CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210951Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDASupplement #	**210951**
/PMC Set (####-#)	3324-1
Product Name:	Apalutamide
Applicant Name:	Janssen
ODE/Division:	**OHOP/DOP1**

SECTION B: /PMC Information

1. PMR/PMC Description

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]"

2. /PMC Schedule Milestones[2, 3]

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

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion,* and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

The results of 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]" that were submitted with the initial NDA were based on an interim analysis, with final OS results not expected until 12/2022 based on projected event rates.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☒ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☒ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** ***[Select either "Yes" or "No" and provide the appropriate responses.]***

☐ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** ***[Go to Q.5]***

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☒ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality**.

Insert electronic signature (usually the Deputy Director for Safety) Signature will be in DARRTS Final version document. KF

Appendix A
PMR/PMC Development Template (FRM-ADMIN-60)
Instructions for Use

[click here to return to the template]

Purpose:
The PMR/PMC Development template (thereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

Who completes this template:
The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

How to complete this template:
The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B "reportable" PMC.[10] The separate templates are then combined into one document for archiving (see "How to archive the completed template").

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

How to archive the completed template:
The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B "reportable" PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.[11] This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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[10] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

[11] A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

Instructions:

SECTION A: Administrative Information [Click here to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

SECTION B: PMR/PMC Information [Click here to return to Section B of the template]

1. **PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

   PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.[12]

   Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

   Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed ***[see Appendix B for examples]***.

2. **PMR/PMC Milestones**: List the PMR/PMC milestones in the specified format.

   Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

   The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

   The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.[13]

[12] The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

[13] "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period

"Other" milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.[14]

SECTION C: PMR/PMC Rationale [Click here to return to Section C of the template]

1. Describe the review issue and the goal of the study or clinical trial.

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.

DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

3. For FDAAA PMRs and 506B PMCs only

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needed to create a well-designed study or clinical trial. See FDA guidance for industry, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

[14] Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

This section applies only to FDAAA PMRs and 506B "reportable" PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS[15] and Sentinel's ARIA[16] system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

***Question 4.a*: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

***Questions 4.b-d*: Explanation of whether FAERS and Sentinel's postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency Memorandum*, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

***Question Q4.e*: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

[15] FDA Adverse Event Reporting System (FAERS)
[16] Active Risk Identification and Analysis (ARIA)

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, in include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

***Question Q4.f*: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.**

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either "type of study" or "type of clinical trial." Do not choose a option under both categories.

SECTION D: PMR/PMC Additional information [Click here to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?

Select "yes" if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

2. This study or clinical trial focuses on the following special population or circumstances:

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select "not applicable."

3. (Complete if applicable) Additional comments about the PMR/PMC.

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 "core" milestones).

Note: Additional milestones also must be tracked by the division (see MAPP 6010.2, *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

SECTION E: PMR/PMC Development Coordinator Statements [Click here to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division's Deputy Director for Safety) who will sign off on the completed Development Template.

1. The PMR/PMC is clear, feasible, and appropriate because (select all that apply):

Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

2. **The following ethical considerations were made with regard to randomized, controlled, clinical trials:**

   This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

   It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

3. **This PMR/PMC has been reviewed for clarity and consistency… reliability of drug quality**.

   This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

APPENDIX B

Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Hepatic Impairment

  Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#

  Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy.

- Drug-Drug Interactions (gastric acid reducing agents)

  Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.

- Drug-Drug Interactions-Induction

  Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

- Anti-Drug Antibody Responses

  Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient's test sample at each sampling point.

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/s/

CHRISTINA D MARSHALL
02/06/2018

KATHERINE M FEDENKO
02/06/2018

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

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

Memorandum

Date: **February 2, 2018**

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

Charlene Wheeler, MSHS, Senior Regulatory Health Project Manager (DOP1)

William Pierce, PharmD, Associate Director for Labeling, (DOP1)

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

CC: Brian Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Erleada® (apalutamide) tablets, for oral use

NDA: 210951

In response to DOP1's consult request dated October 16, 2017, OPDP has reviewed the proposed prescribing information (PI), patient package insert (PPI), container label and blister card labeling for the original NDA submission for Erleada® (apalutamide) tablets, for oral use (Erleada).

OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DOP1 on January 24, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on February 1, 2018.

OPDP has reviewed the attached proposed container label and blister card labeling submitted by the Sponsor to the electronic document room on January 11, and January 18, 2018, and we do not have any comments.

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

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/s/

KEVIN WRIGHT
02/02/2018

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

PATIENT LABELING REVIEW

Date:	February 1, 2018
To:	Julia Beaver, MD Acting Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kevin Wright, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ERLEADA (apalutamide)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 210951
Applicant:	Janssen Research & Development, LLC.

1 INTRODUCTION

On October 10, 2017, Janssen Research & Development, LLC., submitted for the Agency's review an original New Drug Application (NDA) 210951 for ERLEADA (apalutimide) tablets. The purpose of this submission is to seek approval of ERLEADA (apalutamide) for the treatment of patients with non-metastatic castration –resistant prostate cancer (NM-CRPC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on October 16, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ERLEADA (apalutamide) tablets.

2 MATERIAL REVIEWED

- Draft ERLEADA (apalutamide) PPI received on October 16, 2017, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on January 24, 2018.
- Draft ERLEADA (apalutamide) Prescribing Information (PI) received on October 16, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 24, 2018.

3 REVIEW METHODS

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

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

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
02/01/2018

KEVIN WRIGHT
02/01/2018

LASHAWN M GRIFFITHS
02/01/2018

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

NDA	210951
Brand Name	ERLEADA®
Generic Name	Apalutamide (JNJ-56021927; ARN-509)
Sponsor	Janssen Biotech, Inc.
Indication	Treatment of non-metastatic castration-resistant prostate cancer (NM-CRPC)
Dosage Form	Film-Coated Tablet for oral administration
Drug Class	Antagonist of the androgen receptor (AR)
Therapeutic Dosing Regimen	240 mg QD
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Well tolerated up to 480 mg QD; higher doses not tested because of pill burden.
Submission Number and Date	SDN 003; 10/10/2017
Review Division	DOP1

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

A QTc interval prolongation was observed in the dedicated QT study 56021927PCR1019 when apalutamide was administered as 240 mg QD. The largest upper bound of the 2-sided 90% confidence interval (CI) for the change from baseline in QTcF was 16 ms observed at 1 h post-dose on Cycle 3 Day 1. There was no placebo or positive control in this study. Statistically significant positive relationships between apalutamide concentration and ΔQTcF, as well as JNJ-56142060 (active metabolite) concentration and ΔQTcF, were observed.

In this open-label, phase 1b study, 45 male patients with castration-resistant prostate cancer enrolled and received at least one dose of apalutamide. Apalutamide 240 mg once daily was administrated in continuous 28-day treatment cycles.

Overall summary of findings is presented in Table 1 and Table 2:

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Apalutamide 240 mg Once Daily Dosing (FDA Analysis)

Treatment	N	Time (hour)	ΔQTcF Mean (ms)	ΔQTcF 90% CI (ms)
Apalutamide 240 mg QD	42	Cycle 3, Day 1, 1 h post-dose	12.3	8.2, 16.3

Table 2: The QTc Effects (Point Estimates and the 90% CI) at mean peak concentration of apalutamide and its major (active) metabolite at steady state (Cycle 3, Day 1) for Apalutamide 240 mg Once Daily Dosing (FDA Analysis)

Drug/Metabolite moiety	Mean peak concentration (µg/ml)	ΔQTcF Mean (ms)	ΔQTcF 90% CI (ms)
Apalutamide	6.0	14.2	9.4, 19.0
JNJ-56142060 (Metabolite)	5.8	12.1	8.0, 16.2

The study evaluated 240 mg QD dosing, which is the therapeutic dose. This produced mean C_{max} values of 6.0 µg/ml and 5.8 µg/ml for apalutamide and its major metabolite JNJ-56142060, respectively. Simulations based on data collected in DDI studies suggest that: i) ketoconazole (strong CYP3A4 inhibitor) may increase the steady-state C_{max} of apalutamide and active moieties (sum of unbound apalutamide plus the potency-adjusted unbound active metabolite JNJ-56142060) by 38% and 23%, respectively; ii) Gemfibrozil (strong CYP2C8 inhibitor) may increase the steady-state C_{max} of apalutamide and active moieties by 32% and 19%, respectively. The potential effect of severe renal impairment, end stage renal disease or severe hepatic impairment (Child-Pugh C) on PK has not been evaluated. No clinically significant differences in the pharmacokinetics of apalutamide and active metabolite were observed in subjects with mild/moderate renal impairment, or mild/moderate hepatic impairment (Child-Pugh A/B).

2 PROPOSED LABEL

This section contains the sponsor's proposed labeling related to the QTc effects, QT-IRT's proposed labeling and comments to the Division/sponsor regarding the labeling changes.

Sponsor's proposed labeling:

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

(b) (4)

QT-IRT's proposed labeling:

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of maximum therapeutic dose of apalutamide on the QTc interval was assessed in an open-label, uncontrolled, multi-center, single-arm dedicated QT study in 45 patients with castration-resistant prostate cancer. The maximum mean QTcF change from baseline was 12.4 ms (2-sided 90% upper CI: 16.1 ms). An exposure-QT analysis suggested a concentration-dependent increase in QTcF for apalutamide and its active metabolite *[see Warnings and Precautions (5.x)]*.

5.x QTc prolongation

In an uncontrolled open-label ECG study in 45 patients, a concentration-dependent QTc prolongation was observed. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating ERLEADA and monitor these electrolytes periodically during therapy. Avoid ERLEADA in patients with congenital long QT syndrome.

Reviewer's comments to the Division regarding labeling changes:

- The provided language is modeled based on approved labels for Eribulin mesylate (Halaven) and Crizotinib (Xalkori).
- The Division may also consider ECG monitoring for severe renal impairment and severe hepatic impairment because it is not certain whether the effect is due to the drug or metabolite alone and what is the likely impact on exposures of each with these organ impairment scenarios.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Apalutamide (JNJ-56021927; ARN-509) is a potent and specific antagonist of the androgen receptor (AR) that is being developed for the treatment of subjects with prostate cancer. The compound acts through inhibition of androgen receptor (AR) nuclear translocation and AR binding to androgen response elements. Apalutamide binds AR with 5-fold greater affinity than bicalutamide, and induces partial or complete tumor regression in both castration-sensitive and castration-resistant human prostate cancer xenograft models.

3.2 MARKET APPROVAL STATUS

Apalutamide is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 104676 (previous QT-IRT reviews dated 08/10/2015 and 06/23/2017 in DARRTS). The sponsor submitted the study report 56021927PCR1019, including electronic datasets and waveforms to the ECG warehouse.

4.2 QT STUDY

4.2.1 Title

An Open-label Phase 1b QT/QTc Study of JNJ-56021927 (ARN-509) in Subjects with Castration-Resistant Prostate Cancer

4.2.2 Protocol Number

56021927PCR1019

4.2.3 Study Dates

14 Jan 2016 – 20 Sep 2016

4.2.4 Objectives

4.2.4.1 Primary

The primary objective of this study was to evaluate the effects of apalutamide and its active metabolite JNJ-56142060 on ventricular repolarization (QTcF) by using time-matched ECGs at baseline and on study drug.

4.2.4.2 Secondary

- To evaluate the effect of apalutamide on other ECG parameters (heart rate [HR], QT interval, Bazett's QT correction [QTcB] interval, QT interval using study-specific Power [QTcP], RR interval, PR interval, QRS interval, T-wave morphology, and U-wave morphology).
- To evaluate the pharmacokinetics of apalutamide and its metabolite, JNJ-56142060.
- To determine the potential relationship between the plasma concentrations of apalutamide, JNJ-56142060, and QTcF.
- To evaluate the safety of apalutamide.

