CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210951Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

CDTL review is complete and has been added to the NDA/BLA Multidisciplinary Review and Evaluation. My recommendation for this application is regular approval.

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/s/

CHANA WEINSTOCK
02/14/2018

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210951
Priority or Standard	Priority
Submit Date(s)	October 09, 2017
Received Date(s)	October 10, 2017
PDUFA Goal Date	April 10, 2018
Division/Office	DOP1/OHOP
Review Completion Date	February 13, 2018
Established Name	Apalutamide
(Proposed) Trade Name	Erleada
Pharmacologic Class	Androgen receptor inhibitor
Code name	JNJ-56021927, ARN-509
Applicant	Aragon Pharmaceuticals, Inc., represented by Janssen Research & Development, LLC.
Formulation(s)	60 mg tablets
Dosing Regimen	240 mg
Applicant Proposed Indication(s)/Population(s)	ERLEADA is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC).
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	ERLEADA is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC).

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Other	N/A

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

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OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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1 Executive Summary

1.1. Product Introduction

Apalutamide (ARN-509) is a small molecule inhibitor of the androgen receptor (AR) and is not currently approved for any indication or marketed in any country.

The applicant proposed the following indication for approval of this New Molecular Entity (NME):

> *ERLEADA is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC).*

The applicant proposed the following dosing regimen in the labeling for approval:

> *The recommended dose of ERLEADA is 240 mg (four 60 mg tablets) administered orally once daily.*

1.2. Conclusions on the Substantial Evidence of Effectiveness

The management of men with prostate cancer who experience rising prostate-specific antigen (PSA) values after definitive therapy for localized prostate cancer, in the absence of metastatic disease, remains an area of controversy. Patients are often treated with gonadotropin-releasing hormone (GnRH) analogs or undergo bilateral orchiectomy to decrease testosterone to castrate levels. Resistance to these treatments ultimately develops in many patients, with the development of castration-resistant prostate cancer (CRPC). This disease state is marked by an increase in PSA despite castration levels of testosterone. In some patients, overt metastases are found on imaging at the time of CRPC diagnosis. However, because PSA is readily measured in the blood and may increase before overt metastatic disease is present, it is possible for patients to be in a state where their PSA rises, but no measurable disease is discernable on any imaging modality. This pre-metastatic state is termed non-metastatic castration-resistant prostate cancer (NM-CRPC). Patients with NM-CRPC, especially those with a short PSA doubling time (PSADT) (i.e., a PSADT of ≤10 months), are at risk for development of overt metastatic disease and for prostate cancer-specific death. The clinical management of these patients is controversial, with no applicable FDA-approved therapies.

For patients with NM-CRPC and a PSADT <10 months, some clinicians favor various secondary hormonal manipulations and therapies as options (although not FDA-approved). These treatment strategies have not demonstrated a survival benefit in randomized clinical trials in patients who have not received docetaxel-based chemotherapy. In contrast, there are numerous FDA-approved agents available for patients who have metastatic CRPC (i.e., where measurable metastases have been confirmed via radiographic imaging), but the utility of using

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these therapies in the earlier disease state of NM-CRPC is unknown, as these patients were excluded from registrational trials.

The appropriate endpoint to use in trials evaluating agents in the setting of NM-CRPC has been the subject of ongoing debate. Some of these discussions were formally captured at two meetings of the FDA's Oncology Drugs Advisory Committee (ODAC). There was recognition that the transition to a state where the patient developed measurable metastatic disease represented a significant event for patients with NM-CRPC. A consensus emerged that an endpoint looking at metastasis-free survival (MFS) would likely be clinically meaningful as long as it was of sufficient magnitude and was accompanied by data from supportive secondary endpoints such as OS. Thus, MFS is the primary efficacy endpoint used to support the approval of apalutamide in NDA 210951. This approval, in addition to being the first FDA approval of a therapeutic agent in NM-CRPC, is the first to use MFS as an endpoint in this setting.

SPARTAN, the study used to support NDA 210951, was a phase 3 trial of apalutamide in patients with high risk NM-CRPC (i.e., a PSADT of ≤ 10 months). SPARTAN was a multinational, randomized, double-blind, placebo-controlled trial with the primary objective of comparing metastasis-free survival (MFS) in patients randomized to apalutamide or placebo. Secondary objectives were to compare time to metastasis (TTM), progression-free survival (PFS), time to symptomatic progression (SymProg), overall survival (OS), and time to initiation of cytotoxic chemotherapy between the two arms. Patients were randomized in a 2:1 ratio, and randomization was stratified by PSA doubling time (>6 months vs. ≤ 6 months), use of bone sparing agents (yes vs. no), and presence of locoregional disease (N0 vs N1). All patients were to maintain castrate level of testosterone either through ADT (choice of GnRH agonist or antagonist at the investigator's discretion) or through surgical castration.

SPARTAN randomized 1207 patients to apalutamide (N = 806) or placebo (N = 401). Patients were to receive apalutamide at 250 mg orally daily. The dose could be reduced to 180 mg and then to 120 mg in patients with adverse events; no dose re-escalation was allowed. Prior to randomization, patient scans were reviewed by a Blinded Independent Central Review (BICR) and those with distant metastases were excluded. On-study scans were performed by BICR every 16 weeks, with additional scans orderable at investigator discretion if disease progression was suspected and at the end of treatment. Imaging studies included a CT or MRI of the chest, abdomen, and pelvis, plus a bone scan. Areas of abnormal uptake on bone scan were confirmed with a correlative CT or MRI by BICR. Serum PSA was assessed on Day 1 of Cycles 1 to 6, then every 2 cycles from Cycles 7 - 13, and then every 4 cycles, with results done by central laboratory and blinded to subjects, site staff, and applicant.

The results of the analysis of MFS are shown below. This result is supported by multiple sensitivity analyses and the investigator-determined analysis of MFS. The secondary objectives of TTM, PFS, and SymProg were also statistically significant as per the pre-specified hierarchical testing analysis plan. Analysis of OS was performed as an interim analysis, and did not meet the pre-specified statistical significance level based on the O'Brien-Fleming efficacy boundary,

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although these data were not mature with 7.7% deaths in the apalutamide arm and 10.5% in the placebo arm. The additional endpoints of time to initiation of cytotoxic chemotherapy, time to PSA progression, and PFS2 were analyzed as exploratory only.

Table 1. Summary of Efficacy Results. ITT Population, SPARTAN

Endpoint	Number of Events (%)		Median [Months (95% CI)]		HR (95% CI) p-value (log-rank test)[1]
	Apalutamide (N=806)	Placebo (N=401)	Apalutamide	Placebo	
Metastasis Free Survival	184 (23%)	194 (48%)	40.51 (NE, NE)	16.20 (14.59, 18.40)	0.28 (0.23, 0.35) <0.0001
Time to Metastasis	175 (22%)	191 (48%)	40.51 (NE, NE)	16.59 (14.59, 18.46)	0.27 (0.22, 0.34) <0.0001
Progression-Free Survival	200 (25%)	204 (51%)	40.51 (NE, NE)	14.72 (14.49, 18.37)	0.29 (0.24, 0.36) <0.0001
Time to Symptomatic Progression	60 (7%)	59 (15%)	NE (NE, NE)	NE (36.83, NE)	0.45 (0.31, 0.64) <0.0001

[1] All analyses stratified by PSA doubling time, bone-sparing agent use, and locoregional disease status.
NE=Not Estimable

The safety profile of apalutamide in patients with NM-CRPC, a life-threatening disease, is acceptable. There were relatively few discontinuations due to adverse events compared to placebo. Patient-reported outcome data, although exploratory, were supportive of acceptable tolerability compared to placebo. While overall survival data are immature, no decrement in overall survival was observed, and there was a numerical trend to improved overall survival, which increases confidence in the safety of apalutamide. Notable toxicities included rash, weight loss, falls, and fractures. There were rare events of seizure. Adverse events consistent with extended duration of potent androgen deprivation, such as cardiovascular disease, were slightly increased compared to placebo. Recommendations for safe and effective use of apalutamide, including recommends to assess and treat patients at risk for fracture, will be made in labeling, including in patient labeling.

The acceptability of the use of MFS as an endpoint in the setting of NM-CRPC was discussed previously at the FDA's Oncologic Drugs Advisory Committee (ODAC). Thus, the demonstration of a marked improvement in MFS of patients treated with apalutamide compared to placebo, supported by demonstration of statistically significant improvement in the secondary endpoints of TTM, PFS, and SymProg, was considered as evidence of the approvability of apalutamide in this setting. Although the trial excluded patients with PSADT of >10 months, subgroup analyses within the studied population showed similar efficacy across all cutoffs for PSA doubling times, supporting a broader approval. Additionally, given the overall large magnitude of effect demonstrated by SPARTAN, it was felt that the strict cutoff of 10 months would exclude patients in the general population who would be very likely to benefit, for instance those with PSADT slightly higher or those with other poor prognostic features. Thus a broader indication

was granted to allow treating physicians to apply their clinical judgment in selecting patients at higher risk of development of metastatic disease.

The review team recommends that apalutamide be approved for the treatment of adult patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC).

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Patients with castration-resistant prostate cancer with no overt radiographic evidence of metastases (NM-CRPC) are at substantial risk of developing metastatic disease. Currently, there are no FDA-approved therapies for this indication, and management of these patients remains controversial. The FDA's ODAC previously reached consensus that the use of MFS as a primary efficacy outcome measure for trials in NM-CRPC was potentially acceptable if a large magnitude of effect was demonstrated, accompanied by supportive secondary efficacy and safety outcomes. SPARTAN was a phase 3 trial that randomized 1207 patients with BICR-assessed NM-CRPC in a 2:1 ratio to treatment with apalutamide or placebo and used MFS as its primary efficacy endpoint. Patients were followed by BICR-assessed imaging, and investigators were blinded to ongoing PSA assessments. The analysis of MFS, as assessed by independent review, showed a statistically significant and clinically meaningful improvement for the apalutamide arm when compared to placebo. Estimated median MFS was 40.5 months (95% CI: NE, NE) vs. 16.2 months (95% CI: 14.6, 18.4) in the apalutamide and placebo arms, respectively, with a HR 0.28 (95% CI: 0.23, 0.35, P<0.0001). Analysis of the secondary endpoints time to metastasis, progression-free survival, and time to symptomatic progression also significantly favored the apalutamide arm and are supportive.
The safety profile of apalutamide in patients with NM-CRPC, a life-threatening disease, is acceptable. There were relatively few discontinuations due to adverse events compared to placebo. Patient-reported outcome data, although exploratory, were supportive of acceptable tolerability compared to placebo. While overall survival data are immature, no decrement in overall survival was observed and there was a numerical trend to improved overall survival, which increases confidence in the safety of apalutamide. Notable toxicities included rash, weight loss, falls, and fractures. There were rare events of seizure. Adverse events consistent with extended duration of potent androgen deprivation, such as cardiovascular disease, were slightly increased compared to placebo. Recommendations for safe and effective use of apalutamide, including recommendations to assess and treat patients at risk for fracture, will be made in labeling, including in patient labeling. All members of the review team recommended approval of this application or reported that there were no findings that would preclude approval of apalutamide for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC).

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Men who are treated with medical or surgical castration for biochemical recurrence after treatment for localized prostate cancer often develop castration-resistant disease. • In some, overt metastases are found on imaging. However, because PSA is readily measured in the blood and may increase before overt metastatic disease is present, it is possible for patients to have rising PSA but no measurable disease discernable on imaging. This pre-metastatic state is termed non-metastatic castration-resistant prostate cancer (NM-CRPC). • Patients with NM-CRPR, especially those with a short PSA doubling time (PSADT) (i.e., a PSADT of ≤10 months), are at significant risk for development of metastatic disease and prostate cancer-specific death. • Patients with non-metastatic castration-resistant prostate cancer are at a high risk of disease progression to metastatic disease. • Without treatment, these patients have a median MFS of 25 months. • Once a patient develops metastatic disease, median overall survival is 11 months without treatment (JS deBono et al. NEJM 2011)	Patients with a high risk (PSADT <10 months), non-metastatic castration-resistant prostate cancer are at high risk of disease progression to metastatic disease, with resultant morbidity and mortality.
Current Treatment Options	• There are no FDA-approved treatment options in this setting.	There is an unmet need for the development of treatment options with demonstrable improvement in clinical outcomes for patients with NM-CRPC.
Benefit	• Estimated median MFS was 40.5 months (95% CI: NE, NE) vs. 16.2 months (95% CI: 14.6, 18.4) in the apalutamide and placebo arms, respectively, with HR of 0.28 (95% CI: 0.23, 0.35) p<0.0001. • The secondary objectives of TTM, PFS, and SymProg were also statistically significant per the pre-specified hierarchical testing analysis plan.	The observed hazard ratio and difference in median MFS is substantial and clinically meaningful. The magnitude of improvement in MFS is supported by similar magnitude of improvement in the other secondary endpoints of TTM, PFS, and SymProg.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The overall survival data are immature with 24% of the OS events having occurred.	
Risk and Risk Management	• Apalutamide was well-tolerated in most study patients with a low rate of discontinuation due to adverse events • Important risks include falls, fractures, rash, and seizure. • While the incidence of seizure was low, patients at risk for seizure were excluded from SPARTAN. The safety in these patients is unknown. • There was no standardized management of bone density loss in SPARTAN. It is unknown whether adherence to guidelines on bone density loss and fracture risk may have mitigated the increased incidence of fractures.	The safety profile of apalutamide was favorable for patients with NM-CRPC and was generally consistent with long-term androgen deprivation. The most common adverse reaction was rash, which could be managed with corticosteroids and dose interruptions, reductions, or rarely discontinuations. A warning to adhere to established guidance regarding assessment and treatment of bone density loss and fracture risk was added to the label. The safe use of apalutamide can be managed through accurate labeling and routine pharmacovigilance. No REMS is needed.

1.4. Patient Experience Data

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Patient Experience Data Relevant to this Application (check all that apply)

	The patient experience data that was submitted as part of the application, include:	Section where discussed
	✓ Clinical outcome assessment (COA) data, such as	
	✓ Patient reported outcome (PRO) The applicant used two instrument to collect PRO data: FACT-P and EQ-5D-3L	Section 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability and Appendix 19.5.
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

{See appended electronic signature page}

Cross-Disciplinary Team Leader
Chana Weinstock, MD

Reference ID: 4221387

2 Therapeutic Context

2.1. Analysis of Condition

Men with prostate cancer who experience rising prostate-specific antigen (PSA) values after therapy for localized prostate cancer are usually treated with androgen deprivation therapy (ADT), with either medical or surgical castration. This typically results in an initial PSA decrease followed by a period of PSA stability. Ultimately, resistance often develops and patients then develop castration-resistant prostate cancer (CRPC), which is marked by an increase in PSA despite castration levels of testosterone. Because PSA is readily measured in the blood and may increase before overt metastatic disease is present, it is possible for patients to be in a state where their PSA rises but no measurable disease is discernable on any imaging modality. This pre-metastatic state is termed "non-metastatic castration-resistant prostate cancer" (NM-CRPC). The management of these patients is controversial, with no FDA-approved therapies applicable to this population. Generally, patients with NM-CRPC with a short PSA doubling time (PSADT) (i.e., a PSADT of ≤10 months) are at significant risk for development of metastatic disease and prostate cancer-specific death and are considered an especially high-risk group of patients, although other well-known prognostic features exist. The principal surveillance modalilty in these patients is continued PSA monitoring, although the National Comprehensive Cancer Network (NCCN) guidelines also discuss the option of adding imaging surveillance for patients with NM-CRPC with a short PSADT. Despite this recommendation, clinicians may still not routinely monitor high risk patients with NM-CRPC, since frequent PSA monitoring is thought to induce undue anxiety in the absence of an approved intervention.

The transition to a state of measurable metastatic disease represents a significant event for these patients. Despite treatment for metastatic bone disease when it is asymptomatic, most patients will eventually develop skeletal-related events resulting in pain, ineffective hematopoiesis, increased healthcare resource utilization, and progressive complications that are difficult to treat. The delay of metastases and the associated morbidity for as long as possible is, therefore, a primary goal of therapy for men with NM-CRPC. This therapeutic goal is reflected in the use of metastasis-free survival (MFS) as a therapeutic endpoint in this disease setting (refer to section 3.2 for a further discussion of this endpoint in the NM-CRPC setting).

