1.3.3 DEBARMENT CERTIFICATION

Janssen Research & Development, LLC certifies that we did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food Drug and Cosmetic Act in connection with this application.

Digitally signed by BARBARA KOLB
DN: c=US, o=JNJ, ou=Subscribers, cn=BARBARA KOLB, 0.9.2342.19200300.100.1.1=173347
Reason: I am certifying this document.
Date: 2017.09.20 16:32:43 -04'00'

20 September 2017

Barbara Kolb
Senior Director, North America TA Leader
Global Regulatory Affairs, Oncology
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th></th>
<th>NDA # 210951</th>
<th>NDA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
<th>BLA #</th>
<th>BLA Supplement #</th>
<th>Applicant: Janssen Biotech, Inc.</th>
<th>Agent for Applicant (if applicable): N/A</th>
<th>RPM: Charlene Wheeler, MSHS</th>
<th>Division: DOP1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Name:</td>
<td>Erleada®</td>
<td></td>
<td></td>
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<tr>
<td>Established/Proper Name:</td>
<td>apalutamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dosage Form:</td>
<td>Oral Tablets 60 mg</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>NDA Application Type:</td>
<td>☒ 505(b)(1)</td>
<td>☐ 505(b)(2)</td>
<td></td>
<td></td>
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<td>Efficacy Supplement:</td>
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<td>☐ 505(b)(2)</td>
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<tr>
<td>BLA Application Type:</td>
<td>☐ 351(k)</td>
<td>☐ 351(a)</td>
<td></td>
<td></td>
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<td>Efficacy Supplement:</td>
<td>☐ 351(k)</td>
<td>☐ 351(a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

For **ALL 505(b)(2) applications, two months prior to EVERY action:**

- **Review the information in the 505(b)(2) Assessment and submit the draft** to CDER OND IO for clearance.
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

- [ ] No changes
- [ ] New patent/exclusivity *(notify CDER OND IO)*

**Date of check:**

**Note:** If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

### Actions

- Proposed action
- **User Fee Goal Date is April 10, 2018**
- Previous actions *(specify type and date for each action taken)*

- **February 14, 2018**

### Application Characteristics

- **If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?**
  **Note:** Promotional materials to be used within 120 days after approval must have been submitted *(for exceptions, see [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain **N/A**

---

1 The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
2 For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised *(e.g., new listed drug, patent certification revised).*
3 Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Reference ID: 4222532
Review priority:  ☑ Standard  ☒ Priority
Chemical classification (new NDAs only): NME
(confirm chemical classification at time of approval)

☒ Fast Track  ☐ Rx-to-OTC full switch
☒ Rolling Review  ☐ Rx-to-OTC partial switch
☐ Orphan drug designation  ☐ Direct-to-OTC
☐ Breakthrough Therapy designation

(Note: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

REMS:
☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)
  ☐ Yes  ☐ No

- Public communications (approvals only)
  ☒ Office of Executive Programs (OEP) liaison has been notified of action
  ☐ None  ☐ FDA Press Release  ☐ FDA Talk Paper  ☐ CDER Q&As  ☒ Burst
  ☐ Indicate what types (if any) of information were issued

- Exclusivity
  ☒ Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    ☒ No  ☐ Yes
  ☐ If so, specify the type

- Patent Information (NDAs only)
  ☒ Patent Information:
    Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.
  ☒ Verified  ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) (link)
  ☒ Included

Documentation of consent/non-consent by officers/employees (link)
  ☒ Included
### Action Letters

- Copies of all action letters *(including approval letter with final labeling)*
  - Action date February 14, 2018

### Labeling

- Package Insert *(write submission/communication date at upper right of first page of PI)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included
  - Medication Guide
  - Patient Package Insert
  - Instructions for Use
  - Device Labeling
  - None

- Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
  - Included

- Original applicant-proposed labeling
  - Included

- Labels *(full color carton and immediate-container labels)* *(write submission/communication date on upper right of first page of each submission)*
  - Included

- Proprietary Name
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
    - Acceptability letter – 1/5/18
    - Review – 1/3/18

### Labeling reviews *(indicate dates of reviews)*

- RPM: 12/4/17
- DMEPA: 1/23/18, 12/19/17
- DMPP: 2/1/18
- OPDP: 2/2/18
- SEALD: None
- CSS: None
- Product Quality: None
- Other: None

### Administrative / Regulatory Documents

- RPM Filing Review/Memo of Filing Meeting *(indicate date of each review)*
  - 1/26/18
  - Not a (b)(2)

- All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee
  - 1/26/18
  - Not a (b)(2)

- NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*
  - Completed *(Do not include)*

- Application Integrity Policy (AIP) Status and Related Documents
  - [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
  - Applicant is on the AIP
    - Yes
    - No
  - This application is on the AIP
    - Yes
    - No
  - If yes, Center Director’s Exception for Review memo *(indicate date)*
  - If yes, OC clearance for approval *(indicate date of clearance communication)*
    - Not an AP action

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
**Pediatrics (approvals only)**
- Date reviewed by PeRC: 1/10/18
- If PeRC review not necessary, explain: ____

**Breakthrough Therapy Designation**
- Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded): N/A
- CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes): N/A
- CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes): N/A

(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)

**Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)**

- 2/14/18, 2/12/18 x 2, 2/8/18 x 4, 2/7/18 x 2, 2/6/18, 2/2/18, 2/1/18, 1/24/18, 1/18/18, 1/11/18, 1/10/18, 1/5/18, 1/3/18, 12/21/17, 12/20/17, 12/15/17, 12/14/17, 12/13/17 x 2, 12/12/17 x 2, 12/11/17, 12/7/17, 12/6/17, 12/4/17, 11/27/17, 11/6/17, 11/1/17, 10/30/17, 10/23/17, 10/20/17, 10/16/17, 10/11/17

**Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)**

- N/A

**Minutes of Meetings**
- If not the first review cycle, any end-of-review meeting (indicate date of mtg): N/A
- Pre-NDA/BLA or BPD Type 4 meeting (indicate date of mtg): 6/26/17
- EOP2 meeting (indicate date of mtg): 2/28/12
- Mid-cycle Communication (indicate date of mtg): 1/3/18
- Late-cycle Meeting (indicate date of mtg): 2/12/18
- Other milestone meetings (e.g., EOP2a, BPD Type 3, CMC focused milestone meetings) (indicate dates of mtgs)

**Advisory Committee Meeting(s)**
- Date(s) of Meeting(s): No AC meeting

---

### Decisional and Summary Memos

- Office Director Decisional Memo (indicate date for each review): 2/14/18 Multidisciplinary Review
- Division Director Summary Review (indicate date for each review): 2/13/18
- Cross-Discipline Team Leader Review (indicate date for each review): 2/14/18
- PMR/PMC Development Templates (indicate total number): 1

---

### Clinical

- Clinical Reviews

---

Reference ID: 4222532
<table>
<thead>
<tr>
<th>Area</th>
<th>Date(s)</th>
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</thead>
<tbody>
<tr>
<td>Clinical Team Leader Review(s)</td>
<td>See Multidisciplinary Review 2/14/18</td>
</tr>
<tr>
<td>Clinical review(s)</td>
<td>See Multidisciplinary Review 2/14/18, 2/13/8 Memo, 2/12/18 Memo, Filing 2/7/18</td>
</tr>
<tr>
<td>Social scientist review(s) (if OTC drug)</td>
<td>None</td>
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<tr>
<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here □ and include a review/memo explaining why not (indicate date of review/memo)</td>
<td>2/14/18</td>
</tr>
<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)</td>
<td>COA consult – 1/24/18 QT Consult – 1/29/18</td>
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<tr>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)</td>
<td>N/A</td>
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<tr>
<td>Risk Management</td>
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<tr>
<td>REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))</td>
<td>1/30/18</td>
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<td>REMS Memo(s) and letter(s) (indicate date(s))</td>
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<tr>
<td>Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</td>
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<tr>
<td>OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)</td>
<td>12/19/17</td>
</tr>
<tr>
<td>Clinical Microbiology</td>
<td>None</td>
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<td>Clinical Microbiology Team Leader Review(s) (indicate date for each review)</td>
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<td>Clinical Microbiology Review(s) (indicate date for each review)</td>
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<td>Biostatistics</td>
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<td>Statistical Division Director Review(s) (indicate date for each review)</td>
<td>See Multidisciplinary Review 2/14/18</td>
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<td>Statistical Team Leader Review(s) (indicate date for each review)</td>
<td>See Multidisciplinary Review 2/14/18</td>
</tr>
<tr>
<td>Statistical Review(s) (indicate date for each review)</td>
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<td>Clinical Pharmacology</td>
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<td>Clinical Pharmacology Division Director Review(s) (indicate date for each review)</td>
<td>See Multidisciplinary Review 2/14/18</td>
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<td>Clinical Pharmacology Team Leader Review(s) (indicate date for each review)</td>
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<td>Clinical Pharmacology review(s) (indicate date for each review)</td>
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<tr>
<td>OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)</td>
<td>None requested</td>
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</table>

5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).
### Nonclinical

<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
<td>· ADP/T Review(s) <em>(indicate date for each review)</em></td>
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<tr>
<td></td>
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<td></td>
<td>2/14/18</td>
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<tr>
<td></td>
<td>· Supervisory Review(s) <em>(indicate date for each review)</em></td>
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<td>□ See Multidisciplinary Review</td>
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<td></td>
<td>2/14/18, 2/8/18</td>
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<td></td>
<td>· Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
</tr>
<tr>
<td></td>
<td>□ See Multidisciplinary Review</td>
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<tr>
<td></td>
<td>2/14/18, Filing 11/20/17</td>
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<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <em>(indicate date for each review)</em></td>
<td>□ None</td>
</tr>
<tr>
<td>Statistical review(s) of carcinogenicity studies <em>(indicate date for each review)</em></td>
<td>□ No carc</td>
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<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>□ None  Included in P/T review, page</td>
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<td>OSI Nonclinical Inspection Review Summary <em>(include copies of OSI letters)</em></td>
<td>□ None</td>
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### Product Quality

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<tr>
<td></td>
<td>□ 2/2/18</td>
</tr>
<tr>
<td></td>
<td>· Secondary review (e.g., Branch Chief) <em>(indicate date for each review)</em></td>
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<tr>
<td></td>
<td>□ 2/2/18</td>
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<tr>
<td></td>
<td>· Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <em>(indicate date for each review)</em></td>
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<tr>
<td></td>
<td>□ 2/2/18, 11/6/17</td>
</tr>
<tr>
<td>Reviews by other disciplines/divisions/Centers requested by product quality review team <em>(indicate date of each review)</em></td>
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### Environmental Assessment

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<tbody>
<tr>
<td>Categorical Exclusion *(indicate review date) <em>(all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td>□ 1/26/18 See Quality Review</td>
</tr>
<tr>
<td>Review &amp; FONSI <em>(indicate date of review)</em></td>
<td>□</td>
</tr>
<tr>
<td>Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
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### Facilities Review/Inspection

<table>
<thead>
<tr>
<th>Category</th>
<th>Date/Note</th>
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</thead>
<tbody>
<tr>
<td>Facilities inspections *(indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) <em>(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</em></td>
<td>□ Acceptable 1/4/18 See Quality Review</td>
</tr>
<tr>
<td>Withhold recommendation</td>
<td>□</td>
</tr>
<tr>
<td>Not applicable</td>
<td>□</td>
</tr>
</tbody>
</table>

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6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
## Day of Approval Activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
</table>
| For all 505(b)(2) applications:  
  - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) |  
  - No changes  
  - New patent/exclusivity (Notify CDER OND IO) |
| Finalize 505(b)(2) assessment | done |
| For Breakthrough Therapy (BT) Designated drugs:  
  - Notify the CDER BT Program Manager | done |
| For products that need to be added to the flush list (generally opioids):  
  - Notify the Division of Online Communications, Office of Communications | done |
| Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | done |
| If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | done |
| Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name |  
  - Sent email 2/15/18 to have Product Name corrected in DARRTs. |
| Ensure Pediatric Record is accurate | done |
| Send approval email within one business day to CDER-APPROVALS | 2/14/18 |
| Take Action Package (if in paper) down to Document Room for scanning within two business days | 2/15/18 |
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

__________________________________________
AMY R TILLEY
02/15/2018
Jessica,

We would like to have a quick telecon to discuss some of the numbers in the labeling. Can you pull your team together in the next 15 minutes or so to talk to us?

I have also left messages on your office and cell phone numbers.

Christy (for Amy)

Christy Cottrell  
Chief, Project Management Staff  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
Tel: 301-796-4256  
Fax: 301-796-9845  
christy.cottrell@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/

-----------------------------------------------

AMY R TILLEY
02/14/2018
Good Afternoon Barbara,

As the Safety Project Manager for Division of Oncology Product -1, and I am your point of contact for all postmarketing submissions and/or correspondences. I ask that you submit your submissions and/or correspondences the same way that you have done previously; however, email me (cc: project manager assigned to your product) or call me directly for anything concerning postmarketing to ensure adequate and immediate responses to your inquiry.

We have the following postmarketing commitment for your NDA 210951 for your review and agreement:

Submit the analyses and datasets with final report for the clinical trial entitled; “SPARTAN, a phase 3 double-blind, randomized study of apalutamide versus placebo in patients with nonmetastatic castration-resistant prostate cancer [ARN-509-003]”

Final Protocol Submission: 09 /2017
Trial Completion: 12/2022
Final Report Submission: 06/2023

We have suggested milestone dates highlighted in yellow, please let us know if you agree with these dates or include the dates for which are more appropriate. Please respond via email by COB Wednesday, January 31th (if not sooner) with the dates for the milestone followed by submitting your response formally to the NDA.

Thank You,

Christina Marshall, M.S.
Safety Regulatory Health Project Manager
DOP1/OHOP/CDER
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 2123
Silver Spring, MD 20993
Phone: 301-796-3099
Fax: 301-796-9881

Reference ID: 4220839
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA D MARSHALL
02/13/2018
Jessica, the purpose of this email is to let you know we will not be providing the FDA revised PI prior to the teleconference.

Please let me know whether or not Charlene had sent you the call in information for today’s teleconference.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Follow @FD AOncology on Twitter

---

Hi Amy,

I just left you a message a bit before regarding availability of an updated version of the USPI. And is the FDA still planning to have the late-cycle meeting?

Thank you.

Kind Regards,
Jessica
Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Cell: 908.526.5059
Fax: 908.927.2717
Email: jchung18@its.jnj.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, February 08, 2018 3:24 PM
To: Chung, Jessica [JRDUS] <JChung18@ITS.JNJ.com>
Cc: Wheeler, Charlene <Charlene.Wheeler@fda.hhs.gov>; Tilley, Amy <Amy.Tilley@fda.hhs.gov>
Subject: RE: NDA 210951 Erleada - Late Cycle Meeting
Importance: High

Jessica, as per the late cycle meeting agenda sent on February 6, 2018, a revised USPI was sent to you on February 6, 2018. We appreciate your prompt response to the revised USPI, however we have not yet finalized review of your edits. We will send you an updated version shortly.

Regards,
Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Follow @FDAOncology on Twitter

From: Chung, Jessica [JRDUS] [mailto:JChung18@ITS.JNJ.com]
Sent: Thursday, February 08, 2018 1:49 PM
To: Tilley, Amy <Amy.Tilley@fda.hhs.gov>
Cc: Wheeler, Charlene <Charlene.Wheeler@fda.hhs.gov>; Kacuba, Alice <Alice.Kacuba@fda.hhs.gov>
Subject: RE: NDA 210951 Erleada - Late Cycle Meeting

Hi Amy,
I am confirming receipt of this email. Also, thank you to you and Alice for the discussion.

In regards to the late-cycle, do you know what we can anticipate to discuss? Is it possible to provide the topics or the additional USPI comments in advance so that we can be prepared to finalize any remaining labeling comments at the meeting (if still needed).

Thank you.

Kind Regards,
Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Cell: 
Fax: 908.526.5059
Email: jchung18@its.jnj.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, February 08, 2018 12:18 PM
To: Chung, Jessica [JRDUS] <JChung18@ITS.JNJ.com>
Cc: Wheeler, Charlene <Charlene.Wheeler@fda.hhs.gov>; Kacuba, Alice <Alice.Kacuba@fda.hhs.gov>; Tilley, Amy <Amy.Tilley@fda.hhs.gov>
Subject: RE: NDA 210951 Erleada - Late Cycle Meeting
Importance: High

Jessica, the purpose of this email is to let you know that since we are still in label negotiations we would like to keep the Late Cycle Meeting on Feb 12, 2018. Our purpose for keeping the Late Cycle Meeting would be to finalize any label negotiations that may be needed at that time.

We apologize for any inconvenience this may cause.

Kindly confirm receipt of this email.

Regards,
Amy R. Tilley
Regulatory Project Manager
Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Reference ID: 4220651
Hi Amy/Alice,

Based on the review of the briefing package provided by the FDA, Janssen would like to cancel the 12Feb2018 late-cycle meeting at this time. We will also formally submit the cancellation to the NDA 210951.

Thank you.

Kind Regards,
Jessica

Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Cell: 908.526.5059
Email: jchung18@its.jnj.com

Jessica, the purpose of this email is to send you the attached Erleada Late Cycle Briefing Package.

Upon your review of the Briefing Package please let us know whether you want to keep or cancel the Feb 12, 2018, Late Cycle TCON.

Kindly confirm receipt of this email.

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

/s/

----------------------------------------------------

AMY R TILLEY

02/12/2018
Jessica, the purpose of this email is to send you the attached FDA revised PI/PPI for Erleada.

We request your response via email no later than **10 am on Feb 13, 2018**, and as always, please follow up with an official submission to the NDA.

Kindly confirm your receipt of this email.

Regards,

Amy R. Tilley  
Regulatory Project Manager

Center for Drug Evaluation & Research  
Office of Hematology Oncology Products  
Division of Oncology Products 1  
U.S. Food and Drug Administration  
Tel: 301-796-3994  
amy.tilley@fda.hhs.gov  

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Reference ID: 4220670
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/s/

----------------------------------------------------
AMY R TILLEY
02/12/2018
Jessica, as per the late cycle meeting agenda sent on February 6, 2018, a revised USPI was sent to you on February 6, 2018. We appreciate your prompt response to the revised USPI, however we have not yet finalized review of your edits. We will send you an updated version shortly.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Hi Amy,

I am confirming receipt of this email. Also, thank you to you and Alice for the discussion.

In regards to the late-cycle, do you know what we can anticipate to discuss? Is it possible to provide the topics or the additional USPI comments in advance so that we can be prepared to finalize any remaining labeling comments at the meeting (if still needed).

Thank you.
Jessica Chung  
Director, Regulatory Affairs - Oncology  
Janssen Research & Development, LLC  
Phone: 908.927.2717  
Cell: 908.526.5059  
Fax: 908.526.5059  
Email: jchung18@its.jnj.com

Kind Regards,
Jessica

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]  
Sent: Thursday, February 08, 2018 12:18 PM  
To: Chung, Jessica [JRDUS] <JChung18@ITS.JNJ.com>  
Cc: Wheeler, Charlene <Charlene.Wheeler@fda.hhs.gov>; Kacuba, Alice <Alice.Kacuba@fda.hhs.gov>; Tilley, Amy <Amy.Tilley@fda.hhs.gov>  
Subject: RE: NDA 210951 Erleada - Late Cycle Meeting  
Importance: High

Jessica, the purpose of this email is to let you know that since we are still in label negotiations we would like to keep the Late Cycle Meeting on Feb 12, 2018. Our purpose for keeping the Late Cycle Meeting would be to finalize any label negotiations that may be needed at that time.

We apologize for any inconvenience this may cause.

Kindly confirm receipt of this email.

Regards,
Amy R. Tilley  
Regulatory Project Manager  
Center for Drug Evaluation & Research  
Office of Hematology Oncology Products  
Division of Oncology Products 1  
U.S. Food and Drug Administration  
Tel: 301-796-3994  
amy.tilley@fda.hhs.gov

Follow @FDAAncology on Twitter

From: Chung, Jessica [JRDUS] [mailto:JChung18@ITS.JNJ.com]  
Sent: Wednesday, February 07, 2018 5:51 PM

Reference ID: 4219025
Hi Amy/Alice,

Based on the review of the briefing package provided by the FDA, Janssen would like to cancel the 12Feb2018 late-cycle meeting at this time. We will also formally submit the cancellation to the NDA 210951.

Thank you.

Kind Regards,
Jessica

Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Cell: (b) (6)
Fax: 908.526.5059
Email: jchung18@its.jnj.com

Jessica, the purpose of this email is to send you the attached Erleada Late Cycle Briefing Package.

Upon your review of the Briefing Package please let us know whether you want to keep or cancel the Feb 12, 2018, Late Cycle TCON.

Kindly confirm receipt of this email.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Reference ID: 4219025
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

__________________________________________________________

AMY R TILLEY
02/08/2018
Jessica, the purpose of this email is to let you know the attached document that listed the subjects from the apalutamide arm of Study ARN-509-003 with systemic corticosteroid use to treat adverse events of skin rash was useful to the reviewer. Therefore, please officially submit the information to the NDA.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Follow @FDAOncology on Twitter
Hi Amy,

Apologies, please find enclosed the corrected response to the below Clinical IR. This corrected response will be submitted to the NDA 210951 today.

Thanks,
Jessica

Hi Amy,

Attached is the response to the below Clinical IR. The submission will be made via electronic FDA gateway to the NDA 210951 today.

Thank you.

Kind Regards,
Jessica
From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Wednesday, February 07, 2018 3:17 PM
To: Chung, Jessica [JRDUS] <JChung18@ITS.JNJ.com>
Cc: Wheeler, Charlene <Charlene.Wheeler@fda.hhs.gov>; Tilley, Amy <Amy.Tilley@fda.hhs.gov>
Subject: RE: URGENT re NDA 210951 Erleada - Clinical IR

Jessica, my apologies this is a Clinical Information Request.

Thanks,
Amy Tilley

From: Tilley, Amy
Sent: Wednesday, February 07, 2018 3:15 PM
To: Chung, Jessica [JRDUS] (JChung18@ITS.JNJ.com) <JChung18@ITS.JNJ.com>
Cc: Wheeler, Charlene <Charlene.Wheeler@fda.hhs.gov>; Tilley, Amy <Amy.Tilley@fda.hhs.gov>
Subject: URGENT re NDA 210951 Erleada - Statistical IR
Importance: High

Jessica, the purpose of this email is to send you the following Statistical Information Request. We request your response no later than 5 pm today, Feb 7, 2018, and as always follow up with an official submission to the NDA.

Regarding patients with rash who used corticosteroids, you commented “But for most of these patients, corticosteroid use was given specifically for reasons other than rash (e.g., pulmonary infections, polyarthritis, other inflammatory processes). Therefore, we believe that 4% is the more accurate number of subjects managed for rash using corticosteroids.”

Please let us know if there is a way to identify other reasons for corticosteroid use in the adcm.xpt (or other applicable) dataset.

Please confirm receipt of this email.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov
Below is a Listing of subjects from the apalutamide arm of Study ARN-509-003 with systemic corticosteroid use to treat adverse events of skin rash.
<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Subject ID</th>
<th>Concomitant Medication Start Date (Day)</th>
<th>Concomitant Medication End Date (Day)</th>
<th>Medication Class/Standardized Medication Name/Reported Medication Name</th>
<th>Dose/Dose Unit/Frequency/Route</th>
<th>Indication</th>
<th>CM seq</th>
<th>AE seq</th>
<th>AE Preferred Term</th>
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<tr>
<td>Apalutamide</td>
<td>(b) (6)</td>
<td>(b) (6)</td>
<td>(b) (6)</td>
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<td>1/ OINTMENT/DAILY/EPIDURAL</td>
<td>ADVERSE EVENT</td>
<td>42</td>
<td>26</td>
<td>Genital rash</td>
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<tr>
<td></td>
<td>(b) (6)</td>
<td>(437)</td>
<td>(445)</td>
<td>GLUCOCORTICOID/PREDNISONE/PREDNISONE</td>
<td>5/ mg/DAILY/ORAL</td>
<td>ADVERSE EVENT</td>
<td>13</td>
<td>30</td>
<td>Rash maculopapular</td>
</tr>
<tr>
<td></td>
<td>(b) (6)</td>
<td>(36)</td>
<td>(42)</td>
<td>CORTICOSTEROIDS, WEAK, COMBINATIONS WITH ANTIBIOTICS/TERRACORTIR</td>
<td>1 APPLICATION/OINTMENT/PRN/UNKNOWN</td>
<td>ADVERSE EVENT</td>
<td>28</td>
<td>3</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td></td>
<td>(b) (6)</td>
<td>(154)</td>
<td>(b) (6)</td>
<td>CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION/TERRACORTIR MED POLYMXYN B/TERRACORTIR+POLYMXYNE B</td>
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<td>5</td>
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<td>(b) (6)</td>
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<td>ADVERSE EVENT</td>
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<td>Conjunctivitis</td>
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<td>(602)</td>
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<td>50/ mg/DAILY/ORAL</td>
<td>ADVERSE EVENT</td>
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<td>3</td>
<td>Rash generalised</td>
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<tr>
<td></td>
<td>(b) (6)</td>
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<td>(139)</td>
<td>GLUCOCORTICOID/PREDNISONE/PREDNISONE</td>
<td>50/ mg/OTHER/ORAL</td>
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<td>17</td>
<td>3</td>
<td>Urticaria</td>
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<td></td>
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<td>3</td>
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<td>10/ mg/DAILY/ORAL</td>
<td>ADVERSE EVENT</td>
<td>55</td>
<td>13</td>
<td>Rash</td>
</tr>
<tr>
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<td>(100)</td>
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<td>10/ mg/DAILY/ORAL</td>
<td>ADVERSE EVENT</td>
<td>55</td>
<td>14</td>
<td>Rash</td>
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<td>10/ mg/DAILY/ORAL</td>
<td>ADVERSE EVENT</td>
<td>55</td>
<td>12</td>
<td>Rash</td>
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<td>(100)</td>
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<td>10/ mg/DAILY/ORAL</td>
<td>ADVERSE EVENT</td>
<td>55</td>
<td>14</td>
<td>Rash</td>
</tr>
<tr>
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<td>(100)</td>
<td>GLUCOCORTICOID/PREDNISONE/PREDNISONE</td>
<td>10/ mg/DAILY/ORAL</td>
<td>ADVERSE EVENT</td>
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<tr>
<td></td>
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<td>(105)</td>
<td>GLUCOCORTICOID/PREDNISONE/PREDNISONE</td>
<td>5/ mg/DAILY/ORAL</td>
<td>ADVERSE EVENT</td>
<td>56</td>
<td>14</td>
<td>Rash</td>
</tr>
</tbody>
</table>
**LSICM01: Listing of Concomitant Systemic Corticosteroid Medications Use in Subjects with Treatment-emergent Skin Rashes in Apalutamide Treatment Group; Safety Population (Study ARN-509-003)**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Subject ID</th>
<th>Concomitant Medication Start Date (Day)</th>
<th>Concomitant Medication End Date (Day)</th>
<th>Medication Class/Standardized Medication Name/Reported Medication Name</th>
<th>Dose/Dose Unit/Frequency/Route</th>
<th>Indication</th>
<th>CM seq</th>
<th>AE seq</th>
<th>AE Preferred Term</th>
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</thead>
<tbody>
<tr>
<td>(b) (6)</td>
<td>(10)</td>
<td></td>
<td>(14)</td>
<td>GLUCOCORTICOIDS/ BETAMETHASONE/ BETAMETASONE</td>
<td>4/ mg/ DAILY/ ORAL</td>
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<td>2</td>
<td>Rash</td>
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<tr>
<td>(b) (6)</td>
<td>(47)</td>
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<td>(47)</td>
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<td>5/ mg/ ONCE/ INTRAMUSCULAR</td>
<td>ADVERSE EVENT</td>
<td>11</td>
<td>4</td>
<td>Rash</td>
</tr>
<tr>
<td>(b) (6)</td>
<td>(47)</td>
<td></td>
<td>(49)</td>
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<td>4</td>
<td>Rash</td>
</tr>
<tr>
<td>(b) (6)</td>
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<td>(136)</td>
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<td>6</td>
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<tr>
<td>(b) (6)</td>
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<td>50/ g/ PRN/ ORAL</td>
<td>ADVERSE EVENT</td>
<td>16</td>
<td>6</td>
<td>Rash</td>
</tr>
</tbody>
</table>
## Listing of Concomitant Systemic Corticosteroid Medications Use in Subjects with Treatment-emergent Skin Rashes in Apalutamide Treatment Group; Safety Population (Study ARN-509-003)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Subject ID</th>
<th>Concomitant Medication Start Date (Day)</th>
<th>Concomitant Medication End Date (Day)</th>
<th>Medication Class/Standardized Medication Name/Reported Medication Name</th>
<th>Dose/Dose Unit/Frequency/Route</th>
<th>Indication</th>
<th>CM seq</th>
<th>AE seq</th>
<th>AE Preferred Term</th>
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</thead>
<tbody>
<tr>
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<td>(b) (6)</td>
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<td>Urticaria</td>
</tr>
<tr>
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<td>157</td>
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<tr>
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<td>(b) (6)</td>
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<td>40/ mg/ ONCE/ INTRAMUSCULAR</td>
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<td>19</td>
<td>6</td>
<td>Rash</td>
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<td>8/ mg/ QD/ ORAL</td>
<td>ADVERSE EVENT</td>
<td>18</td>
<td>2</td>
<td>Rash erythematous</td>
</tr>
<tr>
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<td>ADVERSE EVENT</td>
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<td>Rash erythematous</td>
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<td>3</td>
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Note: CM seq indicates the sequence number of the concomitant medication record; AE seq indicates the sequence number of the adverse event record.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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AMY R TILLEY
02/08/2018
Jessica, the purpose of this email is to let you know that since we are still in label negotiations we would like to keep the Late Cycle Meeting on Feb 12, 2018. Our purpose for keeping the Late Cycle Meeting would be to finalize any label negotiations that may be needed at that time.

We apologize for any inconvenience this may cause.

Kindly confirm receipt of this email.

Regards,

Amy R. Tilley
Regulatory Project Manager
Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Follow @FDAOncology on Twitter
Kind Regards,
Jessica

Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Cell: (b) (b)
Fax: 908.526.5059
Email: jchung18@its.jnj.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Tuesday, February 06, 2018 4:43 PM
To: Chung, Jessica [JRDUS] <JChung18@ITS.JNJ.com>
Cc: Tilley, Amy <Amy.Tilley@fda.hhs.gov>
Subject: NDA 210951 Erleada - Late Cycle Briefing Package
Importance: High

Jessica, the purpose of this email is to send you the attached Erleada Late Cycle Briefing Package.

Upon your review of the Briefing Package please let us know whether you want to keep or cancel the Feb 12, 2018, Late Cycle TCON.

Kindly confirm receipt of this email.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov
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/s/

----------------------------------------------------
AMY R TILLEY
02/08/2018
Jessica, after conferring with Alice, the labels that were submitted on January 19, 2018 are acceptable at this time.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Hi Amy,

Apologies for the additional email. The team would like to understand if the forthcoming comments will be for all the package labels. More critically as we prepare for launch activities, is it possible to confirm if there are any remaining comments for the bottle package components?

Thank you.
Jessica
Hi Amy - Thank you for the update. Our team will be on standby to address the forthcoming comments.
Yes, I was quick with this email and will continue to include Charlene.

Thank you.
Jessica

Jessica, yes we will have additional revisions to the label. At this time I cannot say when they will be ready to send to you. I will let you know as soon as I can.

Please continue to include Charlene Wheeler on all future emails.

Thanks,

Amy Tilley

Hi Amy,

Good morning.

I wanted to follow up and ask if there might be any more comments anticipated for the package labels. Would you have any updates?

Thank you.

Kind Regards,
Jessica

Jessica Chung
Director, Regulatory Affairs - Oncology
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/s/

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AMY R TILLEY
02/08/2018
Jessica, my apologies this is a Clinical Information Request.
Thanks,
Amy Tilley

Jessica, the purpose of this email is to send you the following Statistical Information Request. We request your response no later than 5 pm today, Feb 7, 2018, and as always follow up with an official submission to the NDA.

Regarding patients with rash who used corticosteroids, you commented “But for most of these patients, corticosteroid use was given specifically for reasons other than rash (e.g., pulmonary infections, polyarthritis, other inflammatory processes). Therefore, we believe that 4% is the more accurate number of subjects managed for rash using corticosteroids.”

Please let us know if there is a way to identify other reasons for corticosteroid use in the adcm.xpt (or other applicable) dataset.

Please confirm receipt of this email.

Regards,
Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

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/s/

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AMY R TILLEY
02/07/2018
Dear Ms. Chung:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Erleada® (apalutamide) oral tablets, 60 mg.