4.2.5 Study Description

4.2.5.1 Design

This was an open-label, multicenter, Phase 1b study with one dose level (240 mg QD) in patients with high-risk non-metastatic castrate resistant prostate cancer (NM-CRPC, defined as having a PSA doubling time of ≤10 months) or metastatic castrate resistant prostate cancer (mCRPC).

4.2.5.2 Controls

There was no placebo or positive control.

4.2.5.3 Blinding

See above.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There was a single treatment arm. All subjects were to receive 240 mg QD apalutamide.

Apalutamide was administered in continuous 28-day treatment cycles. Study drug was to be self-administered daily at home except for Cycle 1 Day 1, Cycle 1 Day 2, and Cycle 3 Day 1 (±2 days), when administration of apalutamide occurred at 9AM (following an overnight fast) at the study site under the supervision of site personnel.

4.2.6.2 Sponsor's Justification for Doses

The purpose of this study was to evaluate the effect of therapeutic doses of apalutamide and its active metabolite, JNJ-56142060, on ventricular repolarization in subjects with CRPC.

Reviewer's Comment: As per the protocol review, because the effect of all intrinsic and extrinsic factors was not known and doses up to 480 mg QD had been shown to be tolerable, the sponsor was advised to consider inclusion of a higher dose. Nevertheless, the sponsor has used the 240 mg QD dose for this study, which is the proposed therapeutic dose for the oncology indication in this submission.

4.2.6.3 Instructions with Regard to Meals

The doses were taken in fasted state on visits.

Reviewer's Comment: Acceptable. High fat meal results in ~16% decrease in C_{max}.

4.2.6.4 ECG and PK Assessments

See appendix 6.2.

Briefly, continuous 12-lead ECGs were collected by a daytime Holter monitor on Cycle 1 Day -1, Cycle 1 Day 1, and Cycle 3 Day 1 between 8:00 AM and 3:00 PM. On Cycle 1 Day 1 and Cycle 3 Day 1, time-matched pharmacokinetic (PK) samples were collected within 5 minutes after the scheduled time point for ECG selection/extraction by the

central reader. Following time points were included: Predose and 1, 2, 3, 4, 5 h post-dose. Holter recordings were sent to a blinded, third-party, central ECG contract laboratory for ECG selection/extraction, ECG interval measurements, and ECG interpretation.

Reviewer's Comment: Acceptable. The timing of ECG/PK sampling seems adequate to capture potential effects at T_{max} (~2 h at the single dose and 1 h at steady state for parent drug, M3 has a very flat profile at steady-state). Because there is considerable accumulation in both drug and metabolite and relatively flat profile over dosing interval for metabolite, the predose measurement at steady state (Cycle 3 Day 1) may not be able to differentiate between direct vs. delayed effects.

4.2.6.5 Baseline

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

4.2.7 ECG Collection

Continuous 12-lead ECGs were collected by a daytime Holter monitor to obtain digital ECGs. ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 45 male patients enrolled and received at least one dose of apalutamide; 43 patients were considered to have completed the study. All 45 enrolled patients were in the safety analysis set, and 43 patients were in the primary analysis set.

The average age (SD) of the 45 patients was 67.4 (7.6) years, ranging from 52 years to 86 years. The majority (42/45, 93.3%) of the patients were White, and all 45 patients were Not Hispanic or Latino.

4.2.8.2 Statistical Analyses

4.2.8.2.1 By-timepoint Analysis

The sponsor analyzed mean change from baseline in QTcF (ΔQTcF) using repeated-measures mixed model. The model and the results are displayed below.

The least square mean changes in QTcF interval from baseline over time and their associated 90% CIs are summarized in Table 3. The least square mean increases from baseline on Cycle 3 Day 1 ranged from 8.0 to 12.4 msec. The least square mean (SE) QTcF change at t_{max} (ie, at approximately 2 hours postdose) on Cycle 1 Day 1 and on Cycle 3 Day 1 were +1.9 (1.6) msec and +12.4 (2.1) msec, respectively. The upper limit of the 90% CI of the least square mean baseline corrected QTcF change at each postdose timepoint was below 10 msec for Cycle 1 Day 1 (maximum of upper limits = 4.5 msec) and above 10 msec, for Cycle 3 Day 1 (maximum of upper limits = 16.0 msec).

Table 3: Least Square Mean and 90% CI in Change from Baseline of QTcF Interval – Mixed Effect Model; Primary Analysis Set (Sponsor's Results)

	Apalutamide			
	N	LS Mean	SE	90% CI
QTcF (msec)				
Cycle 1 Day 1				
Predose	43	-0.7	1.59	(-3.4 ,1.9)
1 hour	41	-0.4	1.62	(-3.1 ,2.3)
2 hour	42	1.9	1.61	(-0.8 ,4.5)
3 hour	42	-3.1	1.61	(-5.8 ,-0.4)
4 hour	42	-2.1	1.61	(-4.8 ,0.6)
5 hour	41	-5.5	1.62	(-8.2 ,-2.8)
Cycle 3 Day 1				
Predose	42	12.0	2.14	(8.4 ,15.5)
1 hour	41	12.3	2.16	(8.7 ,15.9)
2 hour	42	12.4	2.15	(8.8 ,16.0)
3 hour	41	10.9	2.15	(7.3 ,14.5)
4 hour	41	8.2	2.15	(4.6 ,11.8)
5 hour	40	8.0	2.16	(4.4 ,11.6)

Note: A repeated-measures mixed model was used with time point, and baseline value of QTc as fixed effect, and subject as a random effect.

Modified from TPDQTC09 [/SAS/3945/56021927PCR1019/FILES/RE/CSR/PROGRAMS/TPDQTC09.SAS] 15JUL2017, 06:09

Source: Sponsor's clinical study report, Table 10, page 48

Reviewer's Comment: The sponsor's results are consistent with what we found. Please see the reviewer's analyses in section 5.2.1.1.

4.2.8.2.2 Assay Sensitivity

Not Applicable.

4.2.8.2.3 Categorical Analysis

The sponsor's categorical analysis results are displayed in the following Table 4 and Table 5.

Table 4: Incidence Count and Percentage of Subjects with any Pre- and Post-treatment QTcF Greater than 450, 480, and 500 msec; Primary Analysis Set (Sponsor's Results)

	Apalutamide			
	Baseline	Cycle 1 Day 1	Cycle 3 Day 1	Total(C1D1+C3D1)
Analysis set: Primary Analysis Set				43
QTcF (msec)				
>450 - ≤480	12 (27.9%)	6 (14.0%)	20 (46.5%)	20 (46.5%)
>480 - ≤500	0	0	1 (2.3%)	1 (2.3%)
>500	0	0	0	0

Note: Percentages are calculated with the number of subjects in primary analysis set as the denominators.
Only the worst value for a subject is presented.
Note: The Cycle 1 Day 1 Predose measurement and Cycle 1 Day -1 measurements are considered as baseline.

Modified from TPDQTC05A [/SAS/3945/56021927PCR1019/FILES/RE/CSR/PROGRAMS/TPDQTC05A.SAS] 26MAY2017, 04:23

Source: Sponsor's clinical study report, Table 11, page 50

Table 5: Incidence Count and Percentage of Subjects with any QTcF Increase from Baseline Greater than 30 and 60 msec; Primary Analysis Set (Sponsor's Results)

	Apalutamide		
	Cycle 1 Day 1	Cycle 3 Day 1	Total(C1D1+C1D3)
Analysis set: Primary Analysis Set			43
QTcF (msec)			
>30 - ≤60	2 (4.7%)	9 (20.9%)	9 (20.9%)
>60	0	1 (2.3%)	1 (2.3%)

Note: Percentages are calculated with the number of subjects in primary analysis set as the denominators.
Same subject may be counted in both categories.
The time-matched baseline is defined as the mean values of the triplicate ECG measurements taken on Cycle 1 Day -1 (including predose), at the time points matching with those on Cycle 1 Day 1 (including predose) and Cycle 3 Day 1 (including predose).

Modified from TPDQTC07A.RTF] [/SAS/3945/56021927PCR1019/FILES/RE/CSR/PROGRAMS/TPDQTC07A.SAS] 26MAY2017, 04:37

Source: Sponsor's clinical study report, Table 12, page 51

4.2.8.3 Safety Analysis

At the time of the clinical cutoff (CCO) date (20 Sep 2016), there was 1 subject (Subject (b) (6)) that died due to progressive disease on Study Day 120 (>30 days after the last study drug dose). This subject experienced an SAE of Grade 4 General Health deterioration on Study Day 114.

Five subjects experienced at least 1 serious adverse event (SAE). None of the SAEs were considered related to treatment with apalutamide.

Two subjects (Subjects (b) (6) and (b) (6) had dose interruptions during Cycle 2 due to AEs/SAEs, and the planned Cycle 3 Day 1 ECG and PK assessments were not performed. Subject (b) (6) continued treatment with apalutamide and was withdrawn due to progressive disease on Study Day 104. Subject (b) (6) was withdrawn during Cycle 2 (Study Day 55) due to progressive disease.

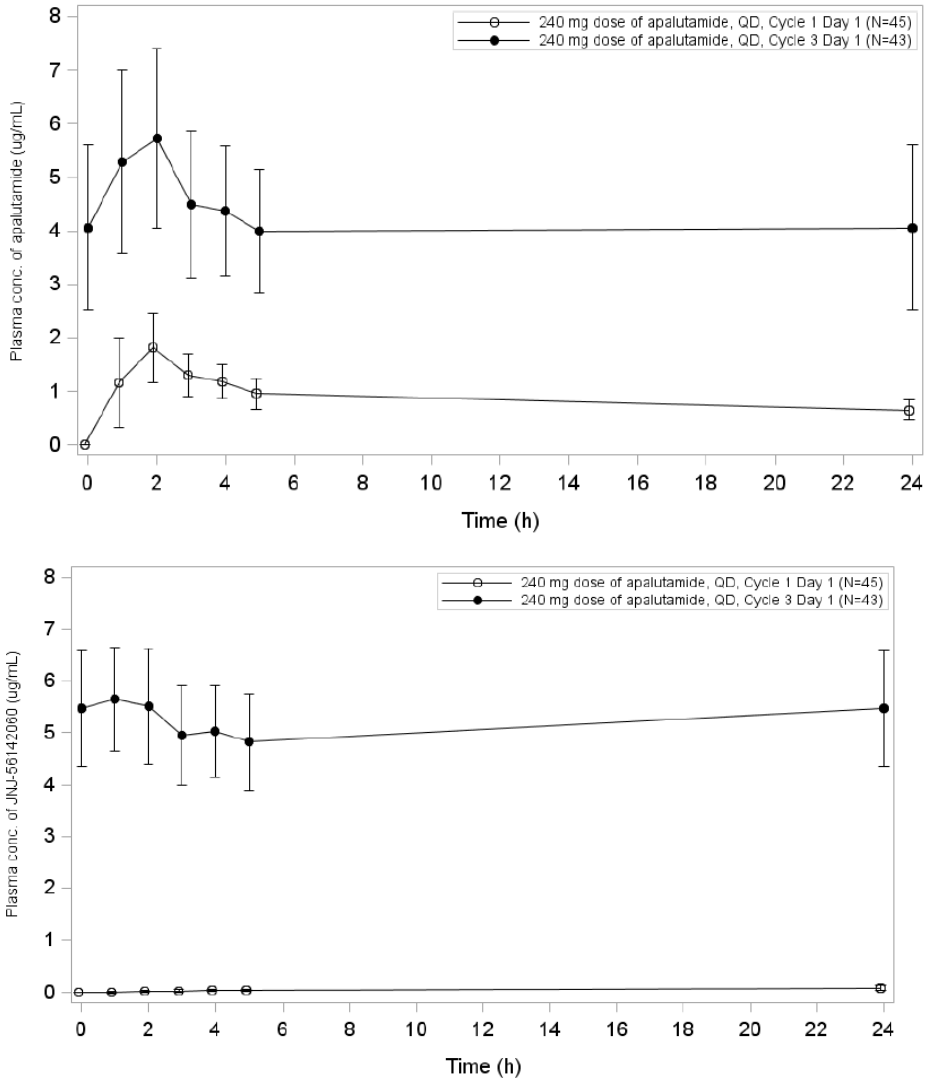
An additional 11 subjects discontinued treatment with apalutamide (ie, a total of 13/45, 29% of subjects discontinued treatment). Ten of the 11 subjects discontinued due to progressive disease, and 1 subject withdrew consent (Subject (b) (6) was experiencing Grade 3 anemia and felt too weak to continue in the study). As of the CCO date 20 Sep 2016, 32 subjects (71%) were continuing treatment with apalutamide.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The mean concentration-time profiles for apalutamide and its major metabolite JNJ-56142060 are illustrated in Figure 1. The PK results are presented in Table 6.

