CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211651Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108708

MEETING PRELIMINARY COMMENTS

Medivation Inc, a wholly-owned subsidiary of Pfizer Inc
Attention: Katarzyna Kowanetz, PhD, RAC
525 Market Street, 36th Floor
San Francisco, CA 94105

Dear Dr. Kowanetz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for talazoparib.

We also refer to your November 17, 2017, correspondence, received November 17, 2017, requesting a meeting to discuss the NDA for talazoparib for the treatment of adult patients with germline BRCA mutated, HER2-negative locally advanced and/or metastatic breast cancer that is currently planned for submission in April 2018.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Clara Lee, Regulatory Project Manager at (240) 402-4809.

Sincerely,

{See appended electronic signature page}

Clara Lee, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology & Oncology Products
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ENCLOSURE: Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Application Number:	IND 108708
Product Name:	Talazoparib
Indication:	The treatment of adult patients with germline BRCA mutated (as detected by an FDA-approved test) human epidermal growth factor receptor 2 (HER2)-negative locally advanced and/or metastatic breast cancer.
Sponsor/Applicant Name:	Medivation Inc, a wholly-owned subsidiary of Pfizer Inc

INTRODUCTION:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 12, 2018, 12:00 PM – 1:00 PM, 10903 New Hampshire Avenue, White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903 between Pfizer, Inc. and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Pfizer has requested a Type B, pre-NDA meeting with the agency to discuss a NDA submission for talazoparib for the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer based on the results from Study 673-301 (C3441009, EMBRACA). NDA submission is currently planned for April 2018.

Clinical studies to be included in the submission are shown in the following table:

Study No.	Study Description	Treatment Regimen (No. of Patients/ Healthy Volunteers)	Status	Included?			
				CSR	SCE (2.7.3)	ISS (5.3.5.3)	SCP (2.7.2)
673-301 (C3441009, EMBRACA)	A Phase 3, open-label, randomized, parallel, 2-arm, multicenter study of talazoparib (BMN 673) vs 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	1 mg/day N=431 enrolled as of April 2017; 412 patients treated 2:1 randomization (talazoparib:physician's choice treatment)	Ongoing	Full	Yes	Yes	Yes
673-201 (C3441008, ABRAZO)	A Phase 2, 2-stage, 2-cohort study of talazoparib (BMN 673) administered to germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer	1 mg/day N=84 enrolled; 83 treated (n=48 in Cohort 1 [platinum pretreated]; n=35 in Cohort 2 [≥3 prior cytotoxic chemotherapies])	Completed	Full	Yes	Yes	Yes
PRP-001 (C3441007)	Phase 1, first-in-human, single-arm, open-label study of oral talazoparib in patients with advanced or recurrent solid tumors	0.025, 0.05, 0.1, 0.2, 0.4, 0.6, 0.9, 1, and 1.1 mg as single dose and QD N=110	Completed	Full	Yes	Yes	Yes
PRP-002	Phase 1, 2-arm, open-label study of oral talazoparib in patients with advanced hematologic malignancies	0.1, 0.2, 0.3, 0.45, 0.9, 1.35, and 2 mg QD N=33	Completed	Abbrev-iated	No	No	Yes
673-103	Phase 1 food-effect study of talazoparib administered to healthy adult male volunteers	0.5 mg as single dose in fasted and fed state (2 doses total); N=18	Completed	Full	No	Yes	Yes
MDV3800-01 (C3441001)	Phase 1 open-label PK and safety study of talazoparib in patients with normal and varying degrees of renal impairment and advanced solid tumors (renal impairment)	0.5 mg QD N=24 (n=6/group) planned	Ongoing	Protocol synopsis[a]	No	No	No, ongoing
MDV3800-02 (C3441002)	Phase 1 open-label PK and safety study of talazoparib in patients with normal and varying degrees of hepatic impairment and advanced solid tumors (hepatic impairment)	0.5 mg QD N=24 (n=6/group) planned	Ongoing	Protocol synopsis[a]	No	No	No, ongoing
MDV3800-03 (C3441003)	Phase 1 open-label study of ^{14}C-talazoparib in patients with advanced solid tumors (mass balance)	1 mg (100 µCi) ^{14}C-talazoparib single dose N=6	Completed	Full	No	No	Yes
MDV3800-04 (C3441004)	Phase 1 open-label study to assess the effect of itraconazole (P-gp inhibitor) and rifampicin (P-gp inducer) on PK of talazoparib following oral dosing in patients with advanced solid tumors (drug–drug interaction)	0.5 mg talazoparib single dose with itraconazole; 1 mg talazoparib single dose with rifampicin N=36 (n=18/group) planned	Ongoing	Protocol synopsis[a]	No	No	No, ongoing
MDV3800-13 (C3441010)	A single-arm, open-label, multicenter, extended-treatment, safety study in patients treated with Talazoparib	1 mg/day (maximum starting dose) or last tolerated dose in the originating study[b]	Ongoing	Protocol synopsis	No	Yes	No
MDV3800-14 (C3441005)	Phase 1 open-label study to evaluate the effect of talazoparib on QT/QTc interval in patients with advanced solid tumors	1 mg QD N=37 treated	Completed	Full	No	Yes	Yes

Status of "Completed" indicates that CSR has been finalized.
BRCA=breast cancer susceptibility (gene); CSR=clinical study report; ISS=integrated summary of safety; N=total number of subjects; n=number of subjects in the particular cohort; NDA=New Drug Application; P-gp=P-glycoprotein; PK=pharmacokinetics; QD=once daily; QTc=corrected QT (interval); SCE=summary of clinical efficacy; SCP=summary of clinical pharmacology; vs=versus.
a. The CSR is expected to be submitted as a postmarketing commitment study.
b. Qualifying studies include PRP-001, MDV3800-01, MDV3800-02, MDV3800-03, MDV3800-04, and MDV3800-14.

In the pivotal study, EMBRACA, patients with germline BRCA mutated locally advanced and/or metastatic breast cancer were randomly assigned (2:1) to receive talazoparib at 1 mg/day or 1 of 4 protocol-specified, physician's choice chemotherapies (capecitabine, eribulin, gemcitabine, or vinorelbine). The primary efficacy endpoint was PFS as determined by the blinded central independent radiology facility (IRF). Secondary objectives were to assess the ORR, overall survival, and safety as compared with the control arm and pharmacokinetics (PK) of talazoparib. Exploratory objectives included quality of life assessed using the European Organization for

Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) / EORTC Quality of Life Questionnaire – Breast Cancer Module (QLQ-BR23) and biomarker research using blood and tumor samples.

A total of 431 patients were randomized to the study at 145 study centers, including 43 sites in the United States. There were 287 patients in the talazoparib arm and 144 patients in the PCT arm. Nineteen (19) patients (1 in the talazoparib arm and 18 in the PCT arm) were randomized but not treated. The data cutoff date was September 15, 2017.