Thank you for your initial agreement to voluntarily participate in the United States Food and Drug Administration’s (FDA’s) Clinical Data Summary Pilot Program (Pilot), as announced by Commissioner Gottlieb on January 16, 2018, and described at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/UCM589210. This letter serves as confirmation that your application has been tentatively selected for inclusion in the Pilot. If your application is approved, as part of the Pilot the FDA will make portions of the clinical study reports (CSRs) for SPARTAN available on FDA’s website, Drugs@FDA. These materials will be posted shortly after approval along with FDA’s review documents (i.e., action package). Your participation in this Pilot has no bearing on our review of the application.

The FDA is conducting this Pilot to assess the potential for improvement in how we make available summary clinical information related to our drug approval decisions. We anticipate that the CSRs, along with FDA’s reviews of the information, will provide a more usable summary of an application’s clinical evidence.

The specific portions of the CSR we intend to post for SPARTAN are described in the following table:

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<tr>
<td>Protocol and amendments</td>
<td>5.3.5.1 – protocol or amendment</td>
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<tr>
<td>Statistical analysis plan</td>
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</tbody>
</table>

As you know, we currently include portions, or further summarized portions, of these CSRs in the text of the medical reviews that are routinely made available after approval. The Pilot will differ from our standard practice for disclosing drug approval information in that the above-named portions of the original CSRs will be separately posted alongside the medical reviews. The FDA will redact the selected portions of the CSRs for trade secrets, confidential commercial
information (CCI), and personal privacy information (PPI), as we currently do when processing these types of documents in response to Freedom of Information Act requests or when posting the medical reviews.

Once the Pilot is complete, we plan to seek public feedback through a Federal Register notice and docket for public comments, and we look forward to learning what we can about how to best support our stakeholders’ needs. Following the posting of your materials as part of the Pilot, our evaluation staff will contact you to request and schedule a voluntary interview. The purpose of this interview is to solicit your feedback and understand your experience with the Pilot and its process. This information will be used as part of an internal analysis of our approach. Any information that you share in this voluntary interview will be anonymized.

If you have any questions, call Charlene Wheeler, Regulatory Project Manager, at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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/s/

JULIA A BEAVER
02/07/2018
Jessica, the purpose of this email is to send you the attached updated PI with the CMC Revisions in Section 11 and a comment.

Sorry for any inconvenience this may have caused.

Please confirm receipt of this email.

Regards,

Amy R. Tilley
Regulatory Project Manager
Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Jessica, the purpose of this email is to send you the attached FDA revised PI and PPI. IMPORTANT: when you respond with your tracked changes document, please incorporate the PI and the PPI into one document and then follow up with an official response to the NDA.

We request your emailed response no later than 12 noon Wednesday, Feb 7, 2018.

Please confirm receipt of this email.

Reference ID: 4217768
Regards,

Amy R. Tilley  
Regulatory Project Manager

Center for Drug Evaluation & Research  
Office of Hematology Oncology Products  
Division of Oncology Products 1  
U.S. Food and Drug Administration  
Tel: 301-796-3994  
amy.tilley@fda.hhs.gov

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/s/

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AMY R TILLEY
02/06/2018
Jessica, the purpose of this email is to send you the attached FDA revised PI and PPI. IMPORTANT: when you respond with your tracked changes document, please incorporate the PI and the PPI into one document and then follow up with an official response to the NDA.

We request your emailed response no later than 12 noon Wednesday, Feb 7, 2018.

- Please confirm receipt of this email.

Regards,

Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994

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Reference ID: 4217699

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/s/

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AMY R TILLEY
02/06/2018
Jessica, the purpose of this email is to let you know that we are in receipt of the email below which states that Janssen consents to the inclusion of NDA 210951 (apalutamide) in the FDA's CSR data transparency pilot aimed to enhance transparency of clinical trial information.

Please be sure to officially submit your consent to participate in the CSR data transparency pilot to the NDA.

Regards,

Amy R. Tilley
Regulatory Project Manager
Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Follow @FDAOncology on Twitter

-----Original Message-----
From: Chung, Jessica [JRDUS] [mailto:JChung18@ITS.JNJ.com]
Sent: Tuesday, February 06, 2018 1:33 PM
To: Kacuba, Alice <Alice.Kacuba@fda.hhs.gov>; Tilley, Amy <Amy.Tilley@fda.hhs.gov>
Subject: FW: NDA 210951: further FDA clarification of CSR transparency pilot
Sensitivity: Confidential

Hi Amy/Alice,

It was nice speaking with you. Thank you for confirming that Janssen will receive a letter of the Agency's decision for Janssen's participation in the pilot. Further that a statement will be included in the apalutamide press release pertaining to the participation in the transparency pilot.

Below is the confirmation that Janssen consents to the inclusion of NDA 210951 (apalutamide) in the FDA's CSR data transparency pilot aimed to enhance transparency of clinical trial information.

If you have any questions, please feel free to contact me.
Thank you.

Kind Regards,

Jessica

Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Cell: [redacted]
Fax: 908.526.5059
Email: jchung18@its.jnj.com

From: Wheeler, Charlene [mailto:Charlene.Wheeler@fda.hhs.gov]
Sent: Monday, February 05, 2018 8:59 AM
To: Kolb, Barbara [JRDUS] <BKolb@its.jnj.com>
Cc: Chung, Jessica [JRDUS] <JChung18@ITS.JNJ.com>; Tilley, Amy <Amy.Tilley@fda.hhs.gov>
Subject: RE: NDA 210951: further FDA clarification of CSR transparency pilot
Sensitivity: Confidential

Morning Barbara,

No decision has been made yet regarding Janssen's participation in the pilot.

Regards,

Charlene Wheeler, MSHS
Senior Regulatory Health Project Manager
Division of Oncology Products 1

Reference ID: 4217613
Dear Charlene,

I am following up to inquire about the FDA transparency pilot of CSR postings. Please advise if you have an update on Janssen's potential participation.

Thank you,

Barbara

Hi Charlene,

Janssen voluntarily consents to the inclusion of NDA 210951 (apalutamide) in the FDA's CSR data transparency pilot aimed to enhance transparency of clinical trial information.

We look forward to the Agency's decision on the participation of NDA 210951 in this pilot program. Thank you for your consideration.
Hi Barbara,

Please see our responses to your questions below. Let me know if you have any additional questions or need further clarification.

Regards,

Charlene Wheeler, MSHS
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Dear Charlene,

Thank you for the informative discussion with the Janssen team on January 18th regarding Voluntary Sponsor Participation of NDA 210951 in the FDA's CSR Data Transparency Pilot.

The team would like further clarification of a few points:

* While FDA indicated during the teleconference that datasets would be out of scope, we understood the entirety of eCTD module 5.3.5.1 is in scope. Module 5.3.5.1 contains individual patient data listings, therefore we wish to clarify that patient listings housed in m5.3.5.1 will be out of scope for the posting. The key concern is due to the potential for ad hoc non-scientific analysis of patient data.

FDA Response: If your application is approved and selected for the pilot, we would not be releasing any data listings housed in 5.3.5.1 as part of the pilot. The scope is to disclose the study report body, document JNJ-56021927 (apalutamide), the protocol and statistical plan for study ARN-509-003 and any relevant amendments or errata to these documents that were subsequently submitted. See below.

* Safety narratives, which often contain detailed clinical histories and data summaries, are included in Module 5.3.5.1. Please clarify that these safety narratives would be redacted for confidentiality or not included in the public posting.

FDA Response: Safety narratives included in the above referenced study report body document would be redacted for confidentiality (i.e., personal privacy, confidential and trade secret information).

* Posting of exploratory analyses and biomarkers included in the CSR (e.g. emergence of resistance mutations on both treatment groups) would invalidate subsequent journal or society embargo restrictions. JRD publication plans for key Congresses are in process and could be impacted by disclosure and invalidation presentation "in context" to the scientific community. For example, if results were made public as part of the FDA transparency pilot prior to there is concern this would be considered a breach of the

Reference ID: 4217613
embargo resulting in the abstract being pulled (and possibly not presented nor published).

Please reply to me to inform Janssen's decision regarding voluntary participation for this application.

FDA Response: This is the type of information that may be summarized in the action package that we currently disclose upon approval. FDA's new molecular entity action packages are posted as soon as the disclosure review is completed, which is on average 5 weeks from the date of approval. In preparing the action packages or other information for disclosure, CDER does not generally consider sponsor plans for further disclosure of the information. We intend to follow the same policy with respect to publication of CSRs included in the pilot.

We recommend discussing the scope of any publication embargo directly with the conference or journal involved to determine whether the scope is narrow enough to prevent invalidation by material published by FDA as part of its regulatory process such as drug approval summaries.

We would appreciate a response regarding your participation in the pilot by next Friday, February 2, 2018.

Thanks and kind regards,

Barbara

From: Wheeler, Charlene [mailto:Charlene.Wheeler@fda.hhs.gov]
Sent: Wednesday, January 17, 2018 12:34 PM
To: Kolb, Barbara [JRDUS] <BKolb@its.jnj.com>
Subject: RE: apalutamide NDA 210951 Sponsor Contact This Week

I would just stick with the disciplines that appear in the clinical summary.

Regards,

Charlene Wheeler, MSHS

Senior Regulatory Health Project Manager
Hi Charlene,

I am acknowledging the email string for a potential discussion with you tomorrow about the pilot program for NDA 210951. I will reach out to the Janssen team for availability since we span time zones.

Other than clinical and statistical information in CSRs, do we need to think of other functional areas that could also be public such as CMC and Nonclinical?

Thank you for the clarification,

Barbara

Hi Jessica,

Thanks for letting me know.

Please let me know if your team is available for a call at 1:30 tomorrow afternoon to discuss the possibility of including your apalutamide application as part of our pilot program.
Hi Charlene,

I am currently sick and out of the office. Could you please include Barbara Kolb on any communications and requests related to the apalutamide NDA 210951 for the remaining part of this week?

Thank you.

Kind Regards,

Jessica

Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Cell: (b) (6)
Fax: 908.526.5059
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/s/

----------------------------------------------------

AMY R TILLEY

02/06/2018

Reference ID: 4217613
Hello Ms. Chung,

The purpose of this email is to provide you with a clinical information request for NDA 210951. Provide your response no later than 10AM on Monday February 5th, 2018. Let me know if you have any questions.

SDTM dataset ie.xpt identifies 117 patients who have failed screening due to not meeting Inclusion Criteria IN01, IN01_1, or IN01_2. Please provide further resolution on the reason for not meeting components of the Inclusion Criteria IN01, IN01_1, or IN01_2 (i.e., histology, PSADT calculated by investigator, invalid or incorrect PSA values, continuous ADT, etc.).

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
02/02/2018
Hello Ms. Chung,

The purpose of this email is to provide you with a statistical information request for NDA 210951. Provide your response no later than 10AM, on Monday, February 5, 2018. Let me know if you have any questions.

As per the Apalutamide CSR page 53, “Of the 925 patients who were ineligible, 517 subjects were ineligible due to the presence of metastatic disease at screening”. Please provide a complete breakdown of reason for treatment failure in the 925 patients screened but considered ineligible for enrollment, or please direct the clinical reviewers as to where in the NDA submission that data is located.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
02/01/2018
Hello Ms. Kolb,

The purpose of this email is to provide you with a labeling IR for NDA 210951. Please accept all changes in the document that you agree with and provide any comments/responses in tracked changed format. Email me your revisions no later than Thursday, February 1, 2018. Your formal response can be submitted after that date. Let me know if you have any questions.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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     /s/

CHARLENE N WHEELER
01/24/2018
PeRC Meeting Minutes
January 10, 2018

PeRC Members Attending:
Lynne Yao
Meshaun Payne
Jacqueline Yancy
Rosemary Addy
Hari Cheryl Sachs
Gerri Bauer
Raquel Tapia
James Travis
Dionna Greene
Victor Baum
Gil Burkhart
Kevin Krudys
Kristiana Brugger
Julia Pinto
Barb Buchs
Jingjing Ye
Raquel Tapia
Mark Rothmann
Susan McCune
Wiley Chambers
Thomas Smith
George Greeley
Adrienne Hornatko Munoz
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<thead>
<tr>
<th>Time</th>
<th>Item</th>
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<tbody>
<tr>
<td>9:00</td>
<td>Agenda</td>
</tr>
</tbody>
</table>
| 9:20 | NDA 210951  
Erleada (apalutamide) Full Waiver with Agreed iPSP |
| 9:35 | Charlene Wheeler  
Prostate Cancer |
| 9:50 | DOP |
| 10:10 | Non-Responsive |
| 10:25 | Non-Responsive |
| 10:40 | Non-Responsive |

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Reference ID: 4210177
Erleada (apalutamide) Full Waiver with Agreed iPSP

- Proposed Indication: Prostate Cancer
- PeRC Recommendations:
  - The PeRC concurred with a full waiver of pediatric studies as outlined in the Agreed iPSP.
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/s/

JACQUILINE A YANCY
01/22/2018
Hello Jessica,

Regarding your question on comment B please see below.

We acknowledge that product strength equivalency statement “Each tablet contains 60 mg of apalutamide.” is presented below the strength on the principal display panels of the pull-out blister card and the carton labeling for the professional sample product. However, since this product strength equivalency statement is not present on all panels where the product strength statement “60 mg” (in purple box) is present, we recommend you to revise the product strength to “60 mg/tablet” or “60 mg per tablet” on all panels of the Pull Out Blister Card, Blister Card Sleeve, and Carton Labeling, so that if the end user overlook the product strength equivalency statement on the principal display panel, they will see that the milligram amount of drug per single unit (e.g., tablet) is 60 mg. This will ensure that there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card.1 Furthermore, our recommendation to add “/tablet” or “per tablet” is only for the blister card components, and is not applicable to the bottle labels.


Regards,
Charlene Wheeler, MSHS
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Could you also let me know when we can anticipate a response to our earlier question on Comment B so that we can address accordingly, if needed?

Thank you.

Kind Regards,
Jessica

Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Fax: 908.526.5059
Email: jchung18@its.jnj.com

From: Chung, Jessica [JRDUS]  
Sent: Tuesday, January 09, 2018 5:02 PM  
To: Wheeler, Charlene  
Subject: RE: NDA 210951 Carton/Container Information Request

Thanks Charlene!

I will discuss your suggestion with the team.

In regards to obtaining the FDA feedback and then for the Sponsor to respond to Comment B, would it be acceptable to provide it with a later due date (although as you know we have been trying to respond to you as early as possible)?

Thank you.
Jessica

From: Wheeler, Charlene [mailto:Charlene.Wheeler@fda.hhs.gov]  
Sent: Tuesday, January 09, 2018 2:11 PM  
To: Chung, Jessica [JRDUS]  
Subject: RE: NDA 210951 Carton/Container Information Request

Hi Jessica,

I haven’t heard back from the review team as yet. My suggestion would be to formally respond to all other items in the IR. Once I hear from them, you can submit a response for comment B.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Hi Charlene,

Apologies for the urgency, in order to provide the revised components for the response in time, would you let me know if a response to the question below is possible for today? We would need to complete annotations by today in order to generate the mock-ups for the response.

Thank you.

Kind Regards,
Jessica

---

From: Chung, Jessica [JRDUS]  [mailto:JChung18@ITS.JNJ.com]
Sent: Tuesday, January 09, 2018 12:43 PM
To: Wheeler, Charlene <Charlene.Wheeler@fda.hhs.gov>
Subject: RE: NDA 210951 Carton/Container Information Request

Hi Charlene,

Regarding comment B, we have a clarification question as follows:
Janssen believes that adding “/tablet” or “per tablet” after “60 mg” (within the deep blue/purple rectangle) adds visual clutter which distracts from the prominence of the dosage strength which is considered “key information” appearing on the principal display panel as well as secondary panels of the Dose Pack. Given that we have included the “product strength equivalency statement”, “Each tablet contains 60 mg of apalutamide.” below the strength on the principal display panels of the DosePack components as well as the Trade and Sample Bottle Labels, will this satisfy the need to add “/tablet” or “per tablet”?

Thank you.

Kind Regards,
Jessica

Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Cell: 908.526.5059
Fax: 908.526.5059
Email: jchung18@its.jnj.com

---

From: Wheeler, Charlene [mailto:Charlene.Wheeler@fda.hhs.gov]
Sent: Monday, January 08, 2018 12:13 PM
To: Chung, Jessica [JRDUS] <JChung18@ITS.JNJ.com>
Subject: RE: NDA 210951 Carton/Container Information Request

Reference ID: 4208611
Hello Ms. Chung,

The purpose of this email is to provide you with an information request regarding the carton/container for NDA 210951. Provide your response no later than Thursday, January 11, 2018. Let me know if you have any questions.

We recommend the following be implemented:

A. Container label
   1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, the expiration date format should be presented in accordance with FDA Guidance (e.g. MMMYYY or MMMDYYYY).

B. Professional Sample Pull Out Blister Card, Blister Card Sleeve, and Carton Labeling
   1. Revise the strength statement “60 mg” in purple box to “60 mg/tablet” or “60 mg per tablet” for clarity.

C. Professional Sample Blister Card Sleeve
   1. Consider presenting the statement “QUESTIONS ON ERLEADATM Tablets?” in sentence case to improve readability. For example, “Questions on ErleadaTM Tablets?”

D. Professional Sample Carton Labeling
   1. Consider presenting the statement “ACCESS AND EDUCATION TOOLS TO HELP YOU START AND STAY ON THERAPY.” in sentence case to improve readability. For example, “Access and education tools to help you start and stay on therapy.”

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
01/18/2018

Reference ID: 4208611
NDA 210951

MID-CYCLE COMMUNICATION

Janssen Research & Development, LLC
Attention: Jessica Chung
Director, Global Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Erleada® (apalutamide) oral tablets, 60 mg.

We also refer to the teleconference between representatives of your firm and the FDA on January 3, 2018. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Charlene Wheeler, MSHS, Senior Regulatory Project Manager at (301) 796-1141.

Sincerely,

Charlene Wheeler, MSHS
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Chana Weinstock, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: January 3, 2018, 11-12PM
Application Number: NDA 210951
Product Name: Erleada® (apalutamide)
Indication: Non-metastatic castration resistant prostate cancer
Applicant Name: Janssen Research & Development, LLC

Meeting Chair: Chana Weinstock, MD
Meeting Recorder: Charlene Wheeler, MSHS

FDA ATTENDEES
Julia Beaver, MD Director, DOP1
Amna Ibrahim, MD Deputy Director, DOP1
Chana Weinstock, MD Clinical Team Lead
Daniel Suzman, MD Clinical Reviewer
Todd Palmby, PhD Pharm/Tox Team Lead
Wei Chen, PhD Pharm/Tox Reviewer
Xiao H. Chen, PhD Office Product Quality, Team Lead
Wentao Fu, PhD Clinical Pharmacology Reviewer
Qi Liu, PhD Clinical Pharmacology Team Lead
Charlene Wheeler, MSHS Senior Regulatory Project Manager

APPLICANT ATTENDEES
Mary Guckert
Kiran Patel
Sudhakar Rao
Caly Chien
Barbara Kolb
Leon Freytor
Jessica Chung
Nancy Micalizzi
Yvonne Wu
Sara Bender
Margaret Yu
Angela Lopez-Gitlitz
Ke Zhang
Arianna Friggeri
Oliver Ackaert
Richard Klep

Reference ID: 4205489
1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No significant issues have been identified to date.

2.0 INFORMATION REQUESTS

Clinical Pharmacology

Reference is made to the Population Pharmacokinetics Report of Study JNJ-56021927 (apalutamide) in the NDA 210951 submission.

1) Provide the following individual data for the patients (N=19) where apalutamide was co-administered with CYP3A inducers:
   a. Apalutamide dosing regimen and PK data
   b. Name of CYP3A4 inducer and dosing regimen
   c. PK sampling schedule related to the dosing
   d. Clarify if there were apalutamide PK data for patients with/without CYP3A inducer co-administered

2) Provide the following individual data for the patients (N=32) where apalutamide was co-administered with CYP2C8 inhibitors:
   a. Apalutamide dosing regimen and PK data
   b. Name of CYP2C8 inhibitor and dosing regimen
   c. PK sampling schedule related to the dosing
   d. Clarify if there were apalutamide PK data for patients with/without CYP2C8 inhibitor co-administered

3) Provide clinical experiences (safety or efficacy observations) of metformin co-administered with apalutamide if available.

Meeting Discussion: The clinical pharmacology responses have been received and are currently being reviewed.
Product Quality

Manufacturing Drug Process:

1) The material dispensing section of all six executed batch records does not match that in the master batch record, in terms of format. It is not clear exactly how much of each ingredient was added into formulation. Provide a tabulated summary of the total amount of each ingredient charged for each registration batch based on the executed batch records.

2) 

3) Please submit plans for verification and maintenance. Normally, maintenance plans include trending of results, periodic method verification, risk analysis if changes are done to the raw materials or process (significant risk triggers verification), and criteria for update and re-validation.

Meeting Discussion: The product quality responses have been received and are currently being reviewed.

Clinical

We are proposing to add information on “Falls and Fractures” to section 5, Warnings and Precautions of the proposed apalutamide package insert and .

Meeting Discussion: The revisions to section 5 have been received and will be reviewed by the clinical team. Further discussion will take place during the labeling negotiations.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT
The review team considers rash and falls/fractures to be the primary safety concerns. With regard to fracture, the review team intends to highlight the risk and potential mitigation strategies in section 5. There is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING
There are no plans, at this time, for an AC meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES
As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is
currently scheduled for **February 12, 2018**. We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

**Additional Meeting Discussion**

FDA indicated that there will be one clinical PMC for this application, which is to submit the analyses and datasets with final report for the clinical trial entitled; “SPARTAN, a Phase 3 double-blind, randomized study of apalutamide versus placebo in patients with non-metastatic castration-resistant prostate cancer [ARN-509-003]”. As per an IR sent to the applicant previously, estimated trial completion date is currently 12/2022, with final report submission anticipated 06/2023.
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/s/

CHARLENE N WHEELER
01/10/2018

CHANA WEINSTOCK
01/11/2018
Hello Ms. Chung,

The purpose of this email is to provide you with an information request regarding the carton/container for NDA 210951. Provide your response no later than Thursday, January 11, 2018. Let me know if you have any questions.

We recommend the following be implemented:

A. Container label
   1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, the expiration date format should be presented in accordance with FDA Guidance (e.g. MMMYYY or MMMDDYYYY).

B. Professional Sample Pull Out Blister Card, Blister Card Sleeve, and Carton Labeling
   1. Revise the strength statement “60 mg” in purple box to “60 mg/tablet” or “60 mg per tablet” for clarity.

C. Professional Sample Blister Card Sleeve
   1. Consider presenting the statement “QUESTIONS ON ERLEADATM Tablets?” in sentence case to improve readability. For example, “Questions on ErleadaTM Tablets?”

D. Professional Sample Carton Labeling
   1. Consider presenting the statement “ACCESS AND EDUCATION TOOLS TO HELP YOU START AND STAY ON THERAPY.” in sentence case to improve readability. For example, “Access and education tools to help you start and stay on therapy.”

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
01/10/2018
NDA 210951

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Janssen Biotech, Inc.
c/o Janssen Research and Development, LLC
920 U. S. Highway 202
P.O. Box 300
Raritan, NJ 08869

ATTENTION: Jessica Chung
Director, Global Regulatory Affairs

Dear Ms. Chung:

Please refer to your New Drug Application (NDA) dated October 9, 2017, received October 10, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apalutamide Tablets, 60 mg.

We also refer to:

- your correspondence, dated and received October 13, 2017, requesting review of your proposed proprietary name, Erleada
- your amendment, dated and received December 7, 2017, to your request for name review

We have completed our review of the proposed proprietary name, Erleada and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, ([https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm](https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm))
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbuleh Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Charlene Wheeler, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
01/05/2018
Hello Ms. Chung,

The purpose of this email is to provide you with a clinical information request for NDA 210951. Provide your response no later than 12 noon on January 8, 2018. Let me know if you have any questions.

The following patients have dates listed in dataset ADTTEEF that are >30 days later than the dates in dataset TU on which they appear to have had independently-assessed metastatic disease first noted by the presence of a new (non-pelvic LN) lesion- please explain the discrepancy in the dates for these patients.

In some cases, this appears to be because the initial NM bone scan and confirmatory CT were separated by a large time interval (e.g. patient )

In other cases, there is a NM bone scan result in dataset TU but no apparent confirmatory CT or Xray result in the TU dataset that was reviewed by independent review.

(e.g. patient )
Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov

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/s/

CHARLENE N WHEELER
01/03/2018
For CDER NDA/BLA reviews only: We are requesting that Division RPMs upload the PeRC PREA Template as a Memo To File into DARRTS in advance of your scheduled PeRC meeting.

Note: The PeRC’s recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. The final PeRC meeting minutes are linked to the NDA/BLA application in DARRTS.

Complete the section(s) of this template that are relevant to your current review. Sections that are not applicable can be deleted.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the required Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Definitions:

Deferral – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impractical; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information MUST be included in the pediatric use section of labeling.
**Partial Waiver** – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

**Pediatric Assessment** – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

**Pediatric Plan** – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

**Pediatric Population/Patient**– 21 CFR 201.57 defines pediatric population(s) and pediatric patient(s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

**Pediatric Record** – A pediatric record is to be completed in DARRTS for either the NDA or supplemental NDA application scheduled for review by the PeRC. The pediatric record indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral.

**Submission Property in DARRTS (REPLACES PEDIATRIC PAGE)** – This process is to be completed in DARRTS for applications to indicate whether the application does or does not trigger PREA or if orphan designation has been granted.
Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☒ Full Waiver ☐ Partial Waiver ☐ Pediatric Assessment ☐ Deferral/Pediatric Plan

BLA/NDA#: NDA 210951

PRODUCT PROPRIETARY NAME: Erleada

APPLICANT/SPONSOR: Janssen Biotech, Inc.

PREVIOUSLY APPROVED INDICATION/S:

(1) N/A

(2) 

(3) 

(4) 

PROPOSED INDICATION/S:

(1) _for the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC)

(2) 

(3) 

(4) 

BLA/NDA STAMP DATE: October 10, 2017

PDUFA GOAL DATE: April 10, 2018

SUPPLEMENT TYPE: N/A

SUPPLEMENT NUMBER: N/A
Does this application provide for (If yes, please check all categories that apply and proceed to the next question):
NEW X active ingredient(s) (includes new combination); □ indication(s); □ dosage form; □ dosing regimen; or □ route of administration?

Did the sponsor submit an Agreed iPSP? Yes □ No □

Are there any changes to the Agreed iPSP that are different than the sponsor’s current pediatric plan? Yes □ No X

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moeity, not just this product.)
Yes □ No X

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes □ No X

If Yes, PMR # NDA #

Does the division agree that this is a complete response to the PMR? Yes □ No □
If Yes, to either question Please complete the Pediatric Assessment Template.
If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.
WAIVER REQUEST

Please attach:

☐ Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor’s proposed language, include the appropriate language under Question 4 in this form.
☒ Pediatric Record

1. Pediatric age group(s) to be waived. 0-18 Years

2. Reason(s) for waiving pediatric assessment requirements (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division’s thinking.)

☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as “Not Feasible.”) If applicable, chose from the adult-related conditions on the next page.

☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (This reason is for Partial Waivers Only)
3. Provide justification for Waiver:
There is no incidence or prevalence of prostate cancer in the pediatric population.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor’s proposed language:
Safety and effectiveness of ERLEADA in pediatric patients have not been established.
Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics
These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis
digestive disorders (gallstones)
acute bacterial exacerbations of chronic bronchitis
dry eye syndrome (keratoconjunctivitis sicca)
(a complication of chronic obstructive pulmonary
dupuytren’s disease and manifestations
disease)
erekctile dysfunction essential thrombocytosis
adjunctive treatment of major depressive disorder
giant cell arteritis
age-related macular degeneration
gout
Alzheimer’s disease
heavy menstrual bleeding associated with uterine fibroids
amyloidosis
Huntington’s chorea
amyotrophic lateral sclerosis
idiopathic pulmonary fibrosis
androgenic alopecia
infertility & reproductive technology
ankylosing spondylitis
juvenile psoriatic arthritis
atherosclerotic cardiovascular disease
memory loss
benign monoclonal gammopathy
menopause and perimenopausal disorders
benign prostatic hyperplasia
mesothelioma
cancer:
microscopic polyangiitis
basal cell and squamous cell skin cancer
myelodysplasia
bladder
myelofibrosis & myeloproliferative disorders
breast
opioid induced constipation in chronic, non-cancer
cervical
pain
colorectal
osteoarthritis
cholangiocarcinoma
overactive bladder
endometrial
Parkinson’s disease
esophageal
paroxysmal nocturnal hemoglobinuria
fallopian tube
plasma cells and antibody production disorders
follicular lymphoma
polycythemia vera
gastric
polymyalgia rheumatica (PMR)
hairy cell leukemia
postmenopausal osteoporosis
hepatocellular
prevention of stroke and systemic embolic events
indolent non-Hodgkin lymphoma
in atrial fibrillation
liposarcoma
psoriatic arthritis
lung (small & non-small cell)
reduction of thrombotic cardiovascular events in
multiple myeloma
patients with coronary artery disease
opharynx (squamous cell)
replacement therapy in males for conditions
ovarian (non-germ cell)
associated with a deficiency or absence of
pancreatic
endogenous testosterone
peritoneal
retinal vein occlusions
prostate
stress urinary incontinence
renal cell
Sjogren’s Syndrome
uterine
temporary improvement in the appearance of
carcinom histiocytic leukemia
caudal lines
treatment of incompetent great saphenous veins
chronic obstructive pulmonary disease
and varicosities
cryoglobulinemia
treatment of Hypoactive Sexual Desire Disorder
degenerative intervertebral disc disease
(HSDD) in postmenopausal women
diabetic peripheral neuropathy/macular edema
type 2 diabetic mellitus with cardiovascular disease
diabetic foot infections
type 2 diabetic nephropathy
diabetic gastroparesis
vascular dementia/vascular cognitive
diabetic retinopathy
disorder/impairment

Template Version 11-1-17

Reference ID: 4200011
DEFERRAL REQUEST

Please attach:  
☐ Pediatric Record

1. Age groups included in the deferral request:

2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:

3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division’s thinking.)
   a. Adult studies are completed and ready for approval
   b. Additional safety or effectiveness data needed (describe)
   c. Other (specify)

4. Provide projected date for the submission of the pediatric assessment (deferral date):

5. Did applicant provide certification of grounds for deferring assessments?  ☐ Yes ☐ No

6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?  ☐ Yes ☐ No

SPONSOR’S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency?  ☐ Yes ☐ No

2. Does the division agree with the sponsor’s plan?  ☐ Yes ☐ No

3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion
and studies submitted)? □ Yes □ No

a. Protocol Submission:
b. Study Completion:
c. Study Submission:

4. Has a Written Request been issued? □ Yes □ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)

5. Has a PPSR been submitted? □ Yes □ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Nonclinical Studies:

Clinical Studies:

Age group and population (indication) in which study will be performed:
This section should list the age group and population exactly as it is in the plan.

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.
**Number of patients to be studied or power of study to be achieved:**

*Example:*

*Study 1:* X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

*Study 2:* This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

**Entry criteria:**

*This section should list pertinent inclusion/exclusion criteria.*

*Example:*

*Entry criteria:* Pediatric patients with disease x diagnosed with laboratory test of LFTs

*Patients must have a negative pregnancy test if female.*

**Clinical endpoints:**

*Example:*

*Study 1:* Clinical outcome and safety will be the primary endpoints.

*Study 2:* The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

**Timing of assessments:**
Example: baseline, week 1, 4, and 6

**Statistical information (statistical analyses of the data to be performed):**

*Example:*

Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, Cmax, Tmax, Cl/F and compared to adults.

**Division comments on product safety:**

*Are there any safety concerns currently being assessed?* □ Yes □ No

*Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies?* □ Yes □ No

*Will a DSMB be required?* □ Yes □ No

**Other comments:**

**Division comments on product efficacy:**

**Division comments on sponsor proposal to satisfy PREA:**

---

**PeRC ASSESSMENT TEMPLATE**

**Please attach:**

---
- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.

- Pediatric Record

Date of PREA PMR:
Description of PREA PMR: (Description from the PMC database is acceptable)

Was Plan Reviewed by PeRC? □ Yes □ No If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:
This section should list the indication(s) exactly as written in the protocols.

Example:
DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics
- Route of administration: Oral
- *Formulation: disintegrating tablet
- Dosage: 75 and 50 mg
- Regimen: list frequency of dosage administration

*If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)
**Types of Studies/ Study Design:**

*Example:*

**Study 1:** Multi-center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.

**Study 2:** PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

---

**Age group and population in which study/ies was/were performed:**

*Example:*

**Study 1:** patients aged X to Y years.

**Study 2:** sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

---

**Number of patients studied or power of study achieved:**

*Example:*

**Study 1:** X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

**Study 2:** powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients.

---

**Entry criteria:**

This section should list pertinent inclusion/exclusion criteria.

