# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 212099Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114769

**MEETING PRELIMINARY COMMENTS**

Bayer HealthCare Pharmaceutical
Attention: Stephanie Mondabon, PhD, MDRA
100 Bayer Blvd.
PO Box 915
Whippany, NJ 07981

Dear Dr. Mondabon:

Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for darolutamide (ODM-201, BAY 1841788).

We also refer to your October 10, 2018, correspondence requesting a meeting to discuss the results of your Phase 3 study 17712 ARAMIS in support of an NDA filing.

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 Jeannette Dinin, Regulatory Project Manager, at (240) 402-4978.

Sincerely,

*{See appended electronic signature page}*

Jeannette Dinin
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

*{See appended electronic signature page}*

V. Ellen Maher, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and 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 114769
**Product Name:** Darolutamide (ODM-201, BAY 1841788)
**Indication:** Non-metastatic castration-resistant prostate cancer (nmCRPC)
**Sponsor/Applicant Name:** Bayer HealthCare Pharmaceutical

**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 December 11, 2018, from 4:00 – 5:00 pm, at 10903 New Hampshire Avenue, White Oak Building 22, Conference Room: 1419, between Bayer HealthCare 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

The purpose of this type B pre-NDA meeting is to discuss the sponsor's plan to submit an NDA in Quarter 1 of 2019 for darolutamide in patients with nmCRPC based on the results of their ARAMIS study. Darolutamide is a second-generation antiandrogen. Both enzalutamide and apalutamide are approved for nmCRPC. The ARAMIS study was conducted under a Special Protocol Assessment (SPA) and was granted Fast Track Designation in July 2016. Patients with a high risk (PSADT<10 months) nmCRPC are at high risk of disease progression to metastatic disease, with resultant morbidity and mortality.

ARAMIS is a randomized, double-blind, placebo-controlled Phase 3 study, conducted in 1509 patients with nmCRPC who were at high risk (PSA doubling time ≤10 months) for developing metastatic disease. Patients were randomized 2:1 in a double-blind manner to either darolutamide 600 mg in patients treated with surgical or chemical androgen deprivation therapy (ADT) vs matching placebo in patients treated with ADT. Patients were stratified by PSA doubling time (≤6 months vs >6 months and ≤10 months) and use of osteoclast-targeted therapy

(yes vs no). Patients received study treatment until confirmed metastasis or an intolerable adverse event (AE).

The primary objective was metastasis free survival (MFS). Secondary objectives were overall survival (OS), time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, time to first symptomatic skeletal event (SSE), and to characterize the safety and tolerability of darolutamide.

The study reached its primary completion for MFS with a data cutoff date of September 3, 2018. The primary analysis of metastasis free survival (MFS) was based on independent central review and showed an overall improvement of 21.9 months for darolutamide (median 40.37 months) compared to placebo (median 18.43 months) with a HR of 0.41, 95% CI [0.342; 0.501] and a p-value of <0.000001. The HRs in the ≤6 month PSADT and the >6 month subgroups were 0.41 and 0.38 respectively. At the time of the primary completion, 136 out of the targeted 240 OS events had occurred. The median OS was not reached in either of the study arms with an observed HR of 0.707 (95% CI 0.501, 0.994) with a 2-sided p-value of 0.0452, trending in favor of darolutamide. The safety profile appears consistent with this class of drugs, with key adverse events such as fracture, falls, fatigue, seizures, and weight decrease experienced at similar rates in both treatment arms. Patients on the treatment arm experienced higher rates of grade 3, 4, and 5 toxicities.

The sponsor is seeking priority review designation based on the magnitude of MFS benefit as well as trend towards improved overall survival.

## 2.0 QUESTIONS/RESPONSES

Question 1: Does the Agency agree with the proposed indication?

**FDA Response: The proposed indication appears to be acceptable. Final decisions concerning indication statements are made following review.**

Question 2: Does the Agency agree that the proposed safety content for the 90-(-120) day safety update report is acceptable?

**FDA Response: Yes.**

Question 3: Does the Agency agree with the approach to use the data from both Phase 1/2 and Phase 3 to assess a time dependency of the darolutamide PK, also considering the separate diastereomers and the active metabolite?

**FDA Response: Your approach appears acceptable. However, the final decision of the adequacy of this approach will be an NDA review issue.**

Question 4: Does the Agency agree that the data from study 17712 ARAMIS support a request of Priority Review?

**FDA Response: A decision concerning priority or standard review will be made at the time of filing. For a priority review designation, you would need to demonstrate that darolutamide would be a significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. We note that both apalutamide and enzalutamide have received approval for the indication you are seeking.**

Question 5: Does the Agency have any comments regarding the approach taken in collecting the Financial Disclosure information in the Phase 3 study 17712 ARAMIS?