Apalutamide is a next generation, orally bioavailable, androgen receptor (AR) inhibitor that inhibits AR nuclear translocation and binding to androgen response elements. This results in the inhibition of downstream transcription of AR-regulated genes. Unlike first-generation anti-androgens that have relatively low AR binding affinity and may exhibit partial agonist activity for the wild-type AR, apalutamide is a potent and selective antagonist of the AR without significant agonist properties.

2.2. Analysis of Current Treatment Option

For patients with metastatic prostate cancer that is castration-resistant, there are numerous FDA-approved treatment options available such as abiraterone, enzalutamide, and docetaxel. In contrast, there are no FDA-approved therapies for patients with castration-resistant prostate cancer but no radiographic evidence of metastasis. Management of these patients remains somewhat controversial, with some opting for observation alone, especially for patients who have a PSADT ≥ 10 months. For patients with a PSADT <10 months, the NCCN guidelines include various secondary hormonal manipulations and therapies as options (although not FDA-approved). Examples include discontinuation of the anti-androgen in patients whose disease progressed on combined androgen blockade to exclude an "anti-androgen withdrawal response," and secondary hormonal therapy. Secondary hormone therapy can be an anti-androgen for patients who initially received medical or survival castration, anti-androgen withdrawal, ketoconazole with or without hydrocortisone, corticosteroid, DES, or other estrogen. These treatment strategies, however, have not demonstrated a survival benefit in randomized clinical trials in patients who have not received docetaxel-based chemotherapy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Apalutamide is a New Molecular Entity (NME) and is not currently marketed in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory history of MFS as a primary efficacy endpoint in NM-CRPC

The primary efficacy endpoint used to support the approval of apalutamide in NDA 210951 is metastasis-free survival (MFS). This approval, in addition to being the first approval of a therapeutic agent in this setting, is the first to use this endpoint in the setting of NM-CRPC. The discussion about which endpoint would be most appropriate to use in this setting took place previously at two meetings of the FDA's Oncology Drugs Advisory Committee (ODAC).

1. The first of these meetings occurred on September 14, 2011. At that time, a non-product specific ODAC was convened to discuss general issues related to the development of drugs for the treatment of patients with NM-CRPC. The committee was asked to consider issues relating to trial design, specific populations, and endpoints in the NM-CRPC setting. During the meeting, many members agreed that the most pressing need for study was in those patients at higher risk for metastatic disease, and rapid PSA doubling time was one method to enrich the population, as this subset typically experiences the worst prognosis. A trial design was proposed for patients with rapid PSA doubling time who had not yet been treated with hormone therapy. These patients would be started on hormone therapy and those who continue to experience rapid PSA doubling would be randomized to either receive or not receive a new compound in combination with second line hormonal therapy.

2. The second ODAC was related to the review of a specific product for potential approval in the NM-CRPC setting. The product under review was denosumab (sBLA 125320/ efficacy supplement 28) for the proposed indication of treatment of NM-CRPC at high risk of developing bone metastasis. On June 27, 2010, Amgen, the applicant for sBLA 125320/28, submitted the results of Trial 20050147, a randomized, double-blind, placebo-controlled trial of 1432 patients with CRPC, considered at high risk for bone metastases, to support approval of this new indication. While the September 2011 non-product specific ODAC had been convened during the sBLA review process, a second meeting was product-specific and met on February 8, 2012.

   The question that FDA asked the committee was: Has denosumab demonstrated a favorable risk/benefit evaluation for the treatment of castration-resistant prostate cancer at high risk for metastasis? In the case of denosumab, a relatively modest reduction in risk (15%) was observed in occurrence of a first bone metastasis-free survival (BMFS) event, 73% of which were asymptomatic, with no demonstrated effects on OS, PFS, or patient

reported outcomes. Other issues were raised as well, including toxicity (osteonecrosis of the jaw), and the fact that denosumab was approved in a later-line of therapy with some question as to the added benefit of administering it earlier in the disease process.

Based on the information presented by the FDA and Amgen, the committee voted 12 to 1 that denosumab did not demonstrate a favorable risk-benefit evaluation for the treatment of men with castration-resistant prostate cancer at high risk for metastasis. Several members felt that the difference in bone metastasis-free survival (BMFS) between the denosumab and placebo arms of the trial was not large enough to establish clear clinical benefit. While there was some discussion of the appropriateness of BMFS as an established surrogate endpoint for clinical benefit, members generally agreed that BMFS could be considered for use as a surrogate endpoint for this purpose because bone metastases can cause significant morbidity in patients with prostate cancer, but only if the magnitude was sufficient. One member stated that approximately one year difference in BMFS would be appropriate to establish clinical benefit.

Members who voted "No" generally agreed that the magnitude of BMFS did not demonstrate a sufficient clinical benefit to offset the risk of adverse events, particularly the morbid complication of osteonecrosis of the jaw in an asymptomatic population. The member who voted "Yes" expressed a desire for additional drug options in this population, and a willingness in this group to tolerate adverse effects. Thus, there was a sense that this endpoint was acceptable if the magnitude of effect were large enough.

Approval of NDA 210951 based on MFS, the primary efficacy endpoint of SPARTAN, would thus essentially establish a new regulatory precedent, although per the previous ODAC discussion, this would be acceptable if a large magnitude of effect was demonstrated in the setting of a favorable safety profile.

Primary regulatory considerations for this application are:

- Does an improvement in the risk of time to first distant metastasis or death confer a clinical benefit in this setting?
- Is the magnitude of the treatment effect on MFS time sufficient to establish a favorable risk-benefit profile in this clinical setting?

Key regulatory history of apalutamide under IND 104676

The following regulatory history outlines key dates and discussions regarding apalutamide that occurred with the Food and Drug Administration under IND 104676. From the outset, following the earlier discussions outlined above that had established the potential acceptability of the use of MFS as a regulatory endpoint in this disease setting, MFS was chosen by the applicant as the primary efficacy endpoint for the proposed registrational phase 3 trial SPARTAN.

February 28, 2012: A Type B End of Phase 2 Meeting was held to discuss the proposed phase 3

ARN-509-003 study (SPARTAN). The applicant proposed to randomize high risk NM-CRPC patients 2:1 to 240mg once daily of apalutamide or placebo, with high risk defined as those patients with a PSA doubling time of < 10 months. The primary efficacy endpoint was to be MFS, defined as time from randomization to death or first evidence of radiographically-detectable bone or soft tissue metastases determined by blinded independent central radiographic review. Key discussion points included:

1. Agreement on a PSA doubling time definition (assessed at randomization)
2. Acceptability of including patients with enlarged pelvic lymph nodes at baseline (b) (4) cm)
3. Acceptability of placebo use given the lack of FDA-approved therapies in this setting.
4. The ability to retain patients with a rising PSA, which was identified by FDA as a potential review issue. In response, the applicant proposed to use a central laboratory and to blind the applicant and investigators to PSA results.
5. The applicant agreed to modify the protocol so an abnormal bone scan would trigger an immediate confirmatory X-ray and/or a CT or MRI.
6. A clarification that localized progression events would be assessed as part of a PFS endpoint, and that the number of patients who discontinue therapy due to PFS events would be a review issue.

November 9, 2012: A Special Protocol Assessment agreement letter was signed by for SPARTAN. FDA noted that "the magnitude of benefit for your primary endpoint will need to be substantially large in order to provide a positive risk-benefit ratio for this largely asymptomatic population. The approval will also depend on the internal consistency and strength of your overall survival, symptomatic progression and PFS results as well as other clinically meaningful measures… in order to support any benefit demonstrated by your surrogate primary endpoint." The BICR charter was reviewed, in which the applicant agreed that all patients would have baseline eligibility confirmed by independent review. Additionally, regarding any new bone scan lesions requiring confirmation by x-ray/CT/MRI, the BICR charter specified that the date of an MFS event would be captured as the date of the bone scan which first noted the lesion that was later confirmed by CT/MRI or X-ray.

December 12, 2013: A Type C meeting was held regarding modifications to ARN-509-003, including;

1. Amendment of the statistical analysis plan to group the overall survival endpoint with other secondary endpoints and to not invalidate all secondary endpoints if OS was not met at the time of the primary analysis.
2. As crossover to apalutamide was not allowed for subjects meeting criteria for the primary endpoint, the applicant proposed to provide abiraterone acetate for these patients as long as they resided in countries where the drug is approved (~95% of the patient population).

FDA agreed to these modifications.

February 9, 2015: FDA agreed to the Initial Pediatric Study Plan (iPSP), in which the applicant proposed a full waiver because prostate cancer does not occur in children.

May 12, 2015: A Type B meeting was held to discuss formulation changes for the apalutamide used in SPARTAN, from capsules to a new tablet formulation. A bioavailability study noted similarity between the two formulations in terms of AUC and Cmax. The sponsor planned the switch when ~ 690 patients had received the capsule, with plans to enroll 150-250 new patients who would receive only the tablet. FDA agreed that data from bioavailability Trial 56021927PCR1011 supported the proposed switch.

June 30, 2016: A Special Protocol Assessment Modification Agreement Letter was issued, incorporating modification to the protocol that decreased visit frequency and associated assessments after cycle 7 from every week to every 2 weeks.

February 24, 2017: A Type A WRO meeting was held in which proposed revisions to the Statistical Analysis Plan (SAP) were discussed. SPARTAN had fully enrolled as of December 2016, and while analysis of the primary endpoint (MFS) at the pre-specified 372 events was projected to occur in May 2017, only 77 death events were projected to occur (compared to the 243 events projected at the time of the SAP design). Because secondary endpoints were projected to be at varying stages of maturity at that point, the applicant proposed hierarchical testing of secondary endpoints in the following order, each at alpha=0.05:

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

FDA agreed to the proposed changes, although FDA asked for a revision of this hierarchical testing procedure so an analysis of OS should be conducted at the time of the MFS analysis with an allocation of a small alpha (type-1 error). Any suggestion of a detrimental effect on survival was noted to be a potential major approvability concern. FDA noted that inclusion of secondary endpoints in labeling would be a review issue and that statistical significance might not be sufficient for inclusion in labeling.

May 4, 2017: FDA sent a Special Protocol Assessment Rescind Agreement letter to the applicant since the changes in the use of supportive secondary endpoints were considered sufficiently large as to invalidate the prior SPA Agreement.

August 11, 2017: FDA granted Fast Track designation to IND 104676 based on topline results of SPARTAN.

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI Consult was requested. 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.

4.2. Product Quality

CMC information provided for ERLEADA (apalutamide) tablets in this NDA has been review by the quality review team in the Office of Pharmaceutical Quality, and is found to be acceptable. The review team recommended approval for the NDA from the product quality standpoint.

There are no outstanding issues related to the Pharmacology and Toxicology safety qualification of any excipients, impurities or degradants for this NDA.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

No companion device or diagnostic is included in this NDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Apalutamide (ARN-509) is a small molecule inhibitor of the androgen receptor (AR). In vitro, apalutamide bound the ligand binding site on AR, impaired nuclear translocation and suppressed DNA binding and transcriptional activation of AR-dependent genes. Apalutamide inhibited androgen induced prostate cancer cell proliferation in vitro. In vivo, apalutamide administration lead to decreased proliferation and increased apoptosis in tumor cells leading to decreased tumor volume in mouse models of human prostate cancer. In mouse xenograft models, apalutamide administration reduced androgen-driven luciferase reporter-gene activity, indicating AR inhibition by apalutamide in vivo. The FDA text for the Established Pharmacologic Class (EPC) of "androgen receptor inhibitor" is both clinically relevant and scientifically valid based on data reviewed.

The intended clinical dose of apalutamide in humans is 240 mg administered orally once daily, and steady state was achieved after 4 weeks. At steady-state, mean C_{max} and AUC values for apalutamide were 6 µg/mL (12.6 µM) and 100 µg*h/mL (209.5 µM*h), respectively.

Four metabolites of apalutamide were identified in rats, dogs, and humans (metabolite M1 [ARN000925], M2 [JNJ-56142047], M3 [JNJ-56142060; ARN000308] and M4 [JNJ-56142021]). The major human metabolite identified in plasm of patients receiving apalutamide was M3, or N-desmethyl apalutamide. Metabolites M1, M2 and M4 were approximately 30-fold less potent against AR binding in vitro compared to apalutamide, while M3 was approximately 3-fold less potent. Apalutamide contributed to 45% and M3 contributed 44% of the total AUC following a single oral dose of 240 mg apalutamide in humans. Given the relative levels of apalutamide and its metabolites in patients, the majority of the AR inhibition is likely due to the parent apalutamide, with a fraction potentially coming from the M3 metabolite.

Seizures occurred in some patients administered apalutamide in clinical trials, consistent with labeled adverse reactions with other androgen receptor inhibitors. The brain-to-plasma ratios for apalutamide were approximately 1:1 in dogs following oral administration. Apalutamide has off-target activity against the $GABA_A$ ion channel at clinically relevant concentrations, inhibiting ligand binding to the $GABA_A$ chloride channel with an IC_{50} of 3.0 µM and $GABA_A$ activity in a tissue-based functional assay with an IC_{50} of 0.88 µM, in vitro. Apalutamide metabolites M2, M3 and M4 inhibited ligand binding to $GABA_A$ in vitro with IC_{50} values of 19, 3.2 and 25 µM, respectively. The metabolite M1 inhibited 10% of radioligand binding at 10 µM in vitro, indicating it has little activity for the $GABA_A$ receptor. Metabolites of apalutamide may contribute to potential off-target toxicity of apalutamide treatment involving the $GABA_A$ receptor, such as seizure. In particular, M3 had similar activity as apalutamide for $GABA_A$ binding in vitro. Apalutamide caused seizures/convulsions in male dogs within 7 to 9 days of oral 25 mg/kg/day doses. The C_{max} in these dogs after a single dose was 7 µg/mL, or 14.7 µM,

which is slightly higher than steady-state C_{max} in humans (6 µg/mL). The C_{max} values were unknown at the time when seizures occurred, but accumulation occurred in dogs between Day 1 and Day 28 of daily oral administration, so exposures on Days 7-9 in these dogs were likely higher than on Day 1 and may have been higher than in dogs administered 10 mg/kg/day for 28 days, which did not experience seizures.

Apalutamide was assessed in single-dose and repeat-dose toxicity studies up to 6-month in male and female rats and 9-months in male dogs. Administration of apalutamide to rats and dogs resulted in changes in the male reproductive organs, consistent with the anti-androgenic pharmacological activity of apalutamide. Toxicities in the reproductive organs included atrophy of the prostate gland, seminal vesicles, and epididymides, and tubular degeneration and/or hyperplasia of the interstitial cells in the testes. The toxicities in the reproductive organs were observed at ≥ 25 mg/kg/day in male rats with 1.4 times the human exposure based on AUC, and at ≥ 2.5 mg/kg/day in male dogs with 0.9 times the human exposure based on AUC. Additional changes following repeated dosing of male and female rats included alteration of tubuloalveolar morphology in the mammary glands, cortical hypertrophy of the adrenal glands, as well as hypertrophy of the pituitary gland. A decrease in red cell mass with a compensatory increase in reticulocytes was observed following repeated dosing in rats. The observed hypercellularity in the bone marrow and/or increased hematopoiesis in the spleen was considered secondary to the decrease in red cell mass. Most observed changes following the administration of apalutamide were the expected anti-androgenic pharmacological effects. Additionally, hepatocellular hypertrophy was observed in rats and bile duct/oval cell hyperplasia was observed in male dogs with concomitant increases in serum alkaline phosphatase (ALP) and cholesterol. In the 26-week female rat study, findings observed after repeated administration of apalutamide were either completely or partially reversible following a 2-month recovery period. Lymphoid depletion of the thymus and hyperplasia of the thyroid gland was only observed after the recovery phase.

QTc prolongation was an adverse reaction identified in some patients administered apalutamide in clinical trials. Nonclinical in vitro and in vivo cardiovascular safety pharmacology studies and single- or repeat-dose toxicology studies in dogs did not identify a significant risk for apalutamide to induce cardiac arrhythmias.

Apalutamide and metabolite M3 did not induce mutations in the bacterial reverse mutation (Ames) assay and were not genotoxic in either the in vitro chromosome aberration test or the in vivo rat micronucleus assay.