*Example:*

**Entry criteria:** Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients had a negative pregnancy test if female.

---

**Clinical endpoints:**

*Example:*

**Study 1:** Clinical outcome and safety were the primary endpoints.
Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed):
This section should list the statistical tests conducted.

Example:
Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control’s response rate.

Study 2: descriptive statistical methods for AUC, Cmax, Tmax, CL/F and compared to adults.

Timing of assessments:
Example:
Baseline, week 2, week 6, and end of treatment
Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.
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/s/

CHARLENE N WHEELER
12/22/2017

CHRISTY L COTTRELL
01/03/2018
Hello Barbara,

The purpose of this email is to provide you with a clin pharm information request for NDA 210951. Your response is requested no later than 2PM on January 5, 2018.

Reference is made to the Population Pharmacokinetics Report of Study JNJ-56021927 (Apalutamide) in NDA 210951 submission.

1. Provide the following individual data for the patients (N=19) where apalutamide was co-administered with CYP3A inducers.
   a. Apalutamide dosing regimen and PK data
   b. Name of CYP3A4 inducer and dosing regimen
   c. PK sampling schedule related to the dosing
   d. Clarify if there were apalutamide PK data for patients with/without CYP3A inducer co-administered.

2. Provide the following individual data for the patients (N=32) where apalutamide was co-administered with CYP2C8 inhibitors.
   a. Apalutamide dosing regimen and PK data
   b. Name of CYP2C8 inhibitor and dosing regimen
   c. PK sampling schedule related to the dosing
   d. Clarify if there were apalutamide PK data for patients with/without CYP2C8 inhibitor co-administered.

3. Provide clinical experiences (safety or efficacy observations) of metformin co-administrated with apalutamide if available.

Let me know if you have any questions.

Regards,

Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
12/21/2017
NDA 210951

INFORMATION REQUEST

Janssen Biotech, Inc.
Attention: Jessica Chung
Director, Global Regulatory Affairs
920 U.S. Highway 202 P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

Please refer to your New Drug Application (NDA) received October 10, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for apalutamide tablet 60mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Manufacturing Drug Process:
The material dispensing section of all six executed batch records do not match that in the master batch record, in term of format. It is not clear exactly how much of each ingredient was added into formulation. Provide a tabulated summary of the total amount of each ingredient charged [(b)(4)] for each registration batch based on the executed batch records.

If you have any questions, please contact me, at (240) 402-5834.

Please respond to Drug Process comments by COB December 22, 2017.

Sincerely,
Kristine F. Leahy - S
Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
The purpose of this email is to provide you with a clinical information request for NDA 210951. Your response is requested no later than 12 pm (eastern standard time) on Thursday December 21, 2017.

1. Please provide a timeline for expected study completion and for submission of the final study report and datasets for SPARTAN, a phase 3 double-blind, randomized study of apalutamide versus placebo in patients with nonmetastatic castration-resistant prostate cancer [ARN-509-003]

Please respond by 1) email to facilitate review 2) official submission to the NDA.

If you have any questions, please feel free to contact me or Charlene Wheeler.

Thank you,

Fatima Rizvi, Pharm D
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-7426 | Email: Fatima.Rizvi@fda.hhs.gov
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/s/

FATIMA M RIZVI
12/20/2017
Hello Ms. Chung,

The purpose of this email is to provide you with a statistical information request for NDA 210951. Your response is requested no later than 2PM on Wednesday, December 20. As I will be out of the office please be sure to copy my colleagues cc’d above.

1. In the study SAP, the symptomatic progression event is defined as:
   • Development of a skeletal-related event: pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy to the bone.
   • Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy.
   • Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

Per the definition, one important requirement is the triggering of a subsequent treatment. Please clarify whether all symptomatic progression events in your analysis have met the event requirements as defined above, particularly for the 15 patients labeled as “symptomatic progression: disease progression on subsequent therapy”. If not, please perform a time to symptomatic progression analysis following the exact event definition in the SAP and submit the SAS dataset used for this analysis.

2. Please also perform an analysis for time to symptomatic progression as specified above using the censoring rule given below:
   For patients who received a new systemic anti-cancer therapy prior to documented symptomatic progression, censor these patients on the date of last visit/assessment showing no symptomatic progression prior to the start of the new systemic anti-cancer therapy.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov

Reference ID: 4196404
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/s/

CHARLENE N WHEELER
12/15/2017
Dear Ms. Chung:

Please refer to your New Drug Application (NDA) received October 10, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for apalutamide tablet 60mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Manufacturing Drug Process:

1. 

2. Please submit plans for verification and maintenance. Normally maintenance plans include trending of results, periodic method verification, risk analysis if changes are done to the raw materials or process (significant risk triggers verification), and criteria for update and re-validation.

If you have any questions, please contact me, at (240) 402-5834.
Please respond to Drug Process comments by COB December 29, 2017.

Sincerely,

Kristine F. Leahy -S
Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hi Jessica,

The purpose of this email is to provide you with an additional clinical information request for NDA 210951. This one will also have a requested response date of Friday, December 15, 2017.

1. The quote below is from the IRC charter provided in 5.3.5.1. Please clarify if PD was determined for any patient based on IRC re-reads of earlier scans. Please identify these patients.

“If progression due to new distant metastases is assessed based on imaging data provided from the sites, and it is determined at a subsequent time point that the imaging assessment provided previously was incorrect, independent reviewers may make corrections as described in SOPs. A re-read may be required in the event it is determined that the assessment provided (and subsequently, read) was erroneous. The corrected data will be provided to Aragon during the data transfer.”

2. Please clarify how patients with bony lesions identified on IRC-reviewed NM bone scan only with no confirmatory CT scan or MRI were handled in terms of determination of PD/MFS events. If there were PD/MFS events identified on the basis of IRC-reviewed NM medicine bone scan only, please provide a list of these patients.

Regards,

Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
12/13/2017
Hello Ms. Chung,

The purpose of this email is to provide you with a clinical information request for NDA 210951. Your response is requested no later than 12PM on Friday, December 15, 2017.

1. There appear to be 132 patients with investigator-identified metastatic lesions on imaging at screening as per the TU dataset who were randomized and treated on-study as per the ADSL dataset. Some of these patients appear to have had pelvic lymph nodes and were stratified as N1 at baseline; however, this does not account for all patients with investigator-identified baseline metastases. Please explain how these patients were eligible for treatment.

2. Please comment on what percentage of patients underwent biopsy at the time of metastasis determination, and where to find information on their pathology reports.

Let me know if you have any questions.

Regards,

Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@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/

CHARLENE N WHEELER
12/13/2017
Hello Ms. Chung,

The purpose of this email is to provide you with a clinical information request for NDA 210951. Your response is requested no later than 12PM on Friday, December 15, 2017.

The following patients appear to have had PD per independent review (per dataset RS) noted at an earlier scan than the date that was used for the independent-review determined MFS event of metastasis (per dataset ADTTEEF). Please comment on the apparent discrepancy.

ARN-509-003-1329-001
ARN-509-003-1826-004
ARN-509-003-2600-001
ARN-509-003-2805-005
ARN-509-003-2811-004
ARN-509-003-3003-002
ARN-509-003-3007-012
ARN-509-003-3115-004
ARN-509-003-3126-003
ARN-509-003-3203-002
ARN-509-003-3508-002
ARN-509-003-3526-001
ARN-509-003-3552-008
ARN-509-003-3574-001
ARN-509-003-3644-008
ARN-509-003-3651-002
ARN-509-003-3661-005
ARN-509-003-4027-001

Let me know if you have any questions.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
12/12/2017
Hello Ms. Chung,

The purpose of this email is to provide you with a statistical IR for NDA 210951. Please provide your initial response by email no later than 2PM on Thursday, December 14, 2017. Your formal submission can be completed after that time.

In the dataset “ADRESP”, we noted that one of the symptomatic progression events was labeled as “Symptomatic Progression - Disease Progression on Subsequent Therapy” and 15 patients (9 in the apalutamide arm and 6 in the placebo arm) with this event were included in the time to symptomatic progression analysis. However, in the SAP this event was not one of the pre-specified events for the time to symptomatic progression analysis. Please clarify this discrepancy.

Let me know if you have any questions.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
12/11/2017
Hello Ms. Chung,

The purpose of this email is to provide you with a PRO IR for NDA 210951. Please see the attachment and complete no later than Thursday, December 14, 2017. Your initial response can be sent to me by email, followed by a formal submission. Let me know if you have any questions.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
As part of FDA’s review of safety and efficacy, we are interested in evaluating patient experience data which includes aspects of healthcare utilization and clinical outcome assessments. Please provide the following analyses, figures and summary tabulations.

**Healthcare Utilization:**

Please provide a table of the incidence of ED visits, hospitalization and supportive care medication and procedures used for each arm by COA assessment window (if no COA assessments used, please record by some reasonable assessment frequency, e.g. monthly, every other month, etc.):

<table>
<thead>
<tr>
<th>Healthcare Utilization</th>
<th>Baseline</th>
<th>Assessment 1</th>
<th>Assessment 2</th>
<th>Assessments X...</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm A N(%)</td>
<td>Arm B N(%)</td>
<td>Arm A N(%)</td>
<td>Arm B N(%)</td>
</tr>
<tr>
<td>ED Visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiemetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidiarrheals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative Procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. EBRT, nephrostomy, venting G tubes, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other: (describe)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable Patients</td>
<td>N=</td>
<td>N=</td>
<td>N=</td>
<td>N=</td>
</tr>
</tbody>
</table>

**Patient-Reported Outcomes**

Please provide the following PRO analyses and tables/figures:

1.) **Patient Disposition**

Provide a figure and table documenting the cumulative patient disposition by arm per PRO assessment window (e.g., q28 days) for all scheduled assessments. Use the following categories, if applicable:

- PRO assessment expected
- PRO assessment not expected due to progression
- PRO assessment not expected due to death
- PRO assessment not expected due to other reasons

2.) **PRO Completion**

Reference ID: 4191856
Provide a figure and table documenting PRO completion rate for each instrument among patients who are expected to have PRO assessments. Provide data for each treatment arm per PRO assessment. Use the following categories:

- All questions completed
- At least 50% completed
- At least one question completed

3.) Overall instrument score (E.g. FACT-G Total Score)

   a. Provide a table of descriptive statistics for the overall score and change from baseline for each PRO assessment by arm.

   b. Provide a line graph of mean overall score and mean of change from baseline for each PRO assessment with both arms and 95% CI.

   c. Provide CDF curves of the overall score and change from baseline for each assessment time for both arms within the first 6 months (to assess acute and subacute patient experience).

4.) Domain level analyses (e.g., multi-question scales and functional measures like physical function, fatigue, etc.)

   a. Provide a table of descriptive statistics for the domain score and change from baseline for each PRO assessment by arm.

   b. Provide a line graph (example below) of mean domain score and mean of change from baseline for each PRO assessment with both arms and 95% CI. Use same y-axis scaling for all graphs assessing the same measure.

Example of mean score over time (physical function)
Example of mean of change from baseline over time (physical function)

![Graph showing change over time](image)

c. Provide CDF curves (example below) of scores and change from baseline for each assessment time for both arms.

![CDF curves for assessment times](image)

5.) Item level analyses

As described below, please provide 2 bar charts for each of the following single items:

- C2- I am losing weight
- C6: I have a good appetite
- GP6: I feel ill
- GP4 “I have pain”
- P1 “I have aches and pains that bother me”
- P3 “My pain keeps me from doing things I want to do”
- GP2 “I have nausea”
- GP1 “I have lack of energy”
- GP5 “I am bothered by the side effects of treatment”
- GF1 “I am able to work (include work at home)
a. Provide a bar chart (example below using QLQC30 items) of the distribution of responses by arm per PRO assessment. Please also include number of patients at each assessment for each arm in or below the bar chart.

![Bar chart showing distribution of responses by arm per PRO assessment.]

<table>
<thead>
<tr>
<th>Visit</th>
<th>Baseline</th>
<th>Vis 2</th>
<th>Vis 3</th>
<th>Vis 4</th>
<th>Vis 5</th>
<th>Vis 6</th>
<th>Vis 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl</td>
<td>1105</td>
<td>1303</td>
<td>1206</td>
<td>1105</td>
<td>1079</td>
<td>1120</td>
<td>1068</td>
</tr>
<tr>
<td>Exp</td>
<td>1106</td>
<td>1304</td>
<td>1207</td>
<td>1106</td>
<td>1080</td>
<td>1121</td>
<td>1068</td>
</tr>
<tr>
<td>N</td>
<td>1147</td>
<td>1106</td>
<td>1105</td>
<td>1105</td>
<td>1105</td>
<td>1120</td>
<td>1068</td>
</tr>
<tr>
<td>A little</td>
<td>58%</td>
<td>60%</td>
<td>59%</td>
<td>60%</td>
<td>60%</td>
<td>59%</td>
<td>60%</td>
</tr>
<tr>
<td>Quite a bit</td>
<td>38%</td>
<td>35%</td>
<td>36%</td>
<td>36%</td>
<td>36%</td>
<td>36%</td>
<td>36%</td>
</tr>
<tr>
<td>Very much</td>
<td>8%</td>
<td>5%</td>
<td>8%</td>
<td>5%</td>
<td>5%</td>
<td>8%</td>
<td>5%</td>
</tr>
</tbody>
</table>

b. Provide a bar chart (example of QLQC30 item) for the distribution of change in response categories from baseline by arm per PRO assessment. Please include number of patients at each assessment for each arm in or below the bar chart.

![Bar chart showing distribution of change in response categories from baseline.]

<table>
<thead>
<tr>
<th>Visit</th>
<th>Vis 2</th>
<th>Vis 3</th>
<th>Vis 4</th>
<th>Vis 5</th>
<th>Vis 6</th>
<th>Vis 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl</td>
<td>1147</td>
<td>1106</td>
<td>1105</td>
<td>1105</td>
<td>1105</td>
<td>1120</td>
</tr>
<tr>
<td>Exp</td>
<td>1106</td>
<td>1304</td>
<td>1207</td>
<td>1106</td>
<td>1080</td>
<td>1121</td>
</tr>
<tr>
<td>N</td>
<td>1147</td>
<td>1106</td>
<td>1105</td>
<td>1105</td>
<td>1105</td>
<td>1120</td>
</tr>
<tr>
<td>Improved</td>
<td>9%</td>
<td>9%</td>
<td>11%</td>
<td>12%</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>Stable</td>
<td>48%</td>
<td>49%</td>
<td>53%</td>
<td>53%</td>
<td>59%</td>
<td>58%</td>
</tr>
<tr>
<td>Worsening 1 point</td>
<td>29%</td>
<td>28%</td>
<td>26%</td>
<td>25%</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>Worsening 2 points</td>
<td>13%</td>
<td>12%</td>
<td>8%</td>
<td>8%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Worsening 3 points</td>
<td>3%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Reference ID: 4191856
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/s/

CHARLENE N WHEELER
12/07/2017
Janssen Research & Development, LLC  
Attention: Jessica Chung  
Director, Global Regulatory Affairs  
920 U.S. Highway 202  
P.O. Box 300  
Raritan, NJ  08869

Dear Ms. Chung:

Please refer to your New Drug Application (NDA) dated October 9, 2017, received October 10, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Erleada® (apalutamide) oral tablets, 60 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. Therefore, the user fee goal date is April 10, 2018. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) VI (refer to: https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm. However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 10, 2018. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

Reference ID: 4191132
In addition, the planned date for our internal mid-cycle review meeting is December 20, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and PLLR Requirements for Prescribing Information 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 in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266
Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Charlene Wheeler, MSHS, Senior Regulatory Project Manager, at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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/s/

JULIA A BEAVER
12/06/2017
Hello Ms. Chung,

The purpose of this message is to provide you with a clinical and statistical information request for NDA 210951. Your response is requested by 12PM on Friday, December 8, 2017.

**Clinical IR:**
Although non-prespecified, please conduct the following subgroup analyses for BICR-assessed MFS, and OS-
1. Patients with baseline radiation or surgery for prostate cancer vs. those who did not undergo such therapy
2. Patients with local progression of disease on-study vs. others
3. Gleason score at baseline
4. PSA doubling time at additional cut-off’s, in addition to 6-month cut-off that was already performed

**Statistics IR:**
1. In the primary MFS analysis, some patients were censored with status listed as “still at risk, on treatment by cutoff” or “still at risk, discontinued treatment by cutoff”, but the censoring dates were earlier than 2017. Please provide clarification on the follow-up status for those patients that were censored early.

Please let me know if you have any questions.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
12/04/2017
NDA 210951

INFORMATION REQUEST

Janssen Biotech, Inc.
Attention: Jessica Chung
Director, Global Regulatory Affairs
920 U.S. Highway 202 P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

Please refer to your New Drug Application (NDA) received October 10, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for apalutamide, tablet, 60mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Manufacturing Drug Process:

1. Only one executed batch record (b)(4) for the six stability batches was submitted in the NDA (15LG2689x). Submit complete executed batch record for all six stability batches with accurate English translation as per 21CFR314.50(d)(1)(ii)(b) and 21CFR314.50(g)(2). The executed batch records should contain material dispensing record, operation parameters, and in-process testing results which should include specification, sampling plan, and testing results.

2. Provide a tabulated summary of all in-process testing results with acceptance criteria of all applicable unite operations of all registration batches, which includes, but not limited to:

3. You indicate that operation parameters are not needed for (b)(4) step due to lower risk of this step (3.2.P.2.3.4.6.3 and 3.2.P.3.3.1.6). We remind you that operation parameters should be specified in the master batch record for all unit operations. These parameters should be either a set point or range with lower and upper limit, supported by data collected from manufacturing of development and/or registration batches. Revise
your master batch record to include those parameters, or alternatively, provide this information with comparatively detailed descriptions in 3.2.P.3.3.

4. The following in-process testing should be performed at least through the initial stage of commercial manufacturing, as recommended by Guidance for Industry, Process validation: General Principles and practices:

Revise the master batch record and/or 3.2.P.3.4 accordingly.

5. You propose to

Revise the manufacturing flowchart as well as the master batch record and/or comparatively detailed descriptions in 3.2.P.3.3 to reflect this process change.

6. Provide reconciliation tables for all six exhibition batches including theoretical yield, maximum and minimum percentages of theoretical yield, and actual yield determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product, wherever is applicable. Provide justification for any significant waste and/or rejections and batch to batch variability.

7. Provide explanation/justification for the specify any waste/reject, identify any root cause and propose preventive measures.

8. The acceptance criterion for assay of is %, as listed in Application 210951 - Sequence 0002 - Specification DS-SPE-28401, while the range is % in Application 210951 - Sequence 0002 - COA A15ID2676. Clarify the difference.

9. Clarify which test method is used to determine the release testing. It is designated as method in 3.2.P.3.4.(specifications), but marked as method in 3.2.P.8.1.4.(stability test).

10. Indicate the actual time during tablet for your registration batches. Explain why this information is not recorded in your executed batch records. Revise your master batch record and/or 3.2.P.3.3 to include this operation perimeter.

11. Additional comments might be forthcoming as the review process proceeds.

Please respond to Manufacturing Drug Process comments by COB November 6, 2017.
Drug Product:
1. For the drug product specifications:
   (1) The data provided in your submission does not justify the proposed limits of NMT % for
       and NMT % for total degradants. Both specification limits to be consistent with the data provided in your submission.
   (2) Include testing for in stability testing.

2. Conduct forced degradation studies of Apalutamide drug product to demonstrate the UPLC method (DS-TMD-20128) is stability indicating and can capture all the potential degradation products if present. About 5-20% degradation should be achieved under different stress conditions. The Photostability testing should follow the conditions recommended in ICH Q1B.

3. For the container closure system for the commercial drug product:
   (1) You have presented two container closure systems in section 3.2.P.7, HDPE bottle and opaque blister. However, section 16 of Prescribing Information only describes HDPE bottle. Clarify if opaque blister will be used for marketing.
   (2) Explain why the count of tablets in opaque blister in stability study is different from that in the proposed carton labeling.
   (3) Provide mock up samples of drug product in the commercial container closure system(s).

4. finished drug product primary stability batches were made from Apalutamide drug substance batches manufactured by Provide stability data of drug substance batches manufactured by

5. The statement at the end of the section in 3.2.P.8.1 is confusing --- "Clearly state the storage conditions for including temperature range and humidity range.

Please respond to drug product comments by COB November 20, 2017.

If you have any questions, please contact me, Kristine Leahy, RPh., Regulatory Business Process Manager, at (240) 402-5834.

Sincerely,

Kristine F. Leahy -S
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 210951

INFORMATION REQUEST

Janssen Biotech, Inc.
Attention: Jessica Chung
Director, Global Regulatory Affairs
920 U.S. Highway 202 P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

Please refer to your New Drug Application (NDA) received October 10, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for apalutamide tablet 60mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Drug Product:**

1) We do not agree with the proposed acceptance criterion of % for in the drug product specification. Tighten the specification limit of Please provide your response by **COB Monday Dec 4, 2017.**

2) Provide revised 3.2.P.5.1, Specification(s) document in Module 3 by **COB Wednesday December 20, 2017.**

**Drug Substance:**

3) Clarify if your regulatory starting material specifications are able to distinguish .

4) Please comment on the M7 mutagenic class of and clarify if this potential process impurity can progress to the API.

Please response to Drug Substance comments by **COB December 20, 2017.**

**Environmental assessment:**

Please refer to CTD section 1.12.14, Environmental Analysis. FDA needs additional data to assist our review of your claim for a categorical exclusion from an environmental assessment.
(EA) under 21 CFR 25.31(b). This need is due to the relevance of apalutamide, an anti-androgen, to substances described in FDA’s guidance for substances with the potential for hormonal effects in the environment (USFDA, 2016). In particular, while the expected introduction concentration (EIC) for apalutamide of \( \mu g/L \) will be less than the 1 ppb (\( \mu g/L \)) exclusion level, a predicted no-effects concentration (PNEC) of less than \( \mu g/L \) appears possible based on another anti-androgen, cyproterone acetate (Kiparissis et al., 2003). While the expected environmental concentration (EEC) would be lower than the EIC due to metabolism, dilution, degradation, and other factors, thus lowering the likelihood of exceeding the PNEC, this would be offset by the uncertainties from the limited toxicity data set, reported insensitivity of current assays (e.g., OECD 230) to anti-androgens, and the potential for cumulative effects across all anti-androgens. Therefore, by **December 8, 2017**, provide (1) available information for determining a more realistic EEC (e.g., metabolism and environmental degradation data); (2) available information for assessing environmental effects for this or similar substances (e.g., aquatic toxicity assay data, “read across” results); and (3) any other available information relevant to assessing the environmental impact of this substance (e.g., environmental risk assessments, fish plasma model results such as those conducted by Nallani et al., 2016).

**References:**


If you have any questions, please contact me, Kristine Leahy, R.Ph., Regulatory Business Process Manager, at (240) 402-5834.

**Sincerely,**

Kristine F. Leahy -S

Kristine Leahy, R.Ph.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Ms. Chung,

The purpose of this email is to provide you with an information request for NDA 210951. Provide your response no later than November 13, 2017. Your initial response should be sent to me by email, followed by a formal submission to the application. Let me know if you have any questions.

Concerning the Biomarker Technical Report (TR2017T-018), please provide a dataset (.xpt format) keyed by unique subject and trial identifiers that includes columns for ARV7 status (at baseline and at first progression (MFS)), each AR point mutation (F877L, T878A, T878A, W742C, L702H, H875Y), AR amplification status, and the respective timing of sample acquisition. Provide justification as to how the threshold of 35 was determined for ARV7 expression (e.g., whether normal samples were used as reference).

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov

Reference ID: 4177237
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/s/

CHARLENE N WHEELER
11/06/2017
Hello Ms. Chung,

The purpose of this email is to provide you with an information request for NDA 210951. Submit model files used to generate final PBPK simulations in your PBPK reports (FK13005 and FK10644) including drug model files, population files, and workspace files (.cmp, .lbr, and .wks).

These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

Submit a sample worksheet to show how the ‘Active unbound fraction’ was calculated in your PBPK report (such as those reported in Table 9 in FK10644).

Submit your response by COB, Nov 6, 2017. Let me know if you have any questions.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
10/30/2017
Hello Ms. Chung,

The purpose of this email is to provide you with a statistical IR for NDA 210951. Please provide your response no later than October 31, 2017. Your initial response can be sent by email, followed by a formal submission to the application. Let me know if you have any questions.

Please submit all versions of the SAP of study SPARTAN with a summary of changes for each amendment.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
10/23/2017
PROPRIETARY NAME
ACKNOWLEDGEMENT

Janssen Biotech, Inc.
c/o Janssen Research and Development, LLC
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869

ATTENTION: Jessica Chung
Director, Global Regulatory Affairs

Dear Ms. Chung:

Please refer to your New Drug Application (NDA) dated October 9, 2017, received October 10, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apalutamide Tablets, 60 mg.

We acknowledge receipt of your correspondence dated and received on October 13, 2017, requesting a review of your proposed proprietary name, Erleada.

If the application is filed, the user fee goal date to review your proposed proprietary name will be January 11, 2018.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (301) 796-0942. For any other information regarding this application, contact Charlene Wheeler, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1141.

Sincerely,

[See appended electronic signature page]

Frances Fahnbulleh, PharmD, RPh
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Reference ID: 4170323
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/s/

FRANCES G FAHNBULLEH
10/20/2017
Dear Ms. Chung:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug: Erleada® (apalutamide) oral tablets, 60 mg

Date of Application: October 9, 2017

Date of Receipt: October 10, 2017

Our Reference Number: NDA 210951

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 9, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).
The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, call Charlene Wheeler, MSHS, Senior Regulatory Project Manager, at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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/s/

CHARLENE N WHEELER
10/16/2017
Hello Ms. Chung,

The purpose of this email is to provide you with a clinical inspection information request for NDA 210951. Please provide protocol Amendments 1-7, specifically showing the annotated changes to the protocol with justifications? Your response is requested no later than Monday, October 16, 2017. Let me know if you have any questions.

Regards,
Charlene Wheeler, MSHS
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-1141
Charlene.Wheeler@fda.hhs.gov
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/s/

CHARLENE N WHEELER
10/11/2017

Reference ID: 4165981
IND 104676

Janssen Research & Development, LLC
Attention: Nancy Micalizzi
Director, Global CMC Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Micalizzi:

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

We also refer to the meeting between representatives of your firm and the FDA on September 7, 2017. The purpose of the meeting was to seek feedback on the mechanistic modeling approach as amended and described in the May 8, 2017, amendment to IND 104676 (S/N 360), in advance of your original NDA submission.

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 Kristine Leahy, RPh., Regulatory Project Manager at (240) 402-5834.

Sincerely,

{See appended electronic signature page}

Paul Seo, Ph.D., Director
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Chemistry- Guidance
Meeting Date and Time: September 7, 2017 10:00 A.M.-11:30 A.M. Eastern Standard Time
Meeting Location: White Oak Building 22, Conference Room: 1415
Application Number: IND 104676
Product Name: Apalutamide 60 mg film-coated tablet
Indication: Non-metastatic castration-resistant prostate cancer
Sponsor Name: Janssen Research & Development, LLC

Meeting Chair: Paul Seo, Ph.D.
Meeting Recorder: Kristine Leahy, RPh.

FDA ATTENDEES
Xiao Hong Chen, Ph.D., Quality Assessment Lead (Acting), OPQ/ONDP Branch II
Paul Seo, Ph.D., Biopharmaceutics Director, OPQ/ONDP/DB
Angelica Dorantes, Ph.D., Biopharmaceutics Branch Chief, OPQ/ONDP/DBI
Okpo Eradiri, Ph.D., Biopharmaceutics Quality Assessment Lead, OPQ/ONDP/DBI
Gerlie Gieser, Ph.D., Biopharmaceutics Reviewer, OPQ/ONDP/DBI
Kimberly Raines, Ph.D., Branch Chief (Acting), OPQ/ONDP/DBIII
Banu Zolnik, Ph.D., Biopharmaceutics Reviewer, OPQ/ONDP/DBI
Yang Zhao, Ph.D., Biopharmaceutics Reviewer, OPQ/ONDP/DBI
Ho-Pi Lin, Ph.D., Biopharmaceutics Reviewer, OPQ/ONDP/DBIII
Min Li, Ph.D., Biopharmaceutics Quality Assessment Lead (Acting), OPQ/ONDP/DBIII
Daniel Suzman, MD., Medical Officer, OND/OHOP/DOP
Kristine Leahy, RPh., Regulatory Business Process Manager, OPQ/OPRO

SPONSOR ATTENDEES
Nancy Micalizzi, Director CMC Regulatory Affairs
Thomas Schultz, Ph.D., Sr. Director, CMC Regulatory Affairs, Reg. Sciences
Christophe Tistaert, Pharm.D., Ph.D., Sr. Scientist, Pharmaceutical Sciences, Preformulation & Biopharmaceutics
Arriana Friggei, Senior Manager, CMC Team Leader
Richard Klep, M.Sc. Associate Director, Analytical Development
Johannes Moes, Pharm.D., Ph.D., Sr. Scientist, Product Development Dissolution Sciences
Wouter Loos, Ph.D., Principal Scientist & Manufacturing Sciences, Drug Product Development & Manufacturing Sciences, Drug Product Development
IND 104676
Page 2

Claire Mackie, Ph. D., Scientific Director, Drug Product Development Biopharmaceutics
Filip Vanhoutte, Ph.D., Scientific Director, Pharmaceutical Sciences, Preformulation & Biopharmaceutics
Jens Ceuleman, Ph.D., Associate Director, Pharmaceutical Sciences, Preformulation & Biopharmaceutics

1.0 BACKGROUND

As follow up to the minutes of the December 6, 2016 Type C Meeting, at which the proposed dissolution test method and mechanistic modeling approach using Physiology-Based Pharmacokinetic Modeling and Simulation were discussed, Janssen submitted an amendment to IND 104676 on May 8, 2017, for FDA’s review and comment. The amendment included a revised interim Modeling & Simulations report, a modeling summary report, and data files comprising the modeling data base, which were provided in a CD-ROM.

The purpose of the meeting was for Janssen to present, discuss, and clarify issues on the mechanistic modeling approach as described in the May 8, 2017 amendment to IND 104676 (S/N 360), in advance of the original NDA submission, which was granted Fast Track Designation. The first portion of the rolling review for the initial NDA was planned for submission the week of September 11, 2017.

2.0 DISCUSSION

FDA Comments provided to the Applicant prior to the meeting

For the model demonstration meeting, FDA would like that you discuss the studies/models supporting the presence of \( b(4) \) in your proposed drug product. Specifically, we would like that you present the model building (conversion of z-factor dissolution model approach to the Johnson model combined with 2-step solubility approach) and its validation in a step-by-step manner. Please discuss in depth the two-step solubility model used as a workaround approach to differentiate the in vivo dissolution rates of \( b(4) \) This would be beneficial for a better understanding of your model.

Please be aware that in the model demonstration meeting, we will not provide an official response to your questions. Our responses will be provided at a later time, after we complete our evaluation of your proposed mechanistic absorption model.

FDA Responses to the Applicant Questions (Post-Meeting)

Question 1:
Does the information provided in the revised Interim Modeling and Simulations report (DS-TEC-979170) and in the Modeling Summary report (DS-TEC-105917) satisfactorily address the Agency’s responses i., ii., iii., iv., and v. to Question 2 as included in the official meeting minutes?

FDA Response to Question 1:

Reference ID: 4163994
The information provided in the revised Interim Modeling and Simulations Report and the Modeling Summary report appears to address the FDA’s comments i, ii, iii, iv, and v to Question 2 in the official meeting minutes dated January 6, 2017. However, the FDA’s determination on the adequacy of the data presented in the reports will be made during the NDA review.

Additionally, to expedite the review process, please address the following in your NDA submission:

a. It appears that the sensitivity of precipitation time in your models may change when the effective permeability (Peff) value reduces. Provide additional data/justifications that the Peff value in your model is adequate. Discuss worst case scenario (i.e. low Peff value) and how it will, or will not alter your conclusions.

b. It appears that simulated Tmax values for some of your models do not agree well with the observed mean data. Discuss the relevance and implications regarding these differences between the predicted and observed values.

c. Provide step-by-step illustrations about how variabilities were included in your population simulations and subsequent calculations for virtual bioequivalence studies and include the supporting files.

d. Provide a table comparing solubility values (model derived solubility and experimentally measured equilibrium solubility) for each of your tested formulations in (b) (4). Provide data for kinetic solubility within the absorption window. Provide a detailed description of the experimental procedures regarding the solubility measurements.

e. Provide the rationale for using FaSSIF in your current 2-step solubility approach.

f. Provide the experimental details for the study exploring the precipitation kinetics of supersaturated apalutamide in FaSSIF spiked with various amounts of (Figure 25 of your Interim Modeling and Simulations report).

g. In your modelling, the dissolution model was switched from z-factor model to Johnson model when simulating the human PK for formulations (b) (4). We suggest you further evaluate your model with the following approach:

   - Using in vitro dissolution data from different formulations with varying amount of (b) (4), to fit Z-factor, and then predict PK. Report the results for this approach, and if there is any difference in simulation results, please explain.

