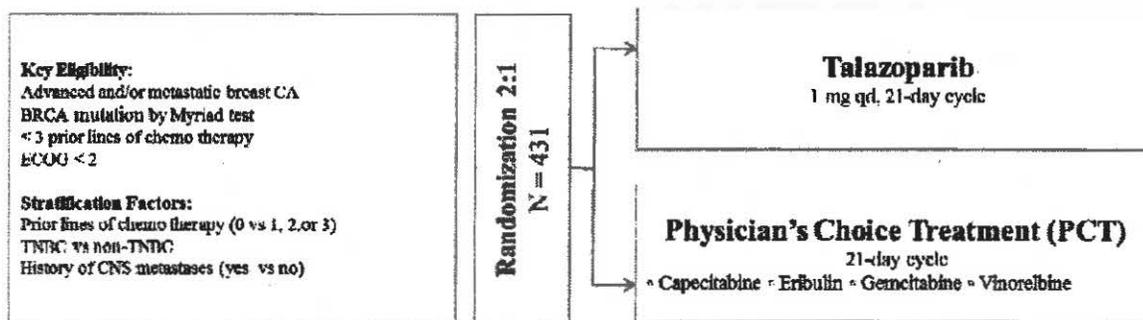
TALZENNA (talozoparib) is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2 negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA approved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

4. REVIEW SUMMARY

4.1. Study Design

To support the clinical indication for talazoparib, Pfizer submitted data from EMBRACA, “A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of Talazoparib (BMN 673) Versus Physician’s Choice in Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens for Metastatic Disease.” In the Phase 3 study, patients were randomly assigned (2:1) to receive talazoparib 1mg/day or one of four protocol-specified, physician’s choice chemotherapies (PCT) (capecitabine, eribulin, gemcitabine or vinorelbine), identified for each patient by the investigator before randomization. A total of 222 study sites enrolled 431 patients over approximately 40 months, and the study closed to enrollment in April 2017.

Figure 1: Study Schematic



BRCA=breast cancer susceptibility gene; CA=cancer; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; N=total number of patients; PCT=physician’s choice treatment; TNBC=triple-negative breast cancer.

Primary Objective: To compare progression-free survival (PFS) of patients treated with talazoparib as a monotherapy relative to those treated with protocol-specified physician’s choice (or healthcare provider’s

choice) of chemotherapy. The primary efficacy endpoint is radiographic PFS, as determined by the central independent radiology facility (IRF) per RECIST version 1.1.

Key Inclusion Criteria: Patients eligible to participate in this study were to meet the following criteria (select criteria shown below) –

- Histologically or cytologically confirmed carcinoma of the breast.
- Locally advanced breast cancer 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 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.
- No more than 3 prior chemotherapy-inclusive regimens for locally advanced and/or metastatic disease.
- 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.

Key Exclusion Criteria: Individuals who met any of the following exclusion criteria (select criteria shown below), were not eligible to participate in the study –

- First-line locally advanced and/or metastatic breast cancer with no prior adjuvant chemotherapy unless the investigator determined that 1 of the 4 cytotoxic chemotherapy agents in the control arm would be otherwise offered to the patient.
- Prior treatment with a PARP inhibitor (not including iniparib).
- Not a candidate for treatment with at least 1 of the treatments of protocol-specified PCTs (capecitabine, eribulin, gemcitabine, vinorelbine).
- Objective disease progression while receiving platinum chemotherapy administered for locally advanced or metastatic disease; patients who received low-dose platinum therapy administered in combination with radiation therapy were allowed.

4.2. Diagnostic Use in Clinical Trial

To be enrolled in the clinical study, patients were required to have documentation of a deleterious or suspected deleterious, mutation in BRCA1 or BRCA2 from Myriad Genetics (Myriad; Salt Lake City, UT) or another laboratory approved by the Sponsor. For trial enrollment, testing conducted by Myriad used a combination of Integrated BRACAnalysis (Myriad's CLIA assay) and BRACAnalysis CDx® test (Myriad CDx assay). The two tests were demonstrated to be in agreement based on previous bridging study results provided under P140020/S009 (NOVA study) and P140020/S012 (OlympiAD study) for the niraparib and olaparib indications, respectively. For BRCA1 or BRCA2 mutation results obtained 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. Only patients with a deleterious, suspected deleterious or pathogenic germline BRCA1/2 mutation were randomized into the pivotal trial. Of the 431 patients randomized into the clinical study, N = 408 (94.6%) were tested centrally by Myriad Genetics (114 were tested with the Integrated BRACAnalysis test and 294 with the BRACAnalysis CDx test). Of the 114 samples tested with the Integrated BRACAnalysis test, 60 were retested with the BRACAnalysis CDx test and shown to have 100% agreement. The remaining 23 patients (5.3%) were enrolled using a non-Myriad laboratory test.

4.3. Efficacy Results

The primary efficacy endpoint was PFS evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and assessed by blinded independent central review (BICR). The study population

consisted of 431 patients with deleterious or suspected deleterious germline *BRCA1* or *BRCA2* -mutated (as detected by central testing conducted by Myriad or local test results) HER2-negative locally advanced or metastatic breast cancer.

In the EMBRACA study, talazoparib treatment demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of PFS over chemotherapy in patients with deleterious or suspected deleterious germline *BRCA1* or *BRCA2*-mutated HER2-negative locally advanced or metastatic breast cancer, with a 46% relative risk reduction of disease progression or death (hazard ratio [HR]: 0.54 [95% confidence interval {CI}: 0.41, 0.71]; $p < 0.0001$). The median PFS by BICR assessment was 8.6 months (95% CI: 7.2, 9.3) in the talazoparib arm and 5.6 months (95% CI: 4.2, 6.7) in the chemotherapy arm. These results are shown in the table below.

The effectiveness of the BRACAnalysis CDx[®] test was based on a subset of 354 (82%) patients with deleterious or suspected deleterious germline *BRCA1/2* mutations for whom prospective and retrospective testing was performed with the BRACAnalysis CDx[®] test. For the remaining 77 patients (18%) whose samples were not available for testing with the BRACAnalysis CDx[®] test, *BRCA1* or *BRCA2* status was determined with the Integrated BRACAnalysis[®] test for 54 patients (18%) or by local assessment for 23 patients (5.3%). As shown in the table below, the clinical outcome data for the 354 patients with confirmed deleterious or suspected deleterious *BRCA1/2* mutation by the BRACAnalysis CDx[®] test was as follows: a 47% reduction in the risk of progression or death, and a median PFS of 8.5 months for talazoparib-treated patients compared with 5.6 months for chemotherapy treated patients. These PFS results are comparable to those observed in the 431 patients in the EMBRACA study, which supports the effectiveness of the device.

PFS by BICR (Intent-to-Treat Population) in the EMBRACA Study		
	Talazoparib	Chemotherapy ^a
Number of patients analyzed, N	N=287	N=144
Events, n (%)	186 (65%)	83 (58%)
Median (95% CI), months	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard Ratio (95% CI); 2-sided P-value	0.54 (0.41, 0.71); <0.0001	
PFS by BICR in BRACAnalysis CDx [®] test Population		
	N=238	N=116
Number of patients analyzed, N		
Events, n (%)	144 (61%)	67 (58%)
Median (95% CI)	8.5 (7.0, 9.3)	5.6 (3.9, 6.7)
Hazard Ratio (95% CI); p-value	0.53 (0.40, 0.72); <0.0001	
a - comparator consisting of healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine).		

5. CONCLUSIONS

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.

6. RECOMMENDATION: P140020/S015 for the BRACAnalysis CDx test will be approved on the same day as NDA 211651 for talazoparib.