**FDA Response: Your approach is reasonable.**

## Additional Comments:

**Clinical**

1. **We note that there was an imbalance in the number of patients who discontinued due to judgement of the investigator (5.7% vs. 16.4%) and personal reason (7.1% vs. 14.1%). In your CSR, please include a sensitivity analysis to address this imbalance.**

**Clinical Pharmacology**

2. **Consider the following recommendations about labeling:**

    a. **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 https://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.**

3. **Address the following questions in the Summary of Clinical Pharmacology:**

    a. **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.**

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

**c. What is the effect of darolutamide on the QT/QTc interval?**

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

**e. 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.**

**f. 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?**

**4. For the clinical pharmacology sections of the original submission:**

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

**b. Provide final study reports 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.**

**c. 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.**

**i. 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.**

**d. 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:**

**a. Standard model diagnostic plots**

**b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line**

**c. Model parameter names and units in tables.**

**d. 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:**

**a. SAS transport files (*.xpt) for all datasets used for model development and validation**

**b. 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**

**c. 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.**

## 3.0 ADDITIONAL INFORMATION

### DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 19, 2018 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 any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined 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. See link to list of relevant molecular targets below. 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 include plans 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 the latest version of the molecular target list, please refer to:
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

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 OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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.

## 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 items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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JEANNETTE L DININ
12/04/2018

VIRGINIA E MAHER
12/04/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114769

**MEETING MINUTES**

Bayer HealthCare Pharmaceutical
Attention: Stephanie Mondabon, PhD, MDRA
100 Bayer Blvd.
PO Box 915
Whippany, NJ 07981

Dear Dr. Mondabon:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ODM-201.

We also refer to the meeting between representatives of your firm and the FDA on September 23, 2015. The purpose of the meeting was to discuss your proposed phase 3 study for newly diagnosed metastatic castration sensitive prostate cancer.

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 Jeannette O'Donnell, Regulatory Project Manager at (240) 402-4978 or email: Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

*{See appended electronic signature page}*

V. Ellen Maher, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

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/s/

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JEANNETTE L O'DONNELL
10/07/2015

VIRGINIA E MAHER
10/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114769

**MEETING PRELIMINARY COMMENTS**

Endo Pharmaceuticals, Inc.
Attention: Tara Chapman, Pharm.D.
Director, Regulatory Affairs
1400 Atwater Drive
Malvern, PA 19355

Dear Dr. Chapman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ODM-201.

We also refer to your August 2, 2013, (amended August 5, 2013), correspondence, received August 2, 2013, requesting a meeting to discuss the Phase 3 development program for ODM-201.

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.

If you have any questions, call me at (301)796-1348.

Sincerely,

*{See appended electronic signature page}*

Modupe Fagbami
Regulatory Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# PRELIMINARY MEETING COMMENTS

**Meeting Type:** Type B
**Meeting Category:** End of Phase 2,

**Meeting Date and Time:** October 10, 2013, at 11:00 am
**Meeting Location:** Building 22, Room 2201

**Application Number:** IND 114769
**Product Name:** ODM-201
**Indication:** Castration-resistant prostate cancer
**Sponsor Name:** Endo Pharmaceuticals, 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 October 24, 2013, at 11:00 am in Building 22, Room 1313 between Endo Pharmaceuticals, 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of 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). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

## BACKGROUND

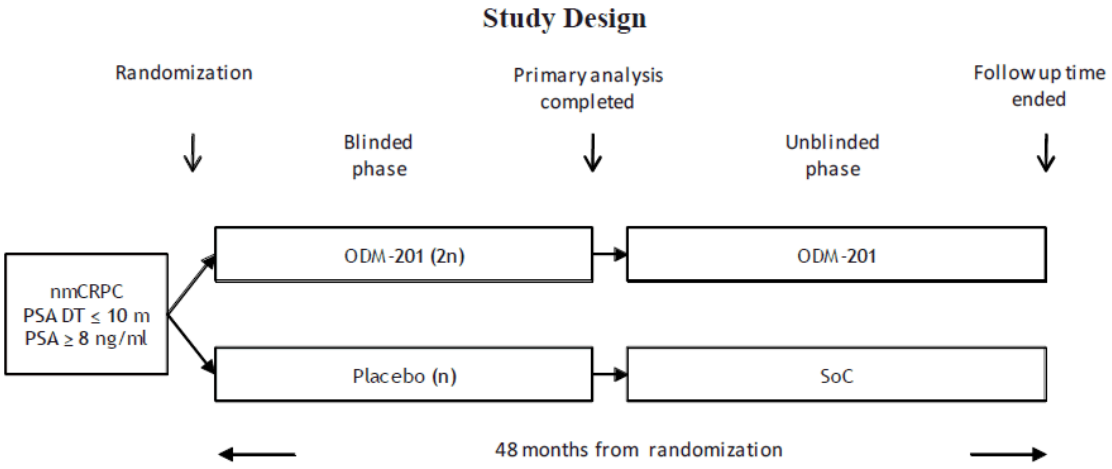
ODM-201 is an oral, nonsteroidal androgen receptor (AR) inhibitor, which potently inhibits binding of androgens to the AR. ODM-201 retains antagonistic properties in cells expressing increased AR