No embryo-fetal developmental toxicology studies were conducted or warranted to support this NDA submission, as the proposed indication does not include females. Due to the male specific indication, the product label includes a contraindication for pregnancy. The product label states that Erleada can cause fetal harm if administered during pregnancy, which is based on inhibition of the androgen receptor, a hormonal signaling pathway critical during development. Male patients with female partners of reproductive potential are advised to use

effective contraception during treatment and for 3 months following the final dose of Erleada. Apalutamide and metabolite M3 have half-lives of approximately 4-5 days in patients with CRPC at steady-state. The applicant's proposed 3-month contraception use following the last dose is acceptable as it is longer than 5 half-lives and an additional 3 weeks to account for the residence time of unejaculated sperm (5 x 5 days = 25 days; 25 days + 21 days = 46 days). This is consistent with current recommendations for a non-genotoxic drug that is expected to be teratogenic based on mechanism of action.

Apalutamide may impair fertility in patients based on results from a fertility and general reproductive performance study in male rats. Daily administration of apalutamide at ≥ 25 mg/kg/day (0.8 times the human exposure based on AUC) for 4 weeks prior to mating resulted in an increase in abnormal sperm cells and dose-related decreases in epidydimal sperm concentration, sperm motility, copulation rate and fertility rate. A reduced number of live fetuses was observed at 150 mg/kg/day (5.7 times the human exposure based on AUC) as evidenced by an increased pre- and/or postimplantation loss in pregnant females. Apalutamide administration also resulted in effects in smaller secondary sex glands (coagulating glands, seminal vesicles, prostate gland) and reduced epidydimal weights. All effects were reversible after a treatment-free period of 8 weeks.

No carcinogenicity studies were conducted or warranted to support this NDA, as the proposed indication was for advanced cancer. Hyperplasia and neoplasms in the ovaries were observed at all tested doses in the 26-week study in female rats, which were considered related to the pharmacological activity of apalutamide. As these findings were pharmacologically driven and only found in female reproductive organs, they do not represent a relevant risk for the indicated population.

The nonclinical data submitted in this NDA are adequate to support approval for the oral daily use of apalutamide for the treatment of patients with non-metastatic, castration-resistant prostate cancer.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

<u>Primary pharmacology</u>
(ARN-509: A novel antiandrogen for prostate cancer. Cancer Res; 2012; 72(6): 1494-1503)
Apalutamide (ARN-509) bound to human lymph node-derived carcinoma cells of the prostate overexpressing the androgen receptor (AR) with an IC50 value of 16 nM. In vitro, the binding affinities of apalutamide to the ligand binding domains of AR and PR, and to full-length ERα and GR demonstrate that it is relatively selective for AR (Table 2).

Table 2. Selectivity of Binding by Apalutamide to AR Versus Other Nuclear Hormone Receptors, ARN-509-003

Relative Binding Affinity (% of highest activity with compounds tested)				
	AR	**PR**	**ERα**	**GR**
Apalutamide	1.2	≤ 0.0005	≤ 0.0005	≤ 0.0002
RU59063[a]	100	1.2	≤ 0.0005	≤ 0.0002
Progesterone [a]	-	100	-	-
Estradiol [a]	-	-	100	-
Dexamethasone [a]	-	-	-	100

(-) indicates that binding of the ligand was not tested in the assay.
AR, androgen receptor; PR, progesterone receptor; ERα, estrogen receptor alpha; GR, glucocorticoid receptor.
[a] RU59063 (non-steroidal androgen), Progesterone, Estradiol, and Dexamethasone were used as 100% activity for AR, PR, ERα and GR binding affinity, respectively.

To assess the impact of apalutamide on nuclear translocation, LNCaP (lymph node-derived carcinoma of the prostate) cells expressing AR tagged with enhanced yellow fluorescent protein (AR-EYFP) were treated with DMSO, R1881, bicalutamide, or apalutamide. In DMSO-treated cells, AR-EYFP was largely localized to the cytoplasm (nuclear: cytoplasmic ratio, 0.7), whereas in R1881-treated cells the receptor was localized predominantly in the nucleus (nuclear: cytoplasmic ratio, 29). Bicalutamide treatment also resulted in a significant amount of nuclear AR (nuclear: cytoplasmic ratio, 13.8). In contrast, much of the AR-EYFP protein remained cytoplasmic (nuclear: cytoplasmic ratio, 2.5) in apalutamide-treated cells, indicating apalutamide inhibits AR nuclear translocation.

To test the effect of apalutamide on DNA binding of AR, LNCaP/AR cells were treated with apalutamide or R1881 or other anti-androgens. AR binding to the enhancer region of PSA or TMPRSS2 target genes was evaluated by chromatin immunoprecipitation (ChIP). AR was not recruited to the enhancer region of PSA or TMPRSS2 target genes after apalutamide treatment. When cotreated with R1881 to activate AR, apalutamide could compete with R1881 and prevent AR from binding to promoter regions. Therefore, apalutamide inhibited AR binding to the PSA or TMPRSS2 gene enhancers with no detectable agonist activity.

The effects of apalutamide on AR-dependent transcription were tested in vitro. To remove cofactor recruitment as a variable that might explain the effects of apalutamide on AR DNA binding, the effects of apalutamide on AR DNA binding was assessed in Hep-G2 cells expressing a VP16-AR fusion protein and an androgen response element (ARE)-driven luciferase. Apalutamide inhibited R1881-induced VP16-AR–mediated transcription with an IC50 value of 0.2 µM. Bicalutamide showed antagonism of VP16-AR–mediated transcription in the presence of R1881 with IC50 of 0.35 µM. These data suggest that apalutamide inhibited AR-dependent gene expression independent of cofactor recruitment.

The in vivo effects of apalutamide on AR-dependent gene transcription were assessed in castrated male immunodeficient mice harboring LNCaP/AR-Luc xenograft tumors (coexpressing exogenous AR and the AR-dependent probasin:luciferase (ARR2-Pb-Luc) reporter). Following 17 days of 10 mg/kg/day oral apalutamide administration, androgen-driven luciferase reporter–gene activity, normalized to tumor volume, was consistently reduced in apalutamide–treated animals compared with vehicle, suggesting that apalutamide inhibited AR-dependent transcription in vivo.

Vertebra-derived carcinoma of the prostate (VCaP) cells were treated with apalutamide for 7 days. Apalutamide failed to stimulate proliferation of VCaP cells and antagonized the proliferative effect of synthetic androgen R1881. Therefore, apalutamide inhibited androgen induced prostate cancer cell proliferation with no apparent stimulatory activity.

To evaluate the effects of apalutamide on tumor growth in vivo, castrated male immunodeficient mice harboring LNCaP/AR-Luc xenograft tumors (coexpressing exogenous AR and the AR-dependent probasin:luciferase (ARR2-Pb-Luc reporter) were orally administered vehicle or apalutamide (10 mg/kg/day) for 17 days. Tumor volumes were measured on Day 28, and Ki-67 immunohistochemistry was carried out on tumor tissue resected 2 hours after the dose on Day 5. TUNEL staining was carried out on tumor tissue resected after final dose on Day 25. On day 28, 7 of 9 vehicle-treated tumors increased in size compared with starting volume, 8 of 10 ARN-509-treated tumors regressed by more than 50% (volume), including two tumors that were no longer palpable. Tumors in mice administered apalutamide exhibited a 60% decrease in proliferative index (vs. vehicle) and a 10-fold increase in apoptotic rate (vs. vehicle) as monitored by Ki-67 staining and TUNEL, respectively.

In vivo antitumor activity of apalutamide was further evaluated in SHO SCID male mice injected with LNCaP/AR-CS cells (Study # DR-10-001-PHARM and DR-10-002-PHARM). Apalutamide exhibited anti-tumor activity at doses from 1 mg/kg to 30 mg/kg (more pronounced at doses ≥10 mg/kg) when administered orally once daily for 7 days (Table 3). Based on anti-tumor efficacy with 10 mg/kg apalutamide in these studies, the applicant hypothesized that a plasma level (AUC) of approximately 160.3 µg*hr/mL would be projected to drive a therapeutic response in humans. Likewise, based on results from additional mouse xenograft studies, the applicant projected an optimal biological dose in humans of ≤ 30 mg/kg/day.

Table 3. Day 28 Tumor Volume and Bodyweight Changes in SHO SCID Mice Injected with LNCaP/AR-CS Cells

Study DR-10-001-PHARM

Agent	Dose	Regimen	T/C*	Bodyweight**	Mortality
Vehicle (control)		QD × 7		0.55%	
ARN-509	1 mg/kg	QD × 7	42.0%	-4.7%	0/7
ARN-509	10 mg/kg	QD × 7	-0.94%	-1.9%	1/8
ARN000034	1 mg/kg	QD × 7	70.0%	-3.1%	0/8
ARN000034	10 mg/kg	QD × 7	11.0%	-5.6%	0/8

Study DR-10-002-PHARM

Agent	Dose	Regimen	T/C*	Bodyweight**	Mortality
Vehicle (control)		QD × 7		101%	0/8
ARN-509	10 mg/kg	QD × 7	-13%	97%	0/8
ARN-509	30 mg/kg	QD × 7	-17%	96%	0/8
ARN-000034	10 mg/kg	QD × 7	1%	100%	0/8
ARN-000034	30 mg/kg	QD × 7	10%	99%	0/8

*T/C, (treated final volume-treated initial volume) / (control final volume-control initial volume) × 100. T/C of 0 denotes tumor stasis.
** Bodyweight is percent change from start of study (pre-dose).
Note: The tables were copied from the applicant's submission.
ARN-509: apalutamide
ARN-000034: enzalutamide

Four metabolites of apalutamide were identified in nonclinical species (metabolite ARN000925 [M1], JNJ-56142047 [M2], JNJ-56142060 (ARN000308)[M3] and JNJ-56142021 [M4]). The major human metabolite identified in plasm of patients receiving apalutamide was M3, or N-desmethyl apalutamide. The activities of M1-M4 were assessed against the AR in a cell-based assay evaluating androgen-induced DNA binding. Metabolites M1, M2 and M4 were approximately 30-fold less potent against AR compared to apalutamide, while M3 was approximately 3-fold less potent.

Secondary Pharmacology

Apalutamide inhibited the GABAA chloride channel by 67% at a concentration of 10 µM in vitro. In a follow-up concentration response study, apalutamide inhibited binding with an IC50 of 3.0 µM, and in a tissue-based functional assay, the in vitro guinea pig ileum bioassay, apalutamide had an IC50 of 0.88 µM for the GABAA receptor. The off-target activity of apalutamide metabolites M1-M4 were screened for their inhibitor activity for GABAA binding. The IC50 values for M2, M3 and M4 were 19, 3.2 and 25 µM, respectively. The metabolite M1 inhibited 10% of radioligand binding at 10 µM in vitro.

Safety Pharmacology

Study title: A Pharmacological Assessment of the Effect of ARN-509 and its Primary Human Metabolite, ARN000308, on the Respiratory System in Male Sprague-Dawley Rats (694182)
GLP compliance: Yes (OECD)

Male albino (Sprague Dawley) rats (6 males/group) were administered a single oral gavage administration of apalutamide or metabolite M3 at 25, 50 and 100 mg/kg. At all doses of apalutamide, there was a slight transient decrease in absolute respiratory rate was noted at 8 and 12 hours post-dose when compared to the pre-dose data from the relevant group. There was a mild compensatory increase in absolute mean tidal volume for animals given 25 mg/kg at 8 hours post-dose, which resulted no change in total pulmonary ventilation. There was no significant compensatory increase in absolute tidal volume at 8 hours post-dose for animals given 50 and 100 mg/kg and no increase at 12 hours for all doses. Therefore, the drop in respiratory rate in these animals led to significant decrease (9-14%) in total pulmonary ventilation. All parameters had returned to normal levels by 72 hours post-dose.

Following the administration of metabolite M3 (ARN000308) at doses of 25, 50 and 100 mg/kg a slight transient decrease in absolute respiratory rate was noted at 8 and 12 hours post-dose when compared to the pre-dose data from the relevant group. There was a mild compensatory increase in absolute tidal volume for the 25 and 100 mg/kg dose groups which resulted no appreciable change in total pulmonary ventilation (absolute minute volume). No compensatory increase in absolute tidal volume was noted in the 50 mg/kg dose group and therefore the drop in respiratory rate led to a decrease (15 and 20%), in total pulmonary ventilation. All parameters had returned to normal levels by 72 hours post-dose.

Study title: Effects of ARN000308 and ARN-509 on Action Potentials in Isolated Canine Cardiac Purkinje Fibers (110513.BSC)

GLP compliance: Yes

Three concentrations of metabolite M3 (ARN000308) and apalutamide (3, 10 and 30 µM) were added sequentially to four isolated, canine Perkinje fiber preparations at three stimulus intervals (basic cycle lengths of 2, 1 and 0.5 s). Metabolite M3 did not induce significant changes. Apalutamide at 3 and 10 µM, but not at 30 µM, induced a statistically significant ($P<0.05$) reduction in action potential amplitude (APA) at a 2s BCL (basic cycle length) (Mean; 0.5 and -1.7 mV, respectively). However, the lack of dose response suggests that these changes may not be biologically significant.

Study title: Effect of JNJ-56021927-AAA and JNJ-56142060-AAA on hERG Tail Currents Recorded from Stably Transfected CHO Cells (794484)
GLP compliance: Yes (OECD)

The potential effect of apalutamide (JNJ-56021927) and metabolite M3 (JNJ-56142060) on hERG channel was investigated at concentrations of 1, 3, 10 and 30 µM using the whole-cell patch clamp electrophysiology technique in CHO-K1 (Chinese Hamster Ovary) cells stably

transfected with hERG. Apalutamide and metabolite M3 produced statistically significant inhibition of the hERG tail current at all tested concentrations. IC50 values for hERG inhibition were 6.17 µM (95% CI = 4.02 to 9.49 µM) and 4.56 µM (95% CI = 3.81 to 5.45 µM) for apalutamide and metabolite M3, respectively, suggesting they are low potency blockers.

Study title: JNJ-56021927-ZAH (ARN-509): Telemetric Evaluation of Cardiovascular Effects in the Conscious Dog (Oral Capsule Administration) (TOX10811)
GLP compliance: no

Conscious telemetered dogs (3/sex) were orally administered apalutamide at 0, 10, 20 and 40 mg/kg (at least 13 days apart) using an escalating dosing design. Heart rate (derived from blood pressure), body temperature, ECG lead II intervals PR, QRS, QT, QT corrected for heart rate (QTcR, QTcB, QTcF and QTcV) and morphology, were recorded starting at least 90 min prior to dosing and for 24 h postdose. No adverse findings were reported.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Rats [^{14}C]ARN-509: Absorption, Distribution, Metabolism and Excretion Studies in the Male Rat after Single Oral Dosing (Study FQA0001) (5 and 50 mg/kg)	Free base or ethanolate salt of apalutamide (n=7) T_{max} (mean): Apalutamide: 8 to 13 hours postdose M3: 12 to 13 hours postdose
Plasma Pharmacokinetics of ARN-509, ARN000308 and ARN000066 in Sprague Dawley Male Rats Following Single Oral Administration of ARN-509 or ARN000308 at Doses of 500, 1000 and 2000 mg/kg (Study DR-13-003-DSD)	T_{max} (mean) Apalutamide: 11 to 12 hour postdose M3: 18 to 24 hours postdose M4: 14 to 24 hours postdose
Pharmacokinetics of ARN000308, the N-desmethylated Metabolite of ARN-509 in Sprague Dawley Male Rats (Study DR-11-014-DSD)	Oral bioavailability bioavailability data for M3 was 77.9%, but no data are available for the parent compound
Dogs Single Dose Pharmacokinetics of ARN-509 in Male Beagle Dogs (Study DR-10-002-DSD)	Oral bioavailability bioavailability of apalutamide was approximately