Clinical Inspection Summary

Date	September 7, 2018
From	Yang-min (Max) Ning, M.D., Ph.D. Susan Thompson, M.D. Kassa Ayalew, M.D., M.P.H. GCPAB/OSI/CDER/FDA
To	Suparna Wedam, M.D. Laleh Amiri Kordestani, M.D. Fatima Rizvi, Pharm. D. DOP1/OHOP/OCE/FDA
NDA #	211651
Applicant	Pfizer, Inc.
Drug	Talazoparib capsules
NME (Yes/No)	Yes
Therapeutic Classification	Inhibitor of mammalian poly-ADP ribose polymerases (PARP)
Proposed Indication(s)	Treatment of adult patients with germline breast cancer susceptibility gene (gBRCA)-mutated, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer
Consultation Request Date	April 16, 2018
Summary Goal Date	September 14, 2018
Action Goal Date	October 16, 2018
PDUFA Date	December 6, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from an open-label, randomized trial (Study 673-301) were submitted to the Agency in support of the proposed indication for talazoparib in this New Drug Application (NDA). Three study sites, as listed in Section III of this summary, were selected for clinical inspection.

The inspectional findings, as summarized below, verified the reported primary efficacy measure with source records at the three sites. There was no evidence of underreporting of adverse events including serious adverse events. Two of the three sites were found to have a few GCP compliance deviations which, to the reviewer's assessments, should neither have a

significant impact on the benefit-risk assessment of the product in study subjects nor have placed study subjects at undue risk.

Based on the inspectional findings and other relevant information contained in the Establishment Inspection Reports, the reviewer considers the submitted data from the inspected sites reliable to support this NDA. Overall, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

Talazoparib is an inhibitor of mammalian poly-ADP ribose polymerases (PARP) including PARP1 and PARP2. To support the proposed indication in this NDA, the applicant submitted clinical data from the key trial (EMBRACA: 673-301) titled “A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of Talazoparib (BMN 673) versus Physician's Choice in Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens for Metastatic Disease”. The primary efficacy measure was progression-free survival (PFS) as assessed by blinded independent central review (ICR) per RECIST v1.1. Tumor response assessments were based on CT and/or MRI scans and were performed at baseline, every 6 weeks (\pm 7 days) from the date of randomization for 30 weeks, and thereafter every 9 weeks (\pm 7 days) until evidence of disease progression as determined by the ICR or initiation of a new antineoplastic therapy.

From October 2013 to April 2017, the trial enrolled 431 subjects at 145 study sites across 16 countries, with 156 subjects from United States.

The review division requested clinical inspections to verify the efficacy and safety data of this trial. Three study sites, as listed in the following section, were selected for clinical inspection based on the number of subjects enrolled by study site and the estimated median PFS in the talazoparib arm that was noticeably longer than the overall median PFS of 8.6 months reported for the same arm.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
Sara Hurvitz UCLA Department of Medicine: Hematology- Oncology, 10945 Le Conte Ave, Ste 3360	Protocol: 673-301 Enrolled: 11	June 4-8, 2018	* NAI

Los Angeles, CA 90095 Email: shurvitz@mednet.ucla.edu Site # 0127			
Louis Fehrenbacher Kaiser Permanente 975 Sereno Dr. Vallejo, CA 94589 Email: lou.fehrenbacher@kp.org Site #: 1321	Protocol: 673-301 Enrolled: 10	May 5-24, 2018	* VAI
Kyung-Hun Lee Seoul National University Hospital 101, Daehak-ro Jongno-gu Seoul 03080 Republic of Korea Email: drleekh@gmail.com Site #: 1366	Protocol: 673-301 Enrolled: 10	July 16-20, 2018	* VAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data is unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Sara Hurvitz, Site 0127

This site was inspected as a data audit for Study Protocol 673-301. The inspection found that 11 of 16 screened subjects were enrolled at the site. At the time of this inspection, the enrollment was closed, with one subject on study treatment and ten subjects off study treatment. The inspection involved reviews of all subjects' source data, eligibility criteria, informed consent forms, treatment assignment, test article accountability records, electronic case report forms (eCRFs), laboratory tests, and comparisons with the efficacy and safety data listings submitted by the applicant to the NDA. The inspection also included a review of study monitoring and conduct, and IRB oversight from 2014 to 2018.

The inspection revealed no significant deficiencies or protocol violations. No Form 483 was issued. All the data regarding the primary endpoint PFS was verified for each subject at the study site, with no discrepancies noted between source documents and the data listings submitted to the NDA. There was no evidence of underreporting of adverse events.

The data reported from Dr. Hurvitz site, associated with Study Protocol 673-301, were consistent with the data submitted to the Agency by the applicant, indicative of data reliability at this site.

2. Dr. Louis Fehrenbacher, Site 1321

This site was inspected as a data audit for Study Protocol 673-301. There were 27 subjects screened at the site and 10 of them enrolled into the study. At the time of the inspection, one subject was receiving the study treatment and nine subjects were discontinued from the study treatment, including three subjects who were deceased. The inspection reviewed all enrolled subjects' source documents and compared them to relevant eCRFs and the data listings submitted to this NDA. The reviewed source data included subjects' informed consent forms, treatment assignments, eligibility criteria, key efficacy records, adverse events (AEs), and related treatment modifications. The inspection also examined the Investigator's oversight and conduct of the study, involving adverse event reporting practices, test article accountability/disposition, training records, and general protocol compliance.

The inspection found that the conduct at this site was generally satisfactory. The treatment assignment of each subject was verified with the source documents. The efficacy measures including PFS, death, and objective response rate were verifiable with the source documents and data listings. There were no missing scans, missing submissions of scans, or discrepancies between the source documents and the submitted data listings for subjects at this site.

There were a number of inspectional observations, which led to a Form 483 issued. These are summarized as follows. For five of the ten enrolled subjects, recordkeeping discrepancies between the source document for AEs end date and eCRFs were identified. For example, no AE end dates were documented on the eCRFs for headache in Subject (b) (6), fatigue in Subject (b) (6), and right toe skin laceration in Subject (b) (6) while the source documents contained the end date for each AE. For some subjects, a second occurrence of the previously reported same AE was not documented on the eCRF. This included tachycardia in Subject (b) (6), flu-like symptoms in Subject (b) (6), dyspnea on exertion in Subject (b) (6) (who had pulmonary embolism documented on the eCRF). In addition, one Subject (b) (6) who was found to have Grade 3 anemia had dizziness reported per the Telephone Encounter document but not on the eCRF.

Two subjects were found to have inaccurate doses and/or no end dates of concomitant medicines reported on the eCRFs. This included Subject (b) (6) whose PRN acetaminophen dose of 500 mg, 2 tablets was reported as 650 mg on the eCRF with no end dates, and Subject (b) (6) whose Cheratussin AC 10-100 mg was reported as 10 mg and whose use of Flonase had no end date on the eCRF. In the Investigator's written response to the Form FDA 483, he acknowledged most of the observations and provided his explanations for some of the observations. For example, Subject (b) (6) had baseline dyspnea and was diagnosed with pulmonary embolism during study,

which resulted in a change in dyspnea. The change was considered a manifestation of the pulmonary embolism. 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.

The data reported from this site, associated with Study Protocol 673-301, appear reliable based on the inspectional findings. The regulatory violations noted above as summarized above represent valid GCP compliance deficiencies but should neither have significant impact on study outcomes nor have put subjects at undue risk. The investigator has implemented corrective and preventive measures to address the compliance issues.