levels, which are commonly found in castration-resistant prostate cancer (CRPC) tissues. ODM-201 diminishes AR signaling by inhibiting testosterone-mediated nuclear translocation of AR. Sponsor notes ODM-201 binds to wild type AR with high affinity and antitumor activity in a VCaP xenograft mouse model was superior compared to the FDA approved antiandrogen,enzalutamide. It has similar affinity to GABA receptors as does enzalutamide, however penetrates poorly into CNS theoretically reducing the seizure risk when compared to other second generation antiandrogens.

ODM-201 has completed testing in a phase 1/2 clinical trial and the purpose of this meeting is to discuss the phase 3 development program for ODM-201. This meeting focuses on non-clinical and clinical aspects and a separate meeting for CMC has been scheduled. The intended indication for ODM-201 with respect to this meeting is the treatment of non-metastatic CRPC patients (b) (4) No crossover will be permitted between study treatments at any time.

Proposed Phase 3 Protocol Design:

The sponsor has included a draft protocol synopsis for a randomized (2:1), placebo-controlled, double-blinded clinical trial in patients with rising prostate specific antigen (PSA) despite castrate levels of testosterone in the absence of radiographic evidence of metastases (non-metastatic CRPC). Patients must be high risk by a predefined definition of PSA ≥8 and/or ≥4 and PSA doubling time (PSADT) of ≤10 months. The primary endpoint is metastases free survival (MFS) by blinded independent review. Other secondary endpoints include overall survival, time to symptomatic metastases, and time to skeletal related event.




Assuming median MFS time of 25 months and 33 months for placebo and ODM- 201, respectively (equivalent to a hazard ratio of 0.75), a total of 427 events is required for the study to achieve 80% power with 2-sided alpha of 0.05. With accrual time of 23 months, minimum follow-up time of 15 months, randomization ratio of 2:1 (ODM-201:placebo) and dropout rate of 12%, approximately 1060 patients will be enrolled in this study.

The purpose of this meeting is to discuss the Phase 3 development program for ODM-201.

Nonclinical

Question 1

Rationale: The nonclinical safety pharmacology and toxicology program for ODM-201 was conducted in accordance with the current ICH Guideline S9 - *Nonclinical Evaluation for Anticancer Pharmaceuticals*. In addition, chronic toxicity studies in rats and dogs are being conducted. All pivotal studies were or will be conducted in accordance with GLP regulations. A tabulated summary of all nonclinical safety studies, along with the details of individual studies and further background information on ODM-201, are provided in this Briefing Book. Briefly, all core safety pharmacology and genotoxicity studies have been completed. Study reports from the 3-month dog and 6-month rat toxicity studies will be available, and a 9-month dog toxicity study will be ongoing when the pivotal Phase 3 clinical study is scheduled to be initiated.

Does the Agency agree that the nonclinical safety pharmacology and toxicology package is sufficient to support ODM-201 Phase 3 clinical studies in the indicated population and that no additional nonclinical safety pharmacology and/or toxicology studies are required?

**FDA RESPONSE: Possibly. The nonclinical studies described in your meeting briefing package appear appropriate to support the proposed Phase 3 clinical trials. However, the adequacy of the resulting data will be determined following our review of the full study reports submitted to your IND. Submit the complete study reports for the repeat-dose GLP toxicology studies in rats (6-months duration) and dogs (3-months duration) described in your briefing package to your IND for our review prior to initiating your Phase 3 clinical trials. In addition, submit the complete study reports for the genetic toxicology studies described in the briefing package to your IND for our review prior to initiating the Phase 3 clinical trial in patients with non-metastatic CRPC. Also, see our responses to Questions 2, 3, 4 and 5.**

Question 2

Rationale: The nonclinical safety pharmacology and toxicology program for ODM-201 was conducted in accordance with the current ICH Guideline S9 - *Nonclinical Evaluation for Anticancer Pharmaceuticals*. In addition, chronic toxicity studies in rats and dogs are being conducted. All pivotal studies were or will be conducted in accordance with GLP regulations. A tabulated summary of all nonclinical safety studies, along with the details of individual studies and further background information on ODM-201 are provided in this Briefing Book. Briefly, all core safety pharmacology and genotoxicity studies have been completed. The 6-month rat toxicity study is ongoing and the 9-month dog toxicity study is in the planning phase. The GLP-compliant in vitro 3T3 phototoxicity study has been completed.

Based on the results of the completed studies, ODM-201 does not represent a genotoxic risk for man. Considering the intended patient population of nmCRPC patients (b) (4) , and as per the current ICH Guideline S9 - *Nonclinical Evaluation for Anticancer Pharmaceuticals* which does not require carcinogenicity studies, it is our understanding that carcinogenicity studies with ODM-201 are not warranted for NDA approval and marketing.