Figure 1: Mean (SD) Plasma Concentration-Time Profiles of Apalutamide (Top Panel) and JNJ-56142060 (Bottom Panel) After Administration of 240 mg Oral Apalutamide Once Daily on Cycle 1 Day 1 and Cycle 3 Day 1



Source: Sponsor's Clinical Study Report 56021927PCR1019, Figure 3 and Figure 4

Table 6: Summary of PK results for apalutamide and its metabolite JNJ-56142060

Analyte	**PK Parameters** (mean±SD, t_{max}: median [range])	**Apalutamide 240 mg qd** Cycle 1, Day 1	**Apalutamide 240 mg qd** Cycle 3, Day 1
Apalutamide	N	45	43
	C_{max}, µg/mL	2.06 ± 0.582	5.95 ± 1.66
	t_{max}, h	2.12 (1.08 – 5.10)	2.10 (1.00 – 4.17)
	AUC_{24h}, µg.h/mL	21.1 ± 4.93	100 ± 31.6
	C_{min}, µg/mL	-	3.72 ± 1.19
	PTR%	-	163 ± 24.7
	$AI_{(Cmax)}$	-	3.09 ± 1.26
	$AI_{(AUC24h)}$	-	4.95 ± 1.69
JNJ-56142060	N	45	43
	C_{max}, µg/mL	0.0919 ± 0.0570	5.85 ± 1.04
	t_{max}, h	24.00 (4.10 – 24.58)	1.10 (0.00 – 4.17)
	AUC_{24h}, µg.h/mL	1.41 ± 0.786	124 ± 23.0
	C_{min}, µg/mL	-	4.66 ± 0.897
	PTR%	-	127 ± 13.3
	$AI_{(Cmax)}$	-	82.1 ± 50.5
	$AI_{(AUC24h)}$	-	122 ± 108
	MPR C_{max}, %	-	105 ± 20.8
	MPR AUC_{24h}, %	-	133 ± 28.0

Source: Sponsor's Clinical Study Report 56021927PCR1019, Table 23 and Table 24

4.2.8.4.2 Exposure-Response Analysis

A linear mixed effects model was fit to the data with ΔQTcF as dependent variable and apalutamide concentration as a predictor and subject as a random effect. The statistical analysis indicated a significant correlation between the change in QTcF from baseline and apalutamide concentration (estimated slope was 2.89 with the associated 90% CI [2.11, 3.67]). Also, a linear mixed effects model was fit to the data with ΔQTcF as dependent variable and JNJ-56142060 concentration as a predictor and subject as a random effect. The statistical analysis indicated a significant correlation between the ΔQTcF and JNJ-56142060 concentration (estimated slope was 2.28 with the associated 90% CI [1.70, 2.85]).

Table 7 below shows the predicted ΔQTcF at mean peak concentrations of apalutamide and JNJ-56142060 with the above models.

Table 7: Predicted ΔQTcF at Mean Peak Plasma Concentration of Apalutamide and JNJ-56142060

Apalutamide

Period	Mean Cmax (ug/mL)	Estimate (msec)	Standard Error	90% CI (msec)
Cycle 1 Day 1	2.0637	2.5763	1.0293	(0.85, 4.31)
Cycle 3 Day 1	5.9472	13.8101	2.4022	(9.77, 17.85)

JNJ-56142060

Period	Mean Cmax (ug/mL)	Estimate (msec)	Standard Error	90% CI (msec)
Cycle 1 Day 1	0.0919	-1.1120	0.9299	(-2.67, 0.45)
Cycle 3 Day 1	5.8472	11.9818	2.0247	(8.58, 15.38)

Source: Sponsor's Clinical Study Report 56021927PCR1019, Table 26 and Table 28

Reviewer's Analysis: The values presented by the applicant for predicted ΔQTcF are comparable to that obtained in reviewer's analysis.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for their primary analysis, which is acceptable since no large changes in heart rate were observed, i.e. mean changes ≤10 bpm (section 5.2.2). Therefore, QTcF is used for all reviewer's assessments.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Apalutamide

The statistical reviewer listed mean of QTcF and used repeated-measures mixed model to analyze the ΔQTcF effect by cycle. The model includes time as a fixed effect. Baseline values are also included in the model as a covariate. The analysis results based on the primary analysis set are listed in the following Table 8.

Table 8: Analysis Results of QTcF and ΔQTcF

			QTcF (ms)		ΔQTcF (ms)			
Cycle	**Day**	**Time (Hour)**	**N**	**Mean (SE)**	**N**	**LSMean**	**SE**	**90% CI**
1	-1	Predose	43	430.1 (2.7)				
		1	42	431.9 (2.7)				
		2	42	432.7 (2.5)				
		3	42	426.5 (2.2)				
		4	42	426.5 (2.2)				
		5	41	425.7 (2.0)				
	1	Predose	43	429.0 (2.1)	43	-0.5	1.3	(-2.7, 1.8)
		1	42	430.1 (2.2)	41	-0.3	1.5	(-2.9, 2.2)
		2	43	432.4 (2.3)	42	1.9	1.8	(-1.0, 4.9)
		3	43	424.8 (2.1)	42	-3.1	1.6	(-5.8, -0.4)
		4	43	425.7 (2.2)	42	-2.2	1.6	(-4.9, 0.5)
		5	43	422.4 (2.4)	41	-5.4	1.9	(-8.6, -2.1)
3	1	Predose	42	441.6 (2.6)	42	11.9	2.0	(8.6, 15.2)
		1	42	442.8 (2.9)	41	12.3	2.4	(8.2, 16.3)
		2	43	442.9 (2.5)	42	12.4	2.2	(8.6, 16.1)

			QTcF (ms)		ΔQTcF (ms)			
Cycle	Day	Time (Hour)	N	Mean (SE)	N	LSMean	SE	90% CI
		3	42	439.3 (2.4)	41	11.1	2.2	(7.4, 14.7)
		4	42	436.5 (2.2)	41	8.3	1.8	(5.2, 11.4)
		5	42	436.1 (2.5)	40	7.7	2.1	(4.1, 11.3)

The largest mean change from baseline in QTcF (ΔQTcF) during Cycle 1 was 1.9 ms with a 90% CI of -1.0 ms to 4.9 ms. The largest mean ΔQTcF during Cycle 3 was 12.4 ms with a 90% CI of 8.6 ms to 16.1 ms.

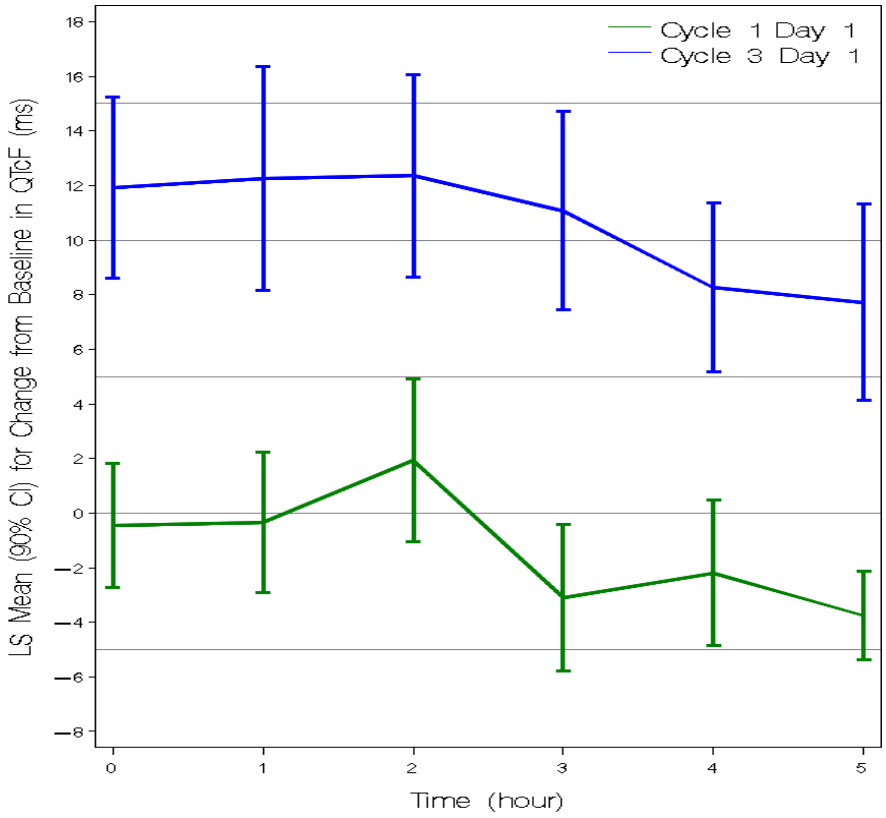
5.2.1.2 Assay Sensitivity Analysis

Not Applicable.

5.2.1.3 Graph of ΔQTcF Over Time

The following figure displays the time profile of ΔQTcF for apalutamide 240 mg once daily.

Figure 2: Mean and 90% CI ΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. No subject's QTcF was above 500 ms.

Table 9: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<=480 ms		480<QTcF<=500 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline/Predose	45	308	32 (71.1%)	278 (90.3%)	13 (28.9%)	30 (9.7%)	0 (0.0%)	0 (0.0%)
Cycle 1 Day 1	45	224	37 (82.2%)	207 (92.4%)	8 (17.8%)	17 (7.6%)	0 (0.0%)	0 (0.0%)
Cycle 3 Day 1	43	253	22 (51.2%)	187 (73.9%)	20 (46.5%)	65 (25.7%)	1 (2.3%)	1 (0.4%)

Table 10 lists the categorical analysis results for ΔQTcF.

Table 10: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms		ΔQTcF>60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Cycle 1 Day 1	44	218	42 (95.5%)	216 (99.1%)	2 (4.5%)	2 (0.9%)	0 (0.0%)	0 (0.0%)
Cycle 3 Day 1	43	247	34 (79.1%)	224 (90.7%)	8 (18.6%)	22 (8.9%)	1 (2.3%)	1 (0.4%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 11. The largest mean change from baseline in HR (ΔHR) during Cycle 1 was 3.1 bpm with a 90% CI of 0.4 bpm to 5.7 bpm. The largest mean ΔHR during Cycle 3 was 2.2 bpm with a 90% CI of -4.6 bpm to 2.6 bpm. No large HR change was found in the study (i.e., mean HR change ≤10 bpm).