3. Dr. Kyung-Hun Lee, Site 1366

This site was also inspected as a data audit for Study Protocol 673-301. There was no previous FDA inspection history for the investigator. This site had 38 subjects screened and 10 subjects enrolled and randomized. As of the time of this inspection, four subjects were in the follow-up phase. The inspection reviewed source documents for all subjects and compared to relevant eCRFs and data listings submitted to the NDA. The reviewed source documents included, but were not limited to, medical records to verify subject eligibility, Institutional Review Board/Ethics committee roster and approvals (initial and continuing reviews, protocol versions, informed consent forms, clarification letters, adverse events, and IDMC updates), selected laboratory and imaging test results in the hospital electronic medical record, dates of baseline and subsequent CTs and MRIs and associated submissions to the central radiology review, date and cause of deaths in medical records and eCRFs, concomitant medications, all serious adverse events and associated reporting. The inspection also reviewed other elements involved in the investigator's conduct and monitoring of the study, including pre-study site training, study staff protocol training, financial disclosures, screening/enrollment log, drug accountability, delegation of authority log and Imaging Data Transmittal Forms.

The inspection revealed no significant deficiencies. Source documents at the site verified the status of each study subject, including dates of disease progression and/or death, with no discrepancies found. There was no evidence of under- or delayed-reporting of adverse events or serious adverse events. On the other hand, the inspection 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.

The data reported from Site 1366, associated with Study Protocol 673-301, appear reliable based on the inspectional findings. The observed late submissions of scans represent valid GCP compliance violations. However, the violations should not have an impact on the primary endpoint given that the status of disease progression from the central review was not affected due to the late submissions and that the protocol-scheduled follow-up scans were performed timely.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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Central Doc. Rm. NDA 211651
Review Division /Division Director/J Beaver
Review Division /Medical Team Leader/L Amiri
Review Division /Project Manager/F Rizvi
Review Division/Medical Officer/S Wedam
OSI/Office Director/D Burrow
OSI/DCCE/ Division Director/N Knin
OSI/DCCE/Branch Chief/K Ayalew
OSI/DCCE/Team Leader/SD Thompson
OSI/DCCE/GCP Reviewer/YM NING
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/

YANGMIN NING
09/10/2018

SUSAN D THOMPSON
09/10/2018

KASSA AYALEW
09/11/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: September 6, 2018
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 211651
Product Name and Strength: Talzenna (Talazoparib) Capsules, 0.25 mg and 1 mg
Applicant/Sponsor Name: Pfizer, Inc.
FDA Received Date: September 4, 2018
OSE RCM #: 2018-715-1
DMEPA Safety Evaluator: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised container labels and the newly proposed carton labeling for Talzenna (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 DISCUSSION

Pfizer stated that they intend to use YYYY MMM DD (e.g., 2017 JAN 31) as the expiration date format instead of the previously recommended format similar to either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017) on the container labels and carton labeling.^b Since the proposed numerical expiration date format consists the full year (YYYY), which would not be confused with the day (DD), we find this proposed expiration date format acceptable from a medication error perspective.

^a Gao, T. Label and Labeling Review for Talzenna (NDA 211651). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JULY 11. RCM No.: 2018-715.

^b NDA 211651 for Talazoparib (PF-06944076, formerly BMN 673, MDV3800) capsules. Response to Information Request – USPI and Updated Container Label. New York (NY): Pfizer Inc. 2018 SEPT 4. Available at <\\cdsesub1\evsprod\nda211651\0027\m1\us\qqr8-16aug2018.pdf>.

We also noted that Pfizer proposed new carton labeling for the 0.25 mg and 1 mg strengths, and we find the proposed carton labeling acceptable from a medication error perspective.

3 CONCLUSION

The revised container labels and the proposed carton labeling for Talzenna is acceptable from a medication error perspective. We have no further recommendations at this time.

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

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/

TINGTING N GAO
09/06/2018

CHI-MING TU
09/06/2018

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

PATIENT LABELING REVIEW

Date: August 20, 2018

To: Julia Beaver, MD
Director
Division of Oncology Products 1 (DOP 1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TALZENNA (talazoparib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 0211651

Applicant: Pfizer, Inc.

1 INTRODUCTION

On April 6, 2018, Pfizer, Inc. submitted for the Agency's review an original New Drug Application (NDA) 0211651 for TALZENNA (talazoparib) capsules for the proposed indication: for the treatment of adult patients with germline breast cancer susceptibility gene (gBRACA)-mutated human epidermal growth factor receptor 2 (HER-2) negative locally advanced or metastatic breast cancer.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP 1) on April 26, 2018 and April 24, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TALZENNA (talazoparib) capsules.

2 MATERIAL REVIEWED

- Draft TALZENNA (talazoparib) capsules PPI received on April 6, 2018, and received by DMPP on August 3, 2018.
- Draft TALZENNA (talazoparib) capsules PPI received on April 23, 2018, and received by OPDP on August 3, 2018.
- Draft TALZENNA (talazoparib) capsules Prescribing Information (PI) received on April 6, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on August 3, 2018.
- Draft TALZENNA (talazoparib) capsules Prescribing Information (PI) received on April 23, 2018, revised by the Review Division throughout the review cycle, and received by OPDP on August 3, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the PPI we:

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

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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/s/

MORGAN A WALKER
08/20/2018

KEVIN WRIGHT
08/20/2018

LASHAWN M GRIFFITHS
08/20/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: August 15, 2018

To: Julia Beaver, M.D., Director
Division of Oncology Products 1 (DOP1)

Fatima Rizvi, PharmD, Regulatory Project Manager, DOP1

William Pierce, PharmD, Associate Director for Labeling, DOP1

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, M.B.A., Team Leader, OPDP

Subject: OPDP Labeling Comments for Talzenna™ (talazoparib) capsules, for oral use

NDA: 211651

In response to DOP1's consult request dated April 26, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and container label for the original NDA submission for Talzenna™ (talazoparib) capsules, for oral use (Talzenna).

OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DOP1(Fatima Rizvi) on August 3, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

OPDP has reviewed the attached proposed container labels submitted by the Sponsor to the electronic document room on April 6, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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

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/s/

KEVIN WRIGHT
08/15/2018

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

IND or NDA	NDA 211651
Brand Name	-
Generic Name	Talazoparib
Sponsor	Pfizer Inc.
Indication	Treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer
Dosage Form	Capsule
Drug Class	PARP inhibitor
Therapeutic Dosing Regimen	1 mg QD
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Same as therapeutic dose for solid tumors
Submission Number and Date	SDN 001; 06 Apr 2018
Review Division	DOP1

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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 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 (Δ QTcF), 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 Δ QTcF and talazoparib concentrations.

In this phase 1, open-label safety study, 37 patients with advanced solid tumors received talazoparib 1 mg QD. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Talazoparib 1 mg QD (FDA Analysis)

		Δ QTcF (ms)			
Day	Time (Hour)	N	Mean	SD	90% CI
1	1	36	3.9	15.9	(-0.6, 8.4)
22	1	30	6.9	14.9	(2.2, 11.5)

The dose used in this study is the proposed therapeutic dose of talazoparib (1 mg QD) and it is also the maximum tolerated dose (MTD). Talazoparib is primarily eliminated by kidney, and patients with moderate/severe renal impairment may have increased exposure. Talazoparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Population PK analysis indicates that concomitant administration of strong P-gp inhibitors with talazoparib increased talazoparib exposure by 45% relative to talazoparib administered alone.

2 PROPOSED LABEL

The following is the sponsor’s proposed QT-related labeling language for section 12.2.

Overall, the language is acceptable to the QT-IRT and we have only minor suggested edits as shown in red font below. We defer the final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of talazoparib on cardiac repolarization was evaluated (b) (4)
 (b) (4)
 (b) (4) in an open label study in 37 patients with advanced solid tumors. Talazoparib had no large (b) (4) QTc (b) (4) (i.e., >20 ms) at the (b) (4) recommended dose (b) (4).

3 BACKGROUND

3.1 PRODUCT INFORMATION

Talazoparib is a potent inhibitor of PARP1 and PARP2, which play important roles in deoxyribonucleic acid (DNA) repair. It is also a lower-potency inhibitor of PARP3, tankyrase 1 (TNKS1, PARP5a), and tankyrase 2 (TNKS2, PARP5b). It is indicated for the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer.