Does the Agency agree that the outlined nonclinical safety pharmacology and toxicology package is sufficient to support product approval and that no additional nonclinical safety pharmacology and/or toxicology studies, including carcinogenicity studies, are required?

**FDA RESPONSE:** **Possibly. We do not have sufficient information about the non-metastatic CRPC patient population to be studied in your proposed Phase 3 clinical trial to determine whether this population falls within the scope of ICH S9. As the expected survival of some of these patients may be relatively long, certain principles within ICH M3(R2) may be applied to the development of ODM-201, as warranted.**

**Carcinogenicity studies may be required to support an indication in the proposed non-metastatic CRPC population. If you do not conduct carcinogenicity studies to support an NDA for ODM-201, provide a justification in your NDA why carcinogenicity studies are not warranted based on the nmCRPC patients studied in the proposed clinical trial (e.g., overall survival, metastasis free survival, time to metastasis, available therapies, etc.). If we determine carcinogenicity studies are warranted to support a nmCRPC indication following our review of an NDA, these studies may be conducted as post-marketing requirements.**

**Also, see our responses to Questions 3, 4 and 5.**

Question 3

Rationale: In the repeat-dose toxicity studies in rats and dogs, comprehensive histopathologic evaluation of male and female reproductive organs has been performed, and all ODM-201 effects were considered to be related to the antiandrogenic properties of the drug. Specifically, administration of ODM-201 resulted in the expected decrease in the size/atrophy of male reproductive organs and other androgen-sensitive tissues. Considering the antiandrogenic effects of ODM-201 and the intended patient population, developmental and reproductive toxicology studies have not been conducted with ODM-201. This is consistent with the current ICH Guideline S9 - *Nonclinical Evaluation for Anticancer Pharmaceuticals*, which states that studies of fertility and early embryonic development (segment I) or peri- and post-natal development (segment III) are not warranted to support clinical trials, registration, or marketing of pharmaceuticals intended for the treatment of patients with advanced cancer. Although embryofetal development toxicity studies (segment II) are generally required for registration and marketing of anticancer drugs, they have not been conducted with ODM-201 because of the male-specific indication of prostate cancer. Moreover, based on the known pharmacologic class effect of antiandrogens,(**Error! Reference source not found.**,**Error! Reference source not found.**) developmental toxicity would be expected; therefore, embryofetal studies are not deemed necessary. This approach is consistent with the registration history of recently approved antiandrogenic drugs, such as Xtandi (enzalutamide) and Zytiga (abiraterone acetate), for which reproductive or developmental toxicity studies were not conducted. In addition, patients are also exposed to LHRH agonist treatment which also affects fertility.



Considering availability of data from the comprehensive histopathologic assessment of male and female reproductive organs from the repeat-dose toxicity studies in both rats and dogs, as well as the intended patient population planned for Phase 3 studies and the therapeutic class of ODM-201, does the Agency agree that reproductive or developmental toxicity studies with ODM-201 will not be required for Phase 3 studies, and subsequent product registration and marketing?

**FDA RESPONSE:** **Possibly. See our response to Question 2. As the nmCRPC population may fall outside the scope of ICH S9, consider recommendations outlined in ICH M3(R2) for reproductive and developmental toxicity studies. Since the proposed clinical trials with ODM-201 will only enroll male patients, you may provide a justification in an NDA for not conducting**

**embryo-fetal development toxicity studies or pre- and postnatal development toxicity studies and propose appropriate labeling. As per ICH M3(R2), nonclinical male fertility studies should be conducted prior to initiating Phase 3 clinical trials. If you do not conduct a male fertility study, submit a justification, including a scientific assessment (e.g., effects on male reproductive organs in repeat-dose toxicity studies, mechanism of action, etc.), to your IND with the relevant nonclinical study reports (e.g., repeat-dose toxicity studies) for why this study is not warranted.**

**Please note, you may need to conduct additional reproductive and developmental toxicity studies to support clinical trials or an NDA for indications not discussed in this meeting briefing package.**

Question 4

Rationale: Both ODM-201 and its metabolite ORM-15341 have been evaluated for absorption of light in the range of 290 to 700 nm. Both ODM-201 and ORM-15341 absorb light in the UVB range of 290-320 nm with the highest absorption at 290 nm, and with the calculated molar absorption coefficient (ε) of 23,100 and 22,500 L $mol^{-1}$ $cm^{-1}$, respectively. As these values exceed the proposed threshold of 1,000 L $mol^{-1}$ $cm^{-1}$ the phototoxicity potential of ODM-201 could not be ruled out.(**Error! Reference source not found.**)



In a QWBA study with ODM-201 in albino and partially pigmented rats, $^{14}C$-radiolabeled ODM-201 was identified in the skin and the eyes (uveal tract and retina) in both rat strains. Consistent with the current draft ICH Guideline S10 - *Photosafety Evaluation of Pharmaceuticals*, specific testing will not be conducted with the metabolite ORM-15341, because this metabolite does not contain any new chromophore.