The outlier analysis results for HR are presented in Table **12**.

Table 11: Analysis Results of HR and ΔHR

			HR (ms)		ΔHR (ms)			
Cycle	Day	Time (Hour)	N	Mean (SE)	N	LSMean	SE	90% CI
1	-1	Predose	43	68.0 (1.8)				
		1	42	67.0 (1.8)				
		2	42	73.0 (1.9)				
		3	42	72.5 (1.8)				
		4	42	76.7 (2.5)				
		5	41	73.4 (1.6)				
	1	Predose	43	68.6 (1.8)	43	-1.8	1.3	(-4.0, 0.4)
		1	42	67.5 (1.8)	41	-2.7	1.3	(-4.8, -0.6)
		2	43	75.0 (2.6)	42	2.9	2.2	(-0.8, 6.7)
		3	43	74.6 (2.5)	42	2.8	2.2	(-0.9, 6.4)
		4	43	76.5 (1.9)	42	3.1	1.6	(0.4, 5.7)
		5	43	74.8 (1.8)	41	2.7	1.4	(0.4, 5.0)
3	1	Predose	42	65.4 (2.0)	42	-4.1	1.1	(-6.0, -2.2)
		1	42	65.0 (2.0)	41	-3.8	1.2	(-5.7, -1.8)
		2	43	69.3 (1.8)	42	-2.8	1.1	(-4.7, -1.0)
		3	42	70.8 (2.5)	41	-1.0	2.2	(-4.6, 2.6)
		4	42	73.0 (2.0)	41	-1.3	1.8	(-4.3, 1.6)
		5	42	72.6 (1.7)	40	0.2	1.1	(-1.7, 2.1)

Table 12: Categorical Analysis for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline/Predose	45	43 (95.6%)	2 (4.4%)	44 (97.8%)	1 (2.2%)
Cycle 1 Day 1	45	42 (93.3%)	3 (6.7%)	45 (100%)	0 (0.0%)
Cycle 3 Day 1	43	41 (95.3%)	2 (4.7%)	41 (95.3%)	2 (4.7%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 13. The largest mean change from baseline in PR (ΔPR) during Cycle 1 was 2.0 ms with a 90% CI of -1.6 ms to 5.6 ms. The largest mean ΔPR during Cycle 3 was 2.6 ms with a 90% CI of -3.7 ms to 4.8 ms. The outlier analysis results for PR are presented in Table 14.

Table 13: Analysis Results of PR and ΔPR

			PR (ms)		ΔPR (ms)			
Cycle	**Day**	**Time (Hour)**	**N**	**Mean (SE)**	**N**	**LSMean**	**SE**	**90% CI**
1	-1	Predose	43	172.4 (3.5)				
		1	42	174.7 (3.8)				
		2	42	174.2 (3.9)				
		3	42	176.7 (4.1)				
		4	41	173.3 (3.9)				
		5	41	173.0 (3.8)				
	1	Predose	43	175.0 (3.6)	43	2.1	2.2	(-1.6, 5.7)
		1	42	175.7 (3.7)	41	2.0	2.1	(-1.6, 5.6)
		2	42	172.3 (3.2)	41	-0.7	1.5	(-3.3, 1.9)
		3	42	174.7 (3.7)	41	-0.0	1.9	(-3.2, 3.1)
		4	43	171.9 (3.6)	41	-1.8	1.8	(-4.9, 1.3)
		5	43	173.5 (3.6)	41	-0.5	1.7	(-3.3, 2.3)
3	1	Predose	42	174.4 (3.5)	42	1.8	2.0	(-1.7, 5.2)
		1	42	174.7 (4.0)	41	0.5	2.6	(-3.7, 4.8)
		2	43	175.4 (3.6)	42	1.7	1.7	(-1.2, 4.6)
		3	41	175.0 (4.0)	40	0.5	2.3	(-3.5, 4.4)
		4	42	171.6 (3.7)	40	-2.5	2.1	(-6.0, 1.0)
		5	42	173.7 (3.8)	40	0.3	1.6	(-2.4, 3.1)

Table 14: Categorical Analysis for PR

	Total N		PR<=200 ms		200<PR<=220 ms		PR>220 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline/Predose	45	307	33 (73.3%)	248 (80.8%)	6 (13.3%)	46 (15.0%)	6 (13.3%)	13 (4.2%)
Cycle 1 Day 1	45	222	35 (77.8%)	182 (82.0%)	8 (17.8%)	36 (16.2%)	2 (4.4%)	4 (1.8%)
Cycle 3 Day 1	43	252	33 (76.7%)	214 (84.9%)	6 (14.0%)	29 (11.5%)	4 (9.3%)	9 (3.6%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 15. The largest mean change from baseline in QRS (ΔQRS) during Cycle 1 was 1.1 ms with a 90% CI of 0.0 ms to 2.2 ms. The largest mean ΔQRS during Cycle 3 was 2.5 ms with a 90% CI of 1.0 ms to 4.0 ms. The outlier analysis results for QRS are presented in Table 16.

Table 15: Analysis Results of QRS and ΔQRS

			QRS (ms)		ΔQRS (ms)			
Cycle	Day	Time (Hour)	N	Mean (SE)	N	LSMean	SE	90% CI
1	-1	Predose	43	92.3 (1.1)				
		1	42	92.2 (1.1)				
		2	42	93.5 (1.2)				
		3	42	92.7 (1.2)				
		4	42	93.3 (1.2)				
		5	41	92.7 (1.3)				
	1	Predose	43	92.8 (1.2)	43	0.3	0.7	(-1.0, 1.5)
		1	42	93.2 (1.1)	41	0.8	0.7	(-0.4, 1.9)
		2	43	94.1 (1.1)	42	0.9	0.7	(-0.3, 2.1)
		3	43	93.5 (1.1)	42	0.7	0.7	(-0.5, 1.9)
		4	43	94.2 (1.1)	42	1.1	0.7	(0.0, 2.2)
		5	43	93.3 (1.1)	41	0.5	0.7	(-0.7, 1.6)
3	1	Predose	42	94.7 (1.3)	42	2.0	1.0	(0.4, 3.6)

			QRS (ms)		ΔQRS (ms)			
Cycle	Day	Time (Hour)	N	Mean (SE)	N	LSMean	SE	90% CI
		1	42	94.1 (1.2)	41	1.4	0.9	(-0.2, 2.9)
		2	43	95.6 (1.2)	42	2.5	0.9	(1.0, 4.0)
		3	42	95.1 (1.2)	41	2.2	0.9	(0.6, 3.7)
		4	42	95.2 (1.2)	41	2.1	0.9	(0.5, 3.6)
		5	42	95.0 (1.3)	40	2.2	0.9	(0.7, 3.7)

Table 16: Categorical Analysis for QRS

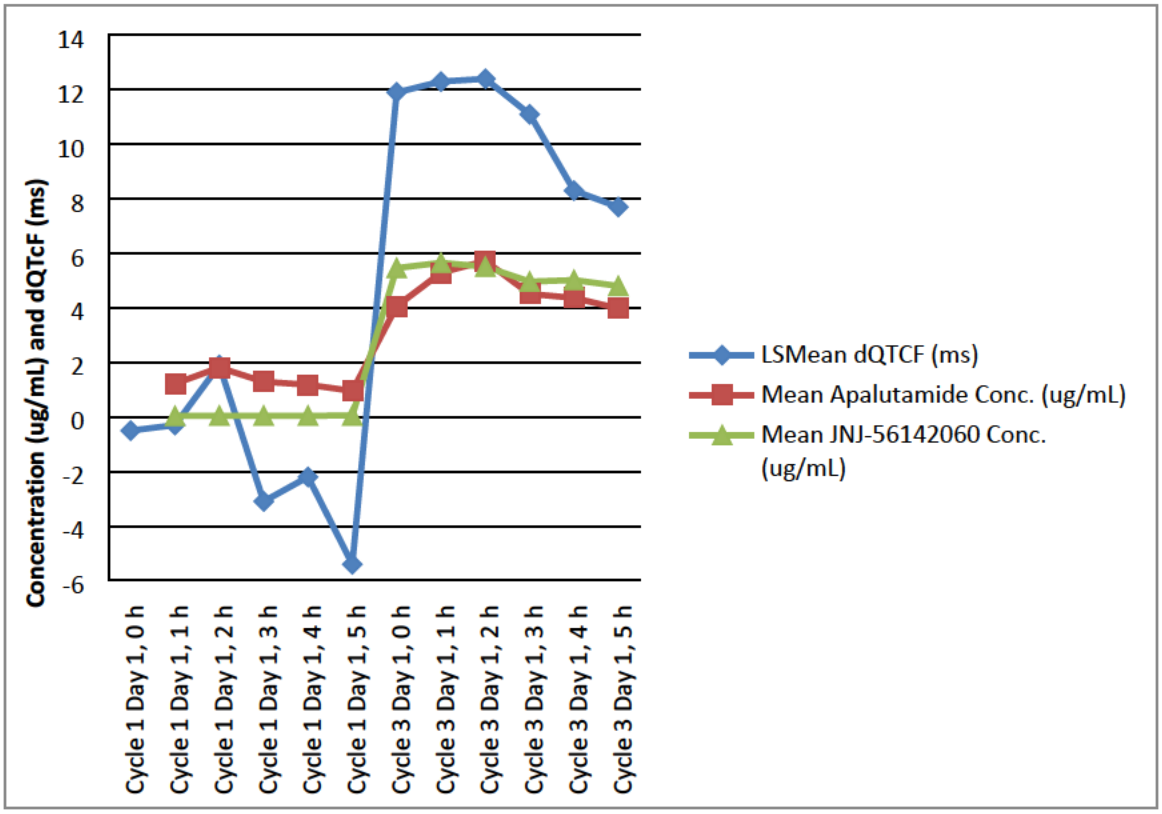
	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline/Predose	45	308	45 (100%)	308 (100%)	0 (0.0%)	0 (0.0%)
Cycle 1 Day 1	45	224	45 (100%)	224 (100%)	0 (0.0%)	0 (0.0%)
Cycle 3 Day 1	43	253	40 (93.0%)	239 (94.5%)	3 (7.0%)	14 (5.5%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean concentration-time profiles for apalutamide and its major metabolite JNJ-56142060 are illustrated in Figure 1.

The juxtaposed time profiles for ΔQTcF (LSmean values obtained from the statistical analysis above) and the concentrations of apalutamide and metabolite JNJ-56142060 are shown in Figure 3 below. The profile for ΔQTcF seems to follow the profile for apalutamide better than the profile for the metabolite JNJ-56142060, although the contribution to the effects from the metabolite cannot be ruled out. Furthermore, the in vitro studies showed similar IC_{50} values for apalutamide and the metabolite for hERG inhibition (refer to Appendix 6.1), and this clinical study shows presence of similar concentrations for both the moieties, which indicates that the potential contribution of metabolite towards QTc effects cannot be ruled out.

Figure 3: Comparative LSMean ΔQTcF and Mean Concentrations of Apalutamide and JNJ-56142060 Time Profiles on Cycle 1 Day 1 and Cycle 3 Day 1



The relationship between ΔQTcF and drug concentrations is visualized in Figure 4 and Figure 5 for apalutamide and JNJ-56142060, respectively. The exposure-response relationship is evaluated using linear mixed effects model with ΔQTcF as dependent variable and apalutamide (or JNJ-56142060) concentration as a predictor and subject as a random effect. There was a statistically significant positive slope ($p<0.05$) for exposure-response relationship for both moieties. Table 17 summarizes the ΔQTcF effects predicted from the models.