**Question 2:**
Does the information provided in the revised Interim Modeling and Simulations report (DS-TEC-979170) and in the Modeling Summary report (DS-TEC-105917) satisfactorily address the following Agency additional comments to Question 2a, as included in the official meeting minutes:

a. regarding calculation of the z-factor and its incorporation within the model?

b. regarding calculation of precipitation time, as required and applicable for -based solid oral formulations?

e. regarding the request for detailed information on the concentration set?

h. regarding the request for inclusion in the model of data showing both BE and lack of BE?
**FDA Response to Question 2:**
The mechanistic absorption model with respect to a, b, and e, appears to address the FDA’s additional comments to Question 2a. With respect to h, it was not fully addressed. The FDA’s determination on the adequacy of the model will be made during the NDA review.

Additionally, we request that you provide in a very detail manner the information and modeling steps used for the 2-step solubility approach in your NDA submission.

**Question 3:**
Does the additional information included in the 08 May 2017 IND amendment (S/N 0360) provide sufficient clarification on Janssen’s use of the Physiology-Based Dissolution test method as input to the Model?

**FDA Response to Question 3:**
The information included in the May 8, 2017 IND amendment, provides sufficient clarification on the use of PBDT test as input to the model.

**Question 4:**
Does the Agency agree that the scope of the testing performed to validate the PBDT method can provide sufficient information to address Agency comment j. to Question 2 as listed in the official meeting minutes?

**FDA Response to Question 4:**
It should be noted that Question 2 j refers to the full development and validation report of the PBDT method, discriminating ability of the PBDT method, and cross-validation with the proposed QC dissolution method. The provided PBDT method development and its discriminating ability appear to address the FDA’s comment to Question 2j. However, regarding the validation of the PBDT method and cross validation with the proposed QC dissolution method, we cannot address your question because your submission did not include sufficient information. Please include this information in your NDA submission.

**Question 5:**
Does the Agency agree, considering the changes incorporated into the interim Modeling and Simulations report, the provision of the Modeling Summary report as well as additional data outlined to validate the PBDT method, that the Model can be considered adequately validated?

**FDA Response to Question 5:**
The modeling approach appears to be reasonable. However, at this stage we cannot provide specific feedback on the adequacy of the validation of the model. This will be determined under the NDA.
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/s/

KRISTINE F LEAHY
10/05/2017

PAUL R SEO
10/05/2017
Aragon Pharmaceuticals  
c/o Janssen Research & Development, LLC  
Attention: Jessica Chung  
Director, Global Regulatory Affairs  
920 U.S. Highway 202, P.O. Box 300  
Raritan, NJ 08869

Dear Ms. Chung:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apalutamide (JNJ-56021927).

We also refer to your June 2, 2017, correspondence, received June 2, 2017, requesting a meeting to discuss the topline results from the ARN-509-003 study and contents of the NDA.

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, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

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

Sincerely,

Virginia E. Maher, MD  
Clinical Team Leader  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments
PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: September 18, 2017
Meeting Location: WO22 Room 1313
Application Number: IND 104676
Product Name: apalutamide (JNJ-56021927)
Indication: Non-metastatic castration resistant prostate cancer
Sponsor/Applicant Name: Aragon 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 September 18, 2017, 12:00 pm – 12:50 pm, Room 1313 between Aragon 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. 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

Apalutamide is a small molecule androgen receptor (AR) inhibitor studied in men with high-risk non-metastatic castration-resistant prostate cancer (NM-CRPC) in the SPARTAN trial (ARN-509-003). SPARTAN was a Phase 3, randomized, double-blind placebo-controlled trial of apalutamide plus androgen deprivation therapy (ADT) versus placebo plus ADT in 1207 men with high-risk NM-CRPC. High-risk was defined by a PSA doubling time of ≤10 months. The primary endpoint was metastasis-free survival (MFS). In a planned interim analysis of the study, there was an improvement in MFS for the apalutamide arm compared to the placebo arm (HR 0.28, 95% CI 0.23-0.35, p<0.0001). Additional secondary endpoints demonstrated statistically significant improvements, including time to metastasis (HR 0.27, p<0.0001), progression-free survival (HR 0.29, p<0.0001), and time to symptomatic progression (HR 0.45, p<0.0001). The study was immature for overall survival, however the HR was 0.70, p=0.07. Of note, the median overall survival of the placebo arm was only 39 months, indicating that high-risk NM-CRPC reflects a life-threatening disease with poor overall survival. Based on these results, the Independent Data Monitoring Committee (IDMC) recommended unblinding the study and all subjects randomized to placebo were offered apalutamide.

Reference ID: 4150519
The Sponsor now plans to submit an NDA for apalutamide. The Sponsor requested Fast Track designation for the apalutamide program for the treatment of patients with high-risk non-metastatic castration-resistant prostate cancer. This designation was granted on August 11, 2017.

2.0 DISCUSSION

Question 1

The Sponsor intends to submit a request for FDA acceptance of a rolling review for the NDA. To enable this, the Sponsor is submitting a Request for Fast Track Designation and is requesting an expedited review by the Agency. Also, the Sponsor is requesting a Priority Review Designation for the NDA. Does the Agency agree with this submission strategy?

Given the advice already provided regarding the above question during the informal August 4, 2017 teleconference, the Sponsor is kindly requesting preliminary comments from the FDA be returned to the Sponsor earlier than the typical timeframe for a meeting scheduled for September 18, 2017. If the FDA preliminary comments require no further discussion, the Sponsor will no longer need to have the meeting.

Sponsor Position:

Men with castration-resistant prostate cancer (CRPC) and a ‘rapidly rising’ prostate specific antigen (PSA) [PSA doubling time (PSADT) <10 months] are at the highest risk for developing imminent metastatic disease. Delaying metastases remains an important unmet medical need for men with a rapid PSADT and NM-CRPC. Although the first evidence of metastatic bone disease is often asymptomatic, if left untreated, most patients eventually develop skeletal-related events resulting in pain, ineffective hematopoiesis, and progressive complications that are difficult to treat. Delaying metastases for as long as possible is therefore, the ultimate goal of therapy in NM-CRPC.

There are no approved treatments for men with high-risk NM-CRPC. The National Comprehensive Cancer Network (NCCN) guidelines recommend regularly scheduled imaging for patients with NM-CRPC with a short PSADT. Despite the recommendation, clinicians are still not routinely monitoring high-risk patients with NM-CRPC, since frequent PSA monitoring induces stress and anxiety with no approved therapies to offer.

The results from Study ARN-509-003 provide compelling evidence of efficacy, representing a 72% reduction in the risk of distant metastases or death, supported by internal consistency from key secondary efficacy endpoints, including notably statistical significance for symptomatic progression (SymProg) and a strong trend for overall survival (OS). The magnitude of the clinical benefits observed balanced by the safety and tolerability profile support a favorable benefit-risk assessment. On July 28, 2017, the Sponsor sent a topline results report to the FDA which provided key efficacy and safety results from Study ARN-509-003 (results are also provided in Appendix 1).
Based on the unmet need in this setting and the results from Study ARN-509-003, the Sponsor proposed to submit a request for Fast Track Designation and a request for Rolling Review (in one submission) to the IND 104676. The FDA provided confirmatory advice on this proposal at the informal teleconference between the FDA and the Sponsor on August 4, 2017, that enabled the Sponsor to proceed with submitting these requests on August 9, 2017. It is further noted that based on the FDA comments/questions from the teleconference, the timelines for the rolling review submission, specifically for the Chemistry, Manufacturing, and Controls Modules 3 and the Office of Scientific Investigations request (Part I-III) have been assessed and accelerated earlier than initially proposed. This is reflected in the proposed rolling review submission schedule submitted along with request for Fast Track Designation to the IND 104676 on August 9, 2017.

The Sponsor also discussed the plan to request a Priority Review Designation for the NDA at the informal teleconference on August 4, 2017. The FDA provided feedback that based on the topline results, the data appear to satisfy the criteria for Priority Review, however the formal assessment will be a review issue when the NDA is submitted. The Sponsor will be requesting Priority Review Designation in the NDA.

**FDA Response:**

*Fast Track designation for the treatment of patients with high-risk non-metastatic castration-resistant prostate cancer was granted August 11, 2017. We agree with your proposal to request Priority Review. As you have noted, this determination will be made at the time of filing.*

**3.0 OTHER IMPORTANT MEETING INFORMATION**

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our June 9, 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:

**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 refusal 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 pedit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

**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 (PLL) (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 PLLR 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/ctd](http://www.fda.gov/ctd).