Based on the above information, an in vitro 3T3 NRU-PT with ODM-201 was conducted. The results from the definitive GLP-compliant in vitro 3T3 assay utilizing appropriate positive control as well as cellular viability and photosensitivity assessments indicate that ODM-201 is not phototoxic. Based on these results and in accordance with the current draft ICH Guideline S10 - *Photosafety Evaluation of Pharmaceuticals*, the Sponsor plans no additional in vitro and/or in vivo phototoxicity studies to support either Phase 3 clinical study or NDA filing. In addition, precautions for protection against sunlight would not be required in the Phase 3 study protocol.

Does the Agency agree that the phototoxicity potential of ODM-201 has been adequately assessed and no further studies are required to support Phase 3 or NDA?

**FDA RESPONSE: Yes, pending our review of the relevant data. Submit all relevant data and study reports to your IND.**

Question 5

Rationale: ODM-201 was tested for mutagenicity in 5 *S* Typhimurium strains up to 5000 µg/plate both in the absence and presence of S9 metabolic activation system. Signs of toxicity to test bacteria as well as precipitation were seen at ≥2500 µg/plate. No evidence of mutagenic activity was seen in this study. ODM-201 was also tested in vitro for induction of chromosome aberrations in cultured peripheral human lymphocytes at up to the cytotoxic or precipitating concentration of 400 µg/mL (1 mM) in the absence and presence of S9 metabolic activation system. ODM-201 increased the frequency of structural chromosome aberrations both in the absence and presence of metabolic

activation at concentrations of ≥200 and 240 µg/mL, respectively, as compared to solvent control. The induction of chromosome aberrations was seen at non-toxic concentrations and the frequencies exceeded the laboratory historical solvent control data. In accordance with the ICH Guideline S2(R1) - *Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*, as a follow-up to positive findings in the in vitro chromosome aberrations study, ODM-201 was tested in a GLP-compliant oral gavage rat micronucleus and comet study at doses up to 1000 mg/kg/day for 3 consecutive days. The study included evaluations of mnPCEs in the bone marrow, potential DNA damage in the liver and duodenum using the single cell gel electrophoresis (comet) assay, and systemic TK exposure assessment. ODM-201 administration at up to 1000 mg/kg/day resulted in systemic drug exposure well above the observed exposure in mCRPC patients following an oral ODM-201 dose of 700 mg bid. The number of mnPCEs in the bone marrow, and DNA migration (comet assay) in the liver and duodenum in ODM-201 treated animals were comparable with the concurrent vehicle control and historical control data. The positive control, EMS, induced clear increases in mnPCEs and DNA damage in hepatocytes and the duodenum, confirming validity and sensitivity of the assay. Based upon these in vivo results, ODM-201 does not represent a genotoxic risk for man.

Based on the negative in vivo genotoxicity study results, the overall weight of evidence from the other genotoxicity studies, and the recommendations from the ICH Guideline S2(R1) - *Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*, ODM-201 is not considered to represent a genotoxic risk for man, and additional genetic toxicology testing is not required to support the planned Phase 3 clinical study or the marketing application. Does the Agency concur?

**FDA RESPONSE: The genetic toxicology studies described in your meeting briefing package appear appropriate to support the proposed Phase 3 clinical trials and an NDA submission for the proposed indications. However, the adequacy of the results of these studies will be determined following our review of the completed study reports submitted to your IND.**

Clinical

Question 6

Rationale: By definition, nmCRPC refers to a disease setting characterized by recurrent PSA increases in the absence of radiographic or clinical evidence of metastases despite castrate levels of testosterone. An elevated PSA level has been linked with shorter bone metastasis-free survival. Data from a study with nmCRPC patients suggest that PSA level greater than 10 ng/mL is independently predictive of bone metastasis-free survival and that PSA levels lower than 7.7 ng/mL are associated with significantly better bone metastasis-free survival compared with PSA levels above 7.7 ng/mL.(**Error! Reference source not found.**) The same study also demonstrated that nmCRPC patients with PSADT between 6.3 and 18.8 months are at a greater risk for developing bone metastasis than patients with PSADT of more than 18.8 months. PSADT of less than 6.3 months carries significantly higher risk for development of bone metastasis than PSADT of more than 6.3 months.



In a recent Phase 3 placebo-controlled study of the effect of denosumab on prevention of bone metastasis or death in patients with nmCRPC, high risk of developing bone metastasis was defined as PSA ≥8.0 ng/mL or PSADT ≤10.0 months, or both (ClinicalTrials.gov identifier NCT00286091).(**Error! Reference source not found.**) This study also confirmed that nmCRPC

patients are indeed at a high risk for developing bone metastases and subsequent death with a median time of 19 months from the event of bone metastasis.