Figure 4: Relationship of ΔQTcF vs. JNJ-56142060 concentration. Error bars represent mean and standard deviation

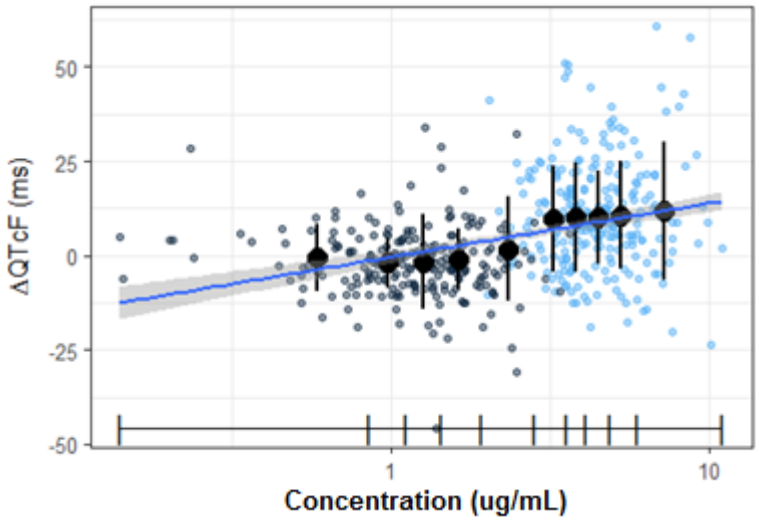


Figure 5: Relationship of ΔQTcF vs. JNJ-56142060 concentration. Error bars represent mean and standard deviation

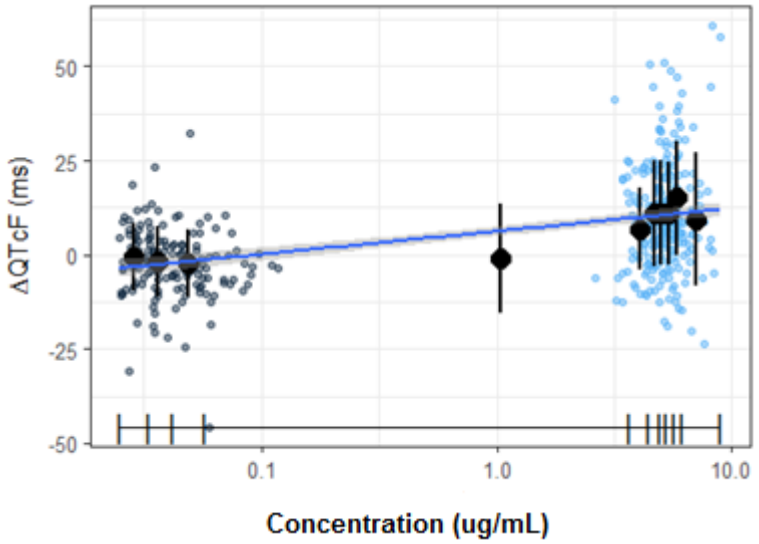


Table 17: The QTc Effects (Point Estimates and the 90% CI) at mean peak concentration of apalutamide and its major (active) metabolite at steady state (Cycle 3, Day 1) for Apalutamide 240 mg Once Daily Dosing (FDA Analysis)

Drug/Metabolite moiety	Mean peak concentration (µg/ml)	ΔQTcF Mean (ms)	ΔQTcF 90% CI (ms)
Apalutamide	6.0	14.2	9.4, 19.0
JNJ-56142060 (Metabolite)	5.8	12.1	8.0, 16.2

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

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

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

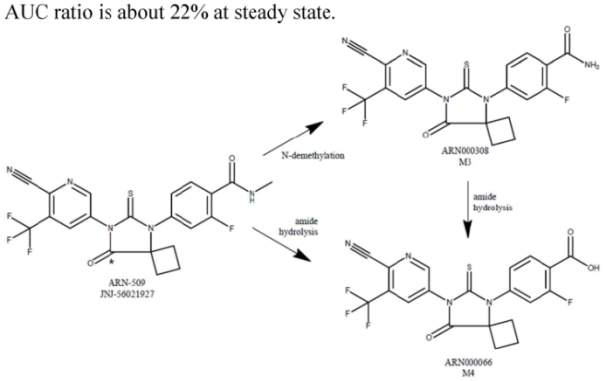
5.4.3 PR and QRS Interval

There are no clinically meaningful effects on the PR and QRS intervals.

- Four subjects had post-baseline PR >220 ms, but 3 of the 4 subjects had abnormal baseline with PR >200 ms (1 of the 3 subjects had baseline PR >220 ms). The changes from baselines for the PR outliers from the 4 subjects were below 15%. Another 9 subjects had post-baseline PR between 200 ms to 220 ms, 6 of them had baseline PR >200 ms.
- Three subjects had post-baseline QRS >110 ms, and baselines for those QRS outliers were all below 110 ms. The changes from baselines for the QRS outliers from the 3 subjects were below 22%.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	240 mg QD	
Maximum tolerated dose (MTD)	The drug was well tolerated up to 480 mg per day. MTD was not achieved because dose-escalation beyond 480 mg per day was impractical due to pill burden (480 mg required 16x 30-mg softgel capsules).	
Principal adverse events	Fatigue, fall, and rash. (These events were selected based upon blinded data from Study ARN-509-003; other events may be added when the study is unblinded[a])	
Maximum dose tested in patients with prostate cancer (PC)	Single Dose	480 mg
	Multiple Dose	480 mg per day for at least 3 cycles (28 days per cycle)
Exposures Achieved at Maximum Tested Dose: 480 mg Mean (%CV)	Single Dose (n=3 in PC patients)	Apalutamide (Parent) C_{max} = 3.56 (21.3%) µg/mL; AUC_{0-24} = 35.5 (4.3%) h*µg /mL; AUC_{0-inf} = 351 (43.8%) h*µg /mL JNJ-56142060 (M3) C_{max} = 0.232 (5.0%) µg/mL; AUC_{0-24} = 1.40 (25.5%) h*µg /mL
	Multiple Dose (n=3 in PC patients)	Parent C_{max} = 11.2 (4.2%) µg/mL; AUC_{0-24h} = 202 (4.8%) h*µg /mL M3 C_{max} = 8.53 (6.1%) µg/mL; AUC_{0-24h} = 181 (1.2%) h*µg /mL
Exposures Achieved at Phase 3 Dose: 240 mg Mean (%CV)	Single Dose (n=3 in PC patients)	Parent C_{max} = 2.97 (13.9%) µg/mL; AUC_{0-24} = 21.9 (12.2%) h*µg /mL; AUC_{0-inf} = 231 (40.3%) h*µg /mL M3 C_{max} = 0.197 (35.2%) µg/mL; AUC_{0-24} = 1.16 (22.7%) h*µg /mL
	Single Dose (n=15 in normal healthy subjects)	Parent C_{max} = 2.70 (18.3%) µg/mL; AUC_{0-24} = 27.0 (16.4%) h*µg /mL; AUC_{0-inf} = 212 (19.8%) h*µg /mL M3 C_{max} = 0.306 (32.0%) µg/mL; AUC_{0-24} = 2.47 (35.7%) h*µg /mL; AUC_{0-inf} = 197 (15.3%) h*µg /mL
	Multiple Dose (n=3 in PC patients)	Parent C_{max} = 7.55 (15.3%) µg/mL; AUC_{0-24h} = 127 (28.7%) h*µg /mL M3 C_{max} = 5.30 (16.8%) µg/mL; AUC_{0-24h} = 119 (16.3%) h*µg /mL
Range of linear PK	30 mg to 480 mg	
Accumulation at steady state, Mean (%CV)	Parent: $Rac_{(AUC)}$ = 5.70 (16.3%) at 240 mg QD M3: $Rac_{(AUC)}$ = 106 (33.1%) at 240 mg QD	
Metabolites	Major metabolite: M3 (JNJ-56142060; ARN000308), which possesses activity against AR with approximately 1/3 the potency of apalutamide. Mean M3-to-^{14}C-radioactivity AUC ratio is 44% after single dose. Mean metabolite-to-parent AUC ratio is about 96% at steady state. Minor metabolite: M4 (JNJ-56142021; ARN000066), not pharmacologic active. Mean M4-to-^{14}C-radioactivity AUC ratio is 2.7% after single dose. Mean metabolite-to-parent AUC ratio is about 22% at steady state. 	
Absorption	Absolute/Relative	F_{abs} = 1.11 (range: 1.08 to 1.13)

	Bioavailability	
	T_{max} Median (range)	Single dose: Parent = 2 hr (1-3); M3 = 168 hr (144-336) Multiple dose: Parent = 1 hr (0.5-2); M3 has a very flat profile at steady state therefore T_{max} is not applicable
Distribution	Vd/F Mean (%CV)	250 L (25%)
	% bound	Parent: 95.8% M3: 94.9%
Elimination	Route	Major: hepatic metabolism (~90%), followed by renal or biliary excretion of downstream metabolites Mass balance: 65% in urine, 24% in feces
	Enzymatic pathways	N-demethylation to M3: CYP2C8 and CYP3A4 Amide hydrolysis to M4: unknown
	Terminal t½ Mean (%CV)	Single dose: Parent = 162 hr (30%); M3 = 242 hr (29%)
	CL/F Mean (%CV)	Single dose: 1.36 L/h (36%) Multiple dose: 2.25 L/h (20%)
Intrinsic Factors	Age	To be assessed by Population PK (see Appendix 3)
	Sex	Not applicable. All studies were conducted in male only.
	Race	To be assessed by Population PK (see Appendix 3)
	Hepatic Impairment	Being evaluated in Study PCR1018 (see Appendix 1)
	Renal Impairment	To be assessed by Population PK (see Appendix 3)
	Disease state	Exposure after single dose was comparable between healthy subjects and patients with prostate cancer.
Extrinsic Factors	Drug interactions	Effect of other drugs on apalutamide Gemfibrozil (CYP2C8 inhibitor): ↑ 68% in AUC of Parent, ↓ 15% in AUC of M3 Itraconazole (CYP3A4 inhibitor): no change in AUC Rifampin (CYP3A4 inducer): To be assessed by PBPK modeling Effect of apalutamide on other drugs Being evaluated in study PCR1020 (see Appendix 1)
	Food Effects	High-fat meal: ↓ 16% in C_{max}, no change in AUC
Expected High Clinical Exposure Scenario	Gemfibrozil (repeated dose) caused a 21% decrease in C_{max} and 68% increase in AUC of apalutamide (single dose).	
Preclinical Cardiac Safety		
Isolated Canine Purkinje Fibers	No biologically significant effects of Parent and M3 on action potential duration, resting membrane potential or V_{max} (maximum rate of depolarization (MRD) measured in volts/second (V/s) at the maximum nominal concentration tested and limit of solubility of 30 µM.	
hERG assay in stably transfected CHO cells	hERG tail current was inhibited: Parent: No-effect concentration = 0.407 µM IC_{50} = 6.17 µM M3: No-effect concentration < 0.407 µM IC_{50} = 4.56 µM	
Telemeteric evaluation of cardiovascular safety in the conscious dog	No effects on blood pressure (systolic, diastolic and mean), heart rate, body temperature, ECG lead II intervals PR, QRS, QT, QT corrected for heart rate (QTcR, QTcB, QTcF and QTcV) or ECG waveform morphology up to the highest dose tested, ie. a single dose of 40 mg/kg body weight. The unbound concentration of Parent and M3 were in the range of the estimated unbound Parent and M3 steady state C_{max} at a dose of 240 mg in patients with CRPC.	
General toxicity studies in the dog up to 39 weeks of treatment	No in vivo cardiovascular effects were noted up to 10 mg/kg/day with exposures in the range of the clinical exposure for Parent and M3.	
Clinical Cardiac Safety		