Type of Study	Major Findings
	100% at 10 mg/kg in dogs
Distribution	
Rats [^{14}C]ARN-509: Absorption, Distribution, Metabolism and Excretion Studies in the Male Rat after Single Oral Dosing (Study FQA0001) Dogs A 13-week Oral Toxicity and Toxicokinetic Study of ARN-509 in Male Dogs with a 60-day Recovery Period (Study TX-509-1002) The distribution of ^{14}C-JNJ-56021927 and ^{14}C-JNJ-56142060 in blood. The protein binding of JNJ-56021927 and JNJ-56142060 in plasma from mouse, rat, dog, rabbit and human and the binding to human ⍰1-acid glycoprotein and albumin (Study FK10658)	<u>Single oral dose of 5, 50 mg/kg, the free base or ethanolate salt</u> widely distributed; greatest in abdominal and brown fat, liver, kidney cortex and medulla, adrenal cortex, pancreas, and Harderian gland and lowest in the lens of the eye, brain and bone surface. <u>Male dogs, daily oral dose of 2.5, 5, 10 mg/kg</u> -Plasma and brain concentrations increased greater than dose-proportionally; -The brain:plasma ratios were approximately 1:1; -The highest fraction was bound to plasma proteins (0.50 to 0.685), and some distributed to blood cells (0.285 to 0.424); -Plasma protein binding was not concentration dependent; -Apalutamide and metabolite M3 were mostly bound to human serum albumin (HSA).
Metabolism	
Rats [^{14}C]ARN-509: Absorption, Distribution, Metabolism and Excretion Studies in the Male Rat after Single Oral Dosing (Study FQA0001) (50 mg/kg) 2-week repeat-dose study (Study VUM00002) (150 mg/kg) *Dogs* The metabolism and excretion of ^{14}C-JNJ-56021927 in male beagle dog after a single oral administration of ^{14}C-JNJ-56021927 at 10 mg/kg (Study FK10704) 3-week repeat-dose study(Study VUM00003) (10 mg/kg/day)	-Apalutamide fraction (65%-12h, 53%-24h) -Metabolite M4 fraction (12%-12h, 15%-24h) -Other metabolites < 10% -M2 and M4 were at highest levels -Apalutamide and M3 were major radioactivity in circulation; -M3 > apalutamide after 72 hours; -M4 was 11- to 19-fold < M3 after 24 hours. The major circulating metabolites were M3 and M4

Type of Study	Major Findings

Table 4. Apalutamide (ARN-509) Metabolite Profiles Across In Vitro and In Vivo Samples*

Metabolite	Rat LM (in Vitro)	Dog LM (In Vitro)	Human LM (In Vitro)	Dog Plasma (In Vitro)	Rat Plasma (150 mg/kg)	Dog Plasma (10 mg/kg)
M1 (Di-Amide)	+	+	+	++++	++	+
M2 (Hydantoin)	+	+	+	++++	++++	++
M3 (N desmethyl)	+	++	+	++	++	+++++
M4 (amide hydrolysis)	++++	++	++	+	+++	+++

\+ Metabolite detectable, but area < 0.5% of total peak area (including ARN-509)
++ Metabolite > 0.5% of total peak area (including ARN-509)
+++ Metabolite > 5% of total peak area (including ARN-509)
++++ Metabolite > 10% of total peak area (including ARN-509)
+++++ Metabolite > 25% of total peak area (including ARN-509)

*In vivo data in above table (copied from the applicant's submission) were summarized based on the study results from the dose range-finding toxicology studies, were pooled from day 14 for the rat study (VUM0002) and day 21 for the dog study (VUM0003)

Excretion	
Rats [^{14}C]ARN-509: Absorption, Distribution, Metabolism and Excretion Studies in the Male Rat after Single Oral Dosing (Study FQA0001) (50 mg/kg) *Dogs* The metabolism and excretion of ^{14}C-JNJ-56021927 in male beagle dog after a single oral administration of 14C-JNJ-56021927 at 10 mg/kg (Study FK10704)	-excretion of total radioactivity(TR) was 34.2% in urine and 58.2% in feces; -50.0% of TR was excreted in bile, remainder in urine (29.7%) and feces (11.2%); -Nearly all TR was recovered after 48 hours; -TR excreted in urine (41.8%) and feces (40.2%). -Cumulative excretion of radioactivity (parent drug and identified metabolites) accounted for 64.2% of the dose in urine and 24.1% of the dose for feces over 1680 hour interval.
TK data from general toxicology studies *Rat* A 26-week repeated dose study in male rats (Study 20054198) 25, 75, 150 mg/kg/day	<u>Male</u> *apalutamide* < dose proportional AUC ranged 135-508 µg*hr/mL C_{max} ranged 7-28 µg/mL $T_{1/2}$: not defined T_{max}: 4 hours Accumulation (1.4 - 1.5)

Type of Study	Major Findings
	Metabolite M3 $AUC_{(0-t)}$ ratios relative to apalutamide ranged from 0.0338 to 0.0545 ≤ 75 mg/kg- > dose proportional ≥ 75 mg/kg- < dose proportional $T_{1/2}$: not defined T_{max}: 12 hours Accumulation (1.2 - 1.5)
A 26-week repeated dose study in female rats (Study 20060308*)* 25, 50, 100, 150 mg/kg/day	<u>Female</u> *apalutamide* ≤ 100 mg/kg- dose proportional ≥ 100 mg/kg- < dose proportional T_{max}: between 4 hours and 12 hours $T_{1/2}$: not defined Accumulation (1.3 - 3.3) *Metabolite M3* $AUC_{(0-t)}$ ratios relative to apalutamide ranged from 0.00852 to 0.0378 ≤ 100 mg/kg- > dose proportional ≥ 100 mg/kg- exposure plateaued T_{max}: 8 hours and 24 hours $T_{1/2}$: not defined Accumulation (2.6 - 7.6)
Dog A 28-day Repeated Dose Study in Male Dogs (study VUM00005) 5, 10, 25 mg/kg/day	*Apalutamide* ≤ 10 mg/kg- > dose proportional <u>5 and 10 mg/kg (Day 28)</u> AUC_{0-24} ranged 116-290 µg*hr/mL C_{max} ranged 6-13 µg/mL $T_{1/2}$: 57 -86 hrs T_{max}: 4 - 7 hours Accumulation (1.2 - 1.3) <u>25 mg/kg</u> (Day 1) AUC_{0-24}: 127 µg*hr/mL C_{max}: 7 µg/mL
A 39-week Repeated Dose Study in Male Dogs (Study 20054199)	*apalutamide* > dose proportional

Type of Study	Major Findings
Daily for 39 weeks 2.5, 5, 10 mg/kg/day	AUC ranged 87-427 µg*hr/mL C_{max} ranged 4-19 µg/mL $T_{1/2}$: not defined T_{max}: 2 and 24 hours No accumulation *Metabolite M3* -AUC(0-t) ratios relative to apalutamide ranged from 0.0338 to 0.0545 < dose proportional $T_{1/2}$: not defined T_{max}: ranged from 2 and 24 hours No accumulation (steady state by Day 28)
TK data from reproductive toxicology studies JNJ-56021927-ZAH: Oral fertility study in the male rat (Study TOX10913)	No TK data provided Estimated exposures: 25 mg/kg/day On Day 28 (study 20054198): AUC_{0-t}: 85 µg*hr/mL C_{max}: 5 µg/mL 150 mg/kg/day On Day 28 (Study UVM00004, a 28-day study in male rats): AUC_{0-24}: 572 µg*hr/mL C_{max}: 31.5 µg/mL

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: A 26-week Repeated Dose Toxicity Study of JNJ-56021927-ZAH by Oral Gavage Administration in Male Rats (study#20054198)

Key Study Findings

- Toxicities involved in the male reproductive system (seminal vesicles, testes, prostate gland, mammary gland, and epididymides), and adrenal gland, bone marrow, pituitary gland, liver;

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 25, 75, 150 mg/kg/day, once daily from Days 1 to

182/183
Route of administration: Oral gavage
Formulation/Vehicle: (b) (4)

(b) (4).
Species/Strain: male Sprague Dawley Crl:CD(SD) rats
Number/Sex/Group: 20/group
Age: 8 weeks old
Satellite groups/ unique design: TK, 8/group (4 control)
Deviation from study protocol affecting interpretation of results: No

Observations and Results:

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	↓ body weight gain beginning on Day 8 Changes compared to the control (%) at the end-of-dosing Dose (mg/kg): 25 / 75 / 150 body weight: ↓5.6 / ↓10* / ↓10* body weight gain: ↓8.4 / ↓15* / ↓15* *: p<0.05
Food Consumption	unremarkable
Ophthalmoscopy	unremarkable
Hematology	Day 183/184 (compared to the control) -↓red cell mass (erythrocytes, hemoglobin, and hematocrit; 0.8 to 0.9x) ↑reticulocytes (1.3 to 1.9x) and red cell distribution width (1.1 to 1.2x), all doses, dose- dependent -↑mean corpuscular hemoglobin (1.0 to 1.1x) and mean corpuscular volume (1.0 to1.1x) at ≥ 75 mg/kg/day -↑in platelets (1.2 to 1.5x), fibrinogen (1.1 to 1.4x), leukocytes (1.1 to 1.3x), and lymphocytes (1.1 to 1.4x) all doses, dose- dependent -similar findings on Day 90/91
Clinical Chemistry	*Day 183/184* *↑alkaline phosphatase (1.3 to 1.9x), blood urea nitrogen (1.3 to 1.6x), cholesterol (1.7 to 3.3x), total protein (up to 1.1x), albumin (up to 1.1x), globulin (up to 1.1x), and creatinine (1.3 to 1.7x)* *all doses, dose- dependent* -similar findings on Day 90/91
Urinalysis	unremarkable
Gross Pathology	Number of Animals with Finding Dose (mg/kg): 0 / 25 / 75 / 150 No. animals per group: 20 / 20 / 20 / 20

Prostate	small		17	19	20
Seminal vesicle	small		14	18	19
Epididymis	small		6	9	11
Testes	discoloration		1	2	6
	small			1	4
	enlarged			2	1

Organ Weights

Change compared to control values (%) in male rats

	Absolute change			Relative change (to BW*)		
Dose (mg/kg)	25	75	150	25	75	150
Adrenal gland	↑17	**↑45[c]**	**↑60[c]**	**↑25[a]**	**↑62[c]**	**↑80[c]**
Pituitary gland	↑11	**↑56[c]**	**↑50[c]**	↑18	**↑74[c]**	**↑70[c]**
Thymus	**↑33[a]**	**↑31[a]**	**↑45[c]**	**↑42[b]**	**↑47[c]**	**↑62[c]**
Liver	↑2	**↑26[c]**	**↑33[c]**	↑3	**↑23[c]**	**↑32[c]**
Spleen	↑10	**↑39[c]**	**↑44[c]**	↑16	**↑55[c]**	**↑60[c]**
Prostate	**↓76[b]**	**↓87[c]**	**↓88[c]**	**↓75[b]**	**↓86[c]**	**↓87[c]**
Epididymides	**↓35[c]**	**↓48[c]**	**↓53[c]**	**↓30[c]**	**↓42[c]**	**↓47[c]**

values in bold are statistically significant (a, p≤0.05; b, p≤0.01; c, p≤0.001)
*BW, Body Weight

Histopathology
Adequate battery: Yes

Dose (mg/kg)	0	25	75	150
No. animals per group	20	20	20	20

	Prostate					
	Atrophy	Minimal		14	5	1
		Mild		6	9	10
		Moderate			4	7
		Severe			2	2
	Seminal vesicle					
	Atrophy	Minimal		15	7	
		Mild		4	7	13
		Moderate			5	5
		Severe			1	2
	Epididymis					
	Atrophy	Minimal		1	2	9
		Mild		1	2	5
		Moderate			1	2
		Severe				3
	Testes					
	Degeneration, seminiferous tubules	Minimal		16	11	11
		Mild				3
		Moderate			4	2
		Severe		1	1	4
	Hyperplasia, interstitial cell	Minimal		3	7	11
		Mild		2	2	2
		Moderate			1	4
		Severe			2	1
	Adenoma, interstitial cell				1	1
	Mammary glands					
	Tubuloalveolar morphology			18	19	17
	Pituitary glands					
	Hypertrophy			5		
	Minimal			12	4	2
		Mild		2	15	17
		Moderate				1
		Severe				
	Liver				1	4
	Hypertrophy, hepatocellular	Minimal				
	Adrenal glands			2	8	15
	Hypertrophy, cortical	Minimal				
	Bone marrow, Femur			3	19	18
	Hypercellular	Minimal				
Toxicokinetics	See ADME/PK section 5.4 above					

Blank: no related findings

Study title/ number: A 26-week Repeated Dose Toxicity Study of JNJ-56021927 by Oral Gavage Administration in Female Rats with a 2-Month Recovery Period (study# 20060308)

Key Study Findings

- Potential apalutamide-related mortality (1 animal) at 150 mg/kg/day, the cause of death was not identified;
- Toxicities in the ovary (including findings of neoplasia), uterus, adrenal gland,

mammary gland, pituitary gland, thyroid gland, liver, spleen, and thymus;
- Except for the liver and spleen, histopathology findings persisted throughout the recovery phase (8 weeks), although generally decreased in incidence and severity;
- Lymphoid depletion of the thymus and hyperplasia of the thyroid gland was observed during the recovery phase but not during the dosing phase.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 25, 50, 100, 150 mg/kg/day, once daily from Days 1 to 182/183

Route of administration: Oral gavage

Formulation/Vehicle: (b) (4)

(b) (4) % w/w/w/w)

Species/Strain: female Sprague Dawley Crl:CD(SD) rats

Number/Sex/Group: 20/group (main), 5/group (recovery, control, 100 mg/kg, and 150 mg/kg)

Age: 8 weeks old

Satellite groups/ unique design: TK, 6/group (4 control)

Deviation from study protocol affecting interpretation of results: No

Observations and Results:

Parameters	**Major findings**
Mortality	

Group	1	2	3	4	5
Dose (mg/kg/day)	0	25	50	100	150
Number of animals	25	20	20	25	25
Unscheduled Euthanasia	0	0	0	0	3
Found Dead	1	3	1	1	2
Total Early Deaths	**1**	**3**	**1**	**1**	**5**
Note: One animal at 150 mg/kg/day had an unknown cause of death, which may be apalutamide-related. All other early deaths were attributed to dosing error.					

Clinical Signs	unremarkable
Body Weights	unremarkable
Food Consumption	unremarkable
Ophthalmoscopy	unremarkable
Hematology	Day 183/184(compared to the control) -↓red cell mass (erythrocytes, hemoglobin, and hematocrit; 0.8 to 0.9x) ↑reticulocytes (1.2 to 1.8x) and red cell distribution width (1.1), LUC (2 x to 2.5x) all doses, dose- dependent -↑in platelets (1.2 to 1.4x, all doses, dose- dependent -↑leukocytes (1.2 to 1.4x), and lymphocytes (1.2 to 1.4x), all doses, dose- dependent

	-↑monocytes (1.3-1.4xx) at ≥ 100 mg/kg -↑fibrinogen (1.2x), ≥ 100 mg/kg) -↓PT (0.9x), ≥ 50 mg/kg -similar findings on Day 88/89 <u>Recovered (compared to the control)</u> Day 205: ↑leukocytes (1.4x) at 100 mg/kg, ↑neutrophils (1.5-2x), ↑LUC (1.3-1.4x) all doses Day 242: ↑leukocytes (1.6x) at 100 mg/kg, ↑neutrophils (1.7-2.5x), all doses
Clinical Chemistry	<u>Day 183/184</u> <u>(compared to the control)</u> ↑ cholesterol (1.6 to 2.4), all doses ↑ globulin (1.1 to 1.3x), Albumin (1.1x), all doses ↑ triglycerides (1.8-2.2x), ALP (1.4x), ≥ 50 mg/kg -similar findings on Day 88/89 <u>Recovery (Day 205, Day 242)</u> unremarkable
Urinalysis	unremarkable
Gross Pathology	

Early Death Animals					
Dose (mg/kg)	0	25	50	100	150
No. animals per group	1	3	1	1	5
Adrenal Gland					
Enlargement					2
Terminal Euthanasia (Day 183/184)					
Dose (mg/kg)	0	25	50	100	150
No. animals per group	19	17	19	19	16
Ovary					
Focus, pale				4	2
Mass		1		3	4
Mammary Gland					
Thick		1	1	2	2
Nodule		1	1	1	2
Adrenal Gland					
Enlargement		1		2	3
Pituitary Gland					
Enlargement, focus, mass		3	2	6	5
Liver					
Enlargement			1	1	1
Recovery Euthanasia (Day 242)					
Dose (mg/kg)	0	25	50	100	150
No. animals per group	5	0	0	5	4
Ovary					
Mass		-	-	4	1
Pituitary Gland					
Enlargement		-	-	1	2