Non-metastatic castration-resistant prostate cancer (nmCRPC) patients (testosterone lower than 1.72 nmol/L [<50 ng/dL] after surgical castration or on ongoing luteinizing hormone-releasing hormone [LHRH] blockade) who are at high risk of developing metastases is proposed to be defined as the patients who have:

- Three (3) consecutive rising prostate-specific antigen (PSA) values at least 2 weeks apart with the last 2 values ≥8 ng/mL within 3 months prior to enrolment, or/and
- PSA level with the last 2 values ≥4 ng/mL and PSA doubling time (PSADT) of ≤10 months.

Does the Agency concur that this is an accurate definition of nmCRPC patients who are at high risk for developing metastases?

**FDA RESPONSE: Yes, PSADT of <10 months and/or PSA ≥8 are reasonable enrichment criteria. Please note however that the inflection point for risk appears closer to a PSA doubling time of 6-8 months (Smith, JCO: 2011). Additionally, your current high risk definition may select some patients with slow growing prostate cancer with PSA above 8 (if doubling time is long) and these patients will dilute your treatment effect. Additional concerns regarding eligibility are listed below:**

- **Patients with significant pelvic lymphadenopathy should be excluded and we would recommend a cutoff of <2cm short axis for pelvic nodes.**
- **Exclude patients with prostate/bladder masses with evidence of baseline hydronephrosis or significant or worsening urethral obstruction.**
- **Please define the method you intend to use to calculate PSA doubling time.**
- **To assure eligibility, consider review of the PSA values by the medical monitor prior to randomization.**

Question 7

Rationale: The main goal for the treatment of high-risk nmCRPC patients is to delay the development of metastases. As non-metastatic patients are mostly asymptomatic from their prostate cancer, delay of the overt metastases needs to be achieved with minimal treatment-associated toxicities. The development of metastases can cause symptoms such as bone pain, can add morbidity and may require additional treatments that may add toxicity, and additional supportive care measures. Metastases also increase the risk of SREs (spinal cord compression, pathologic fracture, or surgery or radiotherapy to a bone lesion), which are serious complications of advanced prostate cancer. Finally, the risk of death from prostate cancer increases with the development of metastases. Because improvement in the MFS can be considered as a clinical benefit for men with high-risk nmCRPC, the Sponsor considers MFS as an appropriate primary efficacy endpoint in the planned Phase 3 clinical trial in these patients. Use of progression-free survival (PFS) as a primary endpoint in confirmatory clinical trials is well established. The magnitude of benefit in MFS that would be considered of clinical benefit was discussed at recent meetings of the Oncologic Drugs Advisory Committee of the FDA (February 8,

2012 FDA Oncologic Drugs Advisory Committee Meeting and September 14, 2011 FDA Oncologic Drugs Advisory Committee Meeting), a minimum improvement of 6 months in MFS was considered by some of the advisors to represent clinical benefit. However, the decision for approval would be based on the overall benefits and risks, including the safety profile of the drug. The proposed Phase 3 study is powered to demonstrate an improvement of 8 months in MFS, which would be considered to be a substantial improvement, particularly if the treatment adds only minimal toxicity.

Based on the Phase 1/2 data of Study 3104001, treatment with ODM-201 700 mg bid demonstrated PSA responses in 75% (6/8) (≥50% decline from baseline, ITT population) and stabilization of bone disease in 86% (6/7) (PP population) of men with mCRPC who were both chemotherapy- and CYP17i-naïve, ODM-201 would be expected to have benefit in earlier disease settings where AR signalling plays a critical role in the pathogenesis of the cancer. Furthermore, Phase 1/2 data available so far suggest that ODM-201 has minimum drug-related AEs, and therefore, is a suitable option for treatment of asymptomatic men with high-risk nmCRPC.

To reduce potential investigator bias, the radiographic assessment of metastases will be conducted by independent, blinded radiologists.

The secondary endpoints of the study will provide supportive data for the clinical benefit of MFS. A delay in the time to development of symptomatic metastases will be assessed, although it is expected that some men will not have symptoms at the time that the metastases are first detected. Overall survival will also be collected, and the data available at the time of the primary analysis of MFS will be presented. However, it is likely that the overall survival data will not be mature at the time of the primary analysis of the study. Overall survival is likely to be affected by the differential use of subsequent therapies in man after they develop metastases and withdraw from the study treatment. Time to a SRE will also be assessed. PSA data will also be collected, but an increase in PSA in the absence of detectable metastases will not be considered an MFS event.

Metastases-free survival (MFS) defined as time between randomization and first occurrence of metastasis or death from any cause is proposed as the primary efficacy endpoint. Radiographic review will be conducted by blinded independent radiologists. Secondary efficacy endpoints will be symptomatic metastases-free survival, time to skeletal-related event (SRE), and overall survival. Exploratory endpoints are time to opiate use for cancer-related pain, time to local disease progression, and time to additional cancer treatment.