Effect of apalutamide on ventricular repolarization	The effect of apalutamide on ventricular repolarization was evaluated in the Phase 2 portion of Study ARN-509-001 at selected clinical sites (refer to Investigator Brochure Section 4.3.6 for further details). As of the data cutoff date of 31 March 2017, 13 subjects remained on study, all receiving apalutamide 240 mg daily (with and without food). The data showed no indication of an effect of apalutamide on heart rate. Subjects in the non-fed/fasted subpopulation showed a small (non-significant) increase in QTcF, but notably, those in the fed/fasted subpopulation all showed an increase from baseline, averaging 20 msec at the start of Cycle 3 and remaining elevated at all ECG time points in the fed/fasted sub-study. There was no evidence for a difference in QTcF between the fed and fasted states. There were no significant effects of apalutamide on the PR or QRS intervals. At present, the clinical QTc data from the ARN-509-001 study show no conclusive evidence of an increase in QTcF with increasing plasma concentration of apalutamide. A Phase 1b QT/QTc study of apalutamide in patients with prostate cancer is currently ongoing (PCR1019, see Appendix 1).
AR=androgen receptor; DDI=drug-drug interaction; GnRHa=gonadotropin releasing hormone analog; PC=prostate cancer; QD=once daily	

[a] The original version of this table was previously provided in a submission dated 16 July 2015 (Serial No 0179), and presented data from the ongoing ARN-509-001 study. The current list of principal adverse events is based only on data from the blinded ARN-509-003 study. In both ARN-509-001 and ARN-509-003, subjects received softgel capsules at study start, and then were switched to the tablet formulation of apalutamide in 2015. Therefore, the current list of principal adverse events includes more data from subjects who received the tablet formulation, which is associated with fewer gastrointestinal-related adverse events compared to the softgel capsules. This list of adverse events may be updated once the ARN-509-003 study is unblinded.

6.2 SCHEDULE OF ASSESSMENTS

Phase	Screening	Treatment Phase (28 day cycles)[a]									Follow-up
Cycle		Cycle 1				Cycle 2		Cycle 3	Cycle X	End of Treatment (EoT)	
Day	Within 28 days	D-1	D1	D2	D15	D1	D15	D1	D1		
Study Procedures											
Screening/Administrative											
Informed consent	X										
Inclusion/exclusion criteria	X										
Medical history and demographics	X										
Prior Prostate Cancer Therapies	X										
Study Drug Administration											
Administer study drug (JNJ-56021927)[b]			X	X	X	X	X	X	X		
Safety Assessments											
Physical Examination	X		X			X		X	X	X	
ECOG PS	X		X			X		X	X	X	
Hematology/ Serum chemistry	X		X		X[c]	X	X[c]	X	X	X	
TSH	X		X			X		X	X	X	
Fasted lipid panel[d]		X							X	X	
Vital signs, height and weight[e]	X		X			X		X	X	X	
Testosterone[f]	X										
ECG[g]											
Pharmacokinetics[g]											
Ongoing Subject Review											
Concomitant therapy	X										X
Adverse events	X										X

Footnotes

[a] Window on Cycle 2 Day 8 includes ± 2 days

[b] Subjects will be dosed with 240 mg QD daily. Treatment cycles will be 28 days.

[c] Potassium, Calcium, Magnesium only

[d] Occurs during baseline and once every 3 cycles from Cycle 4 Day 1 onwards. Includes total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides. Samples for total cholesterol will also be obtained on Cycle 2 Day 1 and on Cycle 3 Day 1

[e] Vital signs include supine blood pressure, pulse/heart rate and respiratory rate. Weight will be recorded at same visits as planned for vital signs. Height will be measured at baseline only

[f] Screening and once every 3 cycles from Cycle 4 Day 1 onwards

[g] See separate PK & ECG table below for details

PK AND ECG TIME AND EVENTS SCHEDULE

Phase	Screening	Treatment Phase (28 day treatment cycle)																												
Cycle		**1**																			**3**									
Cycle Day		*-1*									*1*									2	*1*									
Study Day	Within 28 days	**-1**[1]									1									2	57									
Time		Predose[1]	0a	+1h	+1.5h	+2h	+3h	+3.5h	+4h	+5h	Predose	0	+1h	+1.5h	+2h	+3h	+3.5h	+4h	+5h	Predose	0	Predose	0	+1h	+1.5h	+2h	+3h	+3.5h	+4h	+5h
JNJ-56021927 Dose												X									X		X							
PK blood sample[b]											X		X		X	X		X	X	X[d]		X		X		X	X		X	X
ECG[c]	X	X		X		X	X		X	X	X		X		X	X		X	X			X		X		X	X		X	X
Meal					X			X						X			X								X			X		

[1] There is no dose on Day -1, ECG will be taken at 8:30 am to match the sampling times on Day 1, with the next ECGs taken at 10:00 am, 11:00 am, 12:00 pm, 1:00 pm, and 2:00 pm.

[b] Time-matched PK samples are to be collected within 2 minutes after obtaining the last ECG of a triplicate set.

[c] Triplicate 12-lead EGCs are taken at screening, on Cycle 1 Day -1, on Cycle 1 Day 1, Cycle 1 Day 2, and Cycle 3 Day using standardized equipment. The triplicate ECGs should be taken at most 2 min. apart. If blood sampling or vital signs measurement is scheduled for the same timepoint as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw.

[d] Blood sample should be 24 hours after Day 1 dose.

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

/s/

DHANANJAY D MARATHE
01/29/2018
Simbarashe Zvada was the primary reviewer.

SIMBARASHE P ZVADA
01/29/2018

JANELL E CHEN
01/29/2018

DALONG HUANG
01/29/2018

MOHAMMAD A RAHMAN
01/29/2018

MICHAEL Y LI
01/29/2018

CHRISTINE E GARNETT
01/29/2018

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [optional for SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 210951 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Erleada® Established/Proper Name: apalutamide Dosage Form: Tablets Strengths: 60 mg Route(s) of Administration: Oral		
Applicant: Janssen Agent for Applicant (if applicable): N/A		
Date of Application: October 9, 2017 Date of Receipt: October 10, 2017 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: April 10, 2018	Action Goal Date (if different): February 20, 2018	
Filing Date: December 9, 2017	Date of Filing Meeting: November 20, 2017	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): treatment of individuals with non-metastatic castration-resistant prostate cancer (NM-CRPC)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Staff***		☐ 351(a) ☐ 351(k)

Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***It is the first application for a Qualified Infectious Disease Product (QIDP)*** • ***A Priority Review Voucher (PRV) was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease PRV ☐ Pediatric Rare Disease PRV ☐ Medical Countermeasure PRV
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, follow ICCR process*** ***http://inside.fda.gov:9003/programsinitiatives/combinationproducts/reviewertools/ucm511466.htm***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☒ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division(s) (*if Biosimilar or OTC product*): N/A	
List referenced IND Number(s): IND 104676	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into electronic archive e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				N/A
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		N/A
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature? ***Note: User Fee Staff performs user fee and arrears assessment and notifies RPM if unacceptable for filing. For questions, contact CDER-PDUFA@fda.hhs.gov or CDER-BsUFA@fda.hhs.gov.***	☒	☐		
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No			
505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☒		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		N/A
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD) [**see 21 CFR 314.54(b)(1)]?**	☐	☐		N/A
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR***	☐	☐		N/A

314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.				
• Is there unexpired exclusivity on another listed drug product containing an active moiety that is contained in this application (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		N/A

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year NCE exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

If there is unexpired, 5-year NCE exclusivity on another listed drug product that contains any active moiety contained in this application (and the applicant did not provide a paragraph IV patent certification AND/OR there is more than 1 year left before the NCE exclusivity expires), contact the 505(b)(2) review staff in the Immediate Office of New Drugs prior to filing.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter (available in Other Important Meeting Language in CST). ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☐		N/A
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, contact Office of Orphan Drug Products***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	N/A

Format and Content (must be in eCTD format)				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☐ navigable hyperlinks **If no**, explain.	☒	☐		
Forms and Certifications				
Electronic *forms with electronic signatures are required.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the applicant or an authorized representative (see 21 CFR 54.2(g) and 54.4(a)(1)). If financial disclosure forms are signed by an authorized representative (e.g., a US agent) and not the applicant, request confirmation that the representative is authorized to sign on the applicant's behalf.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		

Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it 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." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is a Field Copy Certification included? • Check eCTD section 1.3.2 for copy of letter notifying the District office that eCTD submission will be submitted to FDA, per the eCTD Technical Conformance Guide (the field offices have access to the EDR). ***If no, request a copy of the letter from the applicant. If applicant did not notify the District office prior to submission, request that applicant provide notification and submit a copy of the letter before the filing date.*** ***Note:*** *Field Copy Certification is not needed if there is no CMC technical section*	☒	☐	☐	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[1]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[2]***	☐	☒		

[1] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829 htm
[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837 htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox.***[3]	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☐	☐ ☐	☐ ☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in***	☐	☐	☒	

[3] To determine whether an OSE consult is needed for REMS and/or any other submission components (e.g., carton and container labeling) refer to "Guide for OND PMs on when to issue consults for OSE."

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

PLLR format before the filing date.				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to the Patient Labeling Team (DMPP)? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	QT-IRT- 10/16/17
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** February 28, 2012	☒	☐		
Pre-NDA/Pre-BLA/BPD Type 4/Pre-Supplement meeting(s)? **Date(s):** 9/18/2017	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 21, 2017

BACKGROUND: NME NDA 210951-apalutamide –androgen receptor inhibitor for the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Charlene Wheeler	Y
	CPMS/TL:	Christy Cottrell	Y
Cross-Discipline Team Leader (CDTL)	Chana Weinstock		Y
Division Director	Julia Beaver		Y
Deputy	Amna Ibrahim		Y
Clinical	Reviewer:	Daniel Suzman Dow-Chung Chi	Y
	TL:	Chana Weinstock	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Wentao Fu	Y
	TL:	Qi Liu	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Simbarashe Zvada	Y
Biostatistics	Reviewer:	Lijun Zhang	Y
	TL:	Jason Schroeder	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wei Chen	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Xiao H. Chen	Y
	RBPM:	Kristine Leahy	Y
• Drug Substance	Reviewer:	Rajan Pragani	Y
• Drug Product	Reviewer:	Xing Wang	Y
• Process	Reviewer:	Lixia Cai	Y
• Microbiology	Reviewer:		
• Facility	Reviewer:	Zhong Li	Y
• Biopharmaceutics	Reviewer:	Banu Zolnik	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Susan Redwood	Y
	TL:	Barbara Fuller	Y
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Kevin Wright	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Tingting Gao	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	Y
	TL:	Elizabeth Everhart	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Susan Thompson	Y

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original 351(a) BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined ○ Reason: *the application did not raise significant safety or efficacy issues*
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**: N/A	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (NME NDAs, Original 351(a) BLAs, and Original 351(k) BLAs)	☐ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☒ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO N/A
• What late submission components, if any, arrived after 30 days?	N/A
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Were the elements of a Formal Communication Plan discussed and agreed upon by the applicant and the review team at the pre-submission meeting? (optional)	☐ YES ☒ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Gideon Blumenthal, MD, Acting Director, OHOP **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program"): December 18, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review ☒ Expedited Review Planned (optional for priority review applications in the Program)
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	If filed, issue Biosimilar Filing Notification letter on day 60 for an original 351(k) BLA
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the Program NME/BsUFA Program Screen in DARRTS (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: October 2017