Organ Weights	Change compared to control values (%) in female rats

	Absolute change				Relative change (to BW)			
Dose (mg/kg)	25	50	100	150	25	50	100	150
Terminal Euthanasia (Day 183/184)								
Adrenal gland	**↑32**	**↑60**	**↑90**	**↑101**	**↑32**	**↑49**	**↑84**	**↑101**
Pituitary gland	↑27	**↑40**	**↑40**	**↑61**	↑25	**↑31**	**↑36**	**↑60**
Liver	**↑19**	**↑47**	**↑81**	**↑75**	**↑18**	**↑38**	**↑75**	**↑74**
Spleen	↑4	**↑16**	**↑39**	**↑28**	↑3	**↑9**	**↑35**	**↑27**
Uterus	**↑48**	**↑51**	**↑44**	↑23	**↑46**	**↑42**	**↑39**	↑21
Heart	↑10	**↑18**	**↑23**	**↑20**	**↑9**	**↑10**	**↑19**	**↑20**
Kidney	↑7	**↑17**	**↑18**	**↑17**	↑6	↑9	**↑14**	**↑16**
Recovery Euthanasia (Day 242)								
Adrenal gland	-	-		↑42	-	-		**↑53**
Pituitary gland	-	-		↑22	-	-	↓12	↑29
Thyroid Gland	-	-			-	-	↑28	**↑39**
Liver	-	-	**↑36**	↑25	-	-	**↑28**	**↑34**
Spleen	-	-	**↑36**	↑13	-	-	↑24	↑19
Thymus	-	-	↓14	↓16	-	-	↓21	↓9
Uterus	-	-	↑20	**↑53**	-	-	↑8	↑56
Heart	-	-	↑25	↑23	-	-	↑18	**↑31**
Kidney	-	-	↑16	↑17	-	-	↑9	**↑25**

Note:
1) values in bold are statistically significant
2) blank: unremarkable
3) (-) no recovery animals assessed
4) BW, Body Weight

Histopathology
Adequate battery: Yes

Terminal Euthanasia (Day 183/184)					
Dose (mg/kg)	0	25	50	100	150
No. animals per group	19	17	19	19	16
Test Article-Related Primary Neoplasms					
Ovary					
Thecoma, benign			1	6	7
Thecoma, malignant				3	2
Granulosa cell tumor, benign				2	
Granulosa cell tumor, malignant		1			
Total Ovarian Neoplasms	**0**	**1**	**1**	**11**	**9**
Non-Neoplastic Findings					
Adrenal Gland					
Hypertrophy, cortex -Minimal		4	4	1	4
-Mild		3	9	9	5
-Moderate			4	8	6
Mammary Gland					
Dilatation, alveolus/duct					
-Minimal		8	7	5	1
-Mild		4	6	10	6
-Moderate		1	3		3
-Marked				1	2
Galactocele		2	3	5	4
Hypertrophy, glandular epithelium					
-Minimal		1	1	4	2

-Mild		1	4	8	10
Vacuolation, glandular epithelium					
-Minimal		5	4	2	2
-Mild		4	7	10	10
Pituitary Gland					
Hyperplasia -Minimal		8	11	8	
-Mild			2	7	5
-Moderate				3	
-Marked			2		1
Liver					
Hypertrophy, hepatocellular, centrilobular -Minimal		3	3	1	3
-Mild		2	10	10	7
-Moderate			5	8	3
-Marked					1
Spleen					
Increased hematopoiesis -Minimal		5	10	7	5
-Mild			3	9	5
Ovary					
Hyperplasia, interstitial cell-Minimal		2	3		2
-Mild		2	8	14	8
-Moderate				2	1
Corpora lutea absent	1	9	15	9	14
Uterus					
Hypertrophy, wall -Minimal	1	6	5	6	4
-Mild	2	4	5	6	5

Recovery Euthanasia (Day 242)			
Dose (mg/kg)	0	100	150
No. animals per group	5	5	4
Primary Neoplasms			
Ovary			
Thecoma, benign		1	1
Granulosa cell tumor, benign		3	2
Non-Neoplastic Findings			
Adrenal Gland			
Hypertrophy, cortex -Minimal		1	1
Mammary Gland			
Galactocele			1
Hypertrophy, glandular epithelium -Mild	1		2
Vacuolation, glandular epithelium -Minimal		1	
-Mild	2	1	3
Pituitary Gland			
Hyperplasia -Minimal		1	2
Thyroid Gland			
Hyperplasia, follicular cell -Minimal		1	1
-Mild		1	
Thymus			
Lymphoid depletion -Minimal	1		

	-Moderate		2		
	-Marked			1	
	Uterus				
	Hypertrophy, wall -Minimal	1		2	
	-Mild		1		
	Ovary				
	Hyperplasia, interstitial cell				
	-Minimal		1	1	
Toxicokinetics	See ADME/PK section 5.4 above				

Study title/ number: A 28-Day Toxicity Study of ARN-509 Administered by Oral Capsule to Male Dogs with a 28-Day Recovery Period (study# VUM00005)

Key Study Findings

- Early euthanasia occurred at 25 mg/kg/day due to instances of convulsions;
- Convulsions (lasting up to 3 minutes), intermittent tremors, and decreased activity were observed at 25 mg/kg;
- Pathologic changes consistent with findings in longer-term studies in dogs (epididymides, prostate, and testes).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 5, 10, 25* mg/kg/day, once daily for 28 days
*The last dose administration at 25 mg/kg/day was conducted on Day 8, and the surviving animals were considered on recovery from Day 9 until termination on Day 29 or 57.
Route of administration: Oral, gelatin capsules
Formulation/Vehicle: (b) (4) (% w/w/w/w)
Species/Strain: male Beagle dogs
Number/Sex/Group: 5/group (main), 3/group (recovery, control, MD, HD)
Age: not provided
Satellite groups/ unique design: none
Deviation from study protocol
affecting interpretation of results: No

Observations and Results:

Parameters	Major findings
Mortality	Three 25 mg/kg/day animals were euthanized due to adverse clinical signs related to convulsions on Day 7 (#D3936), Day 8 (#D3937), or Day 9 (#D3934).

Clinical Signs	< 25 mg/kg: unremarkable 25 mg/kg: convulsions (lasting up to 3 minutes), intermittent tremors, and decreased activity
Other findings were consistent with longer-term studies in dogs reviewed below. Only findings unique to this study were reported here.	
Toxicokinetics	See ADME/PK section 5.4 above

Study title/ number: A 39-week Repeated Dose Toxicity Study of JNJ-56021927-ZAH by Oral Capsule Administration in Male Dogs (study# 20054199)

Key Study Findings

- Decreased body weights and body weight gains
- Toxicities involved in the prostate gland, epididymides, testes, and liver

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2.5, 5, 10 mg/kg/day, once daily from Days 1 to 273
Route of administration: Oral
Formulation/Vehicle: capsule containing (b) (4) % w/w/w/w)
Species/Strain: male Beagle dogs
Number/Sex/Group: 4/group
Age: 6 months old
Satellite groups/ unique design: none
Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control *[include major findings only]*

Parameters	**Major findings**
Mortality	None
Clinical Signs	Unremarkable
Body Weights	

	Change compared to control mean (%)		
Dose (mg/kg)	2.5	5	10
body weight gain	↓30	↓44	↓41
Body weight	↓8	↓12	↓12

Food Consumption	Unremarkable
Ophthalmoscopy	Unremarkable
Electrocardiography	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	

	Change from mean control values (%)					
Dose (mg/kg)	2.5		5		10	
Study Day	182	274	182		182	
ALP	↑28	↑57	↑84	↑157*	↑140	↑245
CHOL	↑58*	↑62*	↑42	↑37	↑66**	↑71*
'*" P<0.05, "**" p<0.01						

Urinalysis: Unremarkable

Gross Pathology: Small epididymis in 1 dog at 10 mg/kg/day

Organ Weights

Change compared to mean control values (%) in male dogs

	Absolute change			Relative change (to BD)		
Dose (mg/kg)	2.5	5	10	2.5	5	10
Epididymis	**↓34.2**	**↓43.8**	**↓59.7**	↓27	↓35.4	**↓53.8**
Prostate	↓85	**↓90.6**	**↓91.5**	↓83	**↓89.2**	**↓90.6**
Kidney	↓22.3	**↓25.3**	**↓26.5**	↑13.7	↑14.2	↓16

values in bold are statistically significant, p ≤ 0.05
*BW, Body Weight

Histopathology
Adequate battery: Yes

Dose (mg/kg)	0	2.5	5	10
No. animals per group	4	4	4	4
Prostate				
Atrophy -Mild		1		
-Moderate		3	3	
-Marked			1	4
Epididymis				
Atrophy -Mild			1	
-Moderate		2		3
-Marked			2	1
Decreased spermatozoa				
-Minimal		1		
-Moderate			3	
-Marked				4
Testes				
Degeneration/Atrophy				
-Minimal		1	1	
-Mild		2	2	1
-Moderate			1	3
Hypertrophy, Leydig cell				
-Minimal			1	
-Mild		1	2	4
Liver				
Hyperplasia, bile duct/oval				
-Minimal		1	3	2
-Mild				2

Toxicokinetics: See ADME/PK section 5.4 above

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: ARN-509 and ARN000308 Bacterial Reverse Mutation Test in Salmonella Typhimurium and Escherichia Coli (Study # 963861)

Key Study Findings:

- Apalutamide and metabolite M3 (ARN000308) did not show any increases in the revertant colony counts in all tester strains in the presence and absence of S9 activation under the test condition (plate incorporation or pre-incubation).

GLP compliance: Yes (OECD)
Test system: Salmonella (TA98, TA100, TA1535, and TA1537), and E. coli strain WP2uvrA
ARN-509 and ARN000308: up to 5000 ug/mL; +/-S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: ARN-509 and ARN000308 In Vitro Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes (Study# 963862)

Key Study Findings

- Cultures treated with apalutamide and metabolite M3 (ARN000308) did not show any substantial increases in the incidence of aberrant metaphases.

GLP compliance: Yes (OECD)
Test system: Human Peripheral Blood Lymphocytes
ARN-509 and ARN000308: up to 500 ug/mL
-S9: 4 hours, 21 hours, + S9: 4 hours,
Study is valid: yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: ARN-509 and ARN000308 Mammalian Erythrocyte Micronucleus Test in Rat Bone Marrow) Study# 963863)

Key Study Findings

- Rats treated with single oral administration of apalutamide or metabolite M3 (ARN000308) at doses up to 2000 mg/kg did not show any notable increases in the incidence of MIE, MME or any remarkable decreases in the proportion of IE.

GLP compliance: Yes (OECD)
Test system: male rats, bone marrow micronuclei; single oral doses of 500, 1000 and 2000 mg/kg
Study is valid: Yes

Other Genetic Toxicity Studies

Study title/ number: In Vivo Mammalian Alkaline Comet Assay in the Liver Cells of Male Rats Following Oral Administration of JNJ-56021927-ZAH (Study# AE44FS.423MICH.BTL)

Key Study Findings

- Rats administration of JNJ-56021927-ZAH at doses up to 150 mg/kg/day on two consecutive days did not cause a significant increase in DNA damage in male rat liver relative to the concurrent vehicle control.

GLP compliance: Yes
Test system: male rats, DNA damage in liver cells; 2 oral doses of 25, 50, 100, 150 mg/kg/dose
Study is valid: Yes

5.5.3. Carcinogenicity

No carcinogenicity study reports were submitted or warranted with this application.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: JNJ-56021927-ZAH: Oral fertility study in the male rat (Study# TOX10913)

Key Study Findings

- Dose-dependent decreases in epidydimal sperm concentration and sperm motility with lower copulation rate and fertility rate;
- Reduced number of viable offspring as evidenced by an increased pre- and/or postimplantation loss;
- All effects observed were reversible after a treatment-free period of 8 weeks.

Conducting laboratory and location	Preclinical Development & Safety, Turnhoutseweg 30, 2340 Beerse, Belgium
GLP compliance:	Yes (OECD)
Methods	
Dose and frequency of dosing:	0, 25 or 150 mg/kg at dose volume 5 mL/kg, once daily for 4 weeks
Route of administration:	oral gavage
Formulation/Vehicle:	a non-aqueous solution containing (b) (4) % w/w/w/w)
Species/Strain:	Male rat/Sprague-Dawley (Crl: CD)
Number/Sex/Group:	20/group* *12 rats/group for sperm evaluation and gross examination of the reproductive organs 20 rats/group for pairing assessment (with untreated females)

Satellite groups:	none
Study design:	**pairing 1:** treated for 4 weeks prior to mating, then remained continuously dosed throughout the first 10-day pairing period **pairing 2 (recovery):** following completion of pairing 1 period, kept untreated for 8 weeks and subjected to a second pairing assessment with a second batch of untreated females
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>no apalutamide-related mortalities</td></tr>
<tr><td>Clinical Signs</td><td>unremarkable</td></tr>
<tr><td>Body Weights</td><td>25 mg/kg: unremarkable
150 mg/kg: ↓ body weight gain at the first week of treatment
(statement provided by the applicant, no data provided)</td></tr>
<tr><td>Food consumption</td><td>unremarkable</td></tr>
<tr><td>Fertility data</td><td>pairing 1:
<table>
<tr><td>Group (mg/kg)</td><td>control</td><td>25</td><td>150</td></tr>
<tr><td>Numbers of animal</td><td>20</td><td>20</td><td>20</td></tr>
<tr><td>Copulation index
(actual numbers of mating males)</td><td>100%
(20)</td><td>95%
(19)</td><td>80%
(16)</td></tr>
<tr><td>No. plugs/No. mating
(mean No. of plugs)</td><td>80/20
(4)</td><td>22/19
(1.16)</td><td>1/16
(0.06)</td></tr>
<tr><td>pre-coital interval</td><td colspan="3">comparable</td></tr>
</table>
pairing 2: unremarkable</td></tr>
<tr><td>Necropsy findings

<u>Gross pathology</u>

<u>Weight of the testes and epididymides</u></td><td>pairing 1:
<table>
<tr><td>Group (mg/kg)</td><td>0</td><td>25</td><td>150</td></tr>
<tr><td>Numbers of animal</td><td>20</td><td>12</td><td>12</td></tr>
<tr><td>small coagulating glands/ seminal vesicles
small prostate</td><td></td><td>2
1</td><td>11
5</td></tr>
<tr><td>relative weight of the left and right epididymis compared to control</td><td>-</td><td>0.66***</td><td>0.58***</td></tr>
</table>
***: p<0.001
pairing 2: unremarkable</td></tr>
<tr><td>Sperm assessment</td><td>pairing 1:
<table>
<tr><td>Group (mg/kg)</td><td>0</td><td>25</td><td>150</td></tr>
<tr><td>Animals: Examined/Total</td><td>11/12</td><td>12/12</td><td>12/12</td></tr>
<tr><td>sperm concentration
Cauda epididymidis
Total Sperm count (million)
(compared with control)
Sperm count (millions/g)</td><td>

185

654</td><td>

126***
(0.68)
664</td><td>

106***
(0.57)
652</td></tr>
<tr><td>Sperm motility
VAP(µm/s)</td><td>
74</td><td>
72</td><td>
68*</td></tr>
</table></td></tr>
</table>

(compared with control)			(0.91)
VSL (µm/s)	51	50	46*
(compared with control)			(0.90)
VCL (µm/s)	146	144	129**
(compared with control)			(0.88)
ALH(µm)	8.3	8.3	7.9**
(compared with control)			(0.95)
Sperm morphology (200 sperms examined)			
Abnormal sperm cells (%)	10.7	13.8	14.8*

VAP: average path, VSL: straight line, VCL curvilinear velocities, ALH: amplitude of the lateral head displacement
*: p< 0.05 **: p<0.01 ***: p<0.001
pairing 2: unremarkable

Litter data
(on Day 14 of presumed pregnancy)

pairing 1:

Group (mg/kg)	0	25	150
No. implantations /pregnant animal	13.8	13.8	11.0
Pre-implantation loss (%)	8.8	12.1	25.5
No. resorptions/ pregnant animal	0.84	1.00	1.00
post-implantation loss (%)	6.2	7.46	14.8
Number of live fetuses/pregnant animal	12.9	12.8	10
No. corpora lutea /pregnant animal Number of dead fetuses/pregnant animal	unremarkable		

pairing 2:

Group (mg/kg)	0	25	150
No. resorptions/ pregnant animal	0.58	1.00	0.79
post-implantation loss (%)	4.03	6.89	5.87
No. corpora lutea /pregnant animal No. implantations /pregnant animal Pre-implantation loss (%) Number of dead fetuses/pregnant animal Number of live fetuses/pregnant animal	unremarkable		

5.5.5. Other Toxicology Studies

Study title/ number: Neutral Red Uptake Phototoxicity Assay of ARN-509 and its Primary Metabolite ARN000308 in Balb/c 3T3 Mouse Fibroblasts (Study# 20020054)

Key Study Findings

- Apalutamide and metabolite M3 (ARN000308) did not demonstrate phototoxicity in this assay.