Does the Agency concur that these endpoints are acceptable to support registration in this indication?

**FDA RESPONSE: Possibly. We remind you that use of metastasis-free survival (MFS) alone to support regulatory approval in the nmCRPC population has not been established. Nonetheless, based on feedback from the 2012 ODAC, MFS may be considered for approval provided the benefit is of large enough magnitude to be likely to predict an improvement in morbidity or mortality in the context of an acceptable safety profile. The absolute benefit of eight months targeted for your trial is on the low end of what ODAC members thought would predict meaningful benefit. It is likely that a difference in median MFS of greater than 8 months will be needed to overcome the uncertainty of this endpoint. The first NDA submission in this indication using this endpoint will likely be presented at an ODAC. Please also see additional clinical comments regarding your secondary endpoints.**

**Evidence of new metastasis by bone scan must be confirmed by x-ray or CT.**

**There is concern that patients may have serum PSA levels checked at their local laboratories and may discontinue study drug based on these results. Make every attempt to minimize these discontinuations. It will be important to examine patient discontinuation between arms due to PSA progression alone. The extent of patient discontinuation and any resulting imbalances will be a review issue.**

**With respect to symptomatic metastasis-free survival, provide details on how you will determine that a metastasis is symptomatic. We would recommend anchoring this with adequately captured patient reported pain data and analgesic use.**

**The extent of missing radiographic assessments should be minimized and will be a review issue.**

**Please adjust the type I error rate for multiple secondary endpoints for which you intend to make efficacy claims. Secondary endpoints analyses are considered supportive only if the primary analysis is positive. Also a claim based on a secondary endpoint should be clinically meaningful and statistically persuasive.**

Question 8

Rationale: Assuming median MFS time of 25 months and 33 months, respectively, for placebo and ODM-201 (equivalent to a hazard ratio of 0.75), a total of 427 events is required for the study to achieve 80% power with 2-sided alpha of 0.05. With accrual time of 23 months, minimum follow-up time of 15 months, randomization ratio of 2:1 (ODM-201:placebo), and dropout rate of 12%, approximately 1060 patients will be enrolled in this study.

A multinational, randomized, double-blind, placebo-controlled, Phase 3 efficacy and safety study of ODM-201 in men with nmCRPC is proposed. Primary comparison between treatment groups will be performed using Cox proportional hazards model. The model will include treatment groups stratified by stratification factors (including PSADT). The sample size is approximately 1060 and analysis will be performed at 427 events to achieve 80% statistical power at 2-sided alpha level of 0.05. The sample size calculation is based on the assumptions of median MFS time of 25 months and 33 months, respectively, for placebo and ODM-201 (equivalent to a hazard ratio of 0.75); accrual time of 23 months and minimum follow-up time of 15 months; randomization ratio of 2:1 (ODM-201:placebo).

Does the Agency agree with the proposed primary analysis and sample size considerations?

**FDA RESPONSE: Please see response to question #7.**

**We recommend that you use a log-rank test stratified by the same factors used at randomization. Please specify how many levels of geographic region will be used in stratification.**

**We recommend that you power the study for OS and conduct an interim analysis of OS at the time of final analysis of MFS.**

Question 9

Rationale: In nonclinical studies, the hERG (10000090) $IC_{10}$ value was 2.3 μM for ODM-201 and 0.8 μM for its active metabolite ORM-15341. Based on these results minor changes in QTc might occur

at total plasma concentrations of the compounds exceeding 13,100 ng/mL and 149,000 ng/mL, respectively. However, the concomitant inhibition of the L-type calcium channel by ODM-201, its main human diastereomer ORM-16555, and metabolite ORM-15341 (11000165) may reverse the effect of hERG channel inhibition on action potential prolongation and reduce the risk for QT prolongation. Furthermore, based on the results of the CV safety pharmacology studies conducted by intravenous administration of ODM-201 and its main human diastereomer ORM-16555 to anesthetized dogs, a slight shortening of the QT interval duration was seen at high exposure levels (at plasma $C_{max}$ levels of ≥9300 ng/mL). Thus, in vivo exposure to ODM-201 in animals has a tendency to decrease rather than increase QT interval duration.

In the Phase 1/ 2 Study 3104001 in patients with mCRPC, the highest measured individual plasma concentrations at steady-state were 9680 ng/mL for ODM-201 and 8560 ng/mL for diastereomer ORM-16555 after 700 mg bid dosing. At the 900 mg bid dose there was no further increase in measured ODM-201 concentration. The highest measured individual plasma concentration for the metabolite ORM-15341 was 15,500 ng/mL after 700 mg bid dosing at steady-state. Thus, the highest observed concentrations in humans at doses up to 900 mg bid are below the threshold observed in hERG studies.