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/s/

CHARLENE N WHEELER
01/24/2018

CHRISTY L COTTRELL
01/26/2018

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA ID C2017201	C2017372
IND/BLA/NDA	210951
Referenced IND for NDA/BLA	
Established Name /Trade	Apalutamide
Sponsor/Applicant	Janssen
Indication	Treatment of non-metastatic castration-resistant prostate cancer
Meeting Type/Deliverable	Not applicable
Sponsor Letter Date/SDN #	SDN 1, 3, and 4
Date of Consult Request	11/17/2017
Review Completion Date	
Review Division	Division of Oncology Products 1 (DOP1)
Clinical Reviewer/Team Leader (TL)	Daniel Suzeman, M.D./ Dow-Chung Chi, M.D.
Review Division Project Manager	Charlene Wheeler
COA Reviewer	Selena Daniels, Pharm.D., M.S.
COA Associate Director	Elektra Papadopoulos, M.D., M.P.H.
Instrument 1	Functional Assessment of Cancer Therapy-Prostate module (FACT-P)
Instrument 2	EuroQol Five Dimensions scale (EQ-5D)
COA Type 1 and Endpoint Concepts	Patient-reported outcome (PRO); prostate cancer symptoms
COA Type 2 and Endpoint Concepts	PRO; health status
Intended Population	Patients with non-metastatic castration-resistant prostate cancer
Internal Meeting Date	Not applicable
Sponsor Meeting/WRO Date	Not applicable

Please check all that apply:

☐Rare Disease/Orphan Designation
☐Pediatric

Daniels, Selena

From: Daniels, Selena
Sent: Friday, January 12, 2018 4:44 PM
To: Suzman, Daniel; Chi, Dow-Chung
Cc: Papadopoulos, Elektra; Kluetz, Paul; COA Staff
Subject: COA Consult for NDA 210951
Attachments: ViewDocument.pdf

Hi Daniel and Dow-Chung,

With regard to consult request for this NDA (attached), you have indicated that the Sponsor's analysis found no statistically significant difference in
time to a clinically meaningful change in FACT-P scores. You have requested COA Staff to ensure that the FDA's analysis is concordant. However, we defer to the Biostatistical reviewer on whether they were able to reproduce this finding. You also may wish to work with the Biostatistical reviewer to look at the distribution of responses, because subsets of patients may show changes not apparent in group means.

With regard to the adequacy of the FACT-P and EQ-5D-3L to support labeling claims, we have the following comments:

- The FACT-P is challenging to interpret because it combines disease-related symptoms, treatment-related symptoms, and disease impacts into its domain and total scores, which makes it difficult to describe results in product labeling. We encourage the use of instruments with well-defined and interpretable domain content.
- The EQ-5D-3L is a generic preference-based measure intended to provide a single health utility index value for use in economic analyses and lacks evidence of content validity for use in estimating clinical benefit for labeling claims. However, we acknowledge that the EQ-5D-5L may be necessary for other regulatory authorities and/or payers.

Please let us know if you have any additional questions related to the COAs. If acceptable, we would like to close out this consult with this email. Thanks.

Have a great holiday weekend!

Warm regards,

Selena

Selena Daniels, PharmD, MS
Clinical Outcome Assessment (COA)Team Leader, COA Staff (Formerly SEALD)
Food & Drug Administration, Center for Drug Evaluation and Research, Office of New Drugs
p:240-402-6021 m: (b) (6) a:10903 New Hampshire Ave, Silver Spring, MD 20993
e:selena.daniels@fda.hhs.gov

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/s/

SELENA R DANIELS
01/24/2018

ELEKTRA J PAPADOPOULOS
01/24/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 23, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 210951
Product Name and Strength:	Erleada (Apalutamide) Tablets, 60 mg
Applicant/Sponsor Name:	Janssen Biotech, Inc.
FDA Received Date:	January 11, 2018 and January 19, 2018
OSE RCM #:	2017-1942-1
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

DOP1 requested that we review the revised Erleada container label and professional sample container label and carton labeling (Appendix A and B) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

Janssen submitted the initial revision of Erleada container label and professional sample container label and carton labeling in response to our previous label and labeling review on January 11, 2018 (Appendix A). However, they provided the following comment in response to our recommendation regarding revising the strength statement "60 mg" in purple box to "60 mg/tablet" or "60 mg per tablet" for the Professional Sample Pull Out Blister Card, Blister Card Sleeve, and Carton Labeling:

[a] Gao, T . Label and Labeling Review for Erleada (NDA 210951). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 19. RCM No.: 2017-1942.

Janssen Biotech, Inc. response:[b]

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"?

In response, we provided the following comment[c]:

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.[d] Furthermore, our recommendation to add "/tablet" or "per tablet" is only for the blister card components, and is not applicable to the bottle labels.

Thus, Janssen submitted second revision of the professional sample blister card container label and blister card carton labeling on January 19, 2018 (see Appendix B).

3 CONCLUSION

The revised Erleada container label and professional sample container label for bottle configurations received on January 11, 2018, and the revised professional sample blister card container label and blister card carton labeling received on January 19, 2018 are acceptable from a medication error perspective. We have no further recommendations at this time.

[b] Chung, J. Personal Communication: NDA 210951 Carton/Container Information Request. Horsham (PA): Janssen Biotech, Inc. 2018 January 8.

[c] Wheeler, C. Personal Communication: NDA 210951 Carton/Container Information Request. FDA, CDER, OND, OHOP, DOP1 (US); 2018 January 18. NDA 210951.

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

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/s/

TINGTING N GAO
01/23/2018

CHI-MING TU
01/23/2018

Clinical Inspection Summary

Date	December 19, 2017
From	Lauren Iacono-Connors, Ph.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation
To	Charlene Wheeler, Regulatory Project Manager Daniel Suzman, Clinical Reviewer Division of Oncology Products 1
NDA #	210951
Applicant	Janssen Research & Development, LLC
Drug	Erleada® (apalutamide; JNJ-56021927; ARN-509)
NME	Yes
Therapeutic Classification	Androgen Receptor Antagonist
Proposed Indication	Non-metastatic Castration-Resistant Prostate Cancer
Consultation Request Date	September 6, 2017 (Submission date: October 10, 2017)
Summary Goal Date	February 2, 2018
Action Goal Date	February 20, 2018
PDUFA Date	April 10, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study ARN-509-003 was submitted to the Agency in support of NDA 210951. Three clinical sites, Dr. Rahul Aggarwal, M.D. (Site 3501), Dr. Julie Graff, M.D. (Site 3524), Dr. Kalpesh Patel, M.D. (Site 3591), and the study sponsor Janssen Research and Development, LLC, were selected for audit.

There were no significant inspectional findings for clinical investigators Dr. Rahul Aggarwal, Dr. Julie Graff, Dr. Kalpesh Patel, and study sponsor Janssen Research and Development, LLC. The data from Study ARN-509-003 submitted to the Agency in support of NDA 210951, appear reliable based on available information.

II. BACKGROUND

Janssen Research and Development, LLC (JRD), on behalf of Janssen Biotech, Inc. (JBI), seeks approval to market apalutamide for the treatment of individuals with non-metastatic castration-resistant prostate cancer (NM-CRPC). The key study supporting this application is Study ARN-509-003.

The following overview of the Study ARN-509-003 is intended as background context for interpreting the inspectional findings.

A total of 1207 subjects were randomized (2:1) to receive apalutamide 240 mg or placebo once daily. Of those randomized, 1201 subjects received at least one dose of study drug. Subjects were to remain on study treatment until documented radiographic progression (development of distant metastases as assessed by BICR), withdrawal of consent, or the development of unacceptable toxicity.

The study was conducted under IND 104676.

Study ARN-509-003 is entitled, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer".

Study Period: Date of first subject enrolled: September 19, 2013
Data cut-off date for analysis: May 19, 2017

Primary efficacy endpoint: The primary efficacy endpoint is Metastasis-Free Survival (MFS), defined as the time from randomization to first evidence of Blinded Independent Central Review [BICR]-confirmed radiographically detectable bone or soft tissue distant metastasis or death due to any cause (whichever occurs earlier) + 1 day.

Objectives of Inspections:

a. Verify MFS as assessed by the clinical investigator
b. Verify Overall Survival (OS)
c. Identification, documentation, and reporting of adverse events (AEs)
d. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI #1: Rahul Aggarwal (Site 3501) UCSF Helen Diller Family Comprehensive Cancer Center, Gateway Medical Building, 1825 Fourth Street, 4th Floor San Francisco, CA 94158	Protocol: ARN-509-003 Subjects: 13	November 6-20, 2017	*VAI
CI #2: Julie Graff (Site 3524) OHSU, 3181 Southwest Sam Jackson Park Road Portland, OR 97239-3079	Protocol: ARN-509-003 Subjects: 25	October 31, 2017 – November 14, 2017	*VAI

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#3: Kalpesh Patel (Site 3591) Arizona Institute Of Urology, 5670 North Professional Park Drive, Suite 100 Tucson, AZ 85704	Protocol: ARN-509-003 Subjects: 11	November 13-17, 2017	*NAI
Sponsor: Janssen Research and Development, LLC 1400 McKean Road PO Box 776 Spring House, PA 19477	Protocol: ARN-509-003 Site Numbers: 3501, 3524, 3591, 1403, 2605, 3007, 3117 and 3400	November 13-21, 2017	*VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Rahul Aggarwal, M.D. (Site 3501)

The site screened 16 subjects and enrolled 13 subjects. A record review was done for all 13 subjects. At the time of this inspection nine subjects had completed the study. The inspection included assessment of all informed consent forms, protocol compliance, subject source data, AE detection and reporting and investigator agreements. The source data was compared to the data listings submitted to the application.

The inspection revealed no significant deficiencies. The primary efficacy endpoint data, as determined by the clinical investigator, were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs. However, there was a protocol violation that affected all enrolled subjects. Specifically, Protocol ARN-509-003, *Section 4., Patient Selection*, specifies that, in part, subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance status of 0 or 1 to be enrolled into the study. Further, Protocol ARN-509-003, *Section 7.1.5., Performance Status*, specifies that the ECOG performance status scale will be used, and will be assessed at Screening and every subsequent clinic visit. Source documents for all 13 enrolled subjects show that after the Cycle 1 visit, the Karnofsky Performance Status (KPS) scale was used for performance instead of the ECOG scale as instructed in the protocol. Results for performance status was reported to the Sponsor as an ECOG

score. However, there was no protocol deviation submitted to the IRB and Sponsor, or a response from the sponsor allowing the KPS to be used and/or the sponsor approval of a conversion table for reporting ECOG scores based on recorded KPS scores.

OSI Reviewer Notes: The site created a Note to File on 11/8/17 regarding the use of a different performance status method during the conduct of this study. Specifically, Dr. Aggarwal explained that the ECOG scale was derived from the KPS scale, and he provided two references that provided "validated" conversion tables between KPS and ECOG, and that the use of the conversion tables should not have had any impact on subject eligibility or secondary efficacy endpoints that involved ECOG performance status. Dr. Aggarwal stated that clinical the use of KPS or ECOG performance status scoring are interchangeable, but promised that moving forward the study team will be re-trained to use performance status metrics as required per protocol.

This inspectional observation was discussed with the DOP1 Clinical Reviewer, Daniel Suzman on December 18, 2017. He agreed that this was a protocol violation but stated that, with exception of the extremes for each of these performance scales, the conversion tables used should reflect a reasonable transcription of KPS to ECOG performance rating. While this is a protocol violation it should not importantly impact study outcomes or have placed subjects at undue risk.