3.2 MARKET APPROVAL STATUS

Talazoparib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

In the GLP study, talazoparib caused a dose-dependent inhibition of IKr. Reduction of current (mean \pm SEM) by $6.7 \pm 0.9\%$, $14.2 \pm 0.4\%$, and $33.4 \pm 1.6\%$ was observed at 10, 30, and 100 μM , respectively. Higher concentrations could not be tested due to talazoparib solubility limitations; therefore, the IKr half-maximal inhibitory concentration (IC_{50}) could not be calculated; it was estimated to be greater than 100 μM , indicating a low hERG liability. The C_{max} at steady-state with 1 mg QD dosing in clinical studies was 0.055 μM (free concentration = 0.0117 μM).

Cardiovascular ECG evaluations were conducted in the 5-day, 28-day and 13-week repeat-dose good laboratory practice (GLP) toxicity studies in dogs. In the repeat dose studies, no significant modifications in heart rate, ECG waveforms, or ECG intervals were observed at the maximum plasma concentration (C_{max}) up to 37.0 ng/mL (0.097 μM), which translates to a 2-fold margin when compared to the clinical steady state C_{max} concentration (21 ng/mL, 0.055 μM) at 1 mg daily.

3.4 PREVIOUS CLINICAL EXPERIENCE

As of the data cutoff date of 30 November 2015, approximately 319 patients with a variety of hematologic malignancies and solid tumors and 18 healthy volunteers received at least 1 dose of talazoparib. The majority of these healthy volunteers and patients were treated in open-label uncontrolled studies, making it difficult to assess the association with talazoparib treatment.

In the phase 1 study, PRP-001 (N = 110), there were 9 patients with 11 adverse events that coded to the cardiac system. There were 3 patients with events of tachycardia, 2 of atrial fibrillation, 2 of supraventricular tachycardia, 1 of angina pectoris, 1 of left bundle branch block, 1 of pericardial effusion, and 1 of ventricular tachycardia. Two of these events (in 2 patients), angina pectoris and atrial fibrillation, were judged to be related to study drug by the investigator. Two events of supraventricular tachycardia were grade 3 (in 2 patients) but assessed as unrelated to study drug; and there were 2 serious adverse events (supraventricular tachycardia and ventricular tachycardia, in 2 patients), neither of which was judged related to study drug. The event of supraventricular tachycardia was in a 70 year old man with a history of recurrent supraventricular tachycardia who came to the hospital with a heart rate of 150. The tachycardia was treated with diltiazem and resolved. The event of ventricular tachycardia was non-sustained and occurred during a Portacath insertion in a 51-year-old woman with a history of palpitations and pericardial effusion. Talazoparib was interrupted, but no other treatment was administered and the event resolved.

ECGs were recorded in this study at baseline, 3 to 4 hours post-dose on days 1 and 35 (for dose escalation phase) or at day 1 of cycle 2 (for dose expansion phase) and at the end of treatment visit, which was to occur ≤ 10 days following the final dose of talazoparib, if clinically indicated. ECG interval data were collected from these recordings retrospectively. Of the 96 patients, with both baseline and postbaseline ECGs based on draft data, 1 patient had a postbaseline QTcF > 500 msec; 1 patient had a postbaseline QTcF > 480 and ≤ 500 msec; and 9 patients (9.4%) had postbaseline QTcF > 450 msec and ≤ 480 msec. One patient had an increase in QTcF from baseline > 60 msec; and 6 patients (6.3%) had an increase from baseline > 30 msec and ≤ 60 msec.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 108708 ([14 Jun 2016](#)). The sponsor's overall proposal of study design for QTc characterization was acceptable to the FDA in the protocol review. A recommendation from QT-IRT about dosing in fasted state on the day of ECG/PK sampling was incorporated by the sponsor in the final study (see Section 4.2.6.3).

The sponsor submitted the study report MDV3800-14, including electronic datasets and waveforms to the ECG warehouse.

4.2 QT STUDY

4.2.1 Title

A Phase 1, Open-Label Study to Assess the Effects of Talazoparib on Cardiac Repolarization in Patients with Advanced Solid Tumors

4.2.2 Protocol Number

MDV3800-14/C3441005

4.2.3 Study Dates

13 Oct 2016 – 22 Jun 2017

4.2.4 Objectives

Primary Objectives:

- To evaluate the effect of talazoparib on cardiac repolarization in patients with advanced solid tumors by assessing the QTc;
- To assess the relationship between plasma talazoparib concentrations and the QTc.

Secondary Objectives:

- To evaluate the safety and tolerability of talazoparib;
- To evaluate the effect of talazoparib on non-QT interval ECG parameters (heart rate, RR, PR, QRS intervals, and ECG morphology);
- To evaluate the PK of talazoparib.

4.2.5 Study Description

4.2.5.1 Design

This is a phase 1, open-label study.

4.2.5.2 Controls

There was no placebo or positive (moxifloxacin) control.

4.2.5.3 Blinding

The study was open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

This was a single arm study. Talazoparib 1 mg QD was given orally for 22 days.

4.2.6.2 Sponsor's Justification for Doses

Reviewer's Comment: The dose used in this study is the proposed therapeutic dose of talazoparib (1 mg QD) and it is also the maximum tolerated dose (MTD).

4.2.6.3 Instructions with Regard to Meals

Talazoparib was to be administered at the study site on Days 1, 2, and 22. Patients were to fast for at least 6 hours before and 2 hours after the doses on Days 1 and 22. Patients could resume eating after the 2-hour postdose PK sample was collected. On other days, talazoparib could have been taken with or without food. The doses on Days 2 and 22 were to be administered at approximately the same clock time (within 1 hour of Time 0) as the Day 1 dose. On Days 3 to 21, patients were to self-administer talazoparib 1 mg QD orally at approximately the same time each morning.

Reviewer's Comment: During protocol review, QT-IRT recommended the sponsor that on the day of ECG/PK measurements, the dosing should be in the fasted state to evaluate effects under maximal extent of C_{max} and that this will aid in optimal collection of ECG/PK samples around T_{max} . Accordingly, the sponsor altered the protocol to have dosing in fasted state on Day 1 and 22 as stated above.

4.2.6.4 ECG and PK Assessments

ECG: Twelve-lead ECGs were recorded continuously by Holter monitor at baseline (day -1), after a single dose of talazoparib (days 1 and 2) and at steady state (day 22). Six-hour recordings were obtained on day -1 (baseline), day 1 (the first day of study drug dosing) and day 22 (steady state).

PK: Predose and 1, 2, 4, and 6 hours on day 1; predose on day 2; and predose, 1, 2, 4, and 6 hours on day 22.

Reviewer's Comment: As per the protocol review, "The proposed sampling for ECGs and PK are appropriate from the perspective of capturing potential effects near T_{max} (1 hour) and delayed effects up to 24 hours post-dose (using pre-dose samples on Day 2 and Day 22 which correspond to 24 hours from previous dose)."

4.2.6.5 Baseline

Time-matched average QT/QTc values on Day -1 were used as baselines.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 38 patients with solid tumors were enrolled in the study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor's results are listed in Table 2.