No interim analysis of PFS by IRF was planned. However, an interim analysis of overall survival was specified at the time the final PFS analysis was performed. The final overall survival analysis is planned to be conducted after approximately 321 deaths occur.

The most frequently selected physician's choice treatment (PCT) was capecitabine (55 patients, 44%), followed by eribulin (50 patients, 40%), gemcitabine (12 patients, 10%), and vinorelbine (9 patients, 7%). The median duration of treatment for talazoparib was 6.1 months (range, 0–36.9 months) compared with 3.9 months (range, 0.2–18.1 months) for PCT overall.

The median PFS by IRF in the talazoparib arm was 8.6 months (95% CI: 7.2, 9.3) compared with 5.6 months (95% CI: 4.2, 6.7) in the PCT arm with an observed hazard ratio (HR) of 0.54 (95% confidence interval [CI]: 0.41, 0.71; $p<0.0001$). Among the 431 patients in the intent-to-treat (ITT) population, PFS events by IRF were observed in 186 patients (65%) in the talazoparib arm and 83 patients (58%) in PCT arm.

An interim analysis of overall survival was performed; there were 163 deaths observed (51% of projected final number of overall survival events), 108 deaths (37.6%) in the talazoparib arm and 55 deaths (38.2%) in the PCT arm. The median overall survival was 22.3 months (95% CI: 18.1, 26.2) in the talazoparib arm compared with 19.5 months (95% CI: 16.3, 22.4) in the PCT arm with a HR of 0.76 (95% CI: 0.55, 1.06) and a p-value of 0.1053.

Confirmed ORRs were 50.2% (95% CI: 43.4%, 57.0%) and 18.4% (95% CI: 11.8%, 26.8%) in the talazoparib arm and the PCT arm, respectively.

The described PRO analyses were prespecified in the Study 673-301 protocol and SAP. An improvement in estimated overall mean change from baseline in global health status/QoL was observed in the talazoparib arm (3.0 [95% CI: 1.2, 4.8]) compared with the PCT arm (-5.4 [95% CI: -8.8, -2.0]) ($p<0.0001$).

Time to clinically meaningful deterioration in the global health status/QoL scale score of the EORTC QLQ-C30 was predefined as the time from randomization to the first observation with a ≥10-point decrease and no subsequent observations with a <10-point decrease from baseline. There was a delay in the time to clinically meaningful deterioration in global health status/QoL in the talazoparib arm (median: 24.3 months [95% CI: 13.8, NR]) compared with the PCT arm (median: 6.3 months [95% CI: 4.9, 12.2]) (HR: 0.38 [95% CI: 0.26, 0.55]; $p<0.0001$).

For the EORTC QLQ-BR23 breast symptoms scale, an improvement was observed in estimated overall mean change from baseline in the talazoparib arm (-5.1 [95% CI: -6.7, -3.5]); whereas, an improvement was observed, but did not reach statistical significance in the PCT arm [-0.1 (95% CI: -2.9, 2.6)]. In addition, there was a difference between both arms (p=0.002) favoring talazoparib.

Time to deterioration in the breast symptoms scale of the EORTC QLQ-BR23 questionnaire was defined as the time from randomization to the first observation with a >10-point increase and no subsequent observations with a <10-point increase from baseline. There was a delay in the time to deterioration in breast symptoms scale in the talazoparib arm (HR: 0.39 [95% CI: 0.20, 0.78]; p=0.005) (median time not reached for either arm).

The most common (>30%) AEs by preferred term in the talazoparib arm were anemia (52.4%), fatigue (50.3%), nausea (48.6%), and headache (32.5%). Most nonhematologic AEs were Grade 1 or 2 in severity. AEs of anemia, thrombocytopenia, headache, platelet count decreased, fatigue, dizziness, arthralgia, asthenia, and back pain were reported more frequently (>5% absolute difference) in the talazoparib arm than in the PCT arm. AEs of hand and foot syndrome, ALT increased, paresthesia, AST increased, and pyrexia were reported more frequently (>5% absolute difference) in the PCT arm than in the talazoparib arm.

2.0 QUESTIONS

Question 1: Does the Agency agree that the efficacy results from the Phase 3 Study 673-301 (C3441009, EMBRACA), together with the data from the supportive Studies 673-201 (C3441008, ABRAZO) and PRP-001 (C3441007), are adequate to support filing and review of an NDA for talazoparib for the proposed indication?

FDA Response to Question 1: Yes.

Question 2: Does the Agency agree that the safety data from the proposed clinical studies in the Integrated Safety Population (pooled data) and additional studies described separately are adequate to support filing and review of an NDA for talazoparib for the proposed indication?

FDA Response to Question 2: Yes. Please include information regarding adverse events of special interest associated with PARP inhibitors (e.g., MDS/AML, pneumonitis, new primary malignancies) across the talazoparib clinical program.

Question 3: Does the Agency agree that the safety and efficacy data summarized in the briefing package could justify a request for priority review of the proposed NDA?

FDA Response to Question 3: Yes. Whether priority review will be granted will be determined at the time of filing.

Question 4: In the event priority review is granted, does the Agency agree with the proposal to provide a 90-day safety update to the NDA that will contain approximately 4 months of additional safety data?

FDA Response to Question 4: Yes.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 27, 2017, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e.,

those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

CLINICAL PHARMACOLOGY

Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

2. What are the exposure-response relationships for efficacy, safety and biomarkers?

3. What is the effect of talazoparib on the QT/QTc interval?

4. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?

5. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.

6. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

1. We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at http://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

2. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

3. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

4. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
   - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
   - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

5. Submit the following for the population pharmacokinetic analysis reports:
   - Standard model diagnostic plots.
   - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
   - Model parameter names and units in tables.
   - Summary of the report describing the clinical application of modeling results. Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

6. Submit the following information and data to support the population pharmacokinetic analysis:
   - SAS transport files (*.xpt) for all datasets used for model development and validation.
   - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

7. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator

c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

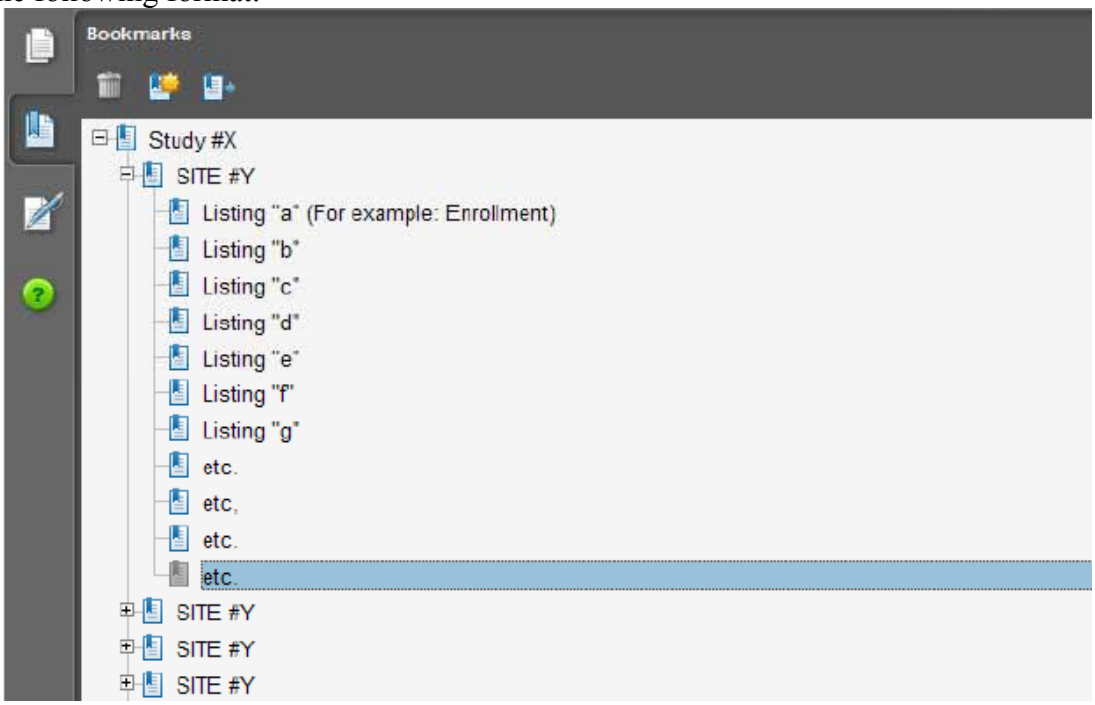
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

CLARA J LEE
02/05/2018

LALEH AMIRI KORDESTANI
02/05/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108708

MEETING PRELIMINARY COMMENTS

Medivation, Inc.
Attention: Katarzyna Kowanetz, PhD
Manager Regulatory, Worldwide Safety and Regulatory
525 Market Street, 36th Floor
San Francisco, CA 94105

Dear Dr. Kowanetz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for talazoparib.

We also refer to your May 12, 2017, correspondence, received May 12, 2017, requesting a meeting to discuss the critical elements of the proposed NDA submission planned for talazoparib for the treatment of germline BRCA-mutated, HER2-negative locally advanced and/or metastatic breast cancer.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Rajesh Venugopal, Regulatory Project Manager at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

ENCLOSURE: Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Application Number:	IND 108708
Product Name:	Talazoparib
Indication:	The treatment of adult patients with germline BRCA-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced and/or metastatic breast cancer
Sponsor/Applicant Name:	Medivation, Inc.

INTRODUCTION

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Tuesday July 18, 2017, 10:30 AM – 11:30 AM, 10903 New Hampshire Avenue, White Oak Building 22, Conference Room: 1309, Silver Spring, Maryland 20903 between Medivation, Inc. and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

Pfizer has requested a pre-NDA meeting to discuss elements of the proposed NDA submission planned for the PARP inhibitor, talazoparib. Study 673-301 (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" is the pivotal study intended to support an NDA submission for talazoparib for the treatment of adult patients with germline BRCA-mutated HER2-negative locally advanced and/or metastatic breast cancer. Top-line results for the EMBRACA study are expected to be available in Q3 2017 with an NDA filing anticipated in early 2018 if the study outcome is positive. In EMBRACA, patients with germline BRCA mutations who received no more than 3 prior cytotoxic chemotherapy regimens for advanced breast cancer were randomly assigned (2:1) to receive talazoparib at 1 mg/day or 1 of 4 protocol-specified, physician's choice chemotherapies (capecitabine, eribulin, gemcitabine, or vinorelbine). The original protocol

excluded patients who received any platinum for advanced breast cancer; however, the eligible population was expanded to allow prior platinum, except for patients considered to have platinum-refractory disease. A total of 222 study sites enrolled 431 patients over approximately 40 months, and the study closed to enrollment in April 2017.

The primary efficacy endpoint is radiographic PFS, as determined by the central independent radiology facility (IRF) per RECIST 1.1. Key secondary endpoints include ORR and OS. For radiographic PFS, a total of 288 PFS events will provide 90% power for a 2-sided log-rank test at a 0.05 significance level to detect a 50% increase in median PFS (hazard ratio [HR] = 0.67). If the 2-sided hypothesis test of PFS is statistically significant, formal hypothesis testing of ORR by investigator between the 2 treatment groups will be performed using the stratified Cochran-Mantel-Haenszel method at a 0.01 significance level. As the OS data are not expected to be mature at time of the PFS analysis, an interim analysis of OS will be conducted at a 0.0001 significance level. No formal hypothesis testing will be performed for OS at the interim analysis. The final analysis of OS will be conducted when approximately 321 deaths occur, which will provide 80% power to detect a 39% increase in median OS (HR = 0.72) using a 2-sided log-rank test with an overall significance level of 0.05. Assuming an exponential distribution of OS, this corresponds to an increase in median OS from 20 to 27.8 months.

The Myriad Genetic Laboratories (Myriad) (CLIA [Clinical Laboratory Improvement Amendments]) BRACAnalysis validated test was initially used to screen patients for Study 673-301. Approximately 30% of all enrolled patients tested positive for BRCA mutations with the CLIA test before the FDA-approved version (BRACAnalysis CDx device) became available. Thereafter, the BRACAnalysis CDx was used to screen patients. In addition, the BRACAnalysis CDx will be used to retest material from any of the initial patients with available samples. Thus, the Sponsor expects to have BRACAnalysis CDx results for >95% of patients in Study 673-301. Less than 5% of patients were enrolled based on local genetic test results and did not have sufficient material for retesting with BRACAnalysis CDx assay.

Study 673-201 (ABRAZO) and Study PRP-001 are to be supportive of the planned NDA. ABRAZO was a Phase 2 study that enrolled patients with locally advanced and/or metastatic breast cancer who had a deleterious germline BRCA1/2 mutation per central assessment in the following 2 parallel cohorts:

- Cohort 1: patients who received prior platinum for metastatic breast cancer and whose disease responded to platinum and remained stable for at least 8 weeks following platinum therapy
- Cohort 2: patients who received 3 or more prior systemic cytotoxic chemotherapy regimens for metastatic breast cancer (platinum therapy for metastatic disease was not permitted)

Eighty-four (84) patients were enrolled in 33 study sites across 5 countries between May 2014 and February 2016: 49 patients in Cohort 1 (platinum pretreated) and 35 patients in Cohort 2 (3 or more prior systemic cytotoxic chemotherapy regimens). Eligible patients had an ECOG performance status ≤1, measurable disease by RECIST 1.1, HER2-negative breast cancer, and adequate hematologic and organ function. There was no limit to endocrine- or immune-based therapies; however, no prior PARP inhibitor therapy was allowed.