**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

Reference ID: 4150519
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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item&lt;sup&gt;1&lt;/sup&gt;</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
= m5
  = datasets
    = bimo
      = site-level
```

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.

<sup>1</sup> 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

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/

__________________________________________
AMY R TILLEY
09/08/2017

__________________________________________
VIRGINIA E MAHER
09/10/2017

Reference ID: 4150519
Yvonne, my apologies as I should have included you on the initial email since you stated yesterday that Jessica Chung was having IT issues.

Please confirm receipt of this email as it is time sensitive.

Thanks,
Amy Tilley

Jessica, the purpose of this email is to send you the following additional IR regarding your submission dated August 15, 2017, SN 385, concerning the apalutamide OSI information for Item I. We request your emailed response as soon as possible but no later than Wednesday, August 23, 2017, then follow up with an official response to the IND.

1. Identify who performed the BIRC function. We did not see this listed in the CRO listings provided.

2. Provide the BIRC Charter used in the conduct of the central review.

3. A GCP sponsor inspection may be conducted, however, it remains unclear what the location is where the "sponsor" inspection will take place. We want one location where the entire Trial Master File may be reviewed by FDA along with appropriate sponsor/CRO personnel to support this inspection.

4. Please confirm that you will include the investigator and BIRC efficacy data in the subject level datalists by site per the OSI Part 2 requests. This is necessary in order to support the clinical investigator site inspections and probable BIRC inspection.

Regards,
Amy R. Tilley
Regulatory Project Manager

Center for Drug Evaluation & Research
Office of Hematology Oncology Products
Division of Oncology Products 1
U.S. Food and Drug Administration
Tel: 301-796-3994
amy.tilley@fda.hhs.gov

Reference ID: 4141098
Dear Amy,

I would like to inform you that the apalutamide OSI information for Item I has been submitted today to the IND 104676 (s/n 0385).

Thank you.

Kind Regards,
Jessica

Jessica Chung
Director, Regulatory Affairs - Oncology
Janssen Research & Development, LLC
Phone: 908.927.2717
Cell: [redacted]
Fax: 908.526.5059
Email: jchung18@its.jnj.com
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------
AMY R TILLEY
08/17/2017
GRANT FAST TRACK ROLLING REVIEW

Aragon Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC.
Attention: Jessica Chung
Director, Global Regulatory Affairs
920 U.S. Highway 202 P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

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

We also refer to your August 9, 2017, request for Fast Track designation. We have reviewed your request and conclude that the required criteria have been met and are designating as a Fast Track development program the investigation of apalutamide for the treatment of patients with high-risk non-metastatic castration-resistant prostate cancer (NM-CRPC). We have also reviewed your request for submission of portions of the modules for review of your planned marketing application and find it acceptable.

If you pursue a clinical development program that does not support use of apalutamide for the treatment of patients with high-risk non-metastatic castration-resistant prostate cancer (NM-CRPC), the application will not be reviewed under the fast track drug development program and submission of sections of the marketing application will not be accepted under this program. For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry: Expedited Programs for Serious Conditions — Drugs and Biologics"¹. This document may be requested from the Office of Communications, Division of Drug Information at 301-796-3400 or 1-888-463-6332.


Reference ID: 4138460
If you have any questions, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Acting Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIA A BEAVER
08/11/2017
IND 104676

MEETING REQUEST-
WRITTEN RESPONSES

Aragon Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC
Attention: Jessica Chung
Director, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ARN-509, JNJ-56021927, and apalutamide.

We also refer to your submission dated May 5, 2017, containing a Type B Pre-NDA meeting request. The purpose of the requested meeting was to discuss the proposed format and content of a planned NDA in eCTD format.

Further reference is made to our Meeting Granted letter dated May 10, 2017, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 26, 2017, background package.

If you have any questions, contact Amy Tilley, Regulatory Project Manager at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

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

{See appended electronic signature page}

Virginia E. Maher, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses

Reference ID: 4116428
Meeting Type: Type B
Meeting Category: Pre-NDA WRO
Application Number: IND 104676
Product Name: apalutamide, ARN-509, and JNJ-56021927
Indication: prostate cancer
Sponsor/Applicant Name: Aragon Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Apalutamide (ARN-509) is a small molecule androgen receptor antagonist. The proposed current indication is for men with high-risk non-metastatic castration-resistant prostate cancer (NM-CRPC) using a dose of 240mg daily. The Sponsor plans to use ARN-509-003 (SPARTAN) to provide primary support for efficacy for this application. Study ARN-509-001, a Phase 1/2 study (N=107) will provide additional safety and efficacy support, while the Phase 1b study 56021927PCR1019 (N=45) will provide additional safety and QT data.

SPARTAN is a Phase 3, randomized, double-blind, placebo-controlled study of men with high-risk NM-CRPC that enrolled 1207 men who were randomized to apalutamide 240mg daily or placebo. High-risk was defined as PSADT ≤ 10 months. The primary endpoint was metastasis-free survival (MFS). This trial reached a Special Protocol Assessment (SPA) agreement based, in part, on recommendations from an Oncologic Drugs Advisory Committee (ODAC) meeting in September 2011 regarding the management of nmCRPC. It was agreed that MFS may be the basis of approval provided it was of sufficient magnitude and was supported by secondary endpoints, including overall survival. In March 2017, the Sponsor reported that there were projected to be only 77 death events as of the date of the analysis of the primary endpoint, as compared to 243 events that were projected at the time of the SAP design. The Sponsor planned to revise the SAP to perform the following hierarchical testing with alpha = 0.05 for each endpoint:

1. TTM
2. PFS
3. Symptomatic progression
4. OS
5. Time to cytotoxic chemotherapy

The Agency responded that the proposed amendment would invalidate the SPA as the agreement was based on internal consistency of secondary endpoints of known clinical value including overall survival. The Agency additionally responded that a large treatment
effect in MFS may be sufficient to allow review of the NDA for regular approval. The Sponsor chose to proceed with the proposed amendment and now requests a Type B meeting regarding format and content of a planned NDA.

2.0 QUESTIONS AND RESPONSES

Clinical Pharmacology and Chemistry, Manufacturing, and Controls (CMC)

Question 1

The Sponsor proposes to conduct 1) a population pharmacokinetic (PK) analysis to characterize the pharmacokinetics of apalutamide and its metabolite JNJ-56142060 following oral dosing, 2) an analysis to explore the relationship between apalutamide exposure and the effect on metastatic free survival, and 3) an analysis to explore the relationship between apalutamide exposure and selected safety endpoints in support of the NDA submission of apalutamide for the treatment of men with high-risk NM-CRPC. Does the Agency agree with the proposed analyses according to the analysis plans attached in Appendix 3 (Population PK) and Appendix 4 (Exposure-response)?

FDA Response: Your population PK and exposure-response analyses plans are generally acceptable. FDA has three recommendations for your consideration:

1. Include Studies 56021927PCR1018 and 56021927PCR1019, if appropriate, in the population PK analysis.
2. Include $C_{\text{max,ss}}$ in the exposure-response analysis.
3. If dose modification rate in Study ARN-509-003 is high, estimate exposure metrics based on the average daily dose up to the time of event or the end of treatment, whichever happens earlier.

Please refer the following submission guidelines for more information: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Question 2

The Sponsor proposes to place the mechanistic absorption modeling reports (used in support of the establishment of proposed clinically relevant specifications for the commercial apalutamide drug product) along with the physiologically based pharmacokinetic (PBPK)-model based reports, in Module 5.3.5.4 Other Study Reports. Does the Agency agree with this proposal?

FDA Response: Yes, your proposal to place the PBPK model based reports in Module 5.3.5.4 is acceptable.
Clinical and Statistics

Question 3

The Sponsor is proposing to submit a Summary of Clinical Safety (SCS) in Module 2.7.4 that will include an Integrated Summary of Safety (ISS) from 3 studies: the pivotal Phase 3 study (Study ARN-509-003), the supporting Phase 1/2 study (Study ARN-509-001), and the QT study (Study 56021927PCR1019). This integration will combine safety data from approximately 950 subjects who received daily doses of apalutamide (240 mg). An example of the proposed tabular format is presented below. Does the Agency agree with this proposal?

Table X: Grouping of Integrated Studies

<table>
<thead>
<tr>
<th>ARN-509-003</th>
<th>ARN-509-001</th>
<th>56021927PCR1019</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=400)(^1)</td>
<td>Apalutamide (N=800)(^1)</td>
<td>Apalutamide (N=100)</td>
<td>Apalutamide (N=45)</td>
</tr>
</tbody>
</table>

\(^1\) Subjects in blinded Study ARN-509-003 (N=1201; safety population) were randomized in a 2:1 ratio to receive apalutamide or placebo. Therefore, approximately 950 subjects in the integrated safety population received apalutamide.

**FDA Response:** Yes, your proposed format for the ISS is acceptable. You should include analyses across trials for safety events of interest including seizure and rash.

Question 4

Given the differences in the pivotal Phase 3 study (ARN-509-003) and Phase 1/2 Study (ARN-509-001), the Sponsor does not plan to include an Integrated Summary of Efficacy (ISE) in the submission. Full clinical study reports will be provided in Module 5 and further discussed in the Clinical Overview (Module 2.5) and in the Summary of Clinical Efficacy (Module 2.7.3). Does the Agency agree with this proposal?

**FDA Response:** Your proposal to not provide an ISE is acceptable.

Question 5

The Sponsor proposes to provide safety narratives for subjects from the pivotal Phase 3 study (ARN-509-003), the supporting Phase 1/2 study (ARN-509-001), and the QT study (56021927PCR1019) who meet the following criteria based on the safety follow-up schedules as defined in the protocols, i.e., within 28 days of last dose of study drug for Studies ARN-509-003 and ARN-509-001, and within 30 days of last dose of study drug for Study 56021927PCR1019:

1. Deaths
2. Treatment-emergent serious AEs
3. Treatment-emergent AEs that lead to treatment discontinuation
4. Treatment-emergent AEs of interest of seizure (any grade)
5. Other treatment-emergent AEs of interest including rash, fractures, fall, and hypothyroidism (grade 3 or higher)
Does the Agency agree with this proposal?

**FDA Response:** Your proposal is acceptable.

**Question 6**

The Sponsor proposes to provide Case Report Forms only for subjects whose narratives are included in the submission. Does the Agency agree with this proposal?

**FDA Response:** Your proposal is acceptable. However, the Agency may request additional CRFs during our review.

**Question 7**

The Sponsor proposes to submit Case Report Tabulations in Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) format (version 3.1.2 or higher) and the analysis datasets in CDISC Analysis Data Model (ADaM) format for the pivotal Phase 3 study (ARN-509-003) only. The Sponsor also proposes to submit the analysis datasets in CDISC ADaM format for the integrated safety data from Studies ARN-509-003, ARN-509-001, and 56021927PCR1019 that support the Summary of Clinical Safety. Does the Agency agree with this proposal?

**FDA Response:** Your proposal is acceptable.

**Question 8**

The Sponsor proposes to use Medical Dictionary for Regulatory Activities Version 19.1 for AEs for the pivotal Phase 3 study (Study ARN-509-003) and the integrated safety data from Studies ARN-509-003, ARN-509-001, and 56021927PCR1019 that support the Summary of Clinical Safety. Does the Agency agree with this proposal?

**FDA Response:** Your proposal is acceptable.

**Question 9**

For the 120-day safety update, the Sponsor proposes to provide an update only for the pivotal Phase 3 Study ARN-509-003 (N=1,201). The cutoff date for the safety update will occur approximately 120 days after the cutoff date of the interim analysis for Study ARN-509-003. Does the Agency agree with this proposal?

**FDA Response:** Your proposal is acceptable.
Regulatory

Question 10

The Sponsor proposes to provide (1) Financial Certification and/or Disclosure information (Form FDA 3454/3455) and (2) the list of principal investigators only for investigators who participated in the pivotal Phase 3 Study (ARN-509-003). (The list of investigators will contain the investigator’s name, address, phone number, and number of subjects enrolled.) Does the Agency agree with this proposal?

FDA Response: Please include the investigator’s e-mail address and fax number. Please see the Office of Scientific Investigation Requests below concerning the data to be submitted.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 10, 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:

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.


**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 (PLL) (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.

**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."

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

- [m5]
  - datasets
    - bimo
      - site-level

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:  

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/

AMY R TILLEY
06/26/2017

VIRGINIA E MAHER
06/26/2017

Reference ID: 4116428
Dear Ms. Chung:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apalutamide (JNJ-56021927).

We also refer to your November 5, 2012, request, received on November 6, 2012, for a special protocol assessment of clinical protocol and to our June 30, 2016, agreement modification letter. The protocol ARN-509-0003 is titled “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer”.

The agreement on this protocol is no longer binding because a substantial scientific issue essential to determining the benefit-risk profile of the drug has been identified after our assessment of this protocol. The initial SPA was predicated on the conduct of a well-designed, well-conducted, internally consistent trial that provides statistically and clinically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. The use of metastasis-free survival as a primary endpoint for non-metastatic castration-resistant prostate cancer is novel and confidence in the meaningfulness of a difference in metastasis-free survival was to be supported by strong consistency in secondary endpoints, particularly overall survival. Thus, the changes to the use of supportive secondary endpoints are sufficiently large as to invalidate the prior SPA Agreement.

If you wish to discuss this issue, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the “Guidance for Industry; Formal Meetings with Sponsors and Applicants for PDUFA Products”. This meeting would be limited to discussion of this protocol.

Reference ID: 4093772
If you have any questions, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Acting Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIA A BEAVER
05/04/2017
IND 104676

MEETING MINUTES

Janssen Research & Development, LLC
Attention: Jessica Chung
Director, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apalutamide (INN-56021927).

We also refer to the meeting between representatives of your firm and the FDA on February 24, 2017. The purpose of the meeting was to discuss 1) the clinical efficacy profile necessary to unblind Study ARN-509-003 and enable review of an NDA submission and 2) the proposed revisions to the Statistical Analysis Plan (SAP).

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, contact Amy Tilley, Regulatory Project Manager at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

(See appended electronic signature page)

Virginia Maher, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 4072716
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Guidance

Meeting Date and Time: February 24, 2107
Meeting Location: Virtual via Email

Application Number: IND 104676
Product Name: Apalutamide (JNJ-56021927)
Indication: Non-metastatic castration-resistant prostate cancer
Sponsor/Applicant Name: Janssen Research & Development, LLC

Meeting Chair: Virginia Maher, MD, Clinical Team Leader
Meeting Recorder: Amy Tilley, Regulatory Project Manager

FDA ATTENDEES
Paul Kluetz, MD, Associate Director for Clinical Science, OHOP
Geoffrey Kim, MD, Director, DOP1
Julia Beaver, MD, Associate Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Virginia Maher, MD, Clinical Team Leader, DOP1
Daniel Suzman, MD, Clinical Reviewer, DOP1
Bindu Kanapuru, MD, Clinical Reviewer, DHP
Shenghui Tang, PhD, Biostatistics Team Leader
Lijun Zhang, PhD, Biostatistics Reviewer
Amy Tilley, Regulatory Project Manager

SPONSOR ATTENDEES
Margaret Yu, Senior Director, Clinical Leader
Angela Lopez-Giltz, Director, Study Responsible Physician
Leon Freytor, Senior Director, Global Regulatory Leader
Jessica Chung, Director, North American Regulatory Leader
Thian Kheoh, Senior Director, Biostatistics Leader
Youyi Shu, Director, Study Statistician
Mary Guckert, Senior Director, Compound Development Team Leader
Kiran Patel, Vice President, Clinical Development, Solid Tumor
Peter Lebowitz, Global Therapeutic Head Oncology

Reference ID: 4072716
1.0 BACKGROUND

ARN-509 is a small molecule androgen receptor antagonist that is currently being evaluated in the ARN-509-003 (SPARTAN) trial of men with high-risk (as defined by PSADT <10 months) non-metastatic castration-resistant prostate cancer (nmCRPC). This trial reached a Special Protocol Assessment (SPA) agreement based, in part, on recommendations from an Oncologic Drugs Advisory Committee (ODAC) meeting on September 14, 2011, regarding the management of nmCRPC. It was agreed that metastasis-free survival (MFS) may be the basis of approval provided it was of sufficient magnitude and was supported by secondary endpoints. The trial was powered to detect an 11 month difference in MFS with 90% power. The current SPA provides for the following testing of secondary endpoints.

1. Group 1, \( \alpha = 0.01 \) with each component tested at 0.025
   a. Time to symptomatic progression
   b. Time to initiation of cytotoxic chemotherapy
   c. Radiographic progression-free survival (rPFS)
   d. Time to metastases (TTM)

2. Group 2, \( \alpha = 0.04 \)
   a. Overall survival (OS)

The Sponsor now reports that the SPARTAN trial has fully enrolled as of December 14, 2016, and that the primary analysis of the primary endpoint (MFS) at the pre-specified 372 events is projected to occur in May 2017. However, there are projected to only be 77 death events, as compared to the 243 events that were projected at the time of the SAP design. The Sponsor notes a similar delay in the time to symptomatic disease endpoint. The Sponsor attributes this to the large increase in the availability of effective therapy with symptomatic and survival benefits that occurred during and after the design of the SPARTAN trial. The Sponsor thus proposes that hierarchical testing instead be performed in the following order, each at \( \alpha = 0.05 \):

1. TTM
2. PFS
3. Symptomatic progression
4. OS
5. Time to cytotoxic chemotherapy

There would be no interim analysis for TTM or PFS, but there would be one interim analysis of symptomatic progression and two interim analyses of OS and time to cytotoxic chemotherapy.

2.0 DISCUSSION

Question 1:

References are made to the February 29, 2012, End-of-Phase 2 meeting, November 9, 2012, Special Protocol Assessment Letter for the ARN-509-003 study, the December 17, 2013, Type C Meeting minutes, and the April 30, 2014 Special Protocol Modification Agreement Assessment Letter (see Appendix 1). During those discussions, the Agency agreed that this single Phase 3 study (ARN-509-003) could support registration of apalutamide for the treatment of men with high-risk NM-CRPC if the magnitude of benefit for the primary endpoint, MFS, is substantially large and the internal consistency and strength of the secondary endpoints are demonstrated.

The treatment landscape for prostate cancer has evolved since the start of Study ARN-509-003. Evidence of the importance of delaying metastasis has emerged, and the challenge of achieving statistical significance in late endpoints (e.g., SymProg and OS) due to the use of effective therapies for metastatic disease has led to further reliance on endpoints like MFS in studies of early prostate cancer. The Sponsor is proposing that a compelling treatment effect in MFS, and an acceptable safety and tolerability profile, will be sufficient to enable the review of the NDA for regular approval in this patient population with unmet medical need.

Does the Agency agree with the proposal?

Sponsor Position:

While MFS is a novel endpoint, delaying progression to metastatic disease is a clinically meaningful endpoint in patients with high-risk early prostate cancer. Using data obtained from United States Surveillance, Epidemiology, and End Results (SEER) cancer registry, patients diagnosed with loco-regional disease who developed metastasis had a significantly higher mortality compared with age-matched controls (HR=4.6, 95% CI: 4.4, 4.7; p<0.0001). In addition, Xie (ESMO 2016) presented data from a meta-analysis of 19 studies in the localized disease setting, showing MFS is highly correlated with OS and could be considered a surrogate for OS. Taken together, these data reinforce the clinical meaning of delaying development of metastatic disease in patients with prostate cancer and point to MFS as a surrogate for other later disease endpoints.

As mentioned previously in Section 5, at the time of the primary analysis of MFS (pre-specified 372 events), fully mature data for 3 of the 5 secondary endpoints is unlikely. The Sponsor has the following explanations for the discordant timing between the maturity of the primary and the secondary endpoints.

Limited data were available for making statistical assumptions for the key secondary endpoints such as OS, in the high-risk NM-CRPC setting at the time the study was designed. Assumptions around the time to development of metastatic disease in the high-risk NM-CRPC population came primarily from a study of bone-targeted therapy (denosumab). The denosumab study
started in February 2006 and the completion date for the primary analysis was July 2010 (NCT0028609). Since that time, life-prolonging therapies (e.g., ZYTIGA® [abiraterone acetate], Xtandi® [enzalutamide], and PROVENGE® [sipuleucel-T]) have become readily available to patients after development of metastatic CRPC (mCRPC). In addition, subjects on the ARN-509-003 study are undergoing imaging evaluations every 4 months, so the detection of metastasis (and the start of subsequent therapy) is likely to occur earlier in the course of their disease. By comparison, nearly half of the subjects with mCRPC who were enrolled in the placebo-controlled Phase 3 study with ZYTIGA plus prednisone (Study COU-AA-302) had more than 10 bone lesions at study entry (Ryan 2013, supplemental appendix). Early treatment when the disease burden is less may render these life-prolonging therapies even more efficacious, leading to delay in achieving a sufficient number of events in SymProg and OS.

Based on ongoing review of blinded data on subjects who have documented metastasis in Study ARN-509-003, 79% are receiving subsequent therapy (abiraterone acetate, docetaxel, enzalutamide or sipuleucel-T). Most of these subjects (68%) received subsequent therapy within 30 days of withdrawal of study treatment. As was previously discussed with the Agency, on-label abiraterone acetate has been made available to subjects on Study ARN-509-003 after development of metastatic disease. As a result, it is expected that the secondary endpoints of SymProg, OS, and CytoChemo will mature much later (please refer to Question 2). Furthermore, as described by Brogliò et al (2009), as the duration of survival post-progression increases, the treatment effect on OS is diluted making it more challenging to show statistical significance. Thus, waiting for additional events to occur might not be sufficient to overcome confounding effects from multiple lines of life-prolonging therapy.

Importantly, ongoing review of the blinded safety and tolerability profile of apalutamide/placebo on Study ARN-509-003 appears favorable. The following summary is based on data from a recent cutoff December 19, 2016 (except for details on rash where the cutoff was September 27, 2016):

- The most common treatment-emergent adverse events (TEAEs) were under the system organ class of Gastrointestinal Disorders and were generally mild.
- Discontinuation due to treatment-related TEAEs was reported in 5% of subjects.
- Rashes of varying grades, often described as maculopapular, were in approximately 15% of subjects, with fewer than 5% of subjects experiencing a Grade 3 rash. These events were primarily managed with drug interruptions, topical steroids, and systemic antihistamines. Of the subjects who experienced a TEAE of rash, 9% discontinued treatment due to rash. Of subjects who were re-challenged after drug interruption, 4% experienced a recurrence of rash.
- Fracture was noted in 6% of subjects overall. However, the Independent Data Monitoring Committee (IDMC) noted an imbalance in fracture risk, and fracture has been
incorporated as an adverse drug reaction in the Investigator’s Brochure. Fractures were associated with an antecedent fall in 55% of these subjects.

- As a possible class effect, seizures are being monitored closely. Two subjects experienced a seizure on Study ARN-509-003. One subject had a seizure that was associated with a fall and significant head trauma. The event was assessed as not related to study drug by the investigator. The second subject who experienced a seizure was found retrospectively to have had a history of febrile seizures.

- Across other apalutamide studies (approximately 3,300 subjects treated), an additional 3 subjects (2 in blinded studies and 1 in an open-label study) have experienced a seizure.

- Deaths due to a TEAE were reported in 0.8% of subjects.

- Overall tolerability is high, with 93% of subjects having had no dose reductions and 78% of subjects having had no dose interruptions.

Delaying metastases remains an important unmet medical need for men with a short PSA doubling time and NM-CRPC. Although the first evidence of metastatic bone disease is often asymptomatic, if left untreated, most patients eventually develop skeletal-related events resulting in pain, ineffective hematopoiesis and progressive complications that are difficult to treat. Therapeutic agents with a large magnitude of benefit on MFS could provide clinical benefit to this patient population.

In conclusion, the data from SEER and Xie reinforce the clinical impact of delaying development of metastatic disease in patients with prostate cancer and justify the use of MFS as a valid surrogate endpoint for overall survival. Additionally, the delay in reaching sufficient events may make OS so confounded by subsequent therapies that a trend will be difficult to observe. Waiting for several years significantly delays the availability of apalutamide, a treatment option for a patient population with an unmet need for whom there is no approved therapy. The Sponsor is proposing that a compelling treatment effect in MFS and an acceptable safety and tolerability profile will be sufficient to enable the review of the NDA for regular approval.

**FDA Response:** A large treatment effect in MFS may be sufficient to allow review of the NDA for regular approval. The decision regarding this proposal will be at your risk. We note that without internal consistency and the strength of the secondary endpoints, the treatment effect on MFS will need to be large to allow confidence in the clinical benefit of apalutamide. We further note that with a small number of death events, there is a risk that due to chance, OS may be worse in patients treated with apalutamide. This risk may be mitigated by allowing for greater maturity of the OS endpoint.
Sponsor Response Q1:

We acknowledge FDA's response.

Meeting Discussion: None

Question 2:

Based on the blinded review of the accumulated events, the Sponsor recently projected that the primary analysis of the MFS endpoint (372 events) will mature in May 2017. However, the secondary endpoints will be at varying stages of maturity when 372 MFS events are reached. While the secondary endpoints of TTM and PFS should track closely with MFS, SymProg, OS, and CytoChemo are unlikely to be mature and are expected to lag behind by several years.

The Sponsor proposes to revise the multiple testing procedure for the secondary endpoints because of the differences in maturations of the secondary endpoints. A hierarchical testing will be performed in the following order: TTM, PFS, SymProg, OS, and CytoChemo, each at alpha=0.05 (2-sided). The testing of SymProg will utilize an adaptive group sequential method, according to the pre-specified O'Brient-Fleming (OBF)-type alpha spending function with possible re-estimation of the required number of events necessary for the next analysis to maintain the desired conditional power. If the testing of SymProg is significant, then OS will be tested similarly using an adaptive group sequential method, followed by testing for CytoChemo.

Does the Agency agree with the testing procedure outlined above?

Sponsor Position:

The primary endpoint of the ARN-509-003 study is MFS. The protocol states that the required number of MFS events is 372 in order to have 90% power to detect an HR of 0.7 at alpha=0.05 (2-sided). The protocol further states that the secondary endpoints will be analyzed at the time of the primary analysis. The secondary endpoints will be subdivided into 2 groups (Group 1: SymProg, CytoChemo, PFS, TTM; Group 2: OS). The statistical testing of the 2 groups will be performed by allocating 0.01 to Group 1 and 0.04 to Group 2 with an overall familywise type I error rate of 0.05.

In the current statistical analysis plan, a Bonferroni procedure will be used to test each of the 4 endpoints in Group 1 at an alpha of 0.0025 (with an overall alpha of 0.01). A group sequential test is planned for the OS endpoint in Group 2 with 2 interim analyses (IAs) and 1 final analysis (FA) utilizing the OBF-type alpha spending function with an overall alpha of 0.04 + g x 0.0025, where g is the number of rejected null hypotheses in Group 1.

At the design stage of the ARN-509-003 study, it was anticipated that by the time of the primary analysis of MFS (i.e., when reaching 372 MFS events), approximately 243 (46% of the maximum number of required) death events would have occurred. Based on the accumulated events in the blinded database as of January 12, 2017, the Sponsor projects that the primary
analysis of the MFS endpoint (372 events) will mature in May 2017, as illustrated in Table 1 and Figure 2.

However, the secondary endpoints will be at varying stages of maturity when 372 MFS events are reached; see Table 1. Based on current projections, events for OS, SymProg, and CytoChemo will lag behind by several years. For each of the 3 endpoints (OS, SymProg, and CytoChemo), assuming HR = 0.75, the required number of events to yield 80% power are 427 (at alpha level 0.05) and 246 (at alpha level 0.2). Figures 3 to 5 provide a projection of the timing to reach 246 and 427 events for OS, SymProg, and CytoChemo, respectively. For example, Figure 3 provides a projection that 246 OS events may not occur until the year 2022 and 427 OS events may not occur until the year 2032. Figure 4 suggests that 246 SymProg events may not occur until the year 2020 and 427 events may not occur until the year 2029.

Figure 2: Projected Number of MFS Events Over Time
Table 1: Observed and Projected Number of Events at Different Clinical Cutoff Dates

<table>
<thead>
<tr>
<th>Endpoint†</th>
<th>Observed Number of Events as of Jan 12, 2017</th>
<th>Predicted Number of Events at Clinical Cutoff of</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>May 05, 2017</td>
<td>Nov 04, 2017</td>
</tr>
<tr>
<td>MFS</td>
<td>297</td>
<td>372</td>
<td>445</td>
</tr>
<tr>
<td>TTM</td>
<td>288</td>
<td>361</td>
<td>432</td>
</tr>
<tr>
<td>PFS</td>
<td>315</td>
<td>394</td>
<td>470</td>
</tr>
<tr>
<td>SymProg</td>
<td>78</td>
<td>100</td>
<td>125</td>
</tr>
<tr>
<td>OS</td>
<td>60</td>
<td>77</td>
<td>96</td>
</tr>
<tr>
<td>CytoChemo</td>
<td>52</td>
<td>66</td>
<td>82</td>
</tr>
</tbody>
</table>

† MFS: metastasis-free survival; TTM: time to metastasis; PFS: progression-free survival; SymProg: time to symptomatic progression; OS: overall survival; CytoChemo: time to cytotoxic chemotherapy

From the last 2 columns of Table 1, even if the Sponsor delays the MFS analysis by 6 months or 12 months from May 2017, the number of events for OS, SymProg, and CytoChemo will continue to lag behind even for a meaningful IA at the time of the primary analysis of MFS. Figure 3, Figure 4, and Figure 5 show the projected number of events for the 3 endpoints indicating that the study could continue for many more years in order to accumulate more events.
**Figure 3: Projected Number of OS Events Over Time**

![Graph showing the projected number of OS events over time with observed and predicted data points, along with 95% pointwise CI.]

**Figure 4: Projected Number of SymProg Events Over Time**

![Graph showing the projected number of SymProg events over time with observed and predicted data points, along with 95% pointwise CI.]

Reference ID: 4072716
Figure 5: Projected Number of CytoChemo Events Over Time

The Bonferroni-type procedure with alpha=0.0025 (2-sided) for testing each of the secondary endpoints in Group 1 as detailed in the current statistical analysis plan lacks power given the projected low event rates particularly for the slow maturing endpoints like SymProg and CytoChemo. Therefore, the Sponsor proposes to revise the multiple testing procedure for the secondary endpoints (Figure 6). The method allows re-estimation of the number of events necessary for the next best opportunity to achieve the desired conditional power. The method controls the familywise type I error rate for the primary and all key secondary endpoints.

A hierarchical testing will be performed in the following order: TTM, PFS, SymProg, OS, and CytoChemo, each at alpha=0.05 (2-sided). As depicted in Figure 6, each endpoint will have a FA but there will be no IA for TTM and PFS, 1 IA for SymProg, and up to 2 IAs for OS and CytoChemo. The testing of SymProg, OS and CytoChemo endpoints will utilize an adaptive group sequential method, according to the pre-specified OBF-type alpha spending function with possible re-estimation of the required number of events necessary for the next analysis to maintain the desired conditional power. If SymProg is significant at the IA, then there will be only 1 IA for OS and CytoChemo (ie, with “IA #2” boxes removed from Figure 6); otherwise there will be 2 IAs for OS and CytoChemo.
The FA of TTM and PFS, IA of SymProg, and the first IAs of OS and CytoChemo will all be performed at the same time as the primary analysis of MFS (372 events).

Assuming that the primary test for MFS is significant at alpha=0.05, TTM will then be tested at alpha=0.05. If significant, then PFS will be tested at alpha=0.05. If PFS is significant, then the Sponsor will perform the IA for SymProg. As mentioned above, for SymProg, assuming HR=0.75, 427 events are required to yield 80% power at alpha=0.05. From Table 1, it is projected that approximately 100 SymProg events will have accumulated at the IA for SymProg, and the information fraction would be approximately \( t = \frac{100}{427} = 0.234 \). The actual information fraction will be used at the time of the analysis and the alpha spend will be adjusted accordingly. Efficacy of SymProg will be concluded if the stratified log-rank test statistic exceeds the critical value derived from the OBF-type alpha spending function.

The SymProg events re-estimation will be based on a conditional power of 90% for the next stage, calculated using the observed treatment effect (hazard ratio). Note that because of the variability associated with the observed hazard ratio, a conditional power of 90% is used in order
to maintain an overall power of approximately 80% if the true hazard ratio is 0.75. The recommended number of SymProg events for the FA should be in the range of 191 (additional 91 events set as the minimum required for the next stage) to 460 (not more than 10% increase on the pre-planned number of events for the next stage). Because the true HR for SymProg is unknown, the minimum number of 191 is chosen to yield at least 80% power to detect an HR of 0.65 at an alpha level of 0.05.

The SymProg events re-estimation will be performed by the independent statistician who supports the IDMC activities. The dissemination and review of the specific results of the IA will be limited to the IDMC. The decision on whether or not to stop the study for efficacy will be made by the IDMC in conjunction with the Sponsor Committee (a small group of Senior Management personnel [Clinician and Statistician] from the Sponsor who have no day-to-day study operation responsibilities).

In order to maintain a strong control of the type I error rate for the SymProg analysis, an inverse normal p-value combination method will be used as the final test. The inverse normal p-value combination method allows flexible adaptations at an IA and creates a valid test that controls the type I error rate in a strong sense analytically. In this proposed design the adaptation is the potential adjustment of the required number of events for the next stage.

The final test statistics for the null hypothesis $H_0$: HR for SymProg $\geq 1$ is defined as

$$Z = w_1 F^{-1}(1 - p_1) + w_2 F^{-1}(1 - p_2),$$

where $F^{-1}(x)$ is the inverse of the standard normal cumulative distribution function, $w_1 = \sqrt{t}$, $w_2 = \sqrt{1 - t}$, $p_1$ denotes the first stage p-value and $p_2$ denotes the second stage p-value.

Critical values for success are calculated based on the OBF-type alpha spending function. The study may be stopped early for efficacy if the interim test statistic exceeds the first stage critical value $z_1$, or stops for success at the second stage, if the final test statistic exceeds the second stage critical value $z_2$. Therefore, the null hypothesis $H_0$ will be rejected either at the first analysis if $F^{-1}(1 - p_1) > z_1$, or at the FA if $Z > z_2$.

The adaptive group sequential testing of OS and CytoChemo will be similar to that of SymProg as described above, except that there is a possibility of 1 more IA to incorporate in the inverse normal p-value combination method. Due to the hierarchical structure of the testing procedure, an outline of some additional technical details is provided in Appendix 2.
**FDA Response:** The proposed change to the testing procedure is acceptable. See response to Question 1 regarding our concern about the strength of the secondary endpoints and their impact on the evaluation of the primary endpoint.

An analysis of overall survival should be conducted at the time of the MFS analysis with an allocation of a small alpha (type-1 error). Any suggestion of a detrimental effect on survival would be a major approvability concern. Please revise the hierarchical testing procedure to reflect the small alpha allocated for the OS analysis at the time of the MFS analysis. Please note that the inclusion of secondary endpoints in labeling will be a review issue and that statistical significance may not be sufficient for inclusion in labeling.

**Sponsor Emailed Response 02:**

We acknowledge FDA's response. We have the following clarification question which we would like to further discuss with the Agency at the meeting.

At the time of the MFS analysis, all secondary endpoints will be analyzed for the Independent Data Monitoring Committee; estimates will be available to enable an assessment of the effect on OS before a formal unblinding. The Sponsor would like to clarify it is inherent in the testing method that alpha allocation for the OS endpoint is required regardless of the significance of the symptomatic progression endpoint. The O'Brien-Fleming-type spending function does allocate alpha at the time of the interim analysis of OS. Does this address the recommendation from the Agency that a small alpha be allocated at the time of the MFS analysis?

**FDA Emailed Response:** Figure 6 shows that the OS interim analysis #1 will be conducted only if the symptomatic progression is significant. The analysis of OS should be conducted regardless of the results of the analysis of symptomatic progression. You should allocate a small amount of alpha for the analysis of OS at the time of the analysis of MFS.

You should provide detailed information on how you will allocate alpha for all your interim analyses in a revised statistical analysis plan.

**Sponsor Emailed Response:** We agree with the Agency's response. We will include the detailed information on how we will allocate alpha for OS interim analysis #1 in the revised statistical analysis plan (SAP).

We plan to submit the agreed-upon changes from this interaction for the protocol and SAP as a protocol amendment and SPA amendment to the IND. We respectfully request the Agency to review the changes as soon as possible.

As a result, we will not need to meet with the Agency today.
Question 3:

Symptomatic progression in Study ARN-509-003 is currently defined as the time from randomization to documentation in the case report form of any of the following (whichever occurs earlier) + 1 day:

- Development of a skeletal-related event (SRE): pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy to the bone

- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy

- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

Does the Agency agree with the proposed addition?

Sponsor Position:
FDA Response: No. (b)(4) is not an accepted marker of symptomatic progression. One concern is that the additional patients you capture by adding this measure to the symptomatic progression composite endpoint may largely include the patients who are not followed by the study site. (b)(4) is likely to be less robust in these patients and may cause the symptomatic progression endpoint to be less interpretable.

Sponsor Response Q3:

We acknowledge FDA’s response.

Meeting Discussion: None

Additional Comments:

1. Indicate the median PSADT among the enrolled patients.

   Sponsor Response Additional Comment 1:

   We acknowledge FDA’s response. The median PSADT among the enrolled and randomized patients is 4.4 months. This analysis is based on pooled data (as of February 16, 2017) from the two treatment arms of the blinded study.

2. If available, provide data regarding duration of subsequent therapy in the two arms.

   Sponsor Response Additional Comment 2:

   We acknowledge FDA’s response. The information will be made available within the clinical study report.

3.0 OTHER IMPORTANT MEETING LANGUAGE INFORMATION

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:
CM360507.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:
m.

4.0  ISSUES REQUIRING FURTHER DISCUSSION

None

5.0  ACTION ITEMS

None

6.0  ATTACHMENTS AND HANDOUTS

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIRGINIA E MAHER
03/21/2017

Reference ID: 4072716
IND 104676

Janssen Research & Development, LLC
Attention: Jessica Chung
Director, Regulatory Affairs, Oncology
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

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

We also refer to the meeting between representatives of your firm and the FDA on December 6, 2016. The purpose of the meeting was to discuss the proposed dissolution test method and mechanic absorption modeling approach using Physiology-Based Pharmacokinetic Modeling and Simulation.

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, Kristine Leahy, RPh., Regulatory Business Process Manager, at (240) 402-5834.

Sincerely,

(See appended electronic signature page)

Anamitra Banerjee, Ph.D.