Table 2: Mean Change from Time-Matched Baseline for ECG Parameters by Nominal ECG Collection Time Point – Central Tendency Analyses (ECG Analysis Population, Sponsor's Results)

Talazoparib 1 mg QD						
Time	n	90% CI of Mean		90% CI of Mean		
		Mean Change from Baseline ¹	Change from Baseline ²	Mean Change from Baseline ¹	Change from Baseline ²	
			QTcF (msec)		QTcB (msec)	
Day 1, 1 hour	36	3.9	(-0.6, 8.4)	0.6	(-3.2, 4.4)	
Day 1, 2 hours	33	3.5	(-0.7, 7.8)	4.7	(0.4, 9.0)	
Day 1, 4 hours	35	1.6	(-1.3, 4.5)	2.9	(-0.6, 6.4)	
Day 1, 6 hours	29	-0.3	(-4.0, 3.4)	-0.4	(-4.3, 3.5)	
Day 2, 0 hour	32	-3.5	(-8.0, 1.1)	-1.7	(-6.2, 2.8)	
Day 22, 0 hour	27	-1.3	(-6.1, 3.6)	-2.4	(-7.0, 2.3)	
Day 22, 1 hour	30	6.9	(2.2, 11.5)	1.1	(-3.8, 6.0)	
Day 22, 2 hours	28	4.7	(-0.2, 9.5)	2.2	(-3.0, 7.4)	
Day 22, 4 hours	30	3.0	(-1.4, 7.3)	1.6	(-3.3, 6.6)	
Day 22, 6 hours	25	0.5	(-4.1, 5.0)	0.0	(-4.7, 4.7)	
			RR Interval (msec)		Heart Rate (bpm)	
Day 1, 1 hour	36	42.9	(10.7, 75.0)	-3.0	(-6.0, 0.1)	
Day 1, 2 hours	33	-7.8	(-34.9, 19.3)	1.4	(-1.2, 4.0)	
Day 1, 4 hours	35	-15.1	(-37.7, 7.6)	1.4	(-0.8, 3.7)	
Day 1, 6 hours	29	2.1	(-16.4, 20.6)	0.1	(-1.5, 1.8)	
Day 2, 0 hour	32	-17.9	(-47.4, 11.7)	2.3	(-0.3, 4.9)	
Day 22, 0 hour	27	16.0	(-25.7, 57.8)	-1.1	(-5.1, 2.8)	
Day 22, 1 hour	30	69.8	(29.3, 110.3)	-6.0	(-9.3, -2.6)	
Day 22, 2 hours	28	30.5	(-4.3, 65.3)	-2.8	(-5.5, -0.1)	
Day 22, 4 hours	30	15.6	(-16.2, 47.4)	-1.4	(-4.7, 1.8)	
Day 22, 6 hours	25	4.1	(-30.9, 39.1)	-0.1	(-3.3, 3.0)	
			PR Interval (msec)		QRS Interval (msec)	
Day 1, 1 hour	36	-2.3	(-4.3, -0.3)	2.9	(0.7, 5.2)	
Day 1, 2 hours	33	-2.2	(-4.3, -0.2)	2.0	(-0.6, 4.6)	
Day 1, 4 hours	35	-3.2	(-5.7, -0.7)	1.1	(-0.8, 3.1)	
Day 1, 6 hours	29	-1.1	(-4.0, 1.8)	0.9	(-1.7, 3.6)	
Day 2, 0 hour	32	-4.5	(-7.1, -1.9)	2.6	(0.3, 4.8)	
Day 22, 0 hour	27	-1.0	(-4.6, 2.5)	0.7	(-2.4, 3.9)	
Day 22, 1 hour	30	0.5	(-3.3, 4.3)	2.6	(-0.2, 5.4)	
Day 22, 2 hours	28	-0.1	(-4.0, 3.9)	1.3	(-1.8, 4.4)	
Day 22, 4 hours	30	-0.1	(-3.1, 3.0)	1.7	(-1.1, 4.4)	
Day 22, 6 hours	25	-2.4	(-5.4, 0.6)	0.7	(-2.5, 3.9)	

Source: Sponsor's clinical study report, Table 24, page 71

Reviewer's Comments: We agree with the sponsor's conclusions. Findings from our independent analysis are consistent with the sponsor's results. Please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

Not Applicable

4.2.8.2.3 Categorical Analysis

In the ECG analysis population, no patients had a maximum post-baseline QTcF, QTcB, or QT interval >500 msec, or a maximum increase from time-matched baseline in QTcF or QTcB >60 msec.

4.2.8.3 Safety Analysis

There were no deaths or adverse events (AEs) of special interest in the study. Three patients (3/37, 8.1%) experienced 5 serious adverse events (SAEs) in the study, most of which were considered as not treatment-related except for the 1 SAE of Anaemia.

- Patient (b) (6) experienced SAEs of Anaemia and Syncope.
- Patient (b) (6) experienced SAEs of Toxicity of various agents and Spontaneous haemorrhage.
- Patient (b) (6) experienced an SAE of large intestinal obstruction.

Of the 37 patients received talazoparib, 6 patients discontinued due to patient withdrawal (3), disease progression (2), and AE (1). There were no permanent discontinuations from talazoparib due to AEs. There were no dose reductions due to AEs in the study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Plasma talazoparib concentrations accumulated following multiple doses. Peak plasma talazoparib concentrations were reached at about the same time following single or multiple doses (Day 1 versus Day 22), with median T_{max} values of 2 hours. On Day 1 and Day 22, the plasma talazoparib geometric mean C_{max} was 4,350 pg/mL and 16,400 pg/mL (for subpopulation of patients who had no prior talazoparib dose modifications), respectively.

Reviewer's comment: Plasma concentration-time profile for talazoparib is shown in reviewer's analysis in Section 5.3.

4.2.8.4.2 Exposure-Response Analysis

Table 3 provides the PK-PD modeling results showing the slopes of the relationships between talazoparib plasma concentration and QTc.

Table 3: Δ QTc versus the Talazoparib Plasma Concentration - Selected Estimates from the Linear Mixed Effects Models (PK-PD Analysis Population)

QT Correction Method	Model Parameter ¹ (Unit)	Talazoparib 1 mg QD		
		Estimate (95% CI)	Standard Error	p-value
QTcF	Intercept term (msec)	4.6 (-3.2, 12.5)	4.0	0.2454
	Concentration slope (msec/ng/mL)	-0.14 (-0.78, 0.50)	0.3216	0.6700
QTcB	Intercept term (msec)	5.9 (-2.5, 14.3)	4.3	0.1681
	Concentration slope (msec/ng/mL)	-0.24 (-0.88, 0.41)	0.3227	0.4668

Source: Selected estimates from the linear mixed effects models; [Tables 14.2.3.22.1 and 14.2.3.22.2 in Cardiac Safety Report](#) (Appendix of Additional Documents).

Abbreviations: CI=confidence interval; PD=pharmacodynamic(s); PK=pharmacokinetic(s); QD=once daily; QTc=QT interval corrected for heart rate; QTcB=QTc based on the Bazett's correction formula; QTcF=QTc based on the Fridericia's correction formula.

1. Linear mixed model was fit for change from baseline versus the plasma concentration (re-scaled to ng/mL), with a treatment-specific intercept, and fixed effects for the intercept, time and treatment dose and random effects for the intercept and plasma concentration.

Reviewer's comments: The sponsor used time as a covariate in the LME model for this design with a single dose level and without any placebo control, which may not be appropriate. Nonetheless, the reviewer's analysis with the usual prespecified model does agree with the sponsor's conclusion that there is no statistically significant positive slope for the concentration-QTc relationship (see Section 5.3).

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for their primary analysis, which is acceptable. Since no large changes in heart rate were observed, i.e., mean changes ≤ 10 bpm (section 5.2.2), no assessment of the QT/RR correction methodology is necessary and QTcF is used for all reviewers' assessments.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Talazoparib

The statistical reviewer listed descriptive statistics for QTcF and the mean change from baseline in QTcF (Δ QTcF). The analysis results are listed in Table 4.