The primary objective was confirmed ORR by central IRF. Secondary objectives included clinical benefit rate at 24 weeks (CBR24), DOR, PFS, OS, and PK. In July 2015, the study met the criterion to proceed to Stage 2 for both cohorts based on investigator review of the objective responses in Stage 1. However, further enrollment was discontinued in February 2016 to facilitate enrollment in the Phase 3 study (673-301), as the eligibility criteria for these 2 studies became overlapping with the issuance of Phase 3 study (673-301) protocol amendment 1.

Efficacy Results for the ABRAZO study by IRF Assessment as of September 1, 2016 are shown in the following table:

	Cohort 1 (N = 48)	Cohort 2 (N = 35)
ORR by IRF, n (% [95% CI])[a]	10 (20.8% [10.5, 35.0])	13 (37.1% [21.5, 55.1])
Median DOR, months (95% CI)[a]	5.8 (2.8, NR)	3.8 (2.8, 10.1)
CBR24, n (% [95% CI])[a]	13 (27.1% [15.3, 41.9])	16 (45.7% [28.2, 63.4])
Median PFS, months (95% CI)[b]	3.9 (2.6, 5.6)	5.6 (4.4, 7.2)

CBR24 = clinical benefit rate at 24 weeks; CI = confidence interval; DOR = duration of response; IRF = independent radiology facility; ITT = intent-to-treat; N = number of patients; NR = not reached; ORR = objective response rate; PFS = progression-free survival.

a. Calculated using the tumor-evaluable population (treated patients with baseline tumor assessment and at least 1 postbaseline tumor assessment) and IRF assessment.

b. Calculated using the ITT population (N = 49 for Cohort 1 and N = 35 for Cohort 2) per analysis plan.

AEs were reported for 81 patients; the most common (>25%) were anemia (52%), fatigue (45%), nausea (42%), diarrhea (33%), thrombocytopenia (33%), and neutropenia (27%). The most common Grade ≥3 AEs (≥10%) were anemia (35%), thrombocytopenia (19%), and neutropenia (15%). Four (4) patients had an AE that resulted in death, none of which was considered related to talazoparib. A total of 23 patients had a serious adverse event; the most common serious adverse events of myelosuppression were anemia (6%) and thrombocytopenia (4%). Four (4) patients had AEs leading to permanent treatment discontinuation.

Study PRP-001 was a Phase 1 first-in-human study that evaluated the safety, PK, pharmacodynamics, and preliminary efficacy of talazoparib in patients with advanced tumors with deoxyribonucleic acid (DNA) repair pathway deficiencies, particularly those associated with BRCA and phosphatase and tensin homolog (PTEN) dysfunction. Enrollment closed in September 2014 with a total of 110 patients.

This study included 20 patients with breast cancer and deleterious germline BRCA mutations who received a median of 3.0 prior chemotherapy regimens (range: 0-6); 8 patients enrolled in the dose-escalation phase and 12 patients in the expansion phase. All 20 patients were treated with talazoparib at 0.60 to 1.1 mg/day, including 14 patients treated at the recommended single-agent talazoparib dose of 1 mg/day. Objective responses (CR or PR) were observed in 7 of the 14 patients (50.0%) with breast cancer and deleterious germline BRCA mutations treated with talazoparib 1 mg/day, including 1 confirmed CR in a patient with a BRCA2 deleterious mutation. Median DOR for the 7 responders who received 1 mg/day was 32 weeks.

Ongoing and completed company-sponsored clinical studies of talazoparib include 5 clinical pharmacology studies in solid tumors, 1 food effect study in healthy volunteers, 1 study in

hematologic malignancies, and 3 studies in solid tumors. An overview of the clinical studies and reports to be included in the NDA are summarized in the following tables:

Study No.	Study Description	Treatment Regimen (No. of Patients/ Healthy Volunteers)	Status	Included?			
				CSR	SCE (2.7.3)	ISS (5.3.5.3)	SCP (2.7.2)
673-301 (C3441009, 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	1 mg/day N = 431 enrolled as of April 2017 2:1 randomization (talazoparib:physician's choice)	Ongoing	Full	Yes	Yes	Yes
673-201 (C3441008, ABRAZO)	A Phase 2, 2-stage, 2-cohort study of talazoparib (BMN 673) administered to germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer	1 mg/day N = 83 treated (n = 48 in Cohort 1 [platinum pretreated]; n =35 in Cohort 2 [≥3 prior cytotoxic chemotherapies])	Completed	Full	Yes	Yes	Yes
PRP-001 (C3441007)	Phase 1, first-in-human, single-arm, open-label study of oral talazoparib in patients with advanced or recurrent solid tumors	0.025, 0.05, 0.1, 0.2, 0.4, 0.6, 0.9, 1, and 1.1 mg as single dose and QD N = 109[a]	Completed	Full	Yes	Yes	Yes
PRP-002	Phase 1, 2-arm, open-label study of oral talazoparib in patients with advanced hematologic malignancies	0.1, 0.2, 0.3, 0.45, 0.9, 1.35, and 2 mg QD N = 33	Completed	Abbre viated	No	No	Yes
673-103	Phase 1 food-effect study of talazoparib administered to healthy adult male volunteers	0.5 mg as single dose; N = 18	Completed	Full	No	No	Yes
MDV3800-01 (C3441001)	Phase 1 open-label PK and safety study of talazoparib in patients with normal and varying degrees of renal impairment and advanced solid tumors (renal impairment)	0.5 mg QD N = 24 (n = 6/group) planned	Ongoing	Protocol synopsis[b]	No	No	No, ongoing
MDV3800-02 (C3441002)	Phase 1 open-label PK and safety study of talazoparib in patients with normal and varying degrees of hepatic impairment and advanced solid tumors (hepatic impairment)	0.5 mg QD N = 24 (n = 6/ group) planned	Ongoing	Protocol synopsis[b]	No	No	No, ongoing
MDV3800-03 (C3441003)	Phase 1 open-label study of ^{14}C-talazoparib in patients with advanced solid tumors (mass balance)	1 mg (100 µCi) ^{14}C-talazoparib single dose N = 6 planned	Ongoing	Full	No	No	Yes
MDV3800-04 (C3441004)	Phase 1 open-label study to assess the effect of itraconazole (P-gp inhibitor) and rifampicin (P-gp inducer) on PK of talazoparib following oral dosing in patients with advanced solid tumors (drug–drug interaction)	0.5 mg talazoparib single dose with itraconazole; 1 mg talazoparib single dose with rifampicin N = 36 (n = 18/group) planned	Ongoing	Protocol synopsis[b]	No	No	No, ongoing
MDV3800-13 (C3441010)	A single-arm, open-label, multicenter, extended-treatment, safety study in patients treated with talazoparib	1 mg/day (maximum starting dose) or last tolerated dose in the originating study[c]	Ongoing	Protocol synopsis	No	Yes	No
MDV3800-14 (C3441005)	Phase 1 open-label study to evaluate the effect of talazoparib on QT/QTc interval in patients with advanced solid tumors	1 mg QD N = 30 planned	Ongoing	Full	No	Yes	Yes