2. Dr. Julie Graff, M.D. (Site 3524)

The site screened 25 subjects and enrolled 14 subjects. A record review was done for all 14 subjects. At the time of this inspection 11 subjects had completed the study. The inspection included assessment of all informed consent forms, protocol compliance, subject source data, AE detection and reporting and investigator agreements. The source data was compared to the data listings submitted to the application.

The inspection revealed no significant deficiencies. The primary efficacy endpoint data, as determined by the clinical investigator, were verifiable with the source records maintained at the site. There were several inspectional observations. One enrolled subject did not meet entry criteria due to taking a medication prohibited by the protocol, and five adverse events were not identified and reviewed until after this inspection was announced.

Protocol ARN-509-003, *Section 4., Patient Selection and Appendix 5,* specifies that concurrent therapy with any of the following (all must have been discontinued or substituted for at least 4 weeks prior to randomization): in part, medications known to lower the seizure threshold, such as Buproprion. Subject (b) (6) was randomized on (b) (6) and received their first dose of study IP on (b) (6). Source documentation for Subject (b) (6) revealed that this subject was on Buproprion (since (b) (6) 200 mg BID) at the time of randomization and first treatment. However, the site did not identify the use of the prohibited medication until (b) (6).

The subject's medical records documented that the subject stopped taking IP from (b) (6) through (b) (6), stopping Bupropion on (b) (6) follow by a 2-week washout period before restarting the study drug. The sponsor stated that the subject could restart the study medication after stopping and Bupropion. The prohibited medication use was reported to the IRB and the use of Bupropion was also listed in the sponsor database for prior and concomitant medications. Subject (b) (6) continued to receive study IP until (b) (6), study day 487. Treatment was discontinued due to progressive disease. This protocol violation should not importantly impact overall study outcomes or subject safety.

The following AEs were not reported to the sponsor, entered into the eCRF, or documented in the clinical study database at the time of this inspection.

Subject ID/ Treatment Arm	**AE**	**Start Date (M/D/Y)**	**Relatedness To Event**	**Grade**
(b) (6) / placebo	Depression	(b) (6)	Possibly related	1
(b) (6) / placebo	Worsening hypertension		Not related	3
(b) (6) / placebo	Ear pain		Not related	1
(b) (6) / apalutamide 240 mg	Skin lesion/neoplasm		Not related	2
(b) (6) / apalutamide 240 mg	Puritis		Possibly related	1

In preparation for this clinical site inspection, the study site staff conducted a comprehensive review of subject medical records for completeness, organization, accuracy. This included the review of study visit notes, which revealed 5 potential AEs that had not been previously identified and documented in the study electronic database. These AEs were found specifically in the clinician's subjective narratives, minor comments and embedded notes, and not necessarily clearly identified as AEs with associated event grading and causality comments. It is for this reason that the study site staff likely did not recognize the events as clinically significant. Nonetheless, these AEs should have been identified, reviewed and entered into the subject records and eCRF.

OSI Reviewer Notes: Dr. Graff concurred with the inspectional observations in a written response, dated 12/1/2017, to the Form FDA 483 inspectional observations. With respect to Subject (b) (6) Dr. Graff stated that it was an oversight that the bupropion use was not identified as exclusionary at screening. Dr. Graff provided a corrective action plan that included the combined use of the list of protocol-prohibited medications (in this case, Study ARN-509-003; Appendix 5), a list of the subject's current medications along with the study-specified inclusion/exclusion criteria during

the screening process. Other preventative actions include re-training site staff, and the development and activation of a "research flag" in the electronic medical records (EMR) for all subjects participating in a research study, thereby notifying all care providers with access to the EMR that the subject is a clinical research participant and that all providers should contact the clinical investigator. The corrective action plan should mitigate these inspectional observations moving forward.

With respect to the 5 AEs that were not reported to the sponsor until after database lock, May 19, 2017, as described above, these unreported AEs were identified during preparation for this FDA inspection. Dr. Graff stated that the root cause was the lack of clear delineation in the subjects' medical records of which "events" are AEs and which are clinically insignificant in the written comments. To mitigate the inspectional findings moving forward, Dr. Graff initiated a process improvement plan that aims to improve contemporaneous AE documentation. The key element is an embedded table in the office visit note template and the electronic medical record. The table is described as an organized, durable record of toxicities from baseline to a protocol-specified end-of-toxicity tracking. The table is expected to optimize consistency and rapid identification of AEs. As of November 15, 2017, the 5 AEs were all source data verified by sponsor representatives and entered into the study database by the sponsor. The clinical site is working closely with the sponsor on the corrective action plan and implementation.

In total, 1207 subjects were randomized to treatment. Of those, 1201 subjects received at least 1 dose of study treatment. The AE dataset submitted to the application included over 12,000 AEs captured from 1156 study subjects during the conduct of the study and prior to the data cut-of date of May 19, 2017. The subjects who had under reported AEs were medically managed throughout the study by this site, and were not at undue risk because of these unreported AEs. Notwithstanding the inspectional observations noted above, the data from Site 3524 submitted to NDA 210951 appear reliable and may be used in support of the respective indication.

3. Dr. Kalpesh Patel, M.D. (Site 3591)

The site screened 18 subjects and enrolled 11 subjects. At the time of this inspection, there are eight subjects who remain on study. A record review was done for 6 enrolled subjects. The inspection included assessment of all informed consent forms, financial disclosure, Form FDA 1572 investigator agreements, clinical monitoring, adverse events, sponsor correspondence, eCRFs, drug accountability, training and IRB correspondence. The source data was compared to the data listings submitted to the application.

The inspection revealed no significant deficiencies. The primary efficacy endpoint data, as determined by the clinical investigator, were verifiable with the source records maintained at the site. There was no evidence of under-reporting adverse events.

4. Janssen Research and Development, LLC

The inspection of Janssen focused on the control, oversight, and management of Study ARN-509-003. The inspection covered roles and responsibilities, protocols, IRB approvals, monitoring plans, written procedures, FDA 1572 forms, data management, site selection, investigator selection, monitor selection/training, investigator non-compliances, escalation process of noncompliant sites, site monitoring visit reports, quality assurance, adverse event reporting, safety reporting, and test article quality assurance and accountability.

Monitoring records were reviewed from eight clinical sites. Actions taken by the sponsor to bring non-compliant clinical sites into compliance were also assessed. Contract agreements and sponsor responsibility transfer agreements were reviewed as appropriate. Reporting practices for AEs, SAEs, and protocol deviations were reviewed. There was no evidence of under-reporting of AEs/SAEs.

Monitoring appeared adequate. GCP noncompliance was identified by clinical monitors at Site 3400, the highest enrolling clinical site. This site was intensely monitored by the sponsor. A summary of key issues identified in the site monitoring reports (MVR) for Site 3400 follows. The site had a backlog of data needing entry into eCRFs, there were out of window bone scans and study visits, and there were potential missing AEs in eCRFs.

OSI Reviewer Notes: The sponsor provided a written response, dated December 3, 2017, to the Form FDA 483 inspectional observations. The sponsor acknowledged the GCP compliance issues identified in MVRs for Site 3400. The sponsor provided summary actions that were taken by the sponsor and/or the site that addressed each deficiency noted in the Form FDA 483. With respect to the data entry backlog, Site 3400 implemented corrective actions by adding addition staff until all data was properly entered in eCRFs. The sponsor implemented data verification visits to confirm completeness of the data in the database by comparison between the eCRF and the source documents for selected data points, adverse events (AE), and concomitant medications. Sponsor personnel directly supervised the data verification process. With respect to out of window study activities, the sponsor informed that there were 79 minor protocol deviations mostly related to study assessments that should not impacted the overall safety of the subjects; for example, out of window study visits, study assessments out of window and/or study assessments not conducted. The site staff had since been retrained to minimize these deviations moving forward.

There was adequate sponsor oversight over the conduct of the study at Site 3400, and extensive support was provided to maintain clinical site GCP compliance and data integrity in the study database.

The data from this sponsor, associated with Study ARN-509-003, submitted to the Agency in support of NDA 210951, appear reliable.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H., Branch Chief
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/s/

LAUREN C IACONO-CONNORS
12/19/2017

KASSA AYALEW
12/19/2017

LABEL AND LABELING REVIEW

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

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

Date of This Review:	December 19, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 210951
Product Name and Strength:	Erleada (Apalutamide) Tablets, 60 mg
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Janssen Biotech, Inc.
Submission Date:	October 10, 2017
OSE RCM #:	2017-1942
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the NDA 210951 review for Erleada, this review evaluates the proposed Erleada container label, professional sample labels and labeling, and Prescribing Information (PI) to identify areas of vulnerability that could lead to medication errors in response to a consult request from Division of Oncology Products 1 (DOP1).

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 PRESCRIBING INFORMATION (PI)

We reviewed Section 2 Dosage and Administration, Section 3 Dosage Forms and Strengths, and Section 16 How Supplied/Storage and Handling of the proposed Erleada PI and determined that the proposed PI could be improved to increase clarity to promote safe use of the product.

3.2 CONTAINER LABEL AND CARTON LABELING

We reviewed the proposed Erleada container label and determined that it is acceptable from a medication error perspective. For the professional sample pull out blister card, blister card sleeve, and carton labeling, we recommend revising the strength presentation to "60 mg/tablet" or "60 mg per tablet" to minimize the risk of confusion.

4 CONCLUSION & RECOMMENDATIONS

The proposed Erleada PI could be improved to increase clarity to promote safe use of this product. The proposed Erleada container label, proposed professional sample pull out blister card, blister card sleeve, and carton labeling could be improved to ensure safe use of the product. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATION FOR THE DIVISION

A. Prescribing Information, Dosage and Administration section
    1. Consider replacing the symbol "≥" and "≤" with their intended meanings to avoid misinterpretation and confusion.

4.2 RECOMMENDATIONS FOR JANSSEN

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

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. MMMYYYY or MMMDDYYYY).[a]

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 ERLEADA™ Tablets?**" in sentence case to improve readability. For example, "**Questions on Erleada™ 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.**"

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

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Erleada that Janssen submitted on October 10, 2017.

Table 2. Relevant Product Information for Erleada	
Initial Approval Date	N/A
Active Ingredient	apalutamide
Indication	treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC)
Route of Administration	Oral
Dosage Form	Tablets
Strength	60 mg
Dose and Frequency	240 mg (four 60 mg tablets) administered orally once daily
How Supplied	Bottle of 120 tablets
Storage	20°C to 25°C
Container Closure	white, opaque, 160-mL high-density polyethylene (HDPE) bottle with (b) (4) closure and induction seal liner containing silica gel desiccant (6 g silicon dioxide in total).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Erleada labels and labeling submitted by Janssen on October 10, 2017.

- Container label
- Professional Sample Pull Out Blister Card
- Professional Sample Blister Card Sleeve
- Professional Sample Carton Labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container label – Bottle of 120 tablets[c]

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

[c] Erleada container label. Available at \\cdsesub1\evsprod\nda210951\0003\m1\us\trade-bottle-label.pdf

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

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TINGTING N GAO
12/19/2017

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12/19/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 210951

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Erleada® (apalutamide) oral tablets, 60 mg

Applicant: Janssen Research & Development, LLC

Receipt Date: October 10, 2017

Goal Date: April 10, 2018

1. Regulatory History and Applicant's Main Proposals

The applicant submitted an NME NDA pursuing approval for Erleada® (apalutamide) oral tablets, 60 mg, for the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

CHARLENE N WHEELER
12/04/2017

CHRISTY L COTTRELL
12/04/2017