Table 4: Analysis Results of QTcF and Δ QTcF

Day	Time (Hour)	QTcF (ms)		Δ QTcF (ms)			
		N	Mean (SD)	N	Mean	SD	90% CI
1	0	36	413.6 (16.9)	33	-3.5	15.5	(-8.1, 1.1)
	1	37	419.5 (19.7)	36	3.9	15.9	(-0.6, 8.4)
	2	37	421.6 (19.7)	33	3.5	14.5	(-0.7, 7.8)

		QTcF (ms)		ΔQTcF (ms)			
Day	Time (Hour)	N	Mean (SD)	N	Mean	SD	90% CI
	4	37	417.1 (16.3)	35	1.6	10.0	(-1.3, 4.5)
	6	35	413.6 (19.5)	29	-0.3	11.8	(-4.0, 3.4)
2	0	33	413.7 (18.4)	32	-3.5	15.3	(-8.0, 1.1)
22	0	30	415.5 (18.8)	27	-1.3	14.8	(-6.1, 3.6)
	1	31	419.8 (22.2)	30	6.9	14.9	(2.2, 11.5)
	2	31	421.8 (22.6)	28	4.7	15.1	(-0.2, 9.5)
	4	31	417.0 (18.8)	30	3.0	13.9	(-1.4, 7.3)
	6	31	412.8 (19.1)	25	0.5	13.3	(-4.1, 5.0)

The largest upper bounds of the 2-sided 90% CI for the mean change from baseline in QTcF were 8.4 ms and 11.5 ms on Days 1 and 22, respectively.

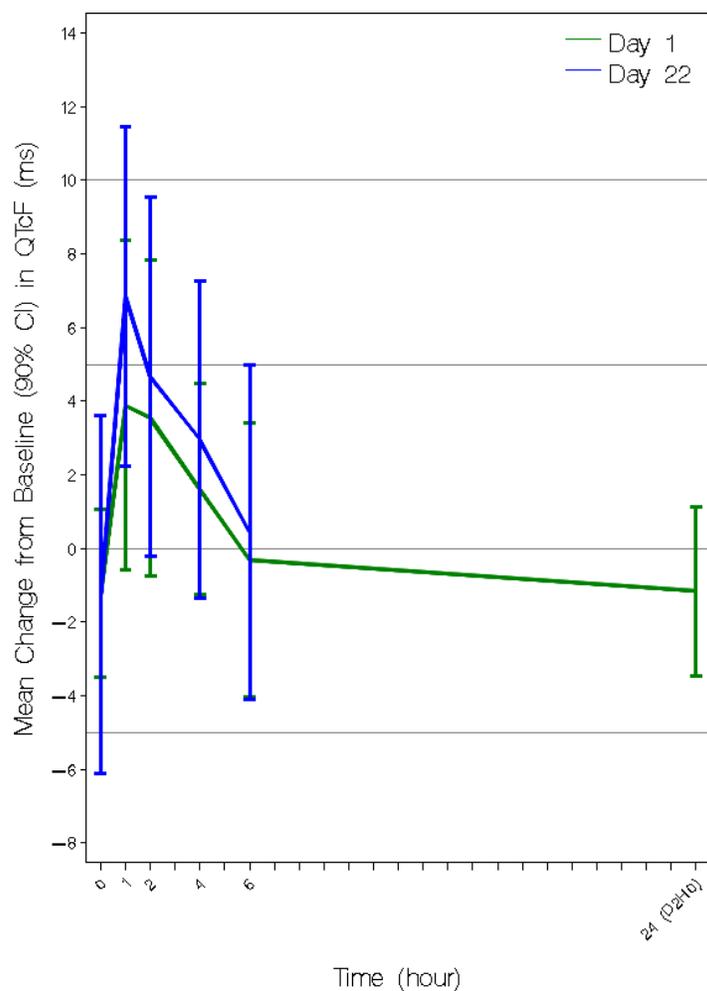
5.2.1.2 Assay Sensitivity Analysis

Not Applicable.

5.2.1.3 Graph of ΔQTcF Over Time

The following figure displays the time profile of ΔQTcF for talazoparib 1 mg QD.

Figure 1: Mean and 90% CI Δ QTcF Timecourse



5.2.1.4 Categorical Analysis

Table 5 lists the number of subjects as well as the number of observations whose QTcF values were between 450 ms and 480 ms and between 480 ms and 500 ms. No subject's QTcF was above 500 ms.

Table 5: Categorical Analysis for QTcF

Treatment Group	Total N		450<QTcF<=480 ms		480<QTcF<=500 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	37	167	3 (8.1%)	4 (2.4%)	0 (0.0%)	0 (0.0%)
Talazoparib 1 mg QD	37	369	4 (10.8%)	14 (3.8%)	1 (2.7%)	1 (0.3%)

Table 6 lists the categorical analysis results for Δ QTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 6: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Δ QTcF \leq 30 ms		30 $<$ Δ QTcF \leq 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Talazoparib 1 mg QD	37	338	29 (78.4%)	326 (96.4%)	8 (21.6%)	12 (3.6%)

5.2.2 Heart Rate Analysis

The point estimates and the 90% confidence intervals are presented in Table 7 for HR. No significant changes in HR was detected.

Table 7: Analysis Results of HR and Δ HR

Day	Time (Hour)	HR (ms)		Δ HR (ms)			
		N	Mean (SD)	N	Mean	SD	90% CI
1	0	36	78.2 (15.6)	33	2.2	8.9	(-0.4, 4.8)
	1	37	73.6 (14.9)	36	-3.0	10.8	(-6.0, 0.1)
	2	37	74.5 (13.0)	33	1.4	8.9	(-1.2, 4.0)
	4	37	81.4 (12.4)	35	1.4	7.8	(-0.8, 3.7)
	6	35	78.0 (13.1)	29	0.1	5.3	(-1.5, 1.8)
2	0	33	77.8 (15.3)	32	2.3	8.7	(-0.3, 4.9)
22	0	30	73.9 (12.1)	27	-1.1	12.0	(-5.1, 2.8)
	1	31	70.9 (12.0)	30	-6.0	10.8	(-9.3, -2.6)
	2	31	71.2 (10.7)	28	-2.8	8.5	(-5.5, -0.1)
	4	31	77.5 (13.4)	30	-1.4	10.4	(-4.7, 1.8)
	6	31	76.9 (10.7)	25	-0.1	9.2	(-3.3, 3.0)

5.2.3 PR Analysis

The point estimates and the 90% confidence intervals are presented in Table 8 for PR interval. No significant changes in PR was detected.

Table 8: Analysis Results of PR and Δ PR

Day	Time (Hour)	PR (ms)		Δ PR (ms)			
		N	Mean (SD)	N	Mean	SD	90% CI
1	0	36	164.2 (24.0)	33	-4.8	7.5	(-7.0, -2.6)
	1	37	167.5 (26.0)	36	-2.3	7.0	(-4.3, -0.3)

		PR (ms)		ΔPR (ms)			
Day	Time (Hour)	N	Mean (SD)	N	Mean	SD	90% CI
	2	37	169.2 (26.9)	33	-2.2	7.1	(-4.3, -0.2)
	4	37	165.1 (25.9)	35	-3.2	8.7	(-5.7, -0.7)
	6	35	166.0 (26.5)	29	-1.1	9.1	(-4.0, 1.8)
2	0	33	164.2 (24.2)	32	-4.5	8.6	(-7.1, -1.9)
22	0	30	168.1 (21.7)	27	-1.0	10.8	(-4.6, 2.5)
	1	31	171.6 (25.4)	30	0.5	12.2	(-3.3, 4.3)
	2	31	171.3 (25.1)	28	-0.1	12.3	(-4.0, 3.9)
	4	31	170.5 (25.7)	30	-0.1	9.9	(-3.1, 3.0)
	6	31	168.3 (25.4)	25	-2.4	8.8	(-5.4, 0.6)

5.2.4 QRS Analysis

The point estimates and the 90% confidence intervals are presented in Table 9 for QRS interval. No significant changes in QRS was detected.