Completed indicates end of study (as defined in protocol) was reached.
BRCA = breast cancer; CSR = clinical study report; N = total number of subjects; n = number of subjects in the particular cohort; NDA = new drug application; P-gp = P-glycoprotein; PK = pharmacokinetics; QD = once daily; QTc = corrected QT (interval); SCE = summary of clinical efficacy; ISS = integrated summary of safety; SCP = summary of clinical pharmacology.

a. PK population.
b. The CSR is expected to be submitted as a postmarketing commitment study.
c. Qualifying studies include PRP-001, MDV3800-01, MDV3800-02, MDV3800-03, MDV3800-04, and MDV3800-14.

DISCUSSION

1. *Does the Agency agree with the proposed content of the NDA presented in Section 6 and the proposed format for data presentation presented in the NDA Table of Contents for Module 2.7 in Appendix 6?*

FDA Response: Yes.

2. *Does the Agency agree that a full integrated summary of efficacy (ISE) is not necessary for the NDA; rather, efficacy results from the Phase 3 and Phase 2 studies will be summarized individually in the summary of clinical efficacy (SCE) (relevant tables and listings will be provided in Module 5)?*

FDA Response: We agree with your plan of not submitting a full ISE for the application. Please ensure you submit detailed SCE documents with the appropriate cross-references to elements in Module 5.

3. *Does the Agency agree that the planned analyses of safety data from individual and pooled clinical studies (PRP-001, 673-201, 673-301, MDV3800-13, and MDV3800-14) are adequate to support the NDA filing and FDA review of talazoparib for the proposed indication?*

FDA Response: Yes, at this time the planned analyses of safety data appear adequate to support filing and review.

4. *Does the Agency agree that the proposed summary of clinical safety (SCS) (described in Section 7.4) is sufficiently detailed to meet the summary requirements of the integrated summary of safety (ISS), as outlined in 21 Code of Federal Regulations (CFR) 314.50(d)(5)(vi)(a) such that a separate ISS is not required (relevant tables and listings will be provided in Module 5)?*

FDA Response: Yes.

5. *Does the Agency agree with the proposal that the NDA include patient narratives for all patients in company-sponsored talazoparib studies with deaths, serious adverse events, permanent discontinuations due to adverse events, and adverse events of special interest as well as case report forms (CRFs) for all patients in Phase 3 Study 673-301 and for patients in company-sponsored studies who have events that meet the narrative criteria described in Section 7.5?*

FDA Response: Yes. In addition, we may ask for additional narratives during review of the application.

6. *Does the Agency agree with the proposal for the content and presentation of clinical pharmacology data, as described in Section 7.6?*

FDA Response: Yes. When conducting exposure-response for efficacy, safety and biomarkers, please provide a justification for the exposure metrics that are used in the exposure-response analyses. If the rate of dose modification/interruption is high, E-R analysis using individual predicted steady state exposures for the average dose each patient received from the beginning of treatment to the time of the event of interest (e.g., ORR, SAE, TEAE, discontinuation, AE of interest) or the end of treatment, whichever happened earlier, may need to be performed.

7. *Does the Agency agree with the proposal to provide the CSRs from the renal impairment (MDV3800-01), hepatic impairment (MDV3800-02), and drug-drug interaction (DDI) (MDV3800-04) studies as postmarketing commitment studies?*

FDA Response: We acknowledge your proposal of potential delay of submission of these CSRs. However, we encourage you to make your best efforts to submit them with initial NDA submission.

8. *Does the Agency agree that Financial Disclosure information will be provided for Studies PRP-001, 673-201, and 673-301?*

FDA Response: Yes.

9. *Does the Agency agree with the proposal that in addition to the planned analyses of efficacy in the Phase 3 study using the intent-to-treat population, the Sponsor will also perform efficacy sensitivity analyses using the subset of patients with BRACAnalysis CDx results in support of the planned NDA and supplemental premarket approval (PMA) filing?*

FDA Response: A bridging study between the two different versions of the Myriad BRACAnalysis test (e.g., CLIA and CDx versions) will not be required if the assays are considered to be equivalent. In the event that a bridging study is not needed, we recommend that you perform the planned analyses of efficacy on the ITT population using the available CLIA and CDx test results combined. Further, a sensitivity analysis should be performed on the approximately 70% of the patients enrolled with the BRACAnalysis CDx results and not the proposed 412 patients who would have BRACAnalysis CDx results available after re-testing. If the results of the sensitivity analysis are similar to the efficacy results obtained from all patients in the ITT population (using the combined CLIA and CDx test results), then the clinical performance of the device can be based on the combined results from the CLIA and CDx versions of the BRACAnalysis test to support a PMA supplement.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 15, 2017, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore,

at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.
For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do

not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and Sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

    a. Location at which Sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other Sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

    b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

    c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

    a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

    b. Subject listing for treatment assignment (randomization)

    c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

    d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol

    e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

    f. By subject listing, of AEs, SAEs, deaths and dates

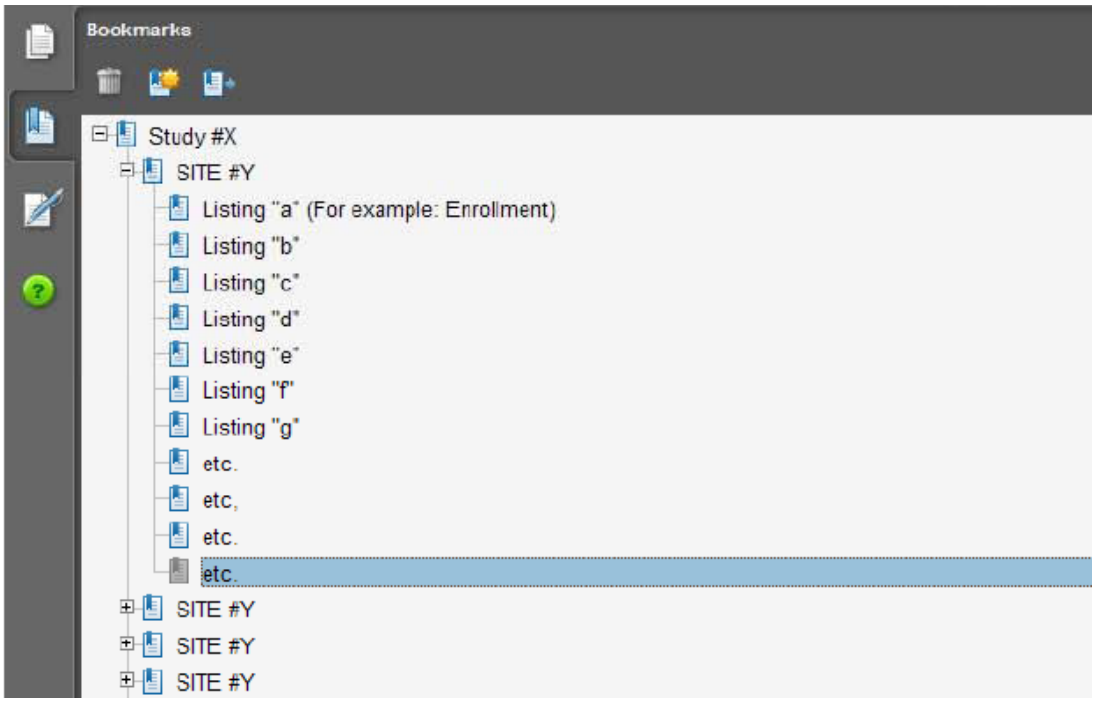
    g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