GLP compliance: Yes

{See appended electronic signature page}

Primary Reviewer	Team Leader
Wei Chen	Todd Palmby

6 Clinical Pharmacology

6.1. Executive Summary

The proposed apalutamide dosing regimen is 240 mg (60 mg × 4 tablets) orally once daily with or without food. The evidence of efficacy was supported by a pivotal Phase 3 randomized, double-blind, placebo-controlled study (Study 003) of apalutamide in combination with androgen deprivation therapy (ADT) in the treatment arm and placebo with ADT in the control arm.

The key review questions focus on appropriateness of apalutamide dose, recommendations for apalutamide dose in patients with hepatic or renal impairment, dose adjustments for apalutamide due to drug-drug interactions (DDIs).

Recommendations

The Office of Clinical Pharmacology Division of Clinical Pharmacology V, Division of Pharmacometrics, and Genomics & Targeted Therapy Group have reviewed the information contained in NDA 210951. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from a Phase 3 Study 003.
General dosing instructions	The proposed apalutamide dosing regimen of 240 mg orally once daily is effective and appears have a manageable safety profile.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is recommended for patients with mild and moderate hepatic impairment. No data are available in patients with severe hepatic impairment. • No dose adjustment is recommended for patients with mild and moderate renal impairment. No data are available in patients with severe renal impairment or end-stage renal disease. • No initial dose adjustment is recommended for patients concomitantly taking a strong CYP2C8 or CYP3A4 inhibitor, consider reducing the dose based on tolerability. • No dose adjustment is recommended for patients concomitantly taking a CYP3A4 and/or CYP2C8 inducer.

Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the Phase 3 Study 003.

Post-Marketing Requirements and Commitments

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Apalutamide and its major active metabolite N-desmethyl apalutamide exhibited dose-proportional increases in exposure across the dose range of 30 mg to 480 mg following both single doses and repeated doses. In vitro, N-desmethyl apalutamide exhibited one-third the AR inhibition potency of apalutamide. The steady-state PK profiles for both apalutamide and N-desmethyl apalutamide after 240 mg apalutamide once daily administration were flat: apalutamide mean (CV%) C_{max}, AUC_{0-24}, and C_{min} were 6.0 µg/mL (28%), 100 µg·h/mL (32%), and 3.7 µg/mL (32%), respectively; N-desmethyl apalutamide mean steady state C_{max}, AUC_{0-24}, and C_{min} were 5.9 µg/mL (18%), 124 µg·h/mL (19%), and 4.7 µg/mL (19%), respectively. An increase in apalutamide apparent clearance (CL/F) was observed with repeat dosing, likely due to auto-induction. The auto-induction effect likely reached its maximum at the recommended dosage because exposure of apalutamide across the dose range of 30 to 480 mg is dose-proportional. There was no time-dependent disposition observed for N-desmethyl apalutamide. Following repeated 240 mg once daily administration, steady-state was generally achieved after 4 weeks. Apalutamide and N-desmethyl apalutamide accumulated with a geometric mean accumulation ratio of 5 and 122, respectively.

ADME Properties

Absorption: The time to reach C_{max} (t_{max}) for apalutamide following administration was 2 hours (range: 1 to 5 hours) after single dose. Apalutamide absolute bioavailability was approximately 100%. Apalutamide showed no clinical significant food effect on exposure (C_{max} and AUC) and t_{max} was delayed about 2 hours with food.

Distribution: The population PK analysis estimated apparent volume of distribution at steady-state for apalutamide and N-desmethyl apalutamide were 276 L and 238 L, respectively. Apalutamide and N-desmethyl apalutamide plasma protein binding values were 96% and 95%, respectively. Blood-to-plasma concentration ratios were 0.79 and 0.78 for apalutamide and N-desmethyl apalutamide, respectively.

Metabolism: Apalutamide is metabolized primarily by CYP2C8 and CYP3A. Following oral administration of a single 240 mg dose of radio-labeled apalutamide to humans, apalutamide and its active metabolite, N-desmethyl apalutamide, were the major circulating drug-derived entity in plasma, representing 45% and 44%, respectively, of the total radio-labeled AUC. No other metabolite was considered to have clinically relevant contribution to efficacy and safety. Metabolism is the main route of elimination of apalutamide. It is metabolized primarily by CYP2C8 and CYP3A4 to form N-desmethyl apalutamide. Apalutamide and N-desmethyl apalutamide are further metabolized to form the inactive carboxylic acid metabolite by carboxylesterase. In vitro and in vivo, apalutamide was identified as a CYP3A4 inducer. Due to CYP3A4 auto-induction, the contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but changes to 40% and 37%, respectively at steady-state.

Excretion: Apalutamide, mainly in the form of metabolites, is eliminated primarily via urine. Following a single oral administration of radiolabeled apalutamide, 89% of the radioactivity was recovered up to 70 days post-dose: 65% was recovered in urine (1.2% of dose as unchanged apalutamide and 2.7% as N-desmethyl apalutamide) and 24% was recovered in feces (1.5% of dose as unchanged apalutamide and 2% as N-desmethyl apalutamide).

Elimination: The CL/F of apalutamide was 1.3 L/h after single dosing and increased to 2.0 L/h at steady-state after once-daily dosing. The CL/F of N-desmethyl apalutamide was 1.5 L/h after single dosing and at steady-state. Based on a population PK analysis, the apparent steady-state half-life for apalutamide and N-desmethyl apalutamide in patients with CRPC was about 4.2 days and 4.6 days, respectively. The apalutamide apparent steady-state half-life from the population PK analysis was similar to the apalutamide mean effective steady-state half-live of about 3 day (range: 3 – 4 days) determined from a pooled dense PK data.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant proposes an oral dosing regimen of 240 mg once daily with or without food. The Phase 3 study 003 evaluated apalutamide at the proposed dose in combination with ADT in the treatment arm (N=806) and placebo with ADT in the control arm (N=401) in patients with NM-CRPC. The proposed dose is effective and has a manageable safety profile.

Therapeutic Individualization

<u>Specific Populations</u>

Patients with Hepatic Impairment: No dose adjustment was recommended for patients with mild or moderate hepatic impairment. In a dedicated hepatic impairment trial, mild (Child-Pugh A; N=8) or moderate hepatic impairment (Child-Pugh B; N=8) had no clinically relevant effect on the plasma exposure of apalutamide and N-desmethyl apalutamide. Plasma exposure of apalutamide was similar in subjects with mild (geometric mean ratios (GMRs): AUC_{inf} 0.95; C_{max} 1.00) and moderate hepatic impairment (GMRs: AUC_{inf} 1.13; C_{max} 1.04) compared with subjects with normal hepatic function. Plasma exposure of N-desmethyl apalutamide was similar in subjects with mild hepatic impairment (GMRs: AUC_{inf} 0.96; C_{max} 0.99) compared with subjects with normal hepatic function. Plasma exposure of N-desmethyl apalutamide was slightly lower in subjects with mild hepatic impairment (GMRs: AUC_{inf} 0.81; C_{max} 0.73) compared with subjects with normal hepatic function. The unbound fraction of apalutamide or N-desmethyl apalutamide was not affected by hepatic impairment. The finding in the dedicated hepatic study were confirmed by the population PK analysis (See Section 19.4.3for detail), which demonstrated that mild hepatic impairment (based on the National Cancer Institute criteria) had no significant influence on the exposure of apalutamide and N-desmethyl apalutamide. The applicant stated that administration of apalutamide is not recommended for patients with severe hepatic impairment.

Patients with Renal Impairment: No dose adjustment was recommended for patients with mild or moderate renal impairment. The PK of apalutamide in patients with severe renal impairment (eGFR ≤ 29 mL/min/1.73m^2) is unknown. Mild (eGFR 60 to 90 mL/min/1.73m^2) and moderate (eGFR 30 to 59 mL/min/1.73m^2) renal impairment had no effect on the exposure of apalutamide and N-desmethyl apalutamide based on a population PK analysis (See Section 19.4.3**.** for detail). Apalutamide and N-desmethyl apalutamide showed low urinary excretion (< 3%) in the mass balance study, renal impairment is not expected to affect the elimination of apalutamide or N-desmethyl apalutamide.

Drug-Drug Interactions

CYP3A4 Inhibitors: In a dedicated drug-interaction study 1012, concomitant itraconazole (a strong CYP3A4 inhibitor) decreased a single dose apalutamide's C_{max} by 22 % without AUC change. Concomitant itraconazole decreased N-desmethyl apalutamide C_{max} by 15 % without AUC change. Apalutamide was identified as a CYP3A4 inducer. Based on physiologically-based PK (PBPK) simulations, the contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but changes to 40% and 37%, respectively at steady-state after 240 mg qd multiple administration due to CYP3A4 auto-induction. PBPK simulation predicted that 400 mg qd ketoconazole (a strong CYP3A4 inhibitors) increased apalutamide C_{max} and AUC_{0-24} at steady state by 38% and 51%. The simulation predicted the active unbound fraction, defined as the unbound fraction of apalutamide plus one-third of the unbound fraction of N-desmethyl apalutamide, increased by 23% and 28% for C_{max} and AUC_{0-24}, respectively. No initial dose adjustment was recommended for concomitant use of a strong CYP3A4 inhibitor based on the predicted active unbound fraction changes. However, consider reducing the apalutamide dose based on tolerability.

CYP2C8 Inhibitors: In study 1012, concomitant 600 mg gemfibrozil (a strong CYP2C8 inhibitor) bid decreased a single dose apalutamide's C_{max} by 21% while AUC_{0-672} and AUC_{inf} increased by 53% and 68%, respectively. Concomitant gemfibrozil decreased N-desmethyl apalutamide C_{max}, AUC_{0-672}, and AUC_{inf} by 45%, 43%, and 15%, respectively. The steady-state PK profile of apalutamide 240 mg once daily coadministration with 600 mg gemfibrozil bid was predicted by a PBPK simulation. The simulation suggested apalutamide and the active unbound fraction C_{max} and AUC_{0-24} increased due to the concomitant: apalutamide C_{max} and AUC_{0-24} increased by 32% and 44%, respectively; active unbound fraction C_{max} and AUC_{0-24} increased by 19% and 23%, respectively. No initial dose adjustment was recommended for concomitant use of a strong CYP2C8 inhibitor. However, consider reducing the apalutamide dose based on tolerability. There was no significant difference in apalutamide exposure (steady state AUC_{0-24} GMR 1.04) in the population PK analysis (Section 19.4.3) of 53 subjects received CYP2C8 inhibitor as co-medication comparing to the apalutamide exposure from 1060 subjects without CYP2C8 inhibitor as co-medication.

CYP3A4/2C8 Inducers: The effects of CYP3A4 or CYP2C8 inducers on the pharmacokinetics of apalutamide have not been evaluated in dedicated clinical study. Based on a PBPK simulation, coadministration of 600 mg qd rifampin, a strong CYP3A4 and moderate 2C8 inducer, decreased the apalutamide steady-state C_{max} and AUC_{0-24} by 25% and 34%, respectively. The simulation predicted active unbound fraction C_{max} and AUC_{0-24} decreased by 15% and 19%, respectively. No dose adjustment was recommended for concomitant use of a CYP3A4/2C8 inducer. There was no significant difference in apalutamide exposure (AUC GMR 0.94) in the population PK analysis (Section 19.4.3) of 24 subjects received CYP3A4 inducer as co-medication comparing to the apalutamide exposure from 811 subjects without CYP3A4 inducer as co-medication.

CYP3A4 Substrates: In study 1020, coadministration of midazolam, a CYP3A4 substrate, with multiple daily doses of 240 mg apalutamide decreased the midazolam AUC by 92%. Substitution for CYP3A4 substrates was recommended when possible or evaluate for loss of efficacy if medication is continued.

CYP2C19 Substrates: In study 1020, coadministration of omeprazole, a CYP2C19 substrate, with multiple daily doses of 240 mg apalutamide decreased the omeprazole AUC by 85%. Substitution for CYP2C19 substrates was recommended when possible or evaluate for loss of efficacy if medication is continued.

CYP2C9 Substrates: In study 1020, coadministration of S-warfarin, a CYP2C9 substrate, with multiple daily doses of 240 mg apalutamide decreased the S-warfarin AUC by 46%. Substitution for CYP2C9 substrates was recommended. Evaluation of efficacy and dose adjustment to maintain optimal plasma concentrations may be necessary if coadministration with apalutamide is unavoidable. If given with warfarin, monitor International Normalized Ratio during initiation and end of apalutamide treatment.

CYP2C8 Substrates: In study 1020, coadministration of pioglitazone, a CYP2C8 substrate, with multiple daily doses of 240 mg apalutamide decreased the pioglitazone AUC by 18%. No dose adjustment for a CYP2C8 substrate was recommended.

P-gp Substrates: In study 1020, coadministration of fexofenadine, a P-gp substrate, with multiple daily doses of 240 mg apalutamide decreased the fexofenadine AUC by 30%. Use caution if substrates of P-gp are coadministered with apalutamide.

BCRP/OATP1B1 Substrates: In study 1020, coadministration of rosuvastatin, a BCRP/OATP1B1 substrate, with multiple daily doses of 240 mg apalutamide decreased the rosuvastatin AUC by 41%. Use caution if substrates of BCRP/OATP1B1 are coadministered with apalutamide.

UDP-Glucuronosyl Transferase (UGT) Substrates: Induction of CYP3A4 by apalutamide suggests that (UGT) may also be induced via activation of the nuclear pregnane X receptor (PXR). Concomitant administration of ERLEADA with medications that are substrates of UGT can result in lower exposure to these medications.

OAT3 Substrates: Apalutamide is not predicted to cause clinically significant changes in exposure of an OAT3 substrate (such as benzylpenicillin) based on FDA 2017 in vitro DDI guidance. No dose adjustment was recommended when an OAT3 substrate is coadministered with apalutamide.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Apalutamide is an AR inhibitor.
Active Moieties	N-desmethyl apalutamide. In vitro, N-desmetyhl apalutamide exhibited about one-third the AR inhibition activity of apalutamide.
QT Prolongation	Estimated ΔQTcF was 12.4 ms (2-sided 90% upper CI: 16.1 ms) at 240 mg once daily dose $C_{max,ss}$.
General Information	
Bioanalysis	Apalutamide and its major metabolite N-desmethyl apalutamide were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as an appendix (Section 19.4.1).