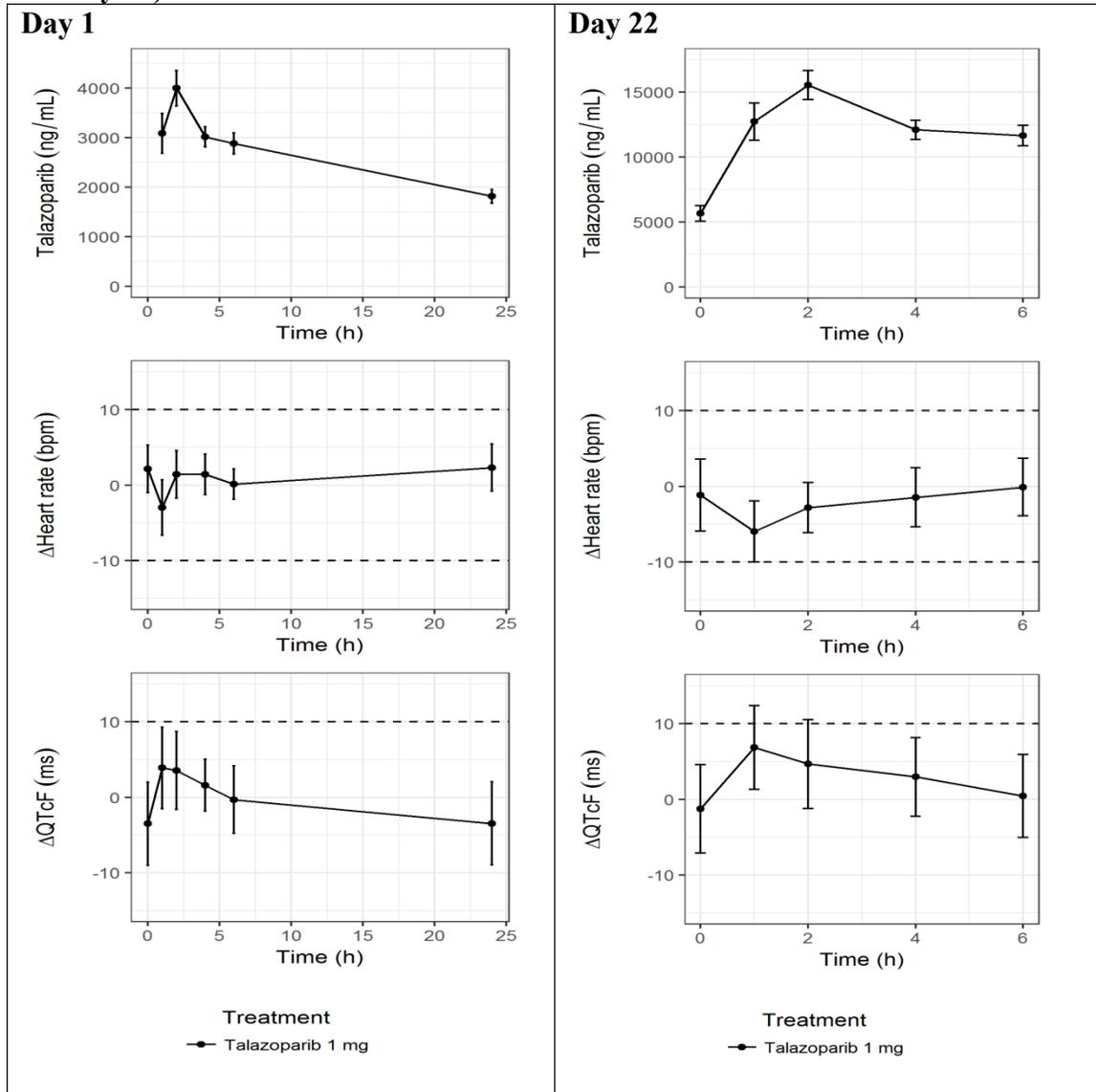
Table 9: Analysis Results of QRS and ΔQRS

		QRS (ms)		ΔQRS (ms)			
Day	Time (Hour)	N	Mean (SD)	N	Mean	SD	90% CI
1	0	36	85.9 (9.2)	33	0.1	8.0	(-2.3, 2.4)
	1	37	87.9 (8.6)	36	2.9	8.1	(0.7, 5.2)
	2	37	87.8 (8.6)	33	2.0	8.7	(-0.6, 4.6)
	4	37	87.3 (8.1)	35	1.1	6.8	(-0.8, 3.1)
	6	35	87.0 (8.5)	29	0.9	8.5	(-1.7, 3.6)
2	0	33	88.0 (8.7)	32	2.6	7.6	(0.3, 4.8)
22	0	30	87.1 (9.3)	27	0.7	9.6	(-2.4, 3.9)
	1	31	88.2 (8.9)	30	2.6	9.0	(-0.2, 5.4)
	2	31	87.9 (8.9)	28	1.3	9.6	(-1.8, 4.4)
	4	31	88.7 (8.9)	30	1.7	8.9	(-1.1, 4.4)
	6	31	87.2 (8.3)	25	0.7	9.5	(-2.5, 3.9)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

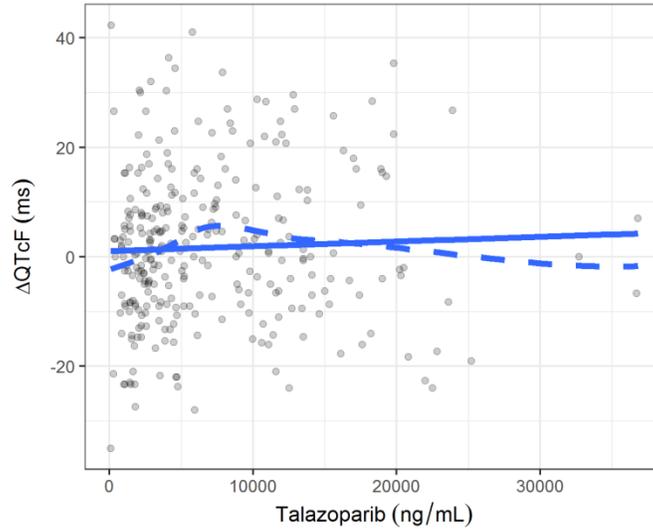
Figure 2 shows the comparison of time profiles for talazoparib, Δ QTcF and Δ HR on Day 1 and Day 22 to evaluate presence of any time delay between concentration and QTc interval and to evaluate any heart rate effects. There does not seem to be any significant delayed effect on QTcF changes or any heart rate effects. Of note, the talazoparib exposure on Day 22 is ~3.8-fold of that on Day 1 and predose concentration on Day 22 is similar to C_{\max} value on Day 1, but there does not appear to be corresponding higher Δ QTcF effect on Day 22.

Figure 2: Time course of Talazoparib concentration, Δ HR, and Δ QTcF (on Day 1 and Day 22)



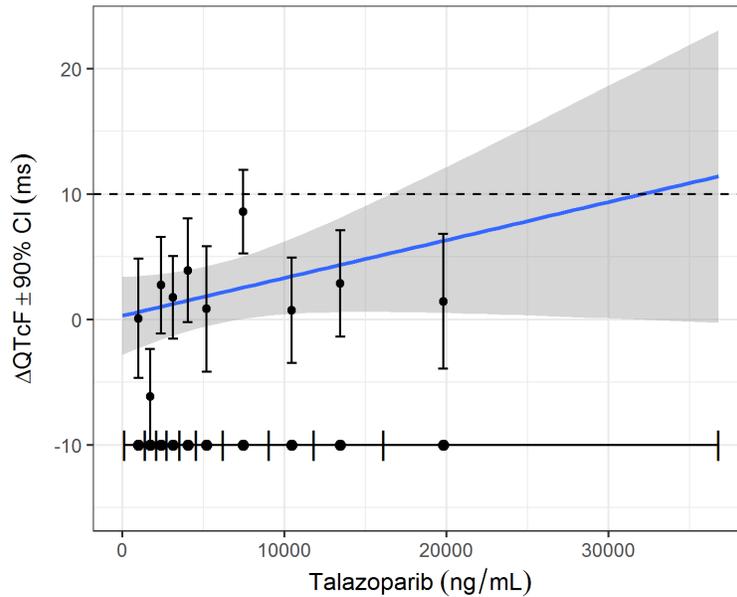
The relationship between drug concentration and Δ QTcF was evaluated to determine if a linear model would be appropriate. Figure 3 shows the relationship between drug concentration and Δ QTcF.