RAJESH VENUGOPAL
07/07/2017

LALEH AMIRI KORDESTANI
07/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108708

MEETING MINUTES

BioMarin Pharmaceuticals, Inc.
Attention: Erin Jones
105 Digital Drive
Novato, CA 94949

Dear Mr. Jones:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMN 673.

We also refer to the meeting between representatives of your firm and the FDA on April 12, 2013. The purpose of the meeting was to discuss the planned Phase 2 and Phase 3 clinical studies and the overall drug development program for BMN 673 to support a New Drug Application (NDA) for treatment of patients with locally advanced and metastatic breast cancer with a BRCA 1 and/or BRCA 2 mutation.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5225.

Sincerely,

{See appended electronic signature page}

Elleni Alebachew, M.S. RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center of Drug Evaluation and Research

Patricia Cortazar, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center of Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	April 12, 2013 10:00 am – 11:00 am
Meeting Location:	FDA WO 22 Room 1315
Application Number:	IND 108708
Product Name:	BMN 673
Indication:	Treatment of patients with locally advanced and metastatic breast cancer with a BRCA 1 and/or BRCA 2 mutation
Sponsor/Applicant Name:	BioMarin Pharmaceuticals, Inc.
Meeting Chair:	Patricia Cortazar, M.D., Medical Team Leader, DOP1
Meeting Recorder:	Elleni Alebachew, M.S. RAC., Regulatory Health Project Manger, DOP1

FDA ATTENDEES

Robert L. Justice, M.D., M.S., Director, DOP1
Amna Ibrahim, M.D., Deputy Director, DOP1
Patricia Cortazar, M.D., Medical Team Leader, DOP1
Laleh Amiri-Kordestani, M.D., Medical Officer, DOP1
W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T., Pharmacology/Toxicology Reviewer
Shenghui Tang, Ph.D., Biostatistics Team Leader
Stella W. Karuri, Ph.D., Biostatistics Reviewer
Qi Liu, Ph.D., Clinical Pharmacology Team Leader
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Reviewer
Reena Philip, Ph.D., Supervisory Microbiologist, CDRH/OIVD/DIHD
Maria Chan, Ph.D., Supervisory Microbiologist, CDRH/OIVD/DIHD
Sharon Liang, Ph.D., Reviewer, CDRH/OVID/DIHD
Elleni Alebachew, M.S. RAC., Regulatory Health Project Manger, DOP1

SPONSOR ATTENDEES

Manish Anand, M.S., Senior Manager, Regulatory Affairs
Lisa Bell, Ph.D., Vice President, Regulatory Affairs
Andrew Dorr, M.D., Consultant
Henry Fuchs, M.D., Chief Medical Officer
Joshua Henshaw, Ph.D., Sr. Scientist, PK/PD
Erin Jones, M.S., Director, Regulatory Affairs
Michael Murtagh, Associate Director, Regulatory Affairs
Len Post, Ph.D., Chief Scientific Officer
Laurie Tsuruda, Ph.D., DABT, Director, Pharmacology and Toxicology
Charlie Zhang, Ph.D., Director, Biostatistics

BACKGROUND

BioMarin requested a type B End-of-Phase 2 meeting to discuss BMN 673 drug development for the treatment of patients with metastatic breast cancer who have a BRCA 1 and/or BRCA 2 germline mutation.

BMN 673 is a poly(ADP-ribose) polymerase (PARP) inhibitor that targets PARP 1 and PARP 2. BMN 673 induces synthetic lethality in tumors with BRCA mutations and in tumors with PTEN deficiencies and other specific alterations such as the EWS-FLI1 translocation in Ewing's sarcoma cells.

BioMarin is currently conducting a phase 1 study (PRP-001) entitled: "First in Human, Single-Arm, Open-label Study of Once a Day, Orally Administered BMN 673 in Patients with Advanced or Recurrent Solid Tumors". A total of 39 patients have been exposed to escalating doses of BMN 673. Three patients experienced dose-limiting toxicities (thrombocytopenia) during dose escalation. Other drug-related adverse events included neutropenia, anemia, alopecia, fatigue and gastrointestinal side effects. Eight patients with metastatic breast cancer were enrolled during dose escalation, including 6 patients with germ-line BRCA mutations. Two of the 6 patients with germ-line mutations who were treated with BMN 673 at doses of 900 and 1000 µg/day, had a partial response. The preliminary data from the Phase 1 study and the clinical data from other PARP inhibitors (ORR: 30%-45%) constitute the basis for BioMarin's hypothesis that BMN 673 may provide clinical benefit to patients with germ-line BRCA mutations.

BioMarin is planning to simultaneously conduct Phase 2 (673-201) and Phase 3 (673-301) studies. Trial 673-301 is an open-label, randomized, parallel, two-arm, multi-center study of BMN 673 versus physician's choice in germ-line BRCA mutation carriers with metastatic breast cancer, who have received no more than two prior chemotherapy regimens for metastatic disease. Study 673-201 is a Phase 2, two-stage, single-arm study of BMN 673 in patients with germ-line BRCA mutation carriers with metastatic breast cancer.

DISCUSSION

Questions and Responses

1. In addition to the IND enabling pharmacology and toxicology program conducted with BMN 673, BioMarin plans to initiate two 13-week repeat dose toxicology studies in rat and dog to support the Phase 3 clinical study. Per ICH S9, BioMarin also plans to conduct embryo-fetal reproductive toxicology studies in the rat and rabbit prior to submission of an NDA.

   Does the Agency agree that the non-clinical toxicology package is adequate to support an NDA for the use of BMN 673 in the proposed indication?