In clinical studies 3104001 and 3014002, there have been no QTcF intervals >480 ms or QTcF prolongations >60 milliseconds from baseline by the data cutoff date. The mean changes in QTcF from baseline in doses of 100, 200, and 700 mg bid (doses with higher number of patients) up to 12 weeks of treatment were all less than 5 milliseconds and the corresponding 95% CIs were all less than 10 milliseconds. There have been no discontinuations or dosage reductions due to QT/QTc interval prolongation in studies 3104001 and 3104002.

Based on the data available it is considered that ODM-201 does not affect QT interval duration in acute and chronic settings and there is no dose-response relationship with the dose of ODM-201.

(b) (4)

**FDA RESPONSE:** (b) (4) **. Per the ICH E14 guidelines, all NMEs with systemic bioavailability should undergo a TQT evaluation to exclude small effects on QT. You should submit a TQT study protocol for QT-IRT review prior to conducting the study. We request that the results of the study be included in your NDA.**

## Regulatory

Question 10

Rationale: The Sponsor proposes to file the original NDA based on 1 pivotal trial in nmCRPC supporting the indication for the treatment of patients with nmCRPC (b) (4) The Sponsor believes that 1 clinical trial is adequate in this population because it remains an unmet medical need. The Sponsor intends to discuss the Phase 3 clinical trial and statistical analysis with the FDA via the SPA process.

The ODM-201 development program consists of two Phase 3 studies, one in nmCRPC and one in mCRPC. It is anticipated that final results from the nmCRPC study will be available for submission before the mCRPC study.

Does the FDA agree that a single study in this indication (nmCRPC) will support approval?

**FDA RESPONSE:**

**Possibly. The magnitude of benefit for your primary end point will need to be large enough to provide a positive risk-benefit ratio for this largely asymptomatic population. The approval will also depend on the internal consistency and strength of your overall survival, symptomatic progression and other clinically meaningful measures (see additional clinical comments) in order to support any benefit demonstrated by your surrogate primary endpoint.**

**In addition, the FDA prefers two adequate and well-controlled trials to demonstrate the effectiveness of an agent. For a single randomized trial to support an NDA, the trial must be well designed, well conducted, well executed, internally consistent and provide statistically and clinically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.**

**Please refer to FDA guidance "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological products*" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf**

Question 11

Rationale: Per the draft Guidance for Industry - *How to Comply with the Pediatric Research Equity Act* (September 2005), a waiver will be requested since prostate cancer does not occur in any pediatric patient populations.

A waiver for pediatric studies will be requested based on the disease not occurring in the pediatric age group. Does the Agency concur?

**FDA RESPONSE:**

**Yes.**

**Additional Comments:**

1. **Regarding proposed secondary endpoints:**
    a. **It will be important to provide data to verify your time to symptomatic metastases endpoint. We would recommend patient reported pain be collected.**
    b. **We have attached a document (Time to Pain Progression SEALD Recommendations Final.doc) which includes recommendations for the measurement of time to pain progression using patient reported outcomes. Time to pain progression may provide additional supportive evidence and be analyzed as an exploratory endpoint. One PRO pain instrument that is commonly used is the Brief Pain Inventory – Short Form (BPI-SF).**

c. **Further recommendations regarding the specifics of your secondary endpoints and their statistical hierarchy will be provided when the full protocol is submitted.**

2. **We recommend including an exploratory analysis of the time to skeletal event which would include only those pathologic fractures that are symptomatic by investigator determination.**

3. **Carefully collect all cancer-related procedure data. An analysis of the time to local cancer-related invasive procedures would be helpful to evaluate benefit in terms of local progression (new nephrostomy, new suprapubic catheter, initial ureteral stenting). This can be done as an exploratory endpoint.**

4. **We would recommend an analysis of time to cytotoxic chemotherapy.**

5. **In the phase 3 protocol,**
   a. **We encourage you to include sparse sampling to explore the exposure-response relationships of ODM-201 for measures of both effectiveness and toxicity. Refer to Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for more information.**
   b. **Consider including cautionary statements about the concomitant use of P-gp inhibitors and CYP2C9 substrates with ODM-201.**

6. **Please address the potential DDI between ODM-201 and a P-gp inhibitor prior to submission of an NDA.**

7. **In the in vitro study 496742, the CYP2C9 inhibition R value result was >1.1 for ODM-201 and the main metabolite, ORM-15341. An in vivo DDI study between ODM-201 and a CYP2C9 substrate is warranted. You may consider using a Physiologically-Based PK (PBPK) approach to explore the DDI potential between ODM-201 and a CYP2C9 substrate drug to further explore the potential for an in vivo DDI prior to conducting a dedicated DDI trial. For more information, refer to the Guidance for Industry found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.**

## PREA REQUIREMENTS

**Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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. Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.**

## 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.**

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10/15/2013