Healthy Volunteers vs. Patients	Following a single 240 mg dose, Mean C_{max} and AUC_{0-24} of apalutamide appeared to be slightly higher in healthy subjects by about 17% to 23% and 30% to 47%, respectively, compared to subjects with CRPC. Comparison of N-desmethyl apalutamide PK between healthy subjects and subjects with CRPC after a single dose of apalutamide was not done.			
Drug exposure at steady state following the therapeutic dosing regimen	At steady-state in study 1019, mean (CV%) C_{max} and $AUC_{0-24,ss}$ values for apalutamide were 6 µg/mL [~13 µM] (28%) and 100 µg.h/mL (32%), respectively; the mean (CV%) C_{max} and $AUC_{0-24,ss}$ values for N-desmethyl apalutamide were 5.9 µg/mL [~13 µM] (18%) and 124 µg.h/mL (19%), respectively.			
Minimal effective dose or exposure	Not available. Apalutamide 240 mg once daily were the only dosing regimen studied for apalutamide in the Phase 3 and Phase 2 clinical trials in NM-CRPC.			
Maximal tolerated dose or exposure	Maximal tolerated dose was not reached in clinical study dosed up to 480 mg once daily.			
Dose Proportionality	Apalutamide showed dose-proportional increase in exposure with increasing doses across the dose range from 30 to 480 mg. See section 19.4.2 for detail.			
Accumulation	At 240 mg once daily dosing steady-state, the mean AUC accumulation ratio for apalutamide and N-desmethyl apalutamide was 5 and 122, respectively.			
Variability	CV% for C_{max} and $AUC_{0-24,ss}$ In patients with CRPC after 240 mg multiple doses Apalutamide: 28% (C_{max}) and 32% ($AUC_{0-24,ss}$). N-desmethyl apalutamide: 18% (C_{max}) and 19% ($AUC_{0-24,ss}$).			
Absorption				
Oral Bioavailability	Absolute oral bioavailability about 100%			
Bioequivalent (BE) tablets/capsule GMR (90% CI)	Almost BE: to-be-market tablets (refer to as tablets in this table) and capsule formulation			
	C_{max}		AUC_{last}	AUC_{INF}
	0.90 (0.79, 1.03)		1.08 (0.95, 1.23)	1.07 (0.94, 1.22)
Oral T_{max}	The T_{max} was 2 hours (range 1 to 5 hours)			
Food effect* for Tablets formulation Fasted/Fed GMR (90% CI)	No clinically relevant food effect. Apalutamide T_{max} (range): Fasted 3.03 (1.00–5.00) hours; Fed 5.05 (2.00–6.00) hours.			
		C_{max}	AUC_{last}	AUC_{INF}
	Apalutamide	0.84 (0.75, 0.94)	0.97 (0.86, 1.09)	0.95 (0.84, 1.06)
	N-desmethyl apalutamide	1.17 (0.98, 1.38)	1.02 (0.94, 1.13)	1.01 (0.93, 1.10)
Food effect* for Capsule formulation Fasted/Fed GMR (90% CI)	No clinically relevant food effect			
		C_{max}	AUC_{0-24}	AUC_{INF}
	Apalutamide	0.86 (0.76, 0.96)	0.95 (0.89, 1.02)	NA
	N-desmethyl apalutamide	0.95 (0.87, 1.05)	1.01 (0.97, 1.06)	NA
Substrate transporter systems [in vitro]	As a substrate of P-gp, Apalutamide was completely absorbed in vivo after oral administration and showed high in vitro passive permeability. P-gp mediated transport is not likely to affect the apalutamide absorption at dose of 240 mg once daily.			
Distribution				
Volume of Distribution	Based on population PK analysis, apparent volume of distribution at steady-state (V_{ss}/F) is 276 L and 236 L for apalutamide and N-desmethyl apalutamide, respectively.			
Plasma Protein	Apalutamide 96%; N-desmethyl apalutamide 95%.			
Blood to Plasma Ratio	Apalutamide 0.79; N-desmethyl apalutamide 0.78.			

Elimination	
Half-life	Apalutamide effective half-life at steady-state 3 days
Clearance	Apalutamide CL/F: at steady-state 2 L/hr; after single dose 1.3 L/hr. N-desmethyl apalutamide CL/F: 1.5 L/hr.
Metabolism	
Primary metabolic pathway(s)	Metabolism is the main route of elimination of apalutamide. Apalutamide primarily metabolized by CYP2C8 and CYP3A4 to form N-desmethyl apalutamide. The contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but changes to 40% and 37%, respectively at steady-state due to CYP3A4 auto-induction. Carboxylesterase also contributes to apalutamide metabolism. N-desmethyl apalutamide is metabolized by carboxylesterase.
Inhibitor/Inducer	Enzymes (CYPs and UGT) In vitro, apalutamide and N-desmethyl apalutamide were identified as CYP3A4 and CYP2B6 inducers. Apalutamide was an inhibitor of CYP2C8 (IC_{50} = 18 µM). It also was identified as an inhibitor of CYP2B6, CYP2C9, CYP2C19, and CYP3A4 with IC_{50} range from 36 to 67 µM. N-desmethyl apalutamide is an inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 with IC_{50} values ranging from 38 to 75 µM. In vivo, apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9. Co-administration of apalutamide 240 mg QD with single oral doses of sensitive CYP substrates resulted in a 92% decrease in the AUC of midazolam (a CYP3A4 substrate), 85% decrease in the AUC of omeprazole (a CYP2C19 substrate), and 46% decrease in the AUC of S-warfarin (a CYP2C9 substrate). Apalutamide did not cause clinically meaningful changes in exposure to pioglitazone (a CYP2C8 substrate). Induction of CYP3A4 by apalutamide suggests that UDP-glucuronosyl transferase (UGT) may also be induced via activation of the nuclear pregnane X receptor (PXR). Transporters In vitro, apalutamide and N-desmethyl apalutamide were weak inhibitors of P-gp with inhibition of digoxin transport (56% for apalutamide and 42% for N-desmethyl apalutamide at 30 µM) and BCRP with inhibition of BCRP-mediated topotecan transport (inhibition of 45% and 33%, respectively, at 30 µM). In vivo, co-administration of apalutamide 240 QD with single oral doses of sensitive transporter substrates resulted in a 30% decrease in the AUC of fexofenadine (a P-gp substrate) and 41% decrease in the AUC of rosuvastatin (a BCRP/OATP1B1 substrate). In vitro, apalutamide showed inhibition of OCT2 (IC_{50} = 27.2 µM), OAT3 (IC_{50} = 12.0 µM) and MATE1 (IC_{50} = 13.8 µM) and MATE-2K (IC_{50} = 37.9 µM) while N-desmethyl apalutamide showed inhibition of OCT2 (IC_{50} = 4.8 µM), OAT3 (IC_{50} = 7.6 µM) and MATE1 (IC_{50} = 17.6 µM) and MATE-2K (32% inhibition at 50 µM). Based on FDA 2017 in vitro DDI guidance, it is predicted that steady-state apalutamide (240 mg once daily) is not expected to have a clinically relevant effect on the exposure to benzylpenicillin (OAT3 substrate)
Excretion	
Primary excretion pathways (% dose) ±SD	In an oral mass balance trial, radioactivity recoveries of dose in urine and feces were 65% (1.2% as apalutamide and 2.7% as N-desmethyl apalutamide) and 24% (1.5% as apalutamide and 2% as N-desmethyl apalutamide), respectively.

**High-fat breakfast (ie, approximately 500 to 600 fat calories, 250 carbohydrate calories, and 150 protein calories).*

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The primary evidence of effectiveness was obtained from phase 3 Study 003.

Study 003 was a randomized (2:1), double-blind, placebo-controlled, multicenter clinical phase 3 study of apalutamide plus androgen-deprivation therapy (ADT) versus placebo plus ADT conducted in patients with NM-CRPC. There was an about two years median metastasis-free

survival (MFS) improvement for the apalutamide arm comparing to the placebo arm as shown in Table 20. The hazard ratio was 0.280 (95% CI: 0.227, 0.346) based on the MFS.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dose 240 mg QD is effective and appears to have a manageable safety profile.

No statistically significant exposure-MFS relationship was found for apalutamide and N-desmethyl apalutamide in study 003. Differences in apalutamide and N-desmethyl apalutamide exposure when 240 mg once daily is administered are not expected to be associated with clinically relevant differences in MFS in subjects with NM-CRPC. These results support that a 240 mg once daily dose of apalutamide provides efficacious exposure in most subjects with NM-CRPC across the exposure range.

In study 003, fatigue, fall, skin rash, weight decrease and arthralgia are the AEs with incidence higher that 10%, at any grade, in NM-CRPC subjects. In study 003, the median treatment duration was 16.9 months and 11.2 months for apalutamide-treated subjects and placebo-treated subjects, respectively. AEs leading to treatment discontinuation was 11% and 7.0% for apalutamide arm and placebo arm, respectively. AEs leading to dose reductions was 11% and 3.3% for apalutamide arm and placebo arm, respectively. Exposure-response analyses suggested lower apalutamide and/or N-desmethyl apalutamide exposure was associated with lower risks for those AEs. The exposure-response analysis suggested dose reduction is likely to improve apalutamide tolerability (**Table 5**). The model results suggested that dose reduction as implemented in study 003 by reducing apalutamide dose to 180 mg, or 120 mg once daily per study protocol, was appropriate for subjects who experience an AE. Seizure occurred in 0.2% of patients receiving apalutamide in Study 003. Exposure-response analysis for seizure could not be established due to limited data.

Skin Rash: In study 003, skin rash were reported for a higher proportion of apalutamide-treated subjects (24%, 191 out of 803 patients) versus placebo-treated subjects (5.5%, 22 out of 399 patients) and this difference persisted (29.6 versus 8.3 events per 100 patient-years) after standardization for longer treatment duration in the apalutamide arm. Events of skin rash were mostly of Grade 1 (8.6% in apalutamide arm; 3.3% in placebo arm) or 2 (10% in apalutamide arm; 2.0% in placebo arm), rarely resulted in hospitalization, generally responded to intervention with corticosteroids and antihistamines, and resolved within approximately 2 months for 81% of subjects affected. Skin rash was the most common reason for treatment discontinuation: 19 subjects (2.4%) in the apalutamide arm and 0 subjects in the placebo arm. Skin rash was the most commonly reported AE leading to both drug interruption (53 subjects (28%) in the apalutamide arm and 5 subjects (23%) in the placebo arm with skin rash) and dose reduction (22 subjects (12%) in the apalutamide arm and 1 subject (4.5%) of in the placebo arm with skin rash). Twenty-nine of 53 subjects in the apalutamide arm had a recurrence of skin rash after restarting apalutamide treatment following drug interruption due to skin rash; 16 of 22 subjects in the apalutamide arm had a recurrence of skin rash at the lower dose after dose reduction due to skin rash. Re-challenge did not result in anaphylactic or high-grade allergic

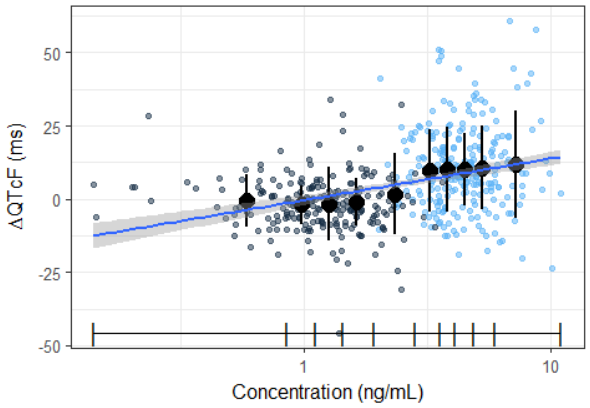
reactions. Events of skin rash ultimately led to study drug being withdrawn for 17 apalutamide-treated subjects (8.9%) and for 0 placebo-treated subjects with such an event.

QT Prolongation: The effect of apalutamide 240 mg once daily on the QTc interval was assessed in an open-label, uncontrolled, multi-center, single-arm dedicated QT study in 45 patients with CRPC. 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 (Figure 1). 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, electrolyte abnormalities and severe hepatic impairment. Correct hypokalemia or hypomagnesemia prior to initiating ERLEADA and monitor these electrolytes periodically during therapy. Avoid ERLEADA in patients with congenital long QT syndrome.

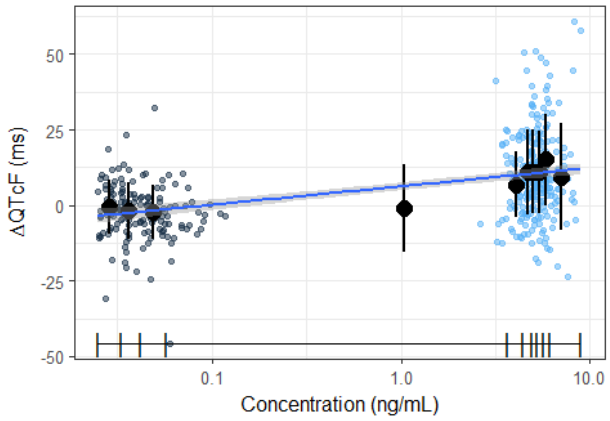
Overall, the proposed 240 mg QD was appropriate based on the efficacy shown in pivotal phase 3 study 003. The safety appears to be manageable with appropriate dose interruptions and/or dose reductions.

Figure 1. Illustration of ΔQTcF against apalutamide or N-desmethyl apalutamide concentration. Error bars represent mean and standard deviation

Apalutamide



N-desmethyl apalutamide



Black open circles Cycle 1 Day 1
Blue open circles Cycle 3 Day 1
Source FDA QT-IRT review on QT/QTc Study 56021927PCR1019

Table 5. Model-based Predicted Incidence for the Treatment-emergent Adverse Events Stratified by Apalutamide Dose Level

Model-Based Incidence, % (95% CI)	Dose Level (Mean Apalutamide AUC_{0-24h})		
	240 mg (AUC_{0-24h} = 120 µg×h/L)	180mg (AUC_{0-24h} = 90 µg×h/L)	120 mg (AUC_{0-24h} = 60 µg×h/L)
Fatigue	31.0 (27.7 – 34.5)	28.4 (25.8 – 31.1)	26.0 (23.5 – 28.7)
Fall	16.0 (13.5 – 19.0)	14.1 (12.2 – 16.3)	12.4 (10.6 – 14.5)
Skin rash	25.8 (22.7 – 29.1)	18.6 (16.4 – 21.1)	13.1 (11.1 – 15.5)
Weight decrease	18.1 (15.5-21.2)	13.6 (11.7-15.8)	10.0 (8.29-12.1)
Arthralgia	16.5 (13.9 – 19.4)	14.0 (12.1 – 16.2)	11.8 (10.0 – 13.9)

Source: Summary of Clinical Pharmacology Studies Table 33 (Section 2.7.2)

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Population PK analysis showed that there are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of apalutamide and N- desmethyl apalutamide.

Hepatic Impairment: No dose adjustment was recommended for patients with mild or moderate hepatic impairment. In a dedicated hepatic impairment trial, mild (Child-Pugh A; N=8) or moderate hepatic impairment (Child-Pugh B; N=8) had no clinically relevant effect on the plasma exposure of apalutamide and N-desmethyl apalutamide. Plasma exposure of apalutamide was similar in subjects with mild (geometric mean ratios (GMRs (90% CI)): AUC_{INF} 0.95 (0.76, 1.18); C_{max} 1.02 (0.77, 1.34)) and moderate hepatic impairment (GMRs(90% CI): AUC_{INF} 1.13 (0.82, 1.57); C_{max} 1.04 (0.74, 1.47)) compared with subjects with normal hepatic function. Plasma exposure of N-desmethyl apalutamide was similar in subjects with mild hepatic impairment (GMRs: AUC_{INF} 0.96 (0.84, 1.11); C_{max} 0.99 (0.73, 1.34)) compared with

subjects with normal hepatic function. Plasma exposure of N-desmethyl apalutamide was slightly lower in subjects with mild hepatic impairment (GMRs: AUC_{INF} 0.81 (0.65, 1.01); C_{max} 0.73 (0.50, 1.07)) compared with subjects with normal hepatic function. The unbound fraction of apalutamide or N-desmethyl apalutamide was not affected by hepatic impairment. The findings in the dedicated hepatic study were confirmed by the population PK analysis (See popPK for detail), which demonstrated that mild hepatic impairment (based on the National Cancer Institute criteria) had no significant influence on the exposure of apalutamide and N-desmethyl apalutamide.

Renal Impairment: No dose adjustment was recommended for patients with mild or moderate renal impairment. The PK of apalutamide in patients with severe renal impairment (eGFR ≤ 29 mL/min/1.73m^2) is unknown. Mild (eGFR 60 to 90 mL/min/1.73m2) and moderate (eGFR 30 to 59 mL/min/1.73m^2) renal impairment had no effect on the exposure of apalutamide and N-desmethyl apalutamidebased on a population PK analysis (See Section 19.4.3 for detail). Apalutamide and N-desmethyl apalutamide showed low urinary excretion (< 3%) in the mass balance study 006, renal impairment is not expected to affect the elimination of apalutamide or N-desmethyl apalutamide.

ARV7 expression: AR splice variants (ARVs) that lack the ligand binding domain are constitutively active in a ligand independent manner. ARV7, the most common splice variant detected in clinical biospecimens, has been associated with resistance to novel AR targeted therapies in prostate cancer (PMID: 25184630, 28384066). Its potential use as a biomarker to assess prognosis and guide treatment selection in advanced prostate cancer, along with reliability of various testing assays, has been extensively discussed in the literature (PMID: 29319382). As part of study ARN-509-003 biomarker exploratory analyses, a total of 326 whole blood samples (126 matched samples collected from patients at both baseline and end of study treatment and 74 unmatched samples collected from patients at the end of treatment) were tested for ARV7 mRNA expression using a real-time polymerase chain reaction (RT-PCR) to determine ARV7 frequency and impact on MFS and PFS2.