Figure 3: Assessment of linearity of concentration-QTc relationship



The linear C-QTc model with random effect on slope and intercept was applied as the default prespecified model and the goodness-of-fit plot is visualized in Figure 4. There was no statistically significant positive relationship between ΔQTcF and talazoparib concentrations (mean slope estimate = 0.3 ms per $\mu\text{g/mL}$; p-value = 0.2).

Figure 4: Observed and Estimated ΔQTcF vs. Talazoparib concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

Patient (b) (6) experienced a SAE syncope. The cause of the syncope was attributed to Anaemia. The patient was also noted to have Grade 3 Thrombocytopenia and Grade 3 Neutropenia which were considered as non-serious adverse events.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. 86.39 % of the ECGs were annotated in the primary lead (lead II), with less than 2.46% of ECGs reported to have significant QT bias per the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically meaningful changes in the PR and QRS intervals were detected.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	1 mg/day	
Maximum tolerated dose	1 mg/day	
Principal adverse events	Gastrointestinal toxicity, myelosuppression, and fatigue	
Maximum dose tested	Single Dose	1.1 mg/day in advanced or recurrent solid tumors; 2 mg/day in advanced hematologic malignancies
	Multiple Dose	1.1 mg/day in advanced or recurrent solid tumors; 2 mg/day in advanced hematologic malignancies.
Exposures achieved at maximum tested dose	Single Dose	MTD: 1 mg/day, N = 5: C _{max} = 10.6 ng/mL (40% CV); AUC ₀₋₂₄ = 85.1 ng·h/mL (34% CV)
	Multiple Dose	MTD: 1 mg/day, N = 6: C _{max} = 21 ng/mL (38% CV); AUC ₀₋₂₄ = 202 ng·h/mL (27% CV)
Range of linear PK	0.025 to 1.1 mg for advanced or recurrent solid tumors; 1 to 2 mg/day for advanced hematologic malignancies	
Accumulation at steady state	At 1 mg/day dose: accumulation = 2.4 (15% CV)	
Metabolites	Low levels of dehydrogenated and mono-oxygenated metabolites.	
Absorption	Absolute/Relative Bioavailability	Not available
	t _{max}	At 1 mg/day dose, day 1: t _{max} = 1.03 h (0.73–2.07); day 35 (steady-state), t _{max} = 1.02 hr (0.75–2) Metabolite: Not applicable

Distribution	Vd/F or Vd	Day 1: Vz/F = 415 L (233–662)
	% bound	Plasma protein binding = 78.7%
Elimination	Route	Renal is primary route of elimination; 44 to 90.6% of the dose was recovered in urine as unchanged parent drug Other minor route of elimination is metabolism.
	Terminal t_½	At 1 mg/day = 50 h (28.6–74.4)
	CL/F or CL	Mean = 5.24 L/h (27% CV)
Intrinsic factors	Age	No effect of age on PK
	Sex	No effect of sex on PK
	Race	Limited data to evaluate
	Hepatic and Renal Impairment	Renal impairment: Mean AUC decreased by 44% in moderate renal impaired patients by population PK analyses. Hepatic impairment: Limited data to evaluate the impact of hepatic impairment on PK.
Extrinsic factors	Drug Interactions	Talazoparib is unlikely to demonstrate clinically significant cytochrome P450 (CYP450) inhibition- or induction-based drug-drug interactions or drug transporter inhibition-based drug-drug interactions when coadministered with corresponding substrates. Study to evaluate the effect of strong P-gp inhibitor or inducer on the PK of talazoparib is planned.
	Food Effects	Food effect study with high fat meal: C _{max} decreased by 46% and no effect on AUCs under fed condition.
Expected high clinical exposure scenario	In patients with severe renal impairment and co-medications with P-gp and BCRP strong inhibitors.	

AUC, area under the plasma concentration-time curve; BCRP, breast cancer resistance protein; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; CYP450, cytochrome P450; MTD, maximum tolerated dose; P-gp, P-glycoprotein; PK, pharmacokinetic; t_½, half-life; T_{max}, time to C_{max}; Vd, apparent volume of distribution; Vd/F, apparent volume of distribution after nonintravenous administration; Vz/F, apparent volume of distribution during terminal phase after nonintravenous administration

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/s/

DHANANJAY D MARATHE

07/17/2018

Youwei Bi was the primary reviewer.

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LABEL AND LABELING REVIEW

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

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

Date of This Review:	July 11, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 211651
Product Name and Strength:	Talzenna (Talazoparib) Capsules, 0.25 mg and 1 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pfizer, Inc.
FDA Received Date:	April 6, 2018
OSE RCM #:	2018-715
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of this NDA, this review evaluates the proposed Talzenna prescribing information (PI) and container labels to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 PRESCRIBING INFORMATION (PI)

We reviewed the proposed Talzenna PI and find it acceptable from a medication error perspective.

3.2 CONTAINER LABEL

We reviewed the proposed Talzenna container labels and determined that they may be improved to promote safe use of the proposed product.

4 CONCLUSION & RECOMMENDATIONS

The proposed Talzenna Prescribing Information is acceptable from a medication error perspective. The proposed Talzenna container labels may be improved to promote safe use of the proposed product.

4.1 RECOMMENDATIONS FOR PFIZER

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. The similarity of the product code numbers in the NDC number has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (b) (4). Revise the product code in the NDC numbers to ensure that the middle 4 digits (XXXX) are different between the strengths.^a
2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format such as MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).^a

^a Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Talzenna received on April 6, 2018 from Pfizer.

Table 2. Relevant Product Information for Talzenna						
Initial Approval Date	N/A					
Active Ingredient	talazoparib					
Indication	Treatment of adult patients with germline BRCA-mutated HER2 negative locally advanced or metastatic breast cancer					
Route of Administration	Oral					
Dosage Form	Capsules					
Strength	0.25 mg and 1 mg					
Dose and Frequency	Recommended dose: 1 mg once daily					
	Dose Modification for Toxicities					
	<table border="1"> <thead> <tr> <th></th> <th>Dose Level</th> </tr> </thead> <tbody> <tr> <td>First dose reduction</td> <td>0.75 mg (three 0.25 mg capsules) once daily</td> </tr> <tr> <td>Second dose reduction</td> <td>0.5 mg (two 0.25 mg capsules) once daily</td> </tr> </tbody> </table>		Dose Level	First dose reduction	0.75 mg (three 0.25 mg capsules) once daily	Second dose reduction
	Dose Level					
First dose reduction	0.75 mg (three 0.25 mg capsules) once daily					
Second dose reduction	0.5 mg (two 0.25 mg capsules) once daily					
How Supplied	0.25 mg: bottle of 30 (b) (4) capsules. 1 mg: bottle of 30 capsules					
Storage	20°C to 25°C (68°F to 77°F)					
Container Closure	(b) (4) high-density polyethylene (HDPE) bottles and (b) (4) closures (b) (4)					

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Talzenna labels and labeling submitted by Pfizer on April 6, 2018.

- Container labels
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container labels



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TINGTING N GAO
07/11/2018

CHI-MING TU
07/11/2018