Branch Chief (Acting), Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: CMC-only

Meeting Date and Time: December 6, 2016, 11:00A.M. – 12:00P.M. EST
Meeting Location: White Oak Building 22, Room 1311

Application Number: IND 104676
Product Name: Apalutamide 60mg tablet
Indication: Treatment of patients with high-risk, non-metastatic castration-resistant prostate cancer (NM CRPC).

Sponsor Name: Janssen Research & Development, LLC

Meeting Chair: Anamitro Banerjee
Meeting Recorder: Kristine Leahy

FDA ATTENDEES
Anamitro Banerjee, Ph.D., Branch Chief (Acting), OPQ/ONDP Branch II
Xiao Hong Chen, Ph.D., Quality Assessment Lead (Acting), OPQ/ONDP Branch II
Gerlie Gieser, Ph.D., Biopharmaceutics Reviewer, OPQ/ONDP
Sandra Suarez, Master Biopharmaceutics Reviewer, OPQ/ONDP
Meng Wang, Biopharmaceutics Reviewer, OPQ/ONDP
Kristine Leahy, RPh., Regulatory Business Process Manager, OPQ/OPRO

SPONSOR ATTENDEES
Leon Freytor, Sr. Director, Global Regulatory Leader Global Regulatory Affairs
Mary Guckert, Clinical Development Compound Leader
Jessica Chung, Director, North American Regulatory Liaison, Clinical Development, Global Regulatory Affairs
Nancy Micalizzi, Director, CMC Regulatory Affairs
Jan Van Gelder, Ph.D., Sr. Scientific Director, Product Development & Manufacturing Sciences
Christophe Tistaert, Pharm.D., Ph.D., Sr. Scientist, Pharmaceutical Sciences, Preformulation & Biopharmaceutics
Caly Chien, Scientific Director, Global Clinical Pharmacology

Reference ID: 4038102
Johannes Moes, Pharm.D., Ph.D., Sr. Scientist, Pharmaceutical Sciences, Dissolution Sciences
Wouter Loos, Ph.D., Principal Scientist, Product Development & Manufacturing Sciences, Drug Product Development
Thomas Schultz, Ph. D., Sr. Director, CMC Regulatory Affairs, Reg. Sciences

1.0 BACKGROUND

The objective of this Type C meeting is to obtain agreement with the FDA regarding the proposed dissolution test method and our mechanistic absorption modeling approach using Physiology-Based Pharmacokinetic Modeling and Simulation.

2. DISCUSSION

**Question 1:**
Does the FDA agree that the proposed dissolution method is appropriate as the regulatory dissolution test method for the commercial apalutamide drug product?

**FDA Response to Question 1:**
Based on the data provided, it appears that the proposed QC dissolution method ('Method C') is adequate for the routine QC testing of the proposed tablet at batch release and during stability testing. The final determination will be made after submission and review of the full dissolution method development and analytical method validation reports.

In your dissolution method development report, we recommend that you provide (if appropriate) the profile similarity (f₂) values, to facilitate our evaluation of the discriminating power of the proposed method for CQAs.

In addition to the presence of tablet hardness, film-coating weight gain, and drug product stability changes, provide data regarding the ability of the proposed QC dissolution method to detect intentional alterations in other CQAs such as levels of parameters.

**Sponsor Response Q1:**
We acknowledge FDA's response.

We will plan to submit the recommended data for the Agency's review as part of the initial NDA submission.

**Meeting Discussion:**
No Discussion was needed during the meeting.

**Question 2:**
Does the FDA agree that the mechanistic absorption model:

a) Is appropriately modeled and validated?
There are insufficient data at this time to reach a conclusion on whether your proposed mechanistic absorption model is appropriately constructed and validated. A decision will be made once the Agency has the opportunity to run the model for verification of the provided results. For this purpose, submit the following information/data as part of an amendment to the IND:

i. A modeling summary report, which provides an overview of the modeling strategy, and details of the modeling procedures including model development, model verification/modification, and model application in a step-wise manner. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.

ii. Detailed information on the inputs used in the construction and validation of the model(s) and simulations. All the physiological and physicochemical parameters as well as their sources should be clearly specified. It is understandable that some input parameters are estimated (optimized). However, when the parameters are optimized, the data source selection, the estimation method, the justification for the optimization algorithm, and the assumption used should be provided.

iii. Although the FDA does not require the use of a specific software, due to substantive differences in software versions, clear identification of software parameters is critical, which should include: name and version of the software, and (for custom modeling software) schematics of model structure and differential equations.

iv. The methodological approach to model validation, model validation results, and sensitivity analyses to evaluate the robustness of the model should be clearly presented. Note that it is generally expected that the clinical data will contribute to establish confidence in the appropriateness of the model in addressing the study question(s).

v. The results of using the verified model to address the study question(s) should be presented using tables, figures and text where appropriate.

vi. The FDA’s final decision regarding the acceptability of the dissolution acceptance criteria/deletion of (b)(4) testing/specification (on) will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of a robust PBPK model predictability.

**Sponsor Response Q2a:**
In the spirit of continued collaboration, we propose to submit the currently available modelling files and dataset to address comments i. through vi., as part of an amendment to the IND. We kindly request the Agency to provide preliminary feedback on the review of these data.
Please note that the model will further be updated to address additional FDA comments a. through j.. The final model will be provided to the Agency when it becomes available. The Sponsor recognizes that the final determination will be made upon receipt of the final data.

In addition, we have the following comments based on a preliminary assessment of your proposed PBPK model:

a. You used dissolution model (z-factor) to build the PBPK model. Clarify how z-factor was calculated based on PBDT profiles, and how z-factor was incorporated into the model.

Sponsor Response Q2a:

FDA comments:
The initial phase of PBDT profiles plays an important role in the z-factor fitting. However, in some of the dissolution profiles, the time points of the initial phase seem not enough to get good fit. In addition, in your submission, provide any other the z-factor fitting profiles used in the modeling and simulation exercise.
b. You mentioned that so that precipitation does not happen in the GI tract. You set precipitation time equal for all formulations based on these findings. However, precipitation time may change with different levels of If this is the case, report the lower limit of and whether has pH dependent solubility.

**Sponsor Response Q2a:**

The target formulation uses Clinical data and PBDT profiles of is available and shows comparable in vivo PK (56021927PCR1007 - treatment arm F) and effective precipitation inhibiting effects. No further investigation was performed towards The below figure is provided in the briefing package Appendix 2, Figure 4 and included below for ease of review.

Additionally, a parameter sensitivity analysis (GastroPlus) on the precipitation time for the target formulation indicated that the mechanistic model of absorption shows very limited sensitivity of the precipitation time as input parameter. This will be included in the final report.

**FDA comments:**

Based on the data provided, the model is not sensitive to precipitation time, which is opposite to the phenomenon observed for BE study of In light of these results, your model may not be applied to supporting changes in.
In addition, the drug is not be fully released in the PBDT when (b) [4] is in the formulation. When (b) [4] were used the dissolution profiles seemed similar, except for the one with the highest release rate. This may generate an inappropriate/narrow range of z-factor when using (b) [4] resulting in no changes in Cmax and AUC due to z-factor/precipitation time.

c. The in vivo results show that total exposure (AUC) is not affected when using (b) [4]. However, PBDT profiles showed that the shapes of dissolution profiles are very different between the use of (b) [4]. This suggests that (b) [4] may not be a biorelevant dissolution medium, and that the use of z-factor may not be reliable. In addition, Figures 6 and 7 (interim modeling and simulations report) show that the drug is not completely dissolved (b) [4]. Therefore, it may be not appropriate to use these profiles to calculate z-factors. Please clarify.

**Sponsor Response Q2a:**
Please refer to the presentation slides provided by the company.

FDA comments:
Please see comments provided under bullet point b.

d. Provide the particle size distribution (d10, d50, d90) of drug substance tested in the study PCR1015.

**Sponsor Response Q2a:**

The particle size distribution has been provided (b) [4] in the briefing package dissolution method development report Appendix 1, Table 55.

<table>
<thead>
<tr>
<th>Table 55:</th>
<th>Particle Size Distribution</th>
<th>Discriminating Capability for</th>
<th>(b) [4] in Drug Product Batches (G023) Used to</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP Batch</td>
<td>Batch</td>
<td>DS Batch</td>
<td>Label</td>
</tr>
<tr>
<td>15B20/G023</td>
<td>14L04/G01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15B25/G023</td>
<td>15A28/G0</td>
<td>15A28/G0</td>
<td>Medium</td>
</tr>
<tr>
<td>15B27/G023</td>
<td>15B09/G01</td>
<td>15B09/G0</td>
<td>Target</td>
</tr>
<tr>
<td>15C02/G023</td>
<td>15B25/G01</td>
<td>15B25/G0</td>
<td>Medium</td>
</tr>
<tr>
<td>15B23/G023</td>
<td>15A19/G0</td>
<td>15A19/G0</td>
<td>Coarse</td>
</tr>
</tbody>
</table>

DP = drug product; DS = drug Substance; * out of normal process range; \* target

Reference ID: 4038102
e. Provide the rationale for the variability values used in the virtual trial population modeling, such as (b) (4) you set.

Sponsor Response Q2a:

FDA comments:
Provide detailed information for the (b) (4) concentration set in your model.

f. The simulated elimination phase does not match the observed data well (refer to Figure 11, interim modeling and simulations report). Provide justification.

Sponsor Response Q2a:
We acknowledge FDA's response. The clearance value will be adjusted in the final model. It is not anticipated that the adjustment will affect the outcome of the BE trial simulation.

g. Provide detailed information of how solubility of (b) (4) and (b) (4) were measured.

Sponsor Response Q2a:
Apparent solubility values of the (b) (4) (b) (4) were derived from the Physiology Based Dissolution Testing profiles (b) (4) To ensure consistency of the biopharmaceutical input parameters between the (b) (4) was also derived from the Physiology Based Dissolution Testing profile.

The conditions include:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

FDA comments: Provide detailed information in terms of the measurement of apparent solubility, such as (b) (4)
h. The model validation step is based on the BA/BE study which demonstrated bioequivalence among the batches/variants tested. We recommend that you challenge the model with data which showed lack of BE.

**Sponsor Response Q2a:**
We acknowledge FDA’s response. The Sponsor will consider the recommendation.

FDA comments: The approvability of the model is highly depending on the ability of the model to predict in vivo data that showed to be not BE. Therefore, we highly recommend that the model is challenged in these terms, ideally with clinical data. In the absence of clinical data, you may consider utilizing data generated to challenge your model with non-BE batch (es).

i. You claimed that you used the same parameters for the human PBPK model to build and obtained good validation. However, the variability of the may be different from the variability in humans. Provide justification for model application.

**Sponsor Response Q2a:**
Please refer to the presentation slides provided by the company.

FDA comments: Clarify whether the same PK parameters were used for the modeling exercise using human data.

j. Submit the full method development and validation report of your proposed PBDT method for review. The PBDT method should discriminate dissolution profiles of batches that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). Provide the complete physiology based dissolution testing data for batches of both strengths (n=12 units/batch; individual, mean, SD, %RSD). The PBDT method should be also cross-validated with the approved QC dissolution method.

**Sponsor Response Q2a:**
Please refer to the presentation slides provided by the company.

**FDA Response Q2b:**
Please refer to the response for the Question 2 (a).

**Sponsor Response Q2b:**
We acknowledge FDA’s response.

**Meeting Discussion:**
Sponsor requested to discuss Question 2a: (c), (i), and (j).
**Regarding Question 2a(c):** The Sponsor indicated that since the proposed QC dissolution method is made to be clinically relevant, there is no plan to develop and validate the PBDT method as another QC method. FDA indicated that at this time the Division of Biopharmaceutics is not ready to accept 2 different methods (1 for routine QC and 1 for PBPK-based biowaivers) but is open to considering the Sponsor’s proposal. Since this case will be setting a precedent, FDA recommended that sponsor demonstrate that the proposed QC method is as predictive as the PBDT method. Additionally, the PBDT method does not require full analytical method validation, but the sponsor should provide the proposal for cross-validation with the proposed QC dissolution method. With respect to cross-validation, the FDA indicated that the setting of the proposed QC dissolution acceptance criteria should reflect the data generated using the PBDT method.

Regarding the adequacy of the PBDT method for generating biorelevant input for the PBPK model and the adequacy of the medium as a biorelevant medium, the FDA recommended that the requested information be submitted as an amendment to the IND. The sponsor noted that the final PBPK model will be available after the FDA evaluation of the IND amendment is received.

**Regarding Question 2a (i):**

**Sponsor’s Response:**
Does the agency agree that:
Potential variability differences between humans and [redacted] are not a concern for mechanistic modeling of absorption using:
- Identical absorption input parameters for both species?
- Default ACAT physiologies differentiating the GI tract of both species?
- PK data from both species to describe distribution and elimination?

**FDA’s Response to Sponsor’s response:** FDA suggested that the Sponsor provide justification for using the same absorption input parameters for [redacted] and humans. Evidence should be provided to demonstrate that the conclusions of the Virtual BE study using the [redacted] are the same as the conclusions derived when using the human model. In other words, the two models should always give the same conclusion: BE or non-BE for the same scenario. The Sponsor plans to submit the current model to the IND and will specify any changes that were implemented or are planned, but the final model will be provided later on when additional data are available.

**Regarding Question 2a(f):**
[See also Discussion under Question 2a(c).]

**Additional Meeting Discussion:**
In response to FDA queries, the sponsor indicated that they are still considering whether controls for (b) and (b) particle size distribution will be part of the proposed specifications, in light of the findings of PBPK modeling and a relative bioavailability study, respectively. The FDA indicated that independently of the PBPK model results, these two quality attributes should be monitored during pharmaceutical development and as part of drug product release and stability studies.

b) Is predictive for in vivo performance of formulation variables and parameters (such as formulation platform, (b) employed, (b) particle size, manufacturing site)?

Please refer to the response for the Question 2 (a).

**Question 3:**
Does the FDA agree that our proposal for setting clinically relevant specifications is appropriately supported by the dissolution method, the mechanistic absorption model, and the in vivo and in-silico data for manufacturing variables known to be relevant for the drug product?

**FDA Response to Question 3:**
Yes, your proposed plan for setting clinically relevant specifications appears acceptable. The final determination will be made upon a thorough review of:

1. The PBPK modeling and simulation results.
2. The dissolution profile data from Phase 3 clinical batches generated using the proposed QC dissolution method, as well as for any other tablet formulations that have been shown in relative BA studies to have comparable PK to these pivotal Phase 3 clinical trial(s).

We remind you that the dissolution acceptance criterion will be determined at the time of NDA submission review, based on the totality of the data provided, including the capability of the dissolution acceptance criterion to reject aberrant/non-bioequivalent batches.

**Sponsor Response Q3:**
We acknowledge FDA’s response.

**Meeting Discussion:**
No Discussion was needed during the meeting.

**Question 4:**
Does the Agency agree that a mechanistic modeling approach may be used to justify the setting of clinically relevant drug product specifications for other critical quality attributes such as (b)?
**FDA Response to Question 4:**
Yes, we agree that mechanistic modeling may be used to justify the setting of clinically relevant specifications (e.g., dissolution, particle size distribution, ...) for the proposed drug product, provided the Agency finds the model as adequately validated. Refer also to the FDA response to Question #2.0

**Sponsor Response Q4:**
We acknowledge FDA’s response.

**Meeting Discussion:**
No Discussion was needed during the meeting.

**Sponsor Slides Attachment:**

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

/s/

KRISTINE F LEAHY
01/06/2017

ANAMITRO BANERJEE
01/06/2017

Reference ID: 4038102
IND 104676

MEETING PRELIMINARY COMMENTS

Aragon Pharmaceuticals, Inc.
c/o Janssen Research and Development, LLC
Attention: Jessica Chung, M.S.
Director, Global CMC Regulatory Affairs
920 U.S. Highway Route 202 P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

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

We also refer to your July 29, 2016, correspondence, received July 29, 2016, requesting a telecon to seek FDA concurrence with the proposed selection of starting materials in the synthesis of the Apalutamide drug substance.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Business Process 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 me, Kristine Leahy, RPh, Regulatory Business Process Manager, at (240) 402-5834.

Sincerely,

{See appended electronic signature page}
Anamitra Banerjee, Ph.D.
Branch Chief (Acting), Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

Reference ID: 3994781
PRELIMINARY MEETING COMMENTS

Meeting Type: C
Meeting Category: CMC only Pre-IND
Meeting Date and Time: October 12, 2016, 10:00A.M. – 11:00A.M. EST
Meeting Location: Teleconference
Application Number: IND 104676
Product Name: Apalutamide
Indication: Proposed treatment of patients with high-risk, non-metastatic castration-resistant prostate cancer (NM-CRPC)
Sponsor/Applicant Name: Aragon Pharmaceuticals c/o Janssen Research and Development

FDA ATTENDEES (tentative)
Anamitro Banerjee, PhD., Branch Chief (Acting), OPQ/ONDP Branch II
Xiao Hong Chen, PhD., Quality Assessment Lead (Acting), OPQ/ONDP Branch II
Kasturi Srinivasarach, PhD., API Branch Chief (Acting) OPQ/ONDP
Raymond Frankovich., Drug Substance Reviewer, OPQ/ONDP
Kristine Leahy, RPh., Regulatory Business Process Manager, OPQ/OPRO

SPONSOR ATTENDEES
Leon Freytor, PhD., Sr. Director, Global Regulatory Affairs Liaison
Nancy Micalizzi, PhD., Director, CMC Regulatory Affairs
Jan Van Gelder, PhD., Sr. Scientific Director, Product Development & Manufacturing Sciences
Wouter Couck, M.Sc., Science Director. API Small Molecule Development
Cyril Benhaim, PhD., Lead Process Chemist, API Small Molecule Development
Jessica Chung, Director, North American Regulatory Liaison

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 12, 2016, 10:00A.M.-11:00A.M. at the FDA between Janssen Research and Development and the FDA. 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 (c.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. Contact the 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 objective of this Type C meeting is to obtain agreement with the Agency regarding the selection of the starting materials in the synthesis of the drug substance.

2.0 DISCUSSION

**Question 1:**
Does the Agency agree with the proposal that (b) (4) are the appropriate starting materials in the synthesis of JNJ-56021927 (b) (4) drug substance?

**FDA Response:**
Yes, we agree. Please report any changes to the synthesis of any of the starting materials and/or to the specification of any of the starting materials to your IND as described in your quality management strategy for each compound.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTINE F LEAHY
10/04/2016

ANAMITRO BANERJEE
10/04/2016
IND 104676

SPECIAL PROTOCOL – AGREEMENT MODIFICATION

Aragon Pharmaceuticals, Inc.
Attention: Jessica Chung
Director, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for ARN-509.

We also refer to your November 5, 2012 request, received on November 6, 2012, for a special protocol assessment of a clinical protocol and to our September 8, 2015, agreement letter. The protocol is titled “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer”.

We acknowledge your submission dated June 8, 2016, received on June 8, 2016, amending the above protocol, which was under a special protocol agreement.

In summary, your amendment makes the following modifications:

1. The frequency of visits after Cycle 7. Starting at Cycle 7, visit frequency will be reduced from every cycle to every 2 cycles. Starting at Cycle 13, visits are reduced to every 4 cycles.

2. Pharmacokinetic sample collection and Patient Reported Outcome questionnaire frequency was revised to reflect the above visit schedule. There was no change in the frequency of tumor assessments.

We have completed our review and, based on the information submitted, agree to these modifications. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as “Special Protocol Assessment Amendment”. This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act (see “Guidance for Industry: Special Protocol Assessment”).

As stated in the “Guidance for Industry: Special Protocol Assessment,” a special protocol assessment documents our agreement that the design and planned analysis of a study can adequately address objectives in support of a regulatory submission. However, final determinations for

Reference ID: 3953609
marketing application approval are made after a complete review of a marketing application and are based on the entire data in the application.

If you have any questions, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tillev@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, M.D.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Reference ID: 3953609
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEOFFREY S KIM
06/30/2016
IND 104676

Aragon Pharmaceuticals, Inc.
c/o Janssen Research and Development, LLC
Attention: Nancy Micalizzi
Director, Global CMC Regulatory Affairs
P.O. Box 300, 920 U.S. Highway Route 202
Raritan, NJ 08869

Dear Ms. Micalizzi:

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

We also refer to the telecon between representatives of your firm and the FDA on June 1, 2016. The purpose of the meeting was to discuss initiation of a Question-based Review for the CMC section of the Apalutamide New Drug Application anticipated to be submitted mid to late 2017.

A copy of the official minutes of the telecon 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 Kristine Leahy RPh., Regulatory Business Process Manager at (240) 402-5834.

Sincerely,

{See appended electronic signature page}

Anamitra Banerjee, Ph.D.
Branch Chief (Acting), Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 3843239
MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: CMC - Guidance
Meeting Date and Time: June 1, 2016, 9:00A.M. – 10:00A.M.
Meeting Location: Teleconference
Application Number: IND 104676
Product Name: Apalutamide
Indication: Proposed treatment of patients with high-risk, non-metastatic castration-resistant prostate cancer (NM-CRPC)
Sponsor Name: Aragon Pharmaceuticals c/o Janssen Research and Development
Meeting Chair: Anamitro Banerjee, Ph.D.
Meeting Recorder: Kristine Leahy, RPh.

FDA ATTENDEES
Lawrence X. Yu, Ph.D., Deputy Director, OPQ
Larisa Wu, Ph.D., Special Assistant to OPQ Deputy Director, OPQ
Sarah Pope-Miksinski, PhD., Office Director, OPQ/ONDP
Thomas Oliver, PhD., Division Director (Acting), OPQ/ONDP
Anamitro Banerjee, Ph.D., Branch Chief (Acting), OPQ/ONDP Branch II
Xiao Hong Chen, Ph.D., Quality Assessment Lead (Acting), OPQ/ONDP Branch II
Kristine Leahy, RPh., Regulatory Business Process Manager, OPQ/OPRO
Teshara Bouie, MSA, Quality Assessment Lead (Acting), OPQ/OPRO

SPONSOR ATTENDEES
Nancy Micalizzi, Director, CMC Regulatory Affairs
Luc Janssens, Ph.D., Sr. Director, CMC Regulatory Affairs
Thomas Schultz, PhD., Sr. Director, CMC Regulatory Affairs
Jan Van Gelder, PhD., Sr. Scientific Director, Product Development & Manufacturing Sciences
Jos Vanhoudt, PhD., Associate Director, CMC Dossier Development Operations
Jessica Chung, Director, North American Regulatory Liaison
Qinling Qu, M.S., Manager, Regulatory Affairs

Reference ID: 3943239
1.0 BACKGROUND

The purpose of the meeting is to discuss the opportunities and mitigate challenges associated with the inclusion of the Question-based Review response document as described in the companion documents to Manual of Policy and Procedure 5015.10. This response document is intended to facilitate review of Chemistry, Manufacturing, and Controls (CMC) information included in the Apalutamid original New Drug Application, which is anticipated to be submitted in 2017.

2. DISCUSSION

**Question 1:**
As stated in MAPP 5015.10, the QbR model is not intended to replace the detailed supportive information in CTD Module 3, however full implementation according to the Agency's MAPP and associated companion documents would require Janssen to substantially supplement, reorganize and relocate CMC information across multiple CTD sections, (in Module 2, and if ICH M4Q is considered, then Module 3 as well). This would require Janssen to institute a substantial revision of the templates currently employed by the Company to draft the Quality section of an NDA.

Therefore, as a first step to initiate the approach, Janssen proposes for this pilot to provide the responses to the QbR questions in a document located separately from Module 2 and 3, such as in Module 1.2 - Reviewers Guide for NDA. This document would be provided in addition to the CMC information provided in traditional CTD format, in Modules 2 and 3. Providing the responses in this location would allow both the Agency and the company to benefit, as it would facilitate a focused QbR review based on a science and risk-based assessment of product quality.

Does the Agency agree with our proposed approach?

**FDA Response to Question 1:**
No. The Agency does not agree with your proposed approach. As we indicated at the teleconference held on May 13, 2016, the response to QbR questions should be provided as one document in Module 2.

**Question 2:**
As stated in MAPP 5015.10, the goal of QbR is to support a more streamlined review, leading to a more focused assessment of the CMC information in a dossier. Janssen intends to provide the Response document as a means to supplement and further clarify the CMC information contained in Modules 2 and 3 of the NDA, and as such it would serve a singular purpose of facilitating review of the NDA. To clarify, we therefore propose the information contained in the responses would not require future lifecycle updates. The CMC information as provided in traditional CTD format Module 3 would remain as the basis for regulatory adherence and any future dossier updates would be made to Module 3 as necessary to ensure regulatory compliance.
Does the Agency agree with our proposed approach?

**FDA Response to Question 2:**
No. All future dossier updates should be made to both Module 2 and 3, as appropriate.

**Meeting Discussion Summary:**
Janssen Research & Development confirmed understanding of the answers to the questions in the meeting package, and had no further questions. However, since the responses were not what Janssen anticipated and incorporated additional broader policy issues, Janssen proposed to have further discussion in a 90 minute face to face meeting outside of the IND, the focus being to further explore innovations in structured submissions. The FDA confirmed that it was open-to hearing new ideas that may facilitate a more efficient review process. The Sponsor’s point of contact will be Nancy Micalizzi. As the discussion moves to cover broader issues, a new Regulatory Business Process Manager (RBPM) will be appointed for the future face to face meeting agreed to in today’s icon. Once assigned, the new RBPM will alert Janssen and receive their information for this upcoming face to face meeting.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANAMITRO BANERJEE
06/08/2016
IND 104676

MEETING PRELIMINARY COMMENTS

Janssen Research & Development, LLC
c/o: Aragon Pharmaceuticals, Inc.
Attention: Kelly Johnson Reid
Director, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Reid:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ARN-509 (INJ-56021927).

We also refer to your correspondence, dated and received May 19, 2015, requesting a meeting to discuss the Clinical Pharmacology development plan to support a New Drug Application (NDA) for the treatment of men with high-risk non-metastatic (M0) castration-resistant prostate cancer (NM-CRPC).

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, contact me at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

Amy R. Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
  Preliminary Meeting Comments

Reference ID: 3804782
PRELIMINARY MEETING COMMENTS

Meeting Type: Type C  
Meeting Category: Guidance  
Meeting Date and Time: August 11, 2015 10:00 am – 11:00 am  
Meeting Location: WO Bldg. 22; Conf. Room 2201  
Application Number: IND 104676  
Product Name: ARN-509 (JNJ-56021927)  
Indication: NM-CRPC  
Sponsor/Applicant Name: Aragon Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for August 18, 2015, 10:00 am, between Aragon Pharmaceuticals, Inc., and the Division of Oncology Products. We are sharing this material to promote a collaborative and successful discussion at the teleconference. The meeting minutes will reflect agreements, important issues, and any action items discussed during the teleconference and may not be identical to these preliminary comments following substantive discussion at the teleconference. 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 teleconference (contact the regulatory project manager (RPM)). If you choose to cancel the teleconference, this document will represent the official record of the teleconference. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. 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. Contact the RPM if there are any major changes to your development plan, the purpose of the teleconference, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the teleconference.

1.0 BACKGROUND

JNJ-56021927 (ARN-509) is an investigational small-molecule non-steroidal androgen receptor (AR) antagonist. The development plan for JNJ-56021927 includes ongoing studies in high-risk non-metastatic castration-resistant prostate cancer (NM-CRPC),

Reference ID: 3804782
The purpose of the meeting is to seek feedback from the FDA on the proposed Clinical Pharmacology Development Plan to support a New Drug Application (NDA) for JNJ-56021927 for the treatment of men with high-risk NM-CRPC.

The sponsor’s development program includes 9 clinical pharmacology studies to be completed prior to NDA submission in conjunction with PK modeling analyses using population-based and physiologically-based approaches, as summarized below:

**PK/ADME:** JNJ-56021927 is absorbed with a T\text{max} from 1 to 3 hours, and a terminal half-life ranging from 130 to 342 hours after single dose. JNJ-56021927 steady-state was achieved after 3 weeks, with an accumulated ratio of 5-7. At steady-state, JNJ-56021927 showed approximately dose-proportional PK over the dose range of 30 to 480 mg daily. JNJ-56021927 was metabolized to its active metabolite JNJ-56142060 (M3), which possesses 1/3 the potency of its parent and had exposure comparable to its parent at steady-state. JNJ-56021927 was completely absorbed in healthy male volunteers, and 88.9% of the total administered \textsuperscript{14}C-radioactive dose was recovered within 42 days, with 64.6% recovered in urine and 24.3% in feces. Less than 4% of the radioactive dose was recovered as JNJ-56021927 in urine and feces, and less than 5% of the radioactive dose was recovered as active metabolite M3 in urine and feces.

**Biopharmaceutics:** The to-be-marketed tablet formulation demonstrated comparable bioavailability relative to the capsule and showed no clinically relevant food effect (Study 56021927PCR1011). A bioavailability study (Study 56021927PCR1017) to support the manufacturing scale up of the tablet formulation is planned.

**Hepatic Impairment:** The sponsor proposed a hepatic impairment PK Study 56021927PCR1018 to evaluate the pharmacokinetics of JNJ-56021927 and M3 in subjects with mild or moderate hepatic impairment compared with subjects with normal hepatic function. Because the life expectancy of patients with Child-Pugh class C hepatic impairment is only 1 to 3 years (with limited treatment options for their liver disease), which is shorter than the median overall survival of approximately 4 years for NM-CRPC patients treated with androgen deprivation therapy alone, patients with severe hepatic impairment are unlikely to benefit from treatment of high-risk NM-CRPC with JNJ-56021927. Therefore, there are no plans to enroll subjects with severe impairment. Administration of JNJ-56021927 will not be recommended in these patients.

**Renal Impairment:** The effect of renal impairment on PK of JNJ-56021927 and M3 will be evaluated using a population PK approach. Based on the snapshot of the clinical database, the population of subjects with mild (n=198) and moderate (n=90) renal impairment is adequate to assess the effect of renal impairment on the exposure to JNJ-56021927 and M3 as part of the population PK analysis. No clinical studies with JNJ-56021927 are being planned in patients with renal impairment or end-stage renal disease.

**Cardiac Safety:** Nonclinical evaluations indicated no evidence of cardiac toxicity for JNJ-56021927 or M3. A ventricular repolarization substudy (n=12) from Study ARN-509-001 showed no evidence of an increase in QTcF with increasing plasma concentration of JNJ-56021927. A QT substudy in SPARTAN is ongoing but due to the limited number of subjects (planned 100 patients with only 9 patients currently enrolled), a new standalone QT study which utilizes the same overall study design (with some modifications) as the current QT substudy in SPARTAN is being proposed.

**Drug-Drug Interaction**
In vitro, JNJ-56021927 is a substrate of CYP3A4 and CYP2C8. A clinical DDI study revealed that the strong CYP3A4 inhibitor itraconazole had no effect on the single-dose PK of JNJ-56021927 and M3. The strong CYP2C8 inhibitor gemfibrozil resulted in an increase in JNJ-56021927 AUC (1.7-fold changes) and no clinically relevant changes in M3 (15% decrease).

In vitro, JNJ-56021927 and M3 have the potential to impact multiple CYP enzymes (CYP3A4, CYP2C9, CYP2C19, and CYP2C8) and transporters (P-gp and BCRP) via inhibition or induction. The induction of CYP3A4 suggests that JNJ-56021927 and M3 will induce other CYP isozymes and drug transporters (e.g., CYP2C and multidrug resistance gene 1 [MDR1]/P-glycoprotein [P-gp]) via activation of pregnane X receptor. In vitro, JNJ-56021927 and M3 are not substrates of BCRP but are weak inhibitors of BCRP and may be clinically relevant in the gut as the $[I]_{\text{IC}_{50}} > 10$. In vitro, JNJ-56021927 and M3 are substrates for P-gp and weak inhibitors for P-gp. JNJ-56021927 and M3 are not substrates for OATP1B1 and OATP1B3. Inhibition of OATP1B1 and OATP1B3 by JNJ-56021927 and M3 is not considered clinically relevant as for JNJ-56021927 the $1+[I]_{\text{IC}_{50}} < 1.25$ and for M3 the $C_{\text{IC}_{50}} < 50$.

The sponsor proposes a multiple-dose clinical DDI study in prostate cancer patients (Protocol 56021927PCR1020) using a cocktail approach to evaluate the in vivo significance of the above findings.

Modeling Analysis

A pooled population PK analysis is planned to assess the potential effects of the intrinsic and extrinsic factors on JNJ-56021927 and M3 exposure. Analysis of parent and metabolite may be conducted separately. A pooled PK/PD analysis is planned to support the selected dosing regimen by evaluating the characteristics of the exposure-response relationships for pharmacological activity, efficacy, and safety of JNJ-56021927. The effect of rifampin (a strong CYP3A inducer and a moderate CYP2C8 inducer) on the PK of JNJ-56021927 at steady-state will be evaluated using physiologically-based pharmacokinetic (PBPK) modeling approach in lieu of a clinical study. A clinical DDI study with rifampin is not planned.

2.0 DISCUSSION

Question 1

Does the Agency agree that the data from Study 56021927PCR1011 adequately address the effect of food on the bioavailability of JNJ-56021927, so that an additional food effect study is not necessary to support registration?

FDA Response: Your proposal appears reasonable. However, the final decision will be an NDA review issue.

Question 2

Given the limited life expectancy of patients with pre-existing severe hepatic impairment (Child-Pugh class C), does the Agency agree that a study of JNJ-56021927 in these patients is not necessary?
**FDA Response:** It may be acceptable to exclude patients with pre-existing severe hepatic impairment independent of the life expectancy of these patients. However, the final decision will be an NDA review issue.

**Question 3**

Does the Agency agree that, given the drug profile, a dedicated study of JNJ-56021927 in subjects with renal impairment is not necessary to support registration?

**FDA Response:** The population PK approach to assess the effect of renal impairment on the exposure to JNJ-56021927 in patients with mild-to-moderate renal impairment may suffice. However, whether a study in subjects with severe renal impairment or ESRD is needed will be an NDA review issue.

**Question 4**

Does the Agency agree that the proposed design of the standalone QTc study along with the QTc data collected in the SPARTAN sub-study are adequate to address the potential for QT/QTc interval prolongation?

**FDA Response:** Yes, we generally agree with the sponsor. Please see Additional Comments concerning the QT study.

**Question 5**

Given that the QTc assessment modifications in support of the proposed indication (see Question 4) do not impact the SPARTAN study protocol, does the Agency agree that triggering a SPA amendment process for SPARTAN is not necessary?

**FDA Response:** Yes.

**Question 6**

Does the Agency agree that the proposed design of the cocktail DDI study and selected probe substrates are adequate to address the in vivo effects of JNJ-56021927 on PK of other drugs?

**FDA Response:** Your proposal appears reasonable. However, the final decision will be an NDA review issue. Please submit your protocol (Protocol 56021927PCR1020) to the Agency for review before initiating the “cocktail” DDI study.
Question 7

Given the observed data in the 56021927PCR1012 study and the proposed design of the cocktail DDI study, does the Agency agree that the proposed PBPK simulation plan is adequate for estimating the effect of rifampin on JNJ-56021927 PK at steady-state dosing of JNJ-56021927?

FDA Response: Your proposed approach seems reasonable. The decision on whether a clinical study estimating the effect of rifampin on JNJ-56021927 PK at steady-state dosing of JNJ-56021927 is needed, depends on the review of your PBPK predictions. The PBPK model of JNJ-56021927 should be able to describe observed PK of JNJ-56021927 and DDI results with itraconazole and gemfibrazil as inhibitors and consider potential auto induction and/or auto-inhibition of CYP3A and CYP2C8. The PBPK model of rifampin should be verified with regard to its ability to describe its effect on probe substrates using literature findings.

Please submit PBPK study report concerning the prediction of rifampin on the PK of JNJ-56021927 for review. Please include PBPK study report and model files that are used to generate final results in any future NDA submission.

Question 8

Does the Agency agree that the proposed Clinical Pharmacology Development Plan, as described, is adequate to support an NDA for the proposed indication?

FDA Response: Your proposed clinical pharmacology development plan is generally acceptable. However, the final decision will be an NDA review issue.

Additional Comments

1. The selected 240-mg q.d. dose is the potential therapeutic dose. Ultimately, the adequacy of the doses will be determined once the final therapeutic dose is established and the effects of all relevant intrinsic and extrinsic factors on the PK of JNJ-56021927 are known. According to you, the drug was well tolerated up to 480 mg per day. You should consider including a 480-mg q.d. cohort in this study.

2. ECG/PK collection times are adequate.
3. Sample size is reasonable. The overall study design is acceptable.
4. We recommend that you incorporate the following elements into your assessment of the ECGs recorded during this study:
   a. Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation
   b. Blinding of ECG readers to treatment, time, and day (i.e., Day -1; Day 1) identifiers
   c. Review of ECGs from a particular subject should be performed by a single reader
   d. Pre-specify the lead for interval measurements
   e. Baseline and on-treatment ECGs should be based on the same lead
5. We are also interested in the effects of JNJ-56021927 on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

6. When you submit your ‘thorough QT study’ report, please include the following items:
   a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
   b. Electronic copy of the study report
   c. Electronic or hard copy of the clinical protocol
   d. Electronic or hard copy of the Investigator’s Brochure
   e. Annotated CRF
   f. A data definition file which describes the contents of the electronic data sets
   g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure response analyses
   h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
   i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
   j. Narrative summaries and case report forms for any
      i. Deaths
      ii. Serious adverse events
      iii. Episodes of ventricular tachycardia or fibrillation
      iv. Episodes of syncope
      v. Episodes of seizure
      vi. Adverse events resulting in the subject discontinuing from the study
   k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows.
   l. A completed Highlights of Clinical Pharmacology Table

7. Advancing in this field – and possibly reducing the burden of conducting QT studies—depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at http://www.cardiac-safety.org/ecg-database/.

Reference ID: 3804782
3.0 OTHER IMPORTANT MEETING INFORMATION

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.

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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. 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. The PSP 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 PSP, including a PSP 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.

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
LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm).

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 1 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
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
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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
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<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
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<tr>
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<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
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<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
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<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
  ❄️ [m5]
  ❄️ datasets
    ❄️ bimo
       ❄️ site-level
```