FDA response: **The non-clinical studies described in your briefing package appear consistent with ICH S9 recommendations and appropriate to support an NDA for the proposed indication, except for the absence of an adequate assessment of genetic toxicology. You will need to investigate the genotoxic potential of BMN 673, as described in ICH S9, to support an NDA. We will make the final determination of the adequacy of your non-clinical studies after reviewing all the data submitted to the NDA.**

Meeting Discussion: **No discussion took place at the meeting.**

2. Following the ongoing Phase 1 clinical studies, BioMarin plans to initiate a Phase 3 multicenter, multinational, randomized, active control clinical study in patients with metastatic breast cancer with a BRCA 1 and/or BRCA 2 germline mutation. In addition, BioMarin plans to evaluate BMN 673 in a Phase 2 multicenter, multinational, open label study in previously-treated metastatic breast cancer patients, and a BRCA 1 and/or BRCA 2 mutation.

   Does the agency agree with the proposed Phase 3 study design?

FDA response: **This question is premature since you only have limited data on the efficacy of BMN 673 in BRCA 1 and 2 mutation carriers with metastatic breast cancer. The responses that you reported from the Phase 1 study in 2 of the 6 patients treated with BMN 673 is hypothesis generating. We strongly recommend that you conduct a Phase 2 trial in the proposed patient population to determine the efficacy and safety of BMN 673. The results from this Phase 2 trial can inform the Phase 3 trial design, including the statistical assumptions and sample size. The Agency would like to meet with you when the results of the Phase 2 study are available to further discuss the Phase 3 trial design.**

In general, we have the following concerns:

- **The acceptability of the Phase 3 trial design will depend upon the efficacy and safety findings from the Phase 2 study.**
- **The determination of what is considered an adequate control arm will depend on the therapies available at the time you submit the Phase 3 trial.**
- **Patients should have received prior standard regimens that are known to benefit patients with breast cancer (anthracyclines, taxanes).**
- **The proposed Phase 3 trial plans to include patients with HER2-positive metastatic breast cancer. These patients should be excluded from the proposed trial since they have several anti-HER2 therapies available that confer clinical benefit.**
- **At the time of the Phase 3 trial submission you should explain the rationale for excluding patients with a history of brain metastases and/or a history of platinum therapy.**
- **Only a clinically meaningful and statistically robust PFS result with acceptable benefit/risk would be considered for approval. Your proposed magnitude of improvement in median PFS (5.6 weeks) is very unlikely to be considered clinically meaningful and sufficient to support approval. See the recent approvals of new breast cancer therapies where either a substantial improvement in PFS or a clinically meaningful improvement in OS was demonstrated. As you are aware**

from the ODAC meeting held on July 23, 2010, there are known problems with PFS interpretation and reproducibility and lack of correlation with overall survival in the metastatic breast cancer trials.

- **We recommend that the trial be adequately powered for OS. OS should be the key secondary endpoint. An interim OS analysis should be performed at the time of the final PFS analysis.**

Meeting Discussion: The sponsor plans to test ORR as the first secondary endpoint followed by OS. FDA reiterated the recommendation that OS should be the first secondary endpoint.

3. Does the Agency agree that the patient population is adequately described in the entry criteria?

FDA response: Please see our response to Question #2.

Meeting Discussion: No discussion took place at the meeting.

4. Does the Agency agree with the selection of a physician's choice comparator arm (limited to vinorelbine, capecitabine, gemcitabine, ixabepilone, and eribulin) in Study 673-301 to assess the efficacy of BMN 673 in this patient population?

FDA response: In the protocol you need to provide the rationale for selecting these therapies in the comparator arm. Please see our response to Question #2.

Meeting Discussion: No discussion took place at the meeting.

5. Does the Agency agree with the proposed primary endpoint of progression free survival (PFS)?

FDA response: See our response to Question #2.

Meeting Discussion: No discussion took place at the meeting.

6. Does the Agency agree with the safety assessments and monitoring frequency to assure patient safety, as outlined in the protocol synopsis?

FDA response: The adequacy of the proposed safety assessments in the Phase 3 trial is unknown since you have not provided us with enough safety information.

Meeting Discussion: No discussion took place at the meeting.

7. Does the Agency agree with the proposed statistical analysis plan (SAP)?

FDA response: See responses to Questions #2, #8, and #9.

Meeting Discussion: No discussion took place at the meeting.

8. Does the Agency agree with the proposed approach to control Type I error for the primary endpoint (PFS) and secondary endpoints OS and ORR?

FDA response: No, see response to Question #2.

Please clarify the order in which secondary endpoints are to be tested; in general, a hierarchical testing procedure is acceptable. Please note that if you use an alpha of 0.05 for the interim analysis of OS analysis as planned, you will have no alpha left for the final OS analysis if the interim OS analysis fails to demonstrate statistical significance. We recommend that you use a group sequential method to determine alpha allocation for the interim and final OS analysis.

Meeting Discussion: The sponsor will propose an analysis for harm based on Pocock boundary, for FDA review and comment. The study will be powered for OS with a hazard ratio of 0.7 to be detected. An interim OS analysis will be performed at the time of the final PFS analysis. Type 1 error rate will be adjusted based on an O'Brien-Fleming boundary type alpha allocation procedure.

9. Does the Agency agree with the proposed testing method for the primary endpoint and the secondary endpoints?

FDA response: Yes. We agree with the proposed testing methods for the primary and secondary endpoints. However, please see responses above.

Meeting Discussion: No discussion took place at the meeting.

10. Does the Agency agree with the proposed statistical considerations, including the stratification factors for randomization, the assumptions underlying proposed sample size and power calculations, and the planned analyses?

FDA response: The stratification factors for randomization appear acceptable. Please note that a statistically significant difference in PFS may not necessarily demonstrate a clinically meaningful difference. See response to Question #8 with regards to the planned analyses.

Meeting Discussion: No discussion took place at the meeting.

11. The clinical pharmacology program at the time of NDA filing will include PK data from the ongoing Phase 1 clinical studies (PRP-001 and PRP-002), the planned Phase 2 study, the planned Phase 3 clinical study, and a planned food effect study. A population PK modeling approach is planned to evaluate the potential effects of patient-specific covariates (e.g., gender, age, weight, and markers of renal/hepatic function) on the PK of BMN 673.

    Does the Agency agree that the proposed clinical pharmacology package supports a NDA for BMN 673 in the proposed indication?