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

Reference ID: 3804782
References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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/

KIM J ROBERTSON
08/11/2015
Kim J. Robertson for Amy Tilley
PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: P3 Guidance
Meeting Date and Time: May 12, 2015
Meeting Location: Teleconference
Application Number: IND 104676
Product Name: JNJ-56021927 (ARN-509)
Indication: Treatment of men with non-metastatic (M0) CRPC
Sponsor/Applicant Name: Aragon Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the Teleconference scheduled for May 12, 2015, 9:00 am – 10:00 am, between Aragon 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. Contact the 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 SPARTAN study randomizes patients with non-metastatic castration-resistant prostate cancer at high risk for the development of metastatic disease to ARN-509 or placebo. The primary endpoint is metastasis-free survival. This is being conducted under a Special Protocol Agreement. Patients are currently receiving 8 softgel capsules of ARN-509 or placebo daily. The sponsor has developed a tablet formulation of ARN-509 and plans to administer the tablet formulation to all patients, both new patients and patients on study. The sponsor has conducted a
bioavailability study and notes that this study shows that the two formulations, softgel capsules and tablets, are similar in terms of AUC and Cmax. The tablet formulation does not require cold storage and will decrease the number of pills from 8 to 4 daily. Further, the sponsor believes that the excipients in the softgel capsules may be causing nausea and diarrhea. The switch to the tablet formulation may decrease these symptoms. The sponsor plans to complete the switch to the tablet formulation by August 2015. At that point, ~690 patients will have received the softgel capsule and 150-250 newly enrolled patients will receive only the tablet formulation.

2.0 DISCUSSION

Question 1:
Does the Agency agree that the data from the bioavailability study 56021927PCR1011 provides sufficient information to demonstrate the comparability of the bioavailability between the softgel capsule and tablet formulations of JNJ-56021927 to support the formulation change from softgel capsules to tablets for the SPARTAN study?

FDA Response:

Yes. The data from Trial 56021927PCR1011 provide sufficient information to support the formulation change in the SPARTAN trial.

Question 2:
Does the Agency agree with the Company’s plan to switch from softgel capsules to tablets for all patients, rather than only new patients?

FDA Response:

Yes. Please clarify the expected duration of exposure for the capsule compared to the tablet in the 690 patients expected to be enrolled by the time of the planned switch.

Question 3:
Does the Agency agree that the proposed descriptive statistical analyses are sufficient to assess the effect of the formulation change on safety and efficacy?

FDA Response:

Descriptive analyses are likely sufficient; however, please address the following in any future NDA submission: The 6 month cut-off for grouping to assess the effect of formulation on efficacy and safety is arbitrary. Since these are exploratory subgroup analyses, also present the efficacy data in terms of metastasis-free survival and PSA response for all 3 groups (capsule only, tablet only and capsule + tablet) and for 2 groups based on greater duration of exposure on the specific formulation (greater duration on tablet versus greater duration on capsule).
Question 4:
Does the Agency agree that a formal BE study to demonstrate BE between softgel capsules and tablets (i.e., commercial formulation) is no longer necessary to support registration of JNJ-56021927 for the treatment of patients with non-metastatic CRPC?

FDA Response:
Yes.

Question 5:
Does the Agency agree that the outlined modifications could be incorporated into a protocol amendment for SPARTAN without triggering a SPA Amendment process?

FDA Response:
You must submit the outlined modifications as a protocol amendment as we cannot a priori determine the impact of the changes. Upon receipt, we will evaluate and make a decision.

It is unlikely that this change will invalidate the SPA agreement.

Additional Comments:
Due to the change in dosage form, generate experimental dissolution profile data to confirm the suitability of your current dissolution method for batch release and stability testing of ARN-509 Tablets.

3.0 OTHER IMPORTANT MEETING INFORMATION

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.

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 (EOP) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. 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. The PSP 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 PSP, including a PSP 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 pdii@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

**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.

**LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

**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 Bioequivalence 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.

Reference ID: 3749741
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.”