FDA response: **No. We have the following comments regarding your clinical pharmacology development program:**

1. **You should submit your plan to address the potential for QT/QTc interval prolongation by BMN 673 for review by the QT/IRT (see ICH E14 guidance found at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf.**

2. **You should further characterize the enzymatic pathways responsible for the metabolic clearance of BMN 673 through *in vitro* screens. The *in vitro* results will determine the need to conduct PK drug interaction trial(s). Refer to the Guidance for Industry entitled "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.**

3. **As a mass balance trial was not conducted, it is not possible to conclude based on the data submitted, that hepatic elimination of your drug is not important for the clearance of BMN 673. In addition to your current exploratory population PK analysis, please also conduct a categorical analysis based on hepatic function (i.e. NCI classification for mild, moderate and severe hepatic impairment, or the Child-Pugh classification). Please also include this categorical analysis based on hepatic function in the final population PK analysis. If adequate representation of moderate and severe hepatic impairment is not possible, then a dedicated hepatic impairment trial should be conducted in order to allow for adequate dose-adjustments in these patient groups.**

4. **Could you please provide your explanation for the increased renal elimination at Day 35 compared to Day 1 in study PRP-001? In addition, you should assess the effect of severe renal impairment on the PK of your drug to allow for appropriate dose-adjustment in this group of patients.**

5. **A population PK approach using Phase 2 and 3 data can be useful to assess the impact of renal and hepatic impairment on BMN 673 PK. We recommend that you enroll a sufficient number of patients with a wide range of hepatic and renal function in your Phase 2 and Phase 3 studies and get enough PK samples from each patient to characterize their PK. You should pre-plan the analysis and power the study to get precise estimates (relative standard error 20%) of the mean clearance parameter in renal and hepatic impaired patients. For further information, see hepatic and renal impairment guidances: (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf).**

6. **Determine bioavailability of the study drug in humans per Guidance for Industry entitled "*Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf.**

7. **If the study drug has pH dependent solubility, determine the potential for a drug-drug interaction with drugs that alter gastric pH (e.g., proton pump inhibitors, histamine receptor antagonists, antacids).**

8. **Based on the FDA Guidance for Industry entitled *Food-Effect Bioavailability and Fed Bioequivalence Studies,* the food-effect trial should be conducted with the highest strength of the drug product intended to be marketed. Your food-effect protocol was not previously submitted for review by FDA. Please provide a rationale for why the 250-µg strength is used in your ongoing food-effect trial (673-101). Submit the results from your food-effect trial and rationale for drug administration with regard to food prior to initiation of your proposed Phase 2 and Phase 3 trials for FDA review.**

Meeting Discussion: No discussion took place at the meeting.

12. Does the Agency agree with the plan to evaluate the potential effects of patient-specific covariates on the PK of BMN 673 in patients using a population PK modeling approach?

FDA response: Your plan appears acceptable provided you address the FDA response to Question #11 above.

Meeting Discussion: No discussion took place at the meeting.

13. Does the Agency agree that the data from the planned Phase 3 randomized, open-label study of BMN 673 (supported with data from the planned Phase 2 study) have the potential to provide adequate safety and efficacy data to support approval in the treatment of patients with advanced metastatic breast cancer with a BRCA 1 and/or BRCA 2 mutation?

FDA response: This question is premature. Please see our response to Question #2.

Meeting Discussion: No discussion took place at the meeting.

14. Upon progression in the proposed Phase 3 study, patients will be allowed to crossover from the comparator arm to BMN 673.

    Does the Agency agree that a statistically significant improvement in PFS supported with an interim OS could support full approval?

FDA response: Possibly. However, as previously stated in our response to Question #2, the PFS improvement should be statistically robust and clinically meaningful supported by a

meaningful improvement in OS. It is very unlikely that the proposed 5.6 week improvement in median PFS will result in a meaningful improvement in OS.

Meeting Discussion: The sponsor asked whether FDA objects to crossover at the time of progression. FDA stated that crossover is acceptable but cautioned that it could impair the ability to demonstrate a survival benefit. An additional risk for the sponsor is if adverse survival is demonstrated for the investigational drug.

15. Does the Agency agree that the overall safety database is adequate to assess BMN 673 in support of a marketing application in patients with advanced metastatic breast cancer with a BRCA 1 and/or BRCA 2 mutation?

FDA response: It is premature to respond to this question. Please see our response to Question #6.

Meeting Discussion: No discussion took place at the meeting.

16. Based on the recent proposal to re-define available therapy in the context of targeted therapy, does the FDA agree metastatic breast cancer with a BRCA 1 and/or BRCA 2 mutation is consistent with an unmet medical need patient population?

FDA response: Please clarify the intent of this question. Are you asking about fast track designation or accelerated approval?

Meeting Discussion: The sponsor clarified that they are asking about accelerated approval and whether there have been any changes in the definition of available therapy based on the molecular target. FDA stated that not at this time.

17. If the Agency agrees that PARP inhibition in a BRCA mutant tumor constitutes a highly targeted therapy for an unmet need, would an objective response rate > 25% in the late line BRCA patients, as identified in the Phase 2 Study 673-201, support approval?

FDA response: It is premature to answer this question without any Phase 2 data. It is unlikely that results of a single-arm study with an objective response rate of 25% would be sufficient to support approval. However, an unprecedented very high response rate might support approval. In addition, the safety profile of a new molecular entity cannot be properly evaluated in a single-arm trial. We strongly encourage you to include in your initial regulatory submission results of one or more, well-designed, well-conducted randomized trials with clinically relevant and statistically significant study results.

You could consider conducting a randomized Phase 2 study and provide information on the ORR improvement over the control arm (standard of care), the duration of response and the safety profile.

Meeting Discussion: No discussion took place at the meeting.

CDRH Comments:

It appears that you intend to use the results of local BRCA Laboratory Developed Tests (LDT) in patient's records to identify patients with BRCA 1 and 2 mutations for possible trial enrollment. We do not recommend that you use results of local BRCA LDTs in patient's records for enrichment in this clinical trial, because your enrollment criteria would be based on a number of different tests, with possibly different interpretation algorithms. We are concerned that this may result in a patient population that may not be representative of the population of breast cancer patients with BRCA mutations (i.e., the population for which BMN 673 will be indicated). Eligibility for BRCA testing should be open to everyone who meets the inclusion/exclusion criteria and based on a single pre-specified protocol to ensure a representative and identifiable population after drug approval.

We recommend you to use a single, analytically validated test to determine BRCA mutation status for enrollment on all patients. This will allow a valid analysis of test/therapy interaction, and will provide a single set of analytical performance parameters to which any new test (if contemplated) could be bridged. Alternatively, we recommend that you use in the clinical trial(s) the test that will be marketed for this indication (i.e., selecting patients for BMN 673 therapy) to avoid having to address discordance when attempting to bridge the patient set to a revised or new test.

If your trial results are sufficient to support approval of an NDA, it will require a companion diagnostic test for BRCA mutations. We encourage you to discuss any plans for a companion diagnostic test with CDRH/OIR through the Pre-Submission process.

For your reference, please refer to the following draft guidance documents on In Vitro Companion Diagnostic Devices and the Pre-Submission Program.
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).

- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm .
In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

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

/s/

PATRICIA CORTAZAR
04/23/2013

ELLENI K ALEBACHEW
04/24/2013