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<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
├── [m5]
│   ├── datasets
│   │   └── bimo
│   │       └── site-level
```

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

Reference ID: 3749741
References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

For general help with eCTD submissions: FSUB@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/

AMY R TILLEY
05/07/2015
IND 104676

ADVICE/INFORMATION REQUEST

Aragon Pharmaceuticals, Inc.
Janssen Research & Development, LLC
Attention: Kelly Johnson Reid
Director, Global Regulatory Affairs
920 US Highway 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Reid:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ARN-509 (JNJ-56021927). We also refer to your submissions dated and received August 28, September 2, 2014, and January 6 and 7, 2015, containing your Initial Pediatric Study Plan (iPSP).

We acknowledge your request for a PREA Waiver of ARN-509 (JNJ-56021927) for the treatment of prostate cancer. We have completed our review of the submission, and we confirm our agreement to your final agreed-upon iPSP. We have no further comments on your PSP. A clean copy of the Agreed iPSP is attached for your reference. However, we remind you that you must also submit a PREA Waiver in your NDA submission.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

Reference ID: 3699480
• if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

• if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

• Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

• Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

SUBMISSION REQUIREMENTS

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Acting Director
Division of Oncology Products I
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosed:
Agreed iPSP

7 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 3699480
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/s/

AMNA IBRAHIM
02/09/2015
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/s/

AMNA IBRAHIM
02/09/2015
IND 104676

MEETING MINUTES

Aragon Pharmaceuticals, Inc.
Attention: Kelly Johnson Reid
Director Global Regulatory Affairs
12780 El Camino Real, Suite 301
San Diego, CA 92130

Dear Ms. Reid:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ARN-509.

We also refer to the meeting between representatives of your firm and the FDA on February 20, 2014. The purpose of the meeting is to obtain advice on the acceptability plans for addressing [b][4] in ARN-509 30 mg softgel capsules.

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, contact Amy Tilley, Regulatory Project Manager at (301) 796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Haripada Sarker, Ph.D.
CMC Lead, Branch II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor Slides

Reference ID: 3457787
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Guidance

Meeting Date and Time: February 20, 2014
Meeting Location: WO22 Rm 1315

Application Number: IND 104676
Product Name: ARN-509
Indication: castration resistant prostate cancer
Sponsor/Applicant Name: Aragon Pharmaceuticals, Inc.

Meeting Chair: Haripada Sarker, Ph.D., CMC Lead, Branch II, ONDQA
Meeting Recorder: Amy Tilley, Regulatory Project Manager

FDA ATTENDEES
Amna Ibrahim, M.D., Deputy Director, DOP1
Virginia Maher, M.D., Clinical Team Leader
Paul Kluetz, M.D., Clinical Reviewer
Haripada Sarker, Ph.D., CMC Lead, ONDQA
Debasis Ghosh, Ph.D., Chemistry Reviewer, ONDQA
Minerva Hughes, Ph.D., Biopharmaceutics Reviewer, ONDQA
Todd Palmby, Ph.D., Pharm/Tox Supervisor, DHOT
Haw-Jyh Chiu, Ph.D., Pharm/Tox Reviewer, DHOT
Elimika Pfuma, Ph.D., Clinical Pharmacology Reviewer
Amy Tilley, Regulatory Project Manager

SPONSOR ATTENDEES
Margaret Yu, Clinical Development Leader
Leon Freytor, Global Regulatory Leader
Kelly Johnson Reid, North American Regulatory Leader
Marco Gottardis, Vice President Oncology
Nancy Micalizzi, CMC Regulatory Affairs
Caly Chien, Clinical Pharmacology
Ann Compernolle, Drug Product Development
Mohamedilas Jimidar, Analytical Technical Integrator
Fillip Marcel Vanhoutte, Pharmaceutical Sciences
Sabine Karin Katrien Inghelbrecht, Drug Product Development
Company Response to FDA Additional Comments #2:

The Company acknowledges the information provided regarding dissolution data and methodology and will take the Agency's recommendations under consideration as we move forward towards registration stability studies on the final drug product formulation.

Meeting Discussion Additional Comment #2:

The sponsor stated that further information will be provided at the appropriate time during development of the final formulation.

3.0 OTHER IMPORTANT MEETING INFORMATION

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

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/s/

HARIPADA SARKER
02/20/2014
Signed-off on behalf of Ali Al Hakim.
IND 104676

MEETING MINUTES

Janssen Research & Development, LLC.
Attention: Kelly Johnson Reid
Director, Global Regulatory Affairs
920 U.S. Highway 202, PO Box 300
Raritan, NJ 08869

Dear Ms. Reid:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ARN-509.

We also refer to the meeting between representatives of your firm and the FDA on December 12, 2013. The purpose of the meeting was to obtain advice regarding the proposed modifications to the ARN-509-003 Study.

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, contact Amy Tilley, Regulatory Project Manager at (301) 796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosures:
Meeting Minutes
Sponsor Slides
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: December 12, 2013 at 11:00 am
Meeting Location: WO Rm 1309

Application Number: IND 104676
Product Name: ARN-509
Indication: Castration-Resistant Prostate Cancer
Sponsor/Applicant Name: Janssen Research & Development, LLC.

Meeting Chair: Virginia Maher, M.D., Clinical Team Leader, DOP1
Meeting Recorder: Amy Tilley, Regulatory Project Manager

FDA ATTENDEES
Jonathan Jarow, M.D., Deputy Director, OHOP
Anthony Murgo, M.D., Director, Division of Oncology Products 1, Associate Office Director for Regulatory Science, OHOP
Amna Ibrahim, M.D., Deputy Director, DOP1
Virginia Maher, M.D., Clinical Team Leader, DOP1
Paul Khuetz, M.D., Medical Officer, DOP1
Kun He, Ph.D., Biostatistics Team Leader
Somesh Chattopadhyay, Ph.D., Biostatistics Reviewer
Rosane Charlab Orbach, Ph.D., Genomics and Targeted Therapy Group, Acting Team Leader
Amy Tilley, Regulatory Project Manager

SPONSOR ATTENDEES
Margaret Yu, M.D., Clinical Leader
Leonid Freytor, Global Regulatory Leader
Kelly Johnson Reid, North American Regulatory Leader
Thian Kheoh, Ph.D., Statistical Leader
Wayne Rackoff, M.D., Clinical
Shibu Thomas, Ph.D., Biomarkers
SPONSOR TELECONFERENCE ATTENDEES
Michael Smith, Ph.D., Compound Development Team Leader
Stephen (Martin) Shreeve, M.D., Study Physician
Qinling Qu, Regulatory Affairs
Claudia Richard, Regulatory Affairs
1.0 BACKGROUND

ARN-509 is a potent and selective orally administered androgen receptor (AR) antagonist. Its mechanism of action is disruption of the androgen-AR interaction and prevention of AR translocation into the nucleus. It has no significant AR agonism which may provide an advantage over other commonly used anti-androgens such as bicalutamide. The compound has demonstrated early signs of clinical activity with an acceptable safety profile in early phase human clinical trials.

The sponsor and the FDA engaged in an end-of-phase 2 meeting in February of 2012 to discuss development of ARN-509 in high risk, non-metastatic castration resistant prostate cancer patients (nm-CRPC). Following feedback from this meeting, a special protocol assessment (SPA) was submitted by the sponsor in September of 2012 for protocol ARN-509-003, a multicenter, randomized, double-blind, Phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer. An agreement letter was issued for this SPA November 9, 2012. The purpose of this Type C meeting is to discuss several proposed modifications to the ARN-509-003 (“SPARTAN”) protocol.

2. DISCUSSION

Question 1

The Company proposes to amend the statistical analysis plan as follows: a) the overall survival endpoint will be grouped with the other secondary endpoints (note that the secondary endpoints themselves remain unchanged); b) with the regrouping of the secondary endpoints and the use of the Hochberg procedure to control for multiplicity, the formal interim analysis of overall survival is no longer necessary; and c) inclusion of a survival update at approximately 70% of total events. Does the Agency agree with each of these changes?

Company Position

The Company proposes to regroup the key secondary endpoint and the other secondary endpoints into a single group of secondary endpoints (overall survival, time to symptomatic progression, time to initiation of cytotoxic chemotherapy, radiographic progression-free survival [rPFS], and time to metastasis [TTM]). To control for multiple testing, the analysis of these endpoints will be carried out using the Hochberg procedure. As currently specified in the protocol, the primary endpoint is metastasis-free survival (MFS), while the key secondary endpoint is overall survival, and other secondary endpoints are time to symptomatic progression, time to initiation of cytotoxic chemotherapy, rPFS, and TTM (Appendix 2, Section 3.2). The current planned statistical analysis for these key and other secondary endpoints is to statistically test these endpoints at the time when the planned number of MFS events is observed (Appendix 2, Section 13.2). The order of the statistical testing is first to determine significance for MFS. If the MFS endpoint is significant, the testing order is overall survival followed by the testing of the other secondary endpoints in the order listed above. Determination of statistical significance on overall survival at the time of mature MFS follows the O'Brien-Fleming boundary as implemented by the Lan-DeMets alpha spending function. Statistical significance can be declared if the observed p value is 0.0019 or less (Appendix 4,
Section 5). The Company considers this testing procedure to be unnecessarily stringent for the following reasons:

(1) Based on previous overall survival data in studies where the patient population has more advanced disease (metastatic CRPC, no prior chemotherapy), it is highly improbable to achieve statistical significance for overall survival at the time of the mature MFS analysis. In the Phase 3 COU-AA-302 study of ZYTIGA plus prednisone (or prednisolone) in patients with asymptomatic or mildly symptomatic mCRPC, at 43% of death events, the hazard ratio (HR) for overall survival was 0.75, p=0.0097. The HR was similar for the IMPACT study of Sipuleucel-T (HR=0.78, p=0.03). For Study ARN-509-003, the theoretical likelihood of significance is approximately 14% (HR of 0.64 or better would be required to declare significance).

With the regrouping of the secondary endpoints, the formal interim analysis for overall survival is being removed and the Hochberg procedure will be used to control for multiplicity. Additionally, because the interval between the time of the MFS analysis and the total expected number of death events is approximately 27 months, the Company proposes to perform a survival update when approximately 70% of the total events are observed. This update is projected to occur approximately 12 months from the time of the analysis of the MFS endpoint.

(2) The results for the secondary endpoints could be considered clinically meaningful in this early disease patient population if the magnitude of improvement is large. A clinically meaningful improvement could be defined as a trend in overall survival (p value of ≤0.2) and statistically significant improvement in 2 of the remaining secondary endpoints (time to symptomatic progression, time to initiation of cytotoxic chemotherapy, rPFS, and TTM).

A summary of proposed changes to the protocol is provided in Appendix 3. The red-line changes for the protocol and SAP are provided in Appendix 2 and Appendix 4, respectively.

**FDA Response Q1:**

Possibly. We require further discussion and clarification regarding the rationale for this change and the specifics of your proposed analysis of the secondary endpoints. Please be prepared to discuss the following:

a. The timing of the analysis of the secondary endpoints;
b. Provide the details of the proposed Hochberg procedure and state whether it will include OS; and
c. Provide your assumptions, effect size and power for how overall survival will be tested at the time of the secondary endpoint analysis.

An interim analysis of survival should be conducted at the time of the MFS analysis. While we might not expect improvement in OS to reach statistical significance, we will be interested in seeing a trend toward improvement in OS to support MFS. One possibility
would be to perform a hierarchical analysis of secondary endpoints (with or without a Hochberg procedure) in which the clinically relevant secondary endpoints you wish to include in labeling are tested prior to OS. Please note that the inclusion of these endpoints in labeling will be a review issue. A final analysis of OS should be provided when available.

Company Response Q1:

Please refer to the presentation slides provided by the sponsor.

Meeting Discussion Q1:

FDA agreed with the sponsor that a statistical plan which does not invalidate all secondary endpoints if OS is not met at the time of the primary endpoint analysis may be acceptable. The specifics of how to achieve this will require further discussion.

Question 2

The Company proposes to implement a multivariate analysis adjusting for baseline factors as a sensitivity analysis for the metastasis-free survival (MFS) primary endpoint and the overall survival secondary endpoint. Does the Agency agree with this proposal?

Company Position

Baseline factors such as performance status, lactate dehydrogenase, and alkaline phosphatase are prognostic factors in patient populations with metastatic disease. Any small imbalance between treatment groups in the baseline factors may affect the outcome measures. The Company proposes to conduct a multivariate analysis adjusting for baseline prognostic factors as a sensitivity analysis. Baseline factors will be assessed by first evaluating each factor separately. If the observed p value is 0.05 or less, then that baseline factor will be included in the multivariate model. A final model will then be carried out using Cox regression with the inclusion of these baseline factors (Appendix 4).

FDA Response Q2:

The additional pre-specified sensitivity analyses are acceptable. However; for a single study to support an approval, the trial must be statistically persuasive, therefore it would be unlikely that sensitivity analyses would provide adequate support to overcome a lack of statistical significance on your primary efficacy endpoint analysis.

Company Response Q2:

We acknowledge FDA’s response. No further discussion is required.

Meeting Discussion Q2:

None
Question 3

The Company proposes the addition of sensitivity analyses to address the effect of subsequent therapy on metastasis-free survival (MFS), if appropriate, and overall survival endpoints. Does the Agency agree with this proposal?

Company Position

As the number of effective therapies to treat patients with prostate cancer continues to increase, an imbalance in the use of these subsequent therapies between the treatment groups may affect the outcome measures for overall survival, and possibly MFS. Collection of MFS data for all patients, even those who discontinue before documented progression, is planned. Therefore, depending on the percentage of such patients, a sensitivity analysis to address the effect of subsequent therapy on MFS also could be informative. The Company proposes to conduct sensitivity analyses using time varying covariate analysis or other methods to obtain a better estimate of the treatment effect (Appendix 4).

FDA Response Q3:

The additional pre-specified sensitivity analyses are acceptable. See response to question #2.

Company Response Q3:

We acknowledge FDA’s response. No further discussion is required.

Meeting Discussion Q3:

None

Question 4

4a. In an effort to provide uniform access to subsequent therapy, the Company proposes to provide ZYTIGA® as an option for subjects who a) meet the criteria for the primary endpoint, and b) reside in countries where the drug is approved for use in patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (CRPC) before chemotherapy. Does the Agency agree with this proposal?

Company Position

Many of the patients in this study who experience metastatic disease progression will be asymptomatic or mildly symptomatic. In the denosumab study of patients with non-metastatic CRPC, 73% of the patients with a metastatic event had no symptoms. To date, the treatment options for patients who progress on ARN-509 are limited. As of 30 September 2013, ZYTIGA was approved in 63 countries for the treatment of mCRPC in patients who are asymptomatic or mildly symptomatic after failure of ADT and who have not received chemotherapy. Providing ZYTIGA to this patient population may reduce bias introduced through regional variations in access to effective subsequent therapy.
Crossover of patients from the placebo group to ARN-509 is not included in the study protocol in order to preserve the integrity of the overall survival endpoint. Providing ZYTIGA to patients in this study may aid in the retention of patients randomized to the placebo group, who may otherwise withdraw consent to follow up.

Additionally, offering ZYTIGA to patients may minimize requests from investigators and patients to unblind the study before the required number of events for the analysis of the survival endpoint are observed.

A section detailing subsequent therapy with ZYTIGA was added to the proposed amended protocol (Appendix 2, Section 8.9). A summary of all the proposed changes to the protocol based on subsequent therapy with ZYTIGA is provided in Appendix 3.

**FDA Response Q4a:**

The provision of abiraterone acetate to patients who develop metastases is acceptable provided it is equally available to both arms. All subsequent therapies for prostate cancer should be carefully documented. Please clarify that abiraterone will not be provided to patients who discontinue therapy for reasons other than progression to metastatic disease. Please also provide your rationale for making abiraterone available only to countries where it is approved. We are concerned that this may impact the interpretation of your survival results.

**Company Response Q4a:**

Please refer to the presentation slides provided by the sponsor.

**Meeting Discussion Q4a:**

The sponsor clarified their proposal to provide abiraterone in countries where it is approved for use prior to chemotherapy. This is expected to be available to >95% of the patient population. Use will be at the investigator’s discretion. This is acceptable.

4b. ZYTIGA will be used for its marketed indication, however the Company still plans to collect data for serious adverse events while subjects receive ZYTIGA. Does the Agency agree with this approach?

**Company Position**

While ZYTIGA will be used according to the local label, the Company is taking a conservative approach and plans to collect data for serious adverse events while subjects receive ZYTIGA. Collection of survival follow-up information will also continue as described in the protocol (Appendix 2, Section 8.8 and Schedule of Activities).
FDA Response Q4b:

The collection of serious adverse events while patients are receiving subsequent therapy with abiraterone acetate is acceptable.

Company Response Q4b:

We acknowledge FDA's response. No further discussion is required.

Meeting Discussion Q4b:

None

Question 5

The Company proposes to amend the protocol to include exploratory biomarker endpoints. Does the Agency agree with this proposal?

Company Position

Results from a Phase 1 study provide evidence that acquired genetic anomalies in the AR may be associated with resistance to ARN-509 treatment. In this study, 3 of 29 patients developed the F876L mutation; the 3 patients were considered non-responders. Preclinical data show that changes in expression or development of mutations in genes in the AR-axis may lead to resistance to drug treatment. In order to gain additional information on acquired genetic anomalies that may occur in a subset of patients, the Company is considering the inclusion of exploratory biomarker endpoints in Study ARN-509-003. Sample collection will include blood samples and archival formalin-fixed paraffin-embedded (FFPE) tumor samples.

The Company proposes to collect blood samples from 300 patients at multiple time points. Based on the Phase 1 data in patients with later-stage disease, mutations typically occurred by Cycle 12 (range: Cycle 10-15). In earlier-stage disease, it is unknown at what time point the development of mutations may occur. Therefore, the Company proposes collection of blood samples prior to dosing on Day 1 of Cycles 1, 6, 12, 18, 24, and an additional sample at the end-of-treatment visit. A panel of preselected RNA and DNA biomarkers, chosen based on preclinical studies and studies involving enzalutamide, will be used to detect expression changes and the presence of mutations (Appendix 2, Section 7.5).

The Company is also proposing to collect archival FFPE tumor samples from 400 patients to investigate whether high-risk genomic classifiers may identify a more homogeneous population of high-risk patients. This will allow selection of the appropriate high-risk patient population for future studies of ARN-509.

A summary of the proposed additions to the protocol for exploratory biomarkers is provided in Appendix 3. Red-line versions of the protocol and SAP can be found in Appendix 2 and Appendix 4, respectively.
FDA Response Q5:

The proposed exploratory biomarker assessment appears acceptable. Regarding F876L detection in plasma cfDNA, consider a larger sample size to account for potential differences in F876L mutation levels (or sensitivity of plasma cfDNA testing) between patients with metastatic CRPC (as reported by Joseph et al., 2013) and patients with earlier-stage disease.

Company Response Q5:

We have performed power calculations to determine sample size. Assuming lower frequencies (5%) in M0 setting, 300 subjects can achieve sufficient power for correlative analysis based on our calculation on a sliding scale.

Meeting Discussion Q5:

This is acceptable.

Question 6

The Company proposes minor modifications to the PK sampling schedule and the PK analysis plan. Does the Agency agree with these proposals?

Company Position

The Company proposes minor modifications to the PK sampling schedule and the population PK analysis plan. The following changes are being proposed:

- to reduce the number of blood samples taken from the patients
- to restrict the timing of the PK sample collection
- to incorporate a formal population PK analysis
- to remove analysis of the relationship between ARN000066 and efficacy and adverse events
- to revise how concentration data below the lower limit of detection will be handled.

The Company proposes to collect PK samples for each patient on Day 1 of Cycles 1, 2, 3, 6, 12, 18, and 24. The current protocol includes collection of samples at Cycle 36 and yearly thereafter (Appendix 2; Section 8 and Schedule of Activities). The planned collection of 7 samples should be sufficient for the population PK analysis. The data from these samples may also be combined with data from PK samples collected in the Phase 1/2 studies.

The timing of PK sample collection in the current protocol specifies between 0.5 and 4 hours post-dose of ARN-509 on Cycle 1, Day 1 and at any time on the scheduled clinic visit for the
remaining PK samples (Appendix 2, Section 8 and Schedule of Activities). For subjects participating in the PK substudy, PK samples are being collected predose and around T\text{max} (2 and 4 hrs postdose) on Day 1 of Cycles 1 and 3 (see Appendix 8 of the protocol). For all the PK samples after Cycle 1, Day 1 (excluding Cycle 3 for the PK substudy, see table below), the Company proposes to collect predose (trough) samples. Trough PK samples are generally considered to have less "noise" and may be more clinically relevant as they are highly correlated with efficacy. Collection of trough PK samples will also facilitate the assessment of auto-induction of metabolism observed with ARN-509.

<table>
<thead>
<tr>
<th>PK Sample Collection Schedule</th>
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<tr>
<td>Day 1, Cycle #</td>
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<sup>a</sup>Patients participating in the PK substudy only.
<sup>b</sup>This PK sample does not have to be collected for patients participating in the PK substudy.

The Company proposes to remove the summary statistics for the sparse population PK samples. Instead, formal population PK analysis of plasma concentration-time data of ARN-509 will be performed using nonlinear mixed-effects modeling. The population PK analysis results will be presented in a separate report. The rationale for this change is that summary statistics are not required for population PK samples, but could be done as an exploratory analysis for the formal population PK analysis.

The current protocol includes modeling analyses of the relationship of exposure to ARN-509 and its metabolites (ARN000308 [M3] and ARN000066 [M4]) to measures of efficacy and adverse events. However, the metabolite ARN000066 is essentially pharmacologically inactive (30-fold less potent than the parent compound, ARN-509 see Appendix 2, Section 1.1.2). Exposure to ARN-509 and exposure to the metabolite are usually highly correlated. Therefore, the analysis of the relationship between ARN000066 and efficacy and adverse events could be misleading due to the correlation of exposure levels between the metabolite and the parent compound. For these reasons, the Company proposes to remove the planned analysis of the relationship between ARN000066 and measures of efficacy and adverse events.

The Company also proposes to revise the handling of concentrations below the lower limit of quantification (BQL) (Appendix 2, Section 13.4.2). Details of handling of BQL data will be specified in the population PK SAP. Exclusion of BQL data will be dependent on the amount of BQL data, and assigning a numeric value to the BQL data is no longer a commonly used method.

A summary of proposed additions and changes to the protocol is provided in Appendix 3. The red-line version of the protocol is provided in Appendix 2. The current population PK analysis
plan presented in the SAP (Appendix 4) was revised indicating that a separate PK SAP will be provided before database lock for the clinical study report.

**FDA Response Q6:**

**Yes, we agree.**

**Company Response Q6:**

We acknowledge FDA’s response. No further discussion is required.

**Meeting Discussion Q6:**

None

**Question 7**

*Health-related quality of life will be evaluated based on the functional assessment of cancer therapy prostate (FACT-P) instrument. A 10-point change in the FACT-P total score is considered clinically meaningful. Therefore, the Company proposes any subject experiencing a 10-point decrement in FACT-P total score from baseline will be considered to have experienced clinically meaningful deterioration in functional status and well-being. Is this approach to evaluating health-related quality of life acceptable to the Agency?*

**Company Position:**

The FACT-P is a multidimensional, self-reported health-related quality of life instrument specifically designed for patients with prostate cancer. It consists of 27 core items, which assess patient function in 4 domains: Physical, Social/Family, Emotional, and Functional well-being, which is further supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as a global health-related quality of life (HRQL) score (FACT-P total score). Higher scores represent better HRQL. Interpretation of scores includes identification of a responder based on meaningful change threshold. A meaningful change threshold should be identified for each patient population of interest. Cella and colleagues (2009) have identified a meaningful change in late-stage prostate cancer as 6 to 10 points for the FACT-P total score. There is no clearly defined clinically meaningful change threshold for early-stage prostate cancer. The current protocol defines a 16-point improvement (“response”) in global FACT-P score compared with baseline (Appendix 2, Section 13.4.1). Evidence suggests that this may not be appropriate for 2 reasons: 1) 6 to 10 points (ie, considerably less than 16 points) is the recognized range of a minimally important difference in the FACT-P total score; and 2) men with early stage disease are likely to score rather high on the FACT-P at baseline, leaving little room for improvement in the score. In the denosumab study in early prostate cancer, 73% of the metastatic events were asymptomatic. Over time, as a patient progresses with disease or experience treatment-related toxicity, many of them will likely report declines in their FACT-P score. The Company expects that any change observed in subjects in the ARN-509-003 study is likely to be a decrement rather than an improvement (“response”) in scores.
Meaningful change thresholds may be identified for each scale using anchor- or distribution-based methodology. Generally, the preference is to use anchor-based definitions with distribution-based approaches as supportive, although this may not be possible in early stages of development. In such cases, a distribution-based approach may be informative.

Several studies have been conducted patients with early-stage prostate cancer using the FACT-P instrument, which may provide insight into a meaningful change in this patient population. In a small sample (n=40) of patients studied longitudinally in the early stages of disease, the FACT-P baseline scores indicated a mean of 122.7 and standard deviation (SD) of 20.4. Based on a commonly employed distribution method for estimating what is likely to be meaningful change (0.5 SD of baseline scores); a rational threshold for meaningful change would be approximately 10.2. Lee and colleagues (2001) studied men scheduled to undergo 1 of 3 interventions (interstitial brachytherapy, external beam radiotherapy or radical prostatectomy). Baseline means and SDs in this study were 138.4 (17.0), 137.1 (12.1), and 138.3 (14.7), respectively, for the 3 groups, suggesting that a meaningful change threshold may be even lower (ie, 6 to 9 points) than estimates based on the Monga et al study. Note that this change is consistent with the Cella et al. (2009) recommendation of a 6 to 10 point range for the FACT-P total score. For purposes of Study ARN-509-003, the Company proposes to use a threshold for a meaningful decrement in HRQL of 10 points on the FACT-P (total score) based on prior research in later stage (metastatic) disease and the larger of the distribution-based estimations from the literature. The appropriateness of this threshold for change will be explored by performing a distribution-based analysis on FACT-P total baseline study scores in ARN-509-003 as well as examination of cumulative distribution functions that includes a range of change scores for the FACT-P total and domain scores.

**FDA Response Q7:**

The cut-off you select is your decision. This will be an exploratory endpoint and there can be no claims made in the label based on FACT-P results.

While FDA acknowledges the importance of overall patient well-being and health-related quality of life, global HRQL instruments present problems as endpoints in trials intended to support regulatory action for several reasons:

1. Concepts and domains measured are often distal to (far removed from) the impact of treatment and the proximal impacts of treatment on how patients feel and function may not be captured in an HRQL instrument. This creates problems in interpreting HRQL results. Items reflecting personal well-being simply may logically be too far “downstream” to clearly reflect treatment benefit;

2. HRQL may reflect or be impacted by other causal factors that increase variability of the measurement and impair the interpretation of treatment effect. For example, financial well-being is impacted by many causal factors other than how patients survive, feel and function. The inclusion of distal attributes of well-being that typify HRQL questionnaires attenuate the overall ability of the measure to detect change;
(3) Some HRQOL instruments include inappropriate items for drug development trials, e.g., financial or social well-being. Even expected improvements in personal relationships or social participation can be less likely to show change across the duration of the clinical trial;

(4) Establishing a benefit on overall HRQOL would require that all domains that are important to interpreting change in HRQOL were measured, that a general improvement was demonstrated, and that no decrement was demonstrated in any domain; and

(5) HRQOL can be impacted by both the benefits and the risks of treatment. For the purposes of providing evidence of effectiveness and safety for product approval, measurements should allow for independent evaluation of the benefits versus the risks of treatment.

Company Response Q7:

We acknowledge FDA's response. No further discussion is required.

Meeting Discussion Q7:

None

3.0 OTHER IMPORTANT MEETING INFORMATION:

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. 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. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP 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 Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development,
please refer to:

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:

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

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<th>Action Item/Description</th>
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<td>Sponsor</td>
<td>January 2014</td>
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<tr>
<td>Amendment to SPA</td>
<td>Sponsor</td>
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6.0 ATTACHMENTS AND HANDOUTS

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

/s/

VIRGINIA E MAHER
12/17/2013
IND 104676

SPECIAL PROTOCOL - AGREEMENT

Aragon Pharmaceuticals, Inc
Attention: Bao Truong
Director, Regulatory Affairs
12780 El Camino Real, Suite #301
San Diego, CA 92130

Dear Ms. Truong:
Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for ARN-509.

We acknowledge your request dated September 26, 2012, received on September 27, 2012, for a special protocol assessment of a clinical protocol. The protocol is titled Protocol ARN-509-003 A Multicenter, Randomized, Double-Blind, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer.

We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as “Special Protocol Assessment - Amendment”. This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act.

As stated on page 9 in the “Guidance for Industry: Special Protocol Assessment,” a special protocol assessment documents our agreement that the design and planned analysis of a study can adequately address objectives in support of a regulatory submission. However, final determinations for marketing application approval are made after a complete review of a marketing application and are based on the entire data in the application.

We also have the following responses to your questions.

1. Does the Agency agree that the single Phase III Study ARN-509-003 is adequate in design to support initial registration for full approval of ARN-509 for the following indication: “ARN-509 is indicated for the treatment of men with high risk NM-CRPC”?
FDA Response (November 1, 2012):

Possibly. The magnitude of benefit for your primary end point will need to be substantially large in order 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 PFS results as well as other clinically meaningful measures (see additional clinical comments) in order to support any benefit demonstrated by your surrogate primary endpoint.

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 should be well-designed, well-conducted, internally consistent, and provide statistically and clinically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform.


Please note that the indication statement will be evaluated after data review.

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response.

2. Does the Agency agree with the adequacy of the safety monitoring plan? (See Protocol ARN-509-003; Appendix D.)

FDA Response (November 1, 2012):

Given the limited clinical information available for ARN-509, please ensure that frequent examinations of unblinded safety data are performed by the Data Monitoring Committee.

Aragon Response (November 5, 2012):

Aragon acknowledges and agrees with the FDA feedback. Frequent examinations of unblinded safety data will be performed by the Data Monitoring committee (DMC). The protocol has been revised to clarify that the DMC will review the progress of the study and cumulative unblinded safety data on a periodic basis (a minimum of two face to face review meetings per year) as well as serve as the primary reviewers of the efficacy analysis. In addition to the formal face to face meetings, unblinded listings of serious adverse events will be provided to the DMC on a monthly basis (see Section 12 of Protocol ARN-509-003).

3. Does the Agency agree that the use of a placebo-control is appropriate to assess the efficacy and safety of ARN-509 in this patient population? (See Section 3.2.)
FDA Response (November 1, 2012):
Yes.

Aragon Response (November 5, 2012):
Aragon acknowledges the FDA response.

4. Does the Agency agree that Aragon’s plan for how to manage PSA anxiety and early study drop-outs (as outlined in Section 1.4) adequately address the Agency’s concern regarding the ability to keep patients on trial (in either arm) when faced with rising PSA?

FDA Response (November 1, 2012):
The sponsor's plan for minimizing study drop-outs for PSA anxiety appears adequate. Please note that the examination of the number of patients who have discontinued study drug and the cause of discontinuation will be a review issue.

Aragon Response (November 5, 2012):
Aragon acknowledges the FDA response.

5. Does the Agency agree that the target patient population is adequately defined as per the study eligibility criteria? (See Section 3.3.)

   a. Does the Agency agree that the proposed definition of rapidly rising PSA (defined as PSADT ≤ 10 months) appropriately selects for patients who are at high risk for developing metastatic prostate cancer and for dying from prostate cancer?

FDA Response to 5a (November 1, 2012):
Yes.

Aragon Response (November 5, 2012):
Aragon acknowledges the FDA response.

   b. Does the Agency agree that it is acceptable to allow inclusion of patients with prior first-generation anti-androgen treatment (e.g., bicalutamide, nilutamide, or flutamide) but not to mandate prior first-generation anti-androgen for all patients before enrollment into the study?
FDA Response to 5b (November 1, 2012):

Yes. However, unequal distribution of patients who have received prior anti-androgen therapy may affect the interpretation of trial results.

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response.

FDA Response (November 9, 2012):

Please confirm that you will collect all prior prostate cancer-directed therapies on the enrollment CRF. Capture this data with as much granularity as possible including starting and stopping dates when available. Of particular interest is prior anti-androgen use and this should be collected with care to minimize missing data.

Aragon Response (November 9, 2012):

Prior prostate cancer-directed therapies, including LHRH agonists/antagonists, anti-androgens, and/or others, will be captured on the appropriate CRF (e.g., Prior Systemic Therapy for Prostate Cancer) at baseline. Name of the agent and start/stop dates will be captured, when available.

   c. Does the Agency agree with inclusion of patients with pelvic lymph nodes < 2 cm in short axis (N1) located below the iliac bifurcation?

FDA Response to 5e (November 1, 2012):

Yes.

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response.

6. Does the Agency agree that metastasis-free survival (MFS), defined as time from randomization to first evidence of blinded independent central review (BICR)-confirmed radiographically detectable bone or soft tissue distant metastasis or death from any cause, whichever occurs earlier, is an appropriate primary endpoint for demonstration of clinical benefit and for full approval of ARN-509 for treatment of men with high risk NM-CRPC? (See Section 3.4.)

FDA Response (November 1, 2012):

Please see response to Questions 1 and 6d. We strongly recommend you avoid early trial interruption at the interim analysis for OS unless a statistically persuasive overall survival result has been achieved.
Aragon Response (November 5, 2012):

Aragon acknowledges and agrees with the FDA recommendation.

a. Does the Agency agree with the proposed definition of the primary endpoint?

FDA Response to 6a (November 1, 2012):

No. Please see response to 6d concerning the primary endpoint.

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response. Please see below Aragon’s reply to the FDA response to Question 6d regarding the definition of MFS.

b. Does the Agency agree that the primary MFS outcome can be adequately substantiated by the proposed secondary endpoints?

FDA Response to 6b (November 1, 2012):

No. The initiation of a new systemic anti-cancer therapy in and of itself would not be expected to be clinically meaningful unless the toxicity of the subsequent therapy was significantly worse than ARN-509. Given the current availability of immunotherapy and other hormonal therapies with very tolerable toxicity profiles, change Time to Initiation of Systemic Therapy to Time to Initiation of Cytotoxic Chemotherapy. Please also see additional FDA comments.

Aragon Response (November 5, 2012):

Aragon agrees and has changed the secondary endpoint of Time to Initiation of Systemic Therapy to Time to Initiation of Cytotoxic Chemotherapy in the revised protocol and SAP.

Of note, consistent with the FDA Additional Comment 6 below regarding careful collection of subsequent therapies, it is still Aragon’s intent to collect all subsequent prostate cancer therapies (including cytotoxic chemotherapy, immunotherapy and other hormonal therapies) to support the analysis of potential impact of subsequent therapies on overall survival results.

c. Does the Agency agree that a treatment effect on MFS that reflects at least 30% reduction in the risk of metastasis or death relative to the placebo arm would be considered a clinically meaningful benefit in high risk NM-CRPC?

FDA Response to 6c (November 1, 2012):

This will be a review issue. Please see response to question 1.
Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response.

d. Does the Agency agree with our plan for the blinded independent central review (BICR; Section 3.4.2) of radiographic scans to confirm disease progression (development of distant metastases)?

FDA Response to 6d (November 1, 2012):

No. We agree with the use of a BICR. However, we note you plan to exclude new lesions considered bone scan flare from the definition of MFS. Any new bone scan lesions with confirmation of bone metastasis by x-ray/CT/MRI should be captured as a MFS event.

Aragon Response (November 5, 2012):

Aragon agrees that any new bone scan lesions with confirmation of bone metastasis by x-ray/CT/MRI should be captured as a MFS event. Aragon acknowledges that there was an inconsistency in the bone scan assessment as described in the outline of BICR (provided in Section 3.4.2 of the 26 September 2012 SPA Request) and the protocol (Section 7.1.8).

The following sentences have been deleted from the below outline of BICR and will also be reflected in the final BICR Charter before implementation:

Outline of BICR (provided in Section 3.4.2 of the 26 September 2012 SPA Request):

(b) (4) has been contracted by Aragon to provide an independent assessment of subject eligibility, followed by independent radiology review of on-study tumor assessments. During the independent radiology review, radiographic exams will be evaluated and Aragon will be provided with an assessment of tumor progression. This independent review will provide Aragon with an assessment of the Date of Distant Metastasis (for MFS and TTM endpoints) and Date of Progression (for PFS endpoint) for all subjects enrolled in Protocol ARN-509-003.

Eligibility Review: (b) (4) will determine radiographic eligibility for all subjects. Eligibility criteria for study entry require the absence of distant metastases. The independent reviewer will ensure the following:

- The absence of brain metastases,
- The absence of bone metastases, and
The absence of distant soft tissue and visceral disease.

If the independent reviewer is unable to confirm the above eligibility requirements (e.g., due to missing exams), the subject will be considered ineligible.

[ ] will provide Aragon with the results of the eligibility review within 3 days of all scans being submitted and qualified for review.

**Radiology Review:** Trained and approved readers will read subject scans according to a one-reader, sequential time point presentation, rolling read mode paradigm. Aragon will provide Aragon with the Time Point Response (TPR) and the Date of Distant Metastasis and/or Date of Progression for all subjects. Response assessments performed by designated readers are an independent function and not subject to input from Aragon, its designees, or any site involved in this clinical trial. In an effort to avoid the introduction of bias to the reading sessions, the data received by the readers at [ ] will be limited to data that is relevant to an independent assessment of tumor response and disease progression.

**Sequential Time Point Presentation Paradigm:** All time points will be completely read in chronological order without access to future images, starting with the Screening time point, then followed by the discrete revelation of each successive time point. The purpose of this approach is to evaluate the therapy in the same manner as the site investigator who evaluates the subject clinically, in real time.

If a change is required to a time point that has previously been read (either on the basis of a correction identified during read QC or because of a “hindsight” change initiated by the independent reviewer based on additional information), the change will be made according to [ ] SOPs. The data in the reading application and in the study database will be concordant. Audit trails will reflect the change.

At each time point, the presence of new lesions will be assessed. Unequivocal new lesions are those that were not present at Screening.

- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings representing something other than tumor).
- New nodal lesions must be pathologic and the reader must believe that it represents new metastatic disease.
- Lesions that are seen (subsequent to Screening) in anatomic locations that were not scanned at Screening will result in progression.
- Lymph nodes:
  - The appearance of a new pelvic lymph node located below the iliac bifurcation is PD if the short axis is \( \geq 20 \) mm. The appearance of a new lymph node located outside the pelvis is PD if the short axis is \( \geq 10 \) mm. In both cases, the short axis must also demonstrate an absolute increase of \( \geq 5 \) mm compared to Screening.
o Growth of a previously normal pelvic lymph node located below the iliac bifurcation is PD if the lymph node’s short axis is ≥ 20 mm. Growth of a previously normal lymph node located outside the pelvis is considered PD if the lymph node’s short axis is ≥ 10 mm. In both cases, the short axis must also demonstrate an absolute increase of ≥ 5 mm compared to Screening.

- If a new lesion is equivocal (e.g., because of its size), continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm the new lesion, then the Date of Distant Metastasis and/or Date of Progression will be the date when the new lesion was first identified.

- A new site of abnormal radiotracer uptake identified on bone scan in an anatomic location thought to be metastatic disease, and not benign intercurrent disease, will result in progression if it can be confirmed by CT or MRI.

- Progression can be assessed based on ≥ one (1) new lesion on bone scan at any time point if the new lesion can be confirmed on CT or MRI.

7. Does the Agency agree with the proposed primary and secondary efficacy analyses, as described in the Statistical Analysis Plan for Study ARN-509-003? (See Section 3.5.)

**FDA Response (November 1, 2012):**

It appears acceptable.

We recommend the following sequence for the secondary endpoints with respect to hierarchical statistical testing:

1. Overall survival
2. Time to symptomatic progression
3. Time to initiation of cytotoxic chemotherapy
4. Radiographic progression-free survival per RECIST with confirmation of bone scan abnormalities by X-ray/CT/MRI
5. Time to metastases

**Aragon Response (November 5, 2012):**

Aragon agrees. The protocol and SAP have been revised to reflect the FDA recommended sequence for hierarchical statistical testing of the secondary endpoints.

8. Does the Agency agree that the overall safety database is sufficient to support registration of ARN-509? (See Section 3.5.)
FDA Response (November 1, 2012):

The proposed overall safety database appears adequate. A final determination will be made after reviewing the data.

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response.

9. Does the Agency agree with the PK sampling in this trial to explore population modeling and exposure-response relationships for efficacy and safety of ARN-509 and the active metabolites? (See Section 3.6.1.)

FDA Response (November 1, 2012):

Yes.

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response.

10. Does the Agency agree with the adequacy of the proposed ECG sub-study as outlined in Appendix 8 of the main Protocol ARN-509-003? (See Section 3.6.2.)

FDA Response (November 1, 2012):

Yes. We have the following additional comments:

1. We recommend that you incorporate the following elements into your assessment of the ECGs recorded during this study:
   a. Blinding of ECG readers to treatment, time, and day (i.e., Day -1; Day 1) identifiers
   b. Review of ECGs from a particular subject should be performed by a single reader
   c. Pre-specify the lead for interval measurements
   d. Baseline and on-treatment ECGs should be based on the same lead

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response.

In response to the FDA recommendation above, Aragon has revised Appendix 8 of the protocol to state that ECGs will be read by independent cardiologists from the central laboratory in a blinded manner and via single reader paradigm. Though the specific lead for interval measurements is not stated in the revised Appendix 8 of the main protocol, the same lead will be used for baseline and on-treatment ECGs.
FDA Response to Question 10 (November 1, 2012):

Yes. We have the following additional comments:

2. We are also interested in the effects of the ARN-503 on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

3. When you submit your QT study report, please include the following items:
   a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
   b. Electronic copy of the study report
   c. Electronic or hard copy of the clinical protocol
   d. Electronic or hard copy of the Investigator's Brochure
   e. Annotated CRF
   f. A data definition file which describes the contents of the electronic data sets
   g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
   h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcL, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcL, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
   i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
   j. Narrative summaries and case report forms for any
      i. Deaths
      ii. Serious adverse events
      iii. Episodes of ventricular tachycardia or fibrillation
      iv. Episodes of syncope
      v. Episodes of seizure
      vi. Adverse events resulting in the subject discontinuing from the study
   k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
   l. A completed Highlights of Clinical Pharmacology Table

4. Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at www.cardiac-safety.org/library.
Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response and additional comments.

FDA Additional Comment 1 (November 1, 2012):

1. **Time to Symptomatic Progression Endpoint**: This composite endpoint, while important as supportive evidence for efficacy, can be problematic and is unlikely to be included in labeling.
   - Elements of symptomatic progression (e.g., radiation, surgery, nephrostomy tube placement, suprapubic catheter insertion, ureteral stenting) should be clearly and prospectively captured in the CRF.
   - Capture the indication for initiation of new systemic therapy carefully in the CRF.
   - Take care to avoid PSA rise or other asymptomatic indications for initiation of new systemic therapy as an event for this endpoint.

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response and will incorporate the comments appropriately.

FDA Additional Comment 2 (November 1, 2012):

2. **Change Time to Initiation of Systemic Therapy to Time to initiation of Cytotoxic Chemotherapy**:
   - Include a single Yes/No question for both on-study and follow up CRFs; Has the patient received cytotoxic chemotherapy since the last visit?
   - Please capture the name of the cytotoxic drug in the CRF.

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response and will incorporate the comments appropriately.

FDA Additional Comment 3 (November 1, 2012):

3. **Bone Scans**: The following may improve the interpretability of Bone Scan Results:
   - include extremities and skull in all exams
   - use digital images for independent review
   - capture reading radiologist/nuclear medicine comments for each overall assessment

Aragon Response (November 5, 2012):

Aragon acknowledges the FDA response

FDA Additional Comment 4 (November 1, 2012):

4. **Definition of MFS Events**:
The number of patients with bone scan abnormalities who do not have an X-ray/CT/MRI done to confirm the lesion will be a review issue.

**Aragon Response (November 5, 2012):**

Aragon acknowledges the FDA response

**FDA Additional Comment 5 (November 1, 2012):**

5. **PRO HROOL:**
   The FDA does not currently recognize FACT-P or EQ-5D as valid PRO instruments for labeling purposes. Nonetheless, we encourage the capture of this data, and results will be reviewed and taken into consideration in the overall risk-benefit assessment of the application.

**Aragon Response (November 5, 2012):**

Aragon acknowledges the FDA response and does not intend to seek labeling claims based on PRO endpoints.

**FDA Additional Comment 6 (November 1, 2012):**

6. **Subsequent Therapies:**
   Careful collection of subsequent prostate cancer therapies will be critical. The analysis of subsequent therapies with respect to the interpretation of overall survival results will be a review issue.

**Aragon Response (November 5, 2012):**

Aragon acknowledges the FDA response. Please also see Aragon’s reply above to the FDA response to Question 6b.

In addition, we sent two additional comments on November 6, 2012.

**FDA Comment 1 (November 6, 2012):**

1. **Prespecify the recommended imaging technique for bone scans (technetium-99 or other).** Record the type of bone imaging performed for each bone scan imaging assessment in the CRF. Differences in bone scan techniques between the arms will be a review issue.

**Aragon Response (November 6, 2012):**

Aragon confirms that Technetium-99m bone scintigraphy (Tc-99m bone scans) is the pre-specified imaging technique for all bone scans. We would also like to note that in the event Technetium-99m (Tc-99m) is unavailable (e.g., isotope supply shortages), Sodium Fluoride
(NaF) PET scans or whole body bone MRI scans could be acceptable as bone imaging alternatives. This information will be clearly reflected in the final BICR Charter.

Aragon confirms that the type of bone imaging performed for each bone scan imaging assessment will be recorded in the CRF.

Aragon acknowledges the FDA comment above (i.e. differences in bone scan techniques between the arms will be a review issue).

**FDA Comment 2 (November 6, 2012):**

2. Prespecify in your BICR charter that the date of an MFS event will be captured as the date of the bone scan which first noted the lesion confirmed by CT/MRI or X-ray.

**Aragon Response (November 6, 2012):**

Aragon agrees with the FDA comment and confirms that the date of an MFS event will be captured as the date of the bone scan which first noted the lesion confirmed by CT/MRI or X-ray. This definition is consistent with our plan and will be stated in the final BICR Charter.

You are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].


Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007,” that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information

When submitting the certification for this application, do not include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to IND 104676, clinical protocol submitted on September 26, 2012, your clinical protocol number, if available, and that it contains the FDA Form 3674 that was to accompany that submission.

If you have already submitted the certification for this submission, please disregard the above.

If you have any questions, call Amy Tilley, Regulatory Project Manager, at (301) 301-796-3994.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMNA IBRAHIM
11/09/2012
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Guidance

Meeting Date and Time: February 28, 2012 11:00 am
Meeting Location: WO Bldg 22, Rm 1309

Application Number: IND 104676
Product Name: ARN-509
Indication: Castration-Resistant Prostate Cancer
Sponsor/Applicant Name: Aragon Pharmaceuticals, Inc.
Meeting Request Date: November 9, 2011
Meeting BGP date: January 26, 2012

Meeting Chair: V. Ellen Maher, M.D., Clinical Team Leader
Meeting Recorder: Amy Tilley, Regulatory Project Manager

FDA ATTENDEES:

Robert Justice, M.D., M.S., Director, DOP1
Amna Ibrahim, M.D., Deputy Division Director, DOP1
V. Ellen Maher, M.D., Clinical Team Leader
Paul G. Klueetz, M.D., Medical Officer
Anne M. Pilaro, Ph.D., Supervisory Toxicologist
Brian Chiu, Ph.D., Senior Toxicologist
Qi Liu, Ph.D., Team Leader, Office of Clinical Pharmacology, DCP5, Internal only
Monica Fisman, Ph.D., Pharmacometrics Reviewer, Telephone
Nitin Mehrotra, Ph.D., Pharmacometrics Reviewer, Telephone
Shenghui Tang, Ph.D., Team Leader, DB 5
Somesh Chattopadhyay, Ph.D., Mathematical Statistician, DB 5
Amy Tilley, Regulatory Project Manager

SPONSOR ATTENDEES:

Aragon Pharmaceuticals, Inc.

Isan Chen, M.D., Chief Medical Officer
Richard Heyman, Ph.D., President and Chief Executive Officer
Edna Chow Maneval, Ph.D., Senior Director, Clinical Development

Reference ID: 3094620
Peter Rix, DABT, Director, Drug Safety and Disposition
Bao Truong, Director, Regulatory Affairs

External Consultant
1.0 BACKGROUND

ARN-509 is a potent and selective orally administered androgen receptor (AR) antagonist. Its mechanism is disruption of the androgen-AR interaction and prevention of AR translocation into the nucleus. It has no significant AR agonism which may provide an advantage over other commonly used anti-androgens such as bicalutamide. In addition, ARN-509 provides a 5-fold greater affinity for the AR than bicalutamide. Preclinical studies revealed seizures at higher doses in beagle dogs as well as deaths in rats (no etiology was found upon pathologic examination). Clinical data for the use of ARN-509 in prostate cancer patients has been obtained in the ongoing ARN-509-001 phase I/II clinical trial. Phase I data from 24 patients treated at doses from 30mg per day to 300mg per day reveal PSA decline >50% in 14/24 patients at all doses. Declines >50% were seen in a third of patients at the 12 week time point. ARN-509 appears to be well-tolerated with no MTD reached. There was one DLT of treatment-related abdominal pain at 300mg, but no other DLT for 5 other patients treated at that dose. The most commonly reported AEs were Fatigue (38%), Nausea (25%), Dyspnea (25%), Peripheral edema (21%) and Arthralgia (21%). There were no deaths and no seizures reported. There is an ongoing phase 2 program at the recommended phase 2 dose of 240mg once daily. Populations being treated include non-metastatic castration resistant prostate cancer (nm-CRPC) who are treatment naive (chemotherapy and abiraterone treatment naive), metastatic CRPC who are treatment naive and metastatic CRPC who chemotherapy naive but have been treated with abiraterone.

In the meeting briefing package, Aragon Pharmaceuticals stated that the planned nonclinical studies to support marketing of ARN-509 will include genetic toxicology studies with ARN-509 and its metabolite ARN000308, safety pharmacology studies on respiratory function with ARN-509 and ARN000308 in rats, and 13-week, repeat-dose toxicity studies with ARN-509 in male rats and dogs.

The sponsor pre-meeting package includes a development plan for the treatment of patients with high-risk, non-metastatic castration resistant prostate cancer patients. The proposed phase 3 clinical protocol (ARN-509-003) intends to randomize high risk nm-CRPC patients 2:1 to 240mg once daily of continuous ARN-509 or placebo. High risk for prostate cancer morbidity or mortality is defined as a PSA doubling time of less than 10 months. The primary efficacy endpoint will be metastasis free survival (MFS) defined as time from randomization to death or first evidence of radiographically-detectable bone or soft tissue metastases determined by blinded independent central radiographic review. Key secondary endpoints include overall survival, time to metastasis, patient reported outcomes (FACT-P and EQ-5D), safety and tolerability and population pharmacokinetics. Patients discontinued from the study due to disease progression will be followed for survival and subsequent anti-cancer agents every 2 months until death, loss of follow-up or withdrawal of consent. The primary efficacy endpoint of MFS will be performed on the ITT population.

The study provides 90% power to detect a 30% reduction in the risk of developing metastases (HR=0.70) for patients receiving ARN-509 with 2-sided alpha of 0.05. There will be one interim analysis for the key secondary endpoint of overall survival performed at the time of the efficacy analysis for MFS. It is estimated that 46% of OS events will have occurred. Using the Lan-
Demets method for group sequential trials with O'Brien-Fleming boundaries, the levels of significance for the interim and final analyses of OS will be 0.0019 and 0.04936 respectively.

The intent of this meeting is to obtain agreement on the adequacy of the proposed toxicology program and to discuss and gain agreement on the acceptability of the proposed phase 3 study plan and statistical analysis plan.

2.0 DISCUSSION

Nonclinical:

1. Does the Agency agree that the nonclinical toxicology studies that have been completed to date and those that are planned are sufficient to support the clinical development and eventual marketing of ARN-509 for the treatment of patients with high risk NM-CRPC? Specifically, does the Agency agree with the plan not to conduct additional repeat-dose toxicity, carcinogenicity, or reproduction toxicology (fertility, embryo-fetal development, or peri-/post-natal development) studies with ARN-509 for the proposed indication? (see Section Error! Reference source not found.)

FDA Response:


FDA agrees that Aragon Pharmaceuticals does not need to conduct additional chronic toxicity studies (specifically in female animals), carcinogenicity or developmental and reproductive toxicity testing to support the proposed indication of high-risk, non-metastatic castration resistant prostate cancer.

Aragon 2-27-2012 Response:

We agree with the Agency’s advice, and genetic toxicology studies with ARN000066 will also be conducted to support marketing of ARN-509 for the proposed indication.

Meeting Discussion:

FDA confirmed that chronic toxicology (6-month studies) will not be required to support an NDA application. FDA further clarified that female animals are not necessary for testing in the 3-month study planned to support clinical development in this patient population.
Clinical:

Regarding the adequacy of the proposed pivotal Study ARN-509-003 entitled, “A Multicenter, Randomized, Double-blinded, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer” (see Section Error! Reference source not found.), to support the approval of ARN-509 for the proposed indication:

2. Is the proposed target patient population adequately defined as per the study eligibility criteria? Specifically, does the Agency agree that the proposed definition of rapidly rising PSA (defined as PSADT ≤ 10 months) appropriately selects patients who are at high risk for developing metastatic prostate cancer and for dying from prostate cancer?

FDA Response:

No. Although non-metastatic castration resistant prostate cancer (nm-CRPC) patients with a PSA doubling time of less than 10 months is a reasonable patient population to study, pelvis lymph nodes in their short axis will be eligible for entry. We recommend excluding patients with lymph nodes > 1 cm in short axis. Alternatively, provide your rationale for including patients with pelvic lymph nodes cm.

Exclude patients with prostate/bladder masses with evidence of baseline hydrenephrosis 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.

Aragon 2-27-2012 Response:

- In response to the Agency’s feedback above, we would like to provide the rationale for including patients with pelvic lymph nodes cm in short axis as follows:
We agree to exclude patients with prostate/bladder masses with evidence of baseline hydronephrosis or significant or worsening urethral obstruction.

PSA doubling time (PSADT) will be calculated using a linear regression model. In the model, the natural logarithm (ln) of PSA will be modeled as a linear function of time. The PSADT will be calculated as the product of ln(2) and the reciprocal of the slope of the regression equation. To ensure accurate and consistent determination of PSADT across all sites, the PSADT formula will be programmed into an IVRS:

- Site staff will enter PSA values in ng/mL and corresponding collection dates into the IVRS:
  - All PSA values must be obtained within 6 months (180 days) prior to randomization
  - There must be at least 2 PSA values collected
  - The first and last PSA values used in the calculation must be separated by at least 8 weeks
- The IVRS will perform the actual PSADT calculation.

To assure eligibility, the IVRS output will be reviewed by the medical monitors.

**Meeting Discussion:**

The sponsor will provide literature to support their decision to include patients with pelvic lymph nodes less than 8 cm on the study. FDA will review this literature and discuss these entry criteria further with the sponsor. The sponsor will exclude patients with locally advanced disease such as a large prostate mass, pre-existing hydronephrosis or urinary outlet obstruction.

The sponsor has clarified their plan to assess PSA doubling at the time of randomization. Their plan appears to be acceptable.

3. Is the proposed use of a placebo-control appropriate to assess the efficacy of ARN-509 in the proposed patient population?

**FDA Response:**

Yes. Given there are no approved therapies in the non-metastatic CRPC setting, the use of a placebo would be acceptable. The availability of frequently used, although off-label, standard second line hormonal therapies such as flutamide, nilutamide, bicalutamide as well as ketoconazole must be made clear in the patient informed consent document. In addition, we are concerned regarding the ability to keep patients on trial (in either arm) when faced with persistently rising PSA. The ability to retain patients with a rising PSA may affect the interpretability of the results and will be a review issue.
Aragon 2-27-2012 Response:

We will implement your recommendation regarding availability of off-label, standard second line hormonal therapies in the patient informed document.

We acknowledge the Agency's feedback on the ability to retain patients with a rising PSA.

Meeting Discussion:

None

4. Does the Agency agree that the primary endpoint of metastasis-free survival (MFS), defined as time from randomization to first evidence of radiographically detectable (bone or soft tissue) metastasis (as determined by a blinded independent central review) or death, whichever occurs earlier, can be an appropriate endpoint for demonstration of clinical benefit in the proposed patient population?

   a. Does the Agency agree with the proposed definition of the primary endpoint?

FDA Response:

No. It is acceptable to use RECIST for detection of soft tissue and visceral metastases. It is not acceptable to use (b) (4) to detect new bone metastases. Please modify the protocol so that an abnormal bone scan will trigger an immediate confirmatory X-ray of the area and, if this is inconclusive, will prompt a CT or MRI scan of the lesion. All scans/films should be reviewed by an independent radiology committee.

Please explain how you will address clinical events related to local growth of prostate cancer such as requirement for trans-urethral resection of the prostate (TURP) or new hydronephrosis thought due to local progression.

Aragon 2-27-2012 Response:

- We agree with the Agency's advice not to use (b) (4) to detect new bone metastases. For the determination of new bone metastases based on bone scans, we plan to modify the protocol as follows:
  - If a new bone metastasis has already been confirmed by CT or MRI, there will be no need for an additional confirmatory X-ray.
  - If a new bone metastasis has already been confirmed by X-ray, there will be no need for an additional confirmatory CT or MRI.
  - If a new bone metastasis is not confirmed by X-ray, then a confirmatory CT or MRI will be performed.
- All scans/films will be reviewed by an independent radiology committee.
- In response to the Agency's request for clarification on how we plan to address clinical events related to local growth of prostate cancer (e.g., local disease...
progression), we intend to capture such events and will evaluate them as part of the planned secondary endpoint of rPFS (radiographic progression-free survival). This change will be reflected in the final protocol.

Meeting Discussion:

The sponsor’s plan appears to be acceptable.

b. Would a treatment effect on MFS that reflects at least 30% reduction in the risk of metastasis or death relative to the placebo arm be considered a clinically meaningful benefit in high risk NM-CRPC?

FDA Response:

Possibly. The final determination of clinically meaningful benefit will be based on the relative and absolute magnitude of improvement in MFS, the results of key secondary endpoints and the safety profile of the product.

Aragon 2-27-2012 Response:

We acknowledge the Agency’s feedback.

Meeting Discussion:

None

5. Does the Agency agree with the proposed primary and secondary efficacy analyses, as described in the draft statistical analysis plan for Study ARN-509-003?

FDA Response:

- Please pre-specify the hypothesis, alpha and power for the analysis of the overall survival.
- For patients who receive non-protocol anti-cancer therapy prior to documented disease progression (development of metastases) or death, MFS should be censored at the last tumor assessment before the start of the new therapy, not at the start of the new therapy.
- To make any efficacy claims based on secondary endpoints, Type I error rate must be adjusted for multiple secondary endpoints.
- Your proposed PRO endpoints are unlikely to support labeling claims. See the PRO Guidance.
Aragon 2-27-2012 Response:

- Although not included in the protocol synopsis, this was outlined in Section 9.2 of our meeting background package. The study is also sized to provide 85% power to detect a 25% reduction (HR = 0.75) in risk of death for patients receiving ARN-509, based on an assumed median overall survival (OS) of 49 months in the placebo arm. The final analysis of OS will occur after approximately 489 deaths have occurred. In order to adjust for a single interim analysis of OS, which will occur only if the primary analysis of MFS is statistically significant, the levels of significance for the interim and final analyses of OS will be 0.0019 and 0.04936, respectively. This will be reflected in the final protocol and statistical analysis plan.

- We agree with the Agency's advice that, for patients who receive non-protocol anticancer therapy prior to documented disease progression (development of metastases) or death, MFS should be censored at the last tumor assessment before the start of the new therapy, not at the start of the new therapy. This will be reflected in the final protocol and statistical analysis plan.

- We acknowledge the Agency's feedback on efficacy claims based on secondary endpoints. Apart from the key secondary endpoint of OS, we do not intend to seek labeling claims based on PROs or any of the other planned secondary endpoints.

Meeting Discussion:

The sponsor presented their plan for blinding patients and investigators to PSA. The sponsor will use a central laboratory and both Aragon and the investigator will be blinded to these results. The number of patients who discontinue without an event will be a review issue.

FDA and the sponsor discussed the handling of patients who develop local disease progression. The sponsor noted that they plan to exclude patients with marked local disease. Patients on both the treatment and placebo arms will receive treatment for local control if necessary. However, this will not be considered a metastasis free survival event. FDA suggests that the requirement for local intervention to the primary tumor or surrounding lymph nodes be considered a PFS event. The number of patients who discontinue due to local disease progression will be a review issue.

6. Assuming treatment with ARN-509 provides a robust MFS improvement and a favorable benefit-risk profile, does the Agency agree that the proposed Phase III Study ARN-509-003 is adequate in design and size to support approval of ARN-509 for the treatment of patients with high risk NM-CRPC?

FDA Response:

No please see responses above.

Furthermore, 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 should be well-designed, well-conducted, internally consistent, and provide statistically and
clinically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform.


Aragon 2-27-2012 Response:

We acknowledge the Agency’s feedback above.

Meeting Discussion:

None

7. Does the Agency have any comments, suggestions or recommendations regarding any aspect of the development of ARN-509 that are not addressed in the preceding questions?

FDA Response:

Figure 7 in the briefing book presents information from the Phase 1 study on the change in PSA with various doses of study drug. This does not show a dose-response effect for ARN-509 and does not provide a basis for the decision to use 240 mg/daily as the recommended Phase 2 dose. In the absence of this information, we strongly recommend that you study more than one dose in a randomized Phase 2 and/or Phase 3 study.

Please provide information on disease status (rather than PSA) following treatment with ARN-509 in your ongoing Phase 1-2 program.

Aragon 2-27-2012 Response:

We acknowledge the Agency’s recommendation. We intend to provide adequate safety and efficacy data from the ongoing Phase I/II program (> 100 patients) to support use of 240 mg/daily in the Phase III study.

Consistent with the Agency’s request above, we will provide information on disease status, in addition to PSA, following treatment with ARN-509 in the ongoing Phase I/II program in the eventual clinical study report.

Meeting Discussion:

None
Additional Comments:

1. Your submitted clinical safety database is limited. The most current safety and efficacy results from your phase 2 program should be provided with the submission of your SPA / final protocol. Please present adverse events as all adverse events and adverse events which occurred after 3 weeks on study drug (steady-state).

   **Aragon 2-27-2012 Response:**

   Per the Agency’s request, we will provide the most current safety (including adverse events as all adverse events and adverse events which occurred after 3 weeks on study drug) and efficacy results from the Phase II program with submission of the final protocol/SPA.

2. Publicly available data from the February 8, 2012 oncology drug advisory committee meeting on denosumab in nm-CRPC noted that the relative risk of developing bone metastases in a clinical trial of nm-CRPC patients went up dramatically at a PSA doubling time cutoff of less than or equal to 8 months. The 8 month cutoff may provide a higher risk population with earlier events and possibly a more pronounced treatment effect.

   **Aragon 2-27-2012 Response:**

   We acknowledge the Agency’s feedback.

3. Your informed consent document will be carefully reviewed to ensure that patients are made aware of standard off-label secondary hormonal agents that are frequently used in this disease setting.

   **Aragon 2-27-2012 Response:**

   We will incorporate the Agency’s feedback in the final informed consent document.

4. A detailed list of prohibited concomitant medications should be included in your full protocol.

   **Aragon 2-27-2012 Response:**

   We will incorporate the Agency’s feedback in the final protocol.

5. If you wish to include data on patient reported outcomes (PRO) assessments in the label, we recommend you consult with the FDA in order to assess the validity of the PRO instruments used prior to the completion of the design of your phase 3 protocol.
Aragon 2-27-2012 Response:

As noted above, apart from the key secondary endpoint of OS, we do not intend to seek labeling claims based on PROs or any of the other planned secondary endpoints.

6. Regarding the phase 3 protocol ARN-509-003, we recommend that you:
   a. Use the results from the food effect study (ARN-509-001) to determine how to dose ARN-509 with regard to food.
   b. Analyze the PK samples for both ARN-509 and the active metabolite ARN00308 in the phase 3 protocol.
   c. Use caution when co-administering strong inhibitors or inducers of CYP3A4 with ARN-509.

Aragon 2-27-2012 Response:

We plan to implement all of these recommendations.

7. During ARN-509 drug development, we remind you to:
   a. Evaluate the in vitro ability of ARN-509 (and its metabolites) to act as substrates, inhibitors or inducers of cytochrome P450 enzymes, conjugating enzymes and transporters to determine the need for drug interaction trial(s). Refer to the Guidance for Industry found at
   b. Use the results from the in vitro cytochrome P450 enzyme inhibitor and inducer studies to determine the need for drug interaction trial(s). Refer to the Guidance for Industry found at
   c. Identify the pathways by which ARN-509 (and its metabolites) are eliminated and excreted to determine the need for organ impairment trial(s). Please refer to the Guidance for Industry found at
      http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf and
   d. Determine bioavailability of ARN-509 in humans per Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations found at
   e. Validate the analytical methods used to determine the concentrations of ARN-509 (and its metabolites). Refer to the Guidance for Industry Bioanalytical Method Validation
f. Explore the exposure-response relationships for ARN-509 (and its metabolites) for measures of both effectiveness and toxicity. Refer to Guidances for Industry found at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and

Aragon 2-27-2012 Response:

We plan to implement all of these recommendations.

8. In an ongoing ventricular repolarization sub-study (see study ARN-509-001), triplicate ECG recordings are performed approximately 2 min apart pre-dose on Cycle 1 Day 1 and prior to blood draws for pharmacokinetic analyses at pre-dose, 4 h (T\text{max}) and 24 h post dose on both Cycle 3 Day 1 and Cycle 3 Day 15 (Appendix B of this package). However, based on the information provided, T\text{max} of the parent, M3 and M4 is 1.5, 8 and 6 h, respectively. ECG samples should be collected at steady state to capture the expected T\text{max} of the parent and the metabolites.

Aragon 2-27-2012 Response:

We acknowledge the Agency’s feedback. As outlined in the meeting background package, we are collecting QT and PK data in the ongoing Phase II study. Data from the ventricular repolarization sub-study, combined with data from Phase I study and pre-clinical evaluations, will further inform the design of additional QT evaluation in the context of your comment.

9. To characterize ARN-509 sponsor should perform an ECG sub-study in oncology patients (Am Heart J 2009; 157:827-836) with the following criteria:

- Study should have an adequate sample size to exclude large effects on the QT interval
- Collect Replicate ECGs with central over-read. ECG samples should be collected at steady state to capture the expected T\text{max} of the parent and the metabolites.
- Time matched ECG and PK sampling at adequate number of time points in the dosing interval to detect immediate and delayed effects on the QT interval.

Aragon 2-27-2012 Response:

Please see our response to Comment #8 above.
3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

None

Minutes Preparer: {See appended electronic signature page}

Amy Tilley
Regulatory Project Manager

Meeting Chair: {See appended electronic signature page}

V. Ellen Maher, M.D.
Clinical Team Leader
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/s/

AMY R TILLEY
02/29/2012

VIRGINIA E MAHER
02/29/2012
LATE-CYCLE COMMUNICATION DOCUMENTS
NDA 210951

LATE-CYCLE MEETING MINUTES

Janssen Biotech, Inc.
c/o Janssen Research & Development, LLC
Attention: Jessica Chung
Director, Global Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chung:

Please refer to your New Drug Application (NDA) dated October 10, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Erleada® (apalutamide) oral tablets, 60 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the Division of Oncology Products 1 (DOP1) on February 12, 2018.

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

If you have any questions, contact Amy Tilley, Regulatory Project Manager at 301-796-3994.

Sincerely,

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

Chana Weinstock, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 12, 2018, 1:00 pm – 2:00 pm
Meeting Location: Teleconference

Application Number: NDA 210951
Product Name: Erleada® (apalutamide)
Applicant Name: Janssen Biotech, Inc.

Meeting Chair: Chana Weinstock, MD, Cross Discipline Team Leader, DOP1
Meeting Recorder: Amy Tilley, Regulatory Project Manager, DOP1

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Chana Weinstock, MD, Clinical Team Leader, DOP1
Daniel Suzman, MD, Clinical Reviewer, DOP1
Dow-Chung Chi, MD, Clinical Reviewer, DOP1
Katherine Fedenko, MS, CRNP, Deputy Director Safety, DOP1
Christina Marshall, Safety Regulatory Health Project Manager
Lijun Zhang, PhD, Biostatistics Reviewer, OTS/OB/DBV
Qi Liu, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCPV
Wentao Fu, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Hisham Qosa, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Simbarashe Zvada, PhD, Pharmacometrics Reviewer, OTS/OCP/DPM
Xiao-Hong Chen, PhD, Chemistry Lead, OPQ/ONDP/DNDPI/NDPBII
Xing Wang, PhD, CMC Reviewer, OPQ/ONDP/DNDPI/NDPBII
Wei Chen, PhD, Pharmacology Toxicology Reviewer, DHOT
Susan Redwood, PhD, DMPP Reviewer, OMP/DMPP
Kelly Jackson, PhD, DMPP Reviewer, OMP/OMPI/DMPP
Kevin Wright, PhD, OPDP Reviewer, OMP/OPDP/DAPRI
Pritpal Singh, PhD, DPV Reviewer, OSE/OPE/DPVII
Naomi Redd, PhD, OSE/DRISK Reviewer, OSE/OMEPRM/DRISK
Shawnetta Jackson, PhD, OSE Project Manager, OSE/PMS
Carolyn McCloskey, MD, OSE Reviewer, OSE/OPE/DEPII
Christy Cottrell, Chief Project Management Staff, DOP1
Amy Tilley, Regulatory Project Manager, DOP1

APPLICANT ATTENDEES
Jessica Chung, MS, Director, Global Regulatory Affairs North America
Sandra Rattray, PhD, Vice President, Global Regulatory Affairs
1.0 BACKGROUND

NDA 210951 was submitted on October 10, 2017 for Erleada® (apalutamide).

Proposed indication: Non-metastatic castration resistant prostate cancer

PDUFA goal date: April 10, 2018

FDA issued a Background Package in preparation for this meeting on February 6, 2018.

2.0 DISCUSSION

1. Introductory Comments:

   Welcome, Introductions, Ground rules, and Objectives of the meeting were stated.

   Meeting Discussion: None

2. Information Requests:

   Meeting Discussion: No outstanding Information Requests at this time.

3. Postmarketing Requirements/Postmarketing Commitments:

   We remind you of your postmarketing commitment:
Meeting Discussion: Reiterated the following to the applicant. No additional discussion.

3324-1 SPARTAN, a phase 3 double-blind, randomized study of apalutamide versus placebo in patients with nonmetastatic castration-resistant prostate cancer [ARN-509-003].

The timetable you submitted on January 26, 2018, states that you will conduct this study according to the following schedule:

- Final Protocol Submission: 09/2017
- Study/Trial Completion: 12/2022
- Final Report Submission: 06/2023

4. Major Labeling issues:

Meeting Discussion: There are no major labeling issues at this time. The FDA revised PI will be sent to the applicant as soon as the labeling review has been completed.

5. Review Plans:

Meeting Discussion: The NDA review is still ongoing.

6. Wrap-up and Action Items:

Meeting Discussion: This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.
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/s/

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AMY R TILLEY
02/15/2018

CHANA WEINSTOCK
02/15/2018
Dear Ms. Chung:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Erleada® (apalutamide) oral tablets, 60 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 12, 2018. Attached is our background package, including our agenda, for this meeting.

Please email a list of your attendees at Charlene.Wheeler@fda.hhs.gov and Amy.Tilley@fda.hhs.gov, at least one week prior to the meeting.

If you have any questions, call Charlene Wheeler, MSHS, Senior Regulatory Project Manager, at (301)-796-1141 or Amy Tilley, Regulatory Project Manager at (301)-796-3994.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package
LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: February 12, 2018, 1-2PM
Meeting Location: T-CON
Application Number: NDA 210951
Product Name: Erleada® (apalutamide)
Indication: Non-metastatic castration resistant prostate
Applicant Name: Janssen Research & Development, LLC

FDA ATTENDEES (tentative)
Julia Beaver, MD Director, DOP1
Amna Ibrahim, MD Deputy Director, DOP1
Chana Weinstock, MD Clinical Team Lead
Daniel Suzman, MD Clinical Reviewer
Todd Palmby, PhD Pharm/Tox Team Lead
Wei Chen, PhD Pharm/Tox Reviewer
Xiao H. Chen, PhD Office Product Quality, Team Lead
Wentao Fu, PhD Clinical Pharmacology Reviewer
Qi Liu, PhD Clinical Pharmacology Team Lead
Charlene Wheeler, MSHS Senior Regulatory Project Manager

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM we may not be prepared to discuss that new information at this meeting.
BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

SUBSTANTIVE REVIEW ISSUES

No substantive review issues have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Information Requests – 10 minutes
   None outstanding.

3. Postmarketing Requirements/Postmarketing Commitments – 10 minutes
   We remind you of your postmarketing commitment:
   
   3324-1 SPARTAN, a phase 3 double-blind, randomized study of apalutamide versus placebo in patients with nonmetastatic castration-resistant prostate cancer [ARN-509-003].

   The timetable you submitted on January 26, 2018, states that you will conduct this study according to the following schedule:

   | Final Protocol Submission:          | 09/2017 |
   | Study/Trial Completion:            | 12/2022 |
   | Final Report Submission:           | 06/2023 |

4. Major Labeling issues – 10 minutes
   Revised USPI will be sent on February 6, 2018 to Applicant.

5. Review Plans – 10 minutes
   NDA review is ongoing.

6. Wrap-up and Action Items – 5 minutes
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/s/

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JULIA A BEAVER
02/06/2018