ARV7 expression was detected in 6.3% (8 out of 126) of patients at baseline (5% in the apalutamide arm and 7.6% in the placebo arm) and in 11 % (22 out of 200) of patients at the end of treatment (9.4% in the apalutamide arm, and 12.5% in the placebo arm). Among the 126 patients with matched samples, 1 patient in the apalutamide arm expressed ARV7 at both baseline and end of treatment. Also, ARV7 expression was detected in end of treatment samples of 13 patients who were ARV7 negative at baseline (7 in the apalutamide arm and 6 in the placebo arm). Apalutamide-treated patients with detectable ARV7 expression at baseline or end of treatment had nominally shorter MFS, compared with apalutamide-treated patients without detectable ARV7 expression (14.7 vs 16.6 months at baseline and 14.0 vs 18.4 months at the end of treatment). This trend was not observed in the placebo arm (7.5 vs 7.3 months at baseline and 7.5 vs 7.4 months at the end of treatment) (Table 6).

The results suggest an association between ARV7 expression and shorter MFS. However, study limitations, including the very small sample size and retrospective nature of the study (only 16.5 % of the ARN-509-003 patients were tested for ARV7 expression) preclude definitive conclusions. Further evaluations with a larger sample size may be more meaningful. Differences in PFS2 were not evaluated by the reviewer.

Table 6: ARV7 expression status in a subset of patients enrolled in Study SPARTAN along with MFS events (N= 126 at baseline and N = 200 at end of treatment)

Time of sample collection for ARV7 testing	Arm	ARV7 status	N	Events	Median MFS (95%CI)
Baseline	Apalutamide	Negative	57	28	16.6 (12.1-22.1)
(N=126)	(N=60)	Positive	3	1	14.7 (NA)
	Placebo	Negative	61	44	7.3 (3.8-10.2)
	(N=66)	Positive	5	5	7.5 (3.5-14.5)
End of treatment	Apalutamide	Negative	87	43	18.4 (14.7-22.2)
(N=200)	(N=96)	Positive	9	5	14.0 (4.4-25.0)
	Placebo	Negative	91	64	7.4 (3.9-10.2)
	(N=104)	Positive	13	11	7.5 (3.5-14.7)

Reviewer table. Exploratory analyses. Source: Technical Report Number: TR2017T-018. N=Sample size, MFS=Metastasis-Free Survival, NA=Not available

Other intrinsic factors: There are no clinically relevant effects of age (median: 72, range: 18-94), race (761 [69.7%] White: 704 not Hispanic or Latino and 75 Hispanic or Latino; 71 [6.5%] Black; 116 [10.6%] Asian: 58 Japanese and 58 Non-Japanese; 11 [1%] Other races; 133 (12.2%) unknown), TB, AST, alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein, and eGFR on the systemic exposure of apalutamide or N-desmethyl apalutamide that would require a dose adjustment based on a population PK analysis. The population analysis dataset comprised 1092 male subjects from which 117 were healthy subjects and 975 with CRPC. Healthy status (healthy or CRPC), body weight (median: 84.1, range: 45-182.1), and serum albumin concentration were statistically associated with apalutamide or N-desmethyl apalutamide PK parameters. Nevertheless, the magnitude of the effect of body weight and serum albumin concentration on the apalutamide or N-desmethyl apalutamide PK parameters in subjects with CRPC was not clinically relevant.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Apalutamide is a CYP2C8 and CYP3A substrate. CYP2C8 and CYP3A moderators have effects on apalutamide and its active metabolite N-desmethyl apalutamide exposures but these effects were not predicted to be clinically relevant. No initial dose adjustment was proposed. However, the applicant recommended to reduce the apalutamide dose based on tolerability when concomitant use with strong CYP2C8 or CYP3A4 inhibitors.

Apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Induction of CYP3A4 by apalutamide suggests that UDP-glucuronosyl transferase (UGT) may also be induced via activation of the nuclear pregnane X receptor (PXR). Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1). Concomitant use with medications that are sensitive substrates of CYP3A4, CYP2C19, CYP2C9, UGT, P-gp, BCRP or OATP1B1 may result in loss of efficacy of these medications.

No clinically relevant food effect was observed with apalutamide. Apalutamide is not ionizable under relevant physiological pH condition. Acid lowering agents (e.g. proton pump inhibitor, H2-receptor antagonist, antacid) are not expected to affect the bioavailability of apalutamide.

<u>Effect of CYP3A4 and CYP2C8 Inhibitors and Inducers on Apalutamide</u>

CYP3A4 Inhibitors: In a dedicated drug-interaction study 1012, concomitant itraconazole (a strong CYP3A4 inhibitor) decreased a single dose apalutamide's C_{max} by 22 % without AUC change. Concomitant itraconazole decreased N-desmethyl apalutamide C_{max} by 15 % without AUC change. Apalutamide was identified as a CYP3A4 inducer. Based on PBPK simulations, the contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but changes to 40% and 37%, respectively at steady-state after 240 mg qd multiple administration due to CYP3A4 auto-induction. physiologically-based PK (PBPK) simulation predicted that 400 mg qd ketoconazole, a strong CYP3A4 inhibitors, increased apalutamide C_{max} and AUC_{0-24} at steady state by 38% and 51%. The simulation predicted the active unbound fraction, defined as the unbound fraction of apalutamide plus one-third of the unbound fraction of N-desmethyl apalutamide, increased by 23% and 28% for C_{max} and AUC_{0-24}, respectively. No initial dose adjustment was recommended for concomitant use of a strong CYP3A4 inhibitor based on the predicted active unbound fraction changes. However, consider reducing the apalutamide dose based on tolerability.

CYP2C8 Inhibitors: In study 1012, concomitant 600 mg gemfibrozil (a strong CYP2C8 inhibitor) bid decreased a single dose apalutamide's C_{max} by 21% while AUC_{0-672} and AUC_{inf} increased by 53% and 68%, respectively. Concomitant gemfibrozil decreased N-desmethyl apalutamide C_{max}, AUC_{0-672}, and AUC_{inf} by 45%, 43%, and 15%, respectively. The steady-state PK profile of apalutamide 240 mg once daily coadministration with 600 mg gemfibrozil bid was predicted by a PBPK simulation. The simulation suggested apalutamide and the active unbound fraction C_{max} and AUC_{0-24} increased due to the concomitant: apalutamide C_{max} and AUC_{0-24} increased by 32% and 44%, respectively; active unbound fraction C_{max} and AUC_{0-24} increased by 19% and 23%,

respectively. In the population analysis, a total of 53 (5.0%) received CYP2C8 inhibitor as co-medication. There was no apparent trend that PK was affected by CYP2C8-inhibiting co-medication based on the limited number of observations. No initial dose adjustment was recommended for concomitant use of a strong CYP2C8 inhibitor. However, consider reducing the apalutamide dose based on tolerability.

CYP3A4/2C8 Inducers: The effects of CYP3A4 or CYP2C8 inducers on the pharmacokinetics of apalutamide have not been evaluated in a dedicated clinical study. Based on a PBPK simulation, coadministration of 600 mg qd rifampin, a strong CYP3A4 and moderate 2C8 inducer, decreased the apalutamide steady-state C_{max} and AUC_{0-24} by 25% and 34%, respectively. The simulation predicted active unbound fraction C_{max} and AUC_{0-24} decreased by 15% and 19%, respectively. In the population analysis, a total 24 subjects (3.0) received CYP3A4 inducer as co-medication. There was no apparent trend that PK was affected by CYP3A4-inducing co-medication based on the limited number of observations. No dose adjustment was recommended for concomitant use of a CYP3A4/2C8 inducer.

<u>Effect of apalutamide on CYP3A4 and CYP1A2 substrates</u>

CYP3A4 Substrates: In study 1020, coadministration of midazolam, a CYP3A4 substrate, with multiple daily doses of 240 mg apalutamide decreased the midazolam AUC by 92%. Substitution for CYP3A4 substrates was recommended when possible or evaluate for loss of efficacy if medication is continued.

CYP2C19 Substrates: In study 1020, coadministration of omeprazole, a CYP2C19 substrate, with multiple daily doses of 240 mg apalutamide decreased the omeprazole AUC by 85%. Substitution for CYP2C19 substrates was recommended when possible or evaluate for loss of efficacy if medication is continued.

CYP2C9 Substrates: In study 1020, coadministration of S-warfarin, a CYP2C9 substrate, with multiple daily doses of 240 mg apalutamide decreased the S-warfarin AUC by 46%. Substitution for CYP2C9 substrates was recommended. Evaluation of efficacy and dose adjustment to maintain optimal plasma concentrations may be necessary if coadministration with apalutamide is unavoidable. If given with warfarin, monitor International Normalized Ratio during initiation and end of apalutamide treatment.

CYP2C8 Substrates: In study 1020, coadministration of pioglitazone, a CYP2C8 substrate, with multiple daily doses of 240 mg apalutamide decreased the pioglitazone AUC by 18%. No dose adjustment for a CYP2C8 substrate was recommended.

UDP-Glucuronosyl Transferase (UGT) Substrates: Induction of CYP3A4 by apalutamide suggests that (UGT) may also be induced via activation of the nuclear pregnane X receptor (PXR). Concomitant administration of ERLEADA with medications that are substrates of UGT can result in lower exposure to these medications.

Transporters related DDI

P-gp Substrates: In study 1020, coadministration of fexofenadine, a P-gp substrate, with multiple daily doses of 240 mg apalutamide decreased the fexofenadine AUC by 30%. Use caution if substrates of P-gp are coadministered with apalutamide.

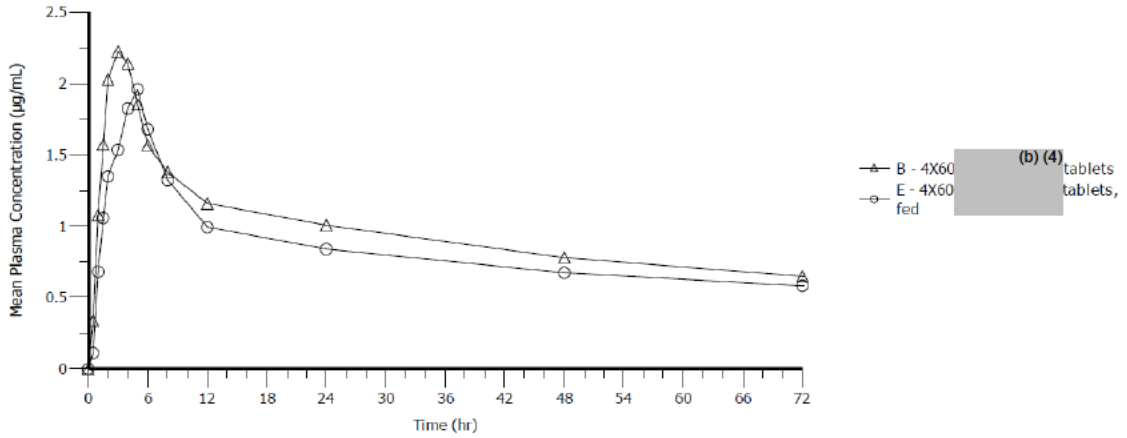
BCRP/OATP1B1 Substrates: In study 1020, coadministration of rosuvastatin, a BCRP/OATP1B1 substrate, with multiple daily doses of 240 mg apalutamide decreased the rosuvastatin AUC by 41%. Use caution if substrates of BCRP/OATP1B1 are coadministered with apalutamide.

OCT2, OAT1, OAT3 and MATEs substrates: In vitro, apalutamide showed inhibition of OCT2 (IC_{50} = 27.2 µM), OAT3 (IC_{50} = 12.0 µM) and MATE1 (IC_{50} = 13.8 µM) and MATE-2K (IC_{50} = 37.9 µM) while N-desmethyl apalutamide showed inhibition of OCT2 (IC_{50} = 4.8 µM), OAT3 (IC_{50} = 7.5 µM) and MATE1 (IC_{50} = 17.6 µM) and MATE-2K (32% inhibition at 50 µM). Based on FDA 2017 in vitro DDI guidance, it is predicted that steady-state apalutamide (240 mg once daily) is not expected to have a clinically relevant effect on the exposure to benzylpenicillin (OAT3 substrate). No dose adjustment was recommended when a OAT3 substrate is coadministered with apalutamide.

Food Effect

To-be-market Tablet Formulation (G023) - (b) (4) Tablets: In an open-label, randomized, parallel-group study 1011, healthy subjects under fasting conditions (≥10 hours) in Treatment B (N=15) and with a high-fat meal (approximately 500 to 600 fat calories, 250 carbohydrate calories, and 150 protein calories) in Treatment E (N=15) were administrated with a dose of 240 mg (4 X 60 mg tablets) apalutamide to-be-market tablets. There was no clinically relevant exposure difference in fed and fasted conditions. The results indicated that C_{max} was decreased by 16% while AUC remained unchanged. Median tmax was delayed about 2 hours with food, Table 7.

Table 7. Mean Plasma Concentration-Time Profiles and Comparative Bioavailability for Apalutamide Under Fasted and Fed Conditions After a 240 mg Single Dose



Parameter (Unit)	Treatment Group [a]	N	Geometric Mean	GMR Test/Reference (%)	90% CI (%)	Total CV (%)
C_{max} (µg/mL)	B	15	2.40			18.5%
	E	15	2.01	83.95	(74.90, 94.11)	
AUC_{last} (µg.h/mL)	B	15	213.52			19.6%
	E	15	206.53	96.73	(85.76, 109.10)	
AUC_{∞} (µg.h/mL)	B	15	222.98			18.5%
	E	14	209.78	94.08	(83.75, 105.70)	

[a] B: 240 mg dose given as 4x60 mg (b) (4) tablets under fasted conditions
E: 240 mg dose given as 4x60 mg tablets under fed condition
Treatment B was used as the reference group.

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods Figure 1 and Table 10 (Section 2.7.1)

Capsule Formulation: Patients with CRPC were dosed with apalutamide 240 mg (8 X 30 mg capsules) once daily in the Phase 2 of study 001. Each treatment cycle in study 001 was 28 days. In a 2-way crossover food effect substudy of study 001, 12 patients were dosed with apalutamide at steady-state, Days 1 and 15 of Cycle3, under fasting conditions (≥10 hours) and with a high-fat/high calorie breakfast (800-1000 calories with approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively). There was no clinically relevant exposure difference in fed and fasted conditions. Mean C_{max} and AUC_{0-24} for apalutamide were slightly higher under Fasted conditions than Fed, Table 8.

Table 8. Summary of PK Parameters for Apalutamide (ARN-509) and N-desmethyl apalutamide (ARN000308) under fasted and fed conditions

Analyte and Statistic	Cmax (µg/mL)		AUC_{0-24} (µg·h/mL)	
	Fasted	Fed	Fasted	Fed
ARN-509				
N	12	12	12	12
Mean (SD)	5.67 (1.84)	4.76 (1.38)	95.3 (29.0)	91.7 (32.0)
Median	5.30	4.38	94.0	80.4
Min, Max	3.56, 9.79	3.19, 7.99	62.5, 161	61.8, 172
CV (%)	32.5	29.0	30.5	34.9
Ln(Parameter) Geo LSM	5.36	4.59	91.8	87.4
LSM Ratio (% of Reference)	85.6		95.2	
90% CI	76.3, 96.0		88.7, 102	
ARN000308				
N	12	12	12	12
Mean (SD)	6.15 (1.93)	5.78 (1.36)	122 (27.7)	124 (30.7)
Median	5.75	5.94	121	118
Min, Max	3.56, 10.7	3.16, 8.52	75.7, 186	73.0, 193
CV (%)	31.4	23.5	22.8	24.8
Ln(Parameter) Geo LSM	5.99	5.71	120	122
Ratio (% of Reference)	95.3		101.1	
90% CI	86.6, 105		96.5, 106	

Abbreviations: CI, confidence interval; Geo LSM, geometric least squares mean; SD, standard deviation.
Reference treatment was Fasted.

Source: Table 8 of Pharmacokinetic Report of Clinical Study Report ARN-509-001 (Section 5.3.3.2)

Effect of Drugs That Elevate the Gastric pH on Apalutamide

Apalutamide (pK_a 9.7, acidic arboxamide moiety) is not ionizable under relevant physiological pH condition, therefore acid lowering agents are not expected to affect the solubility and bioavailability of apalutamide. Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Yes, the to-be-market 60 mg tablet formulation was used in multiple studies including the Phase 3 study 003. Study 003 was initiated using a 30 mg capsule formulation and were later switched to the to-be-market 60 mg tablet formulation. The tablet and capsule was demonstrated to have comparable apalutamide exposures (See 19.4.2 for details).

{See appended electronic signature page}

Wentao Fu
Primary Reviewer

Qi Liu
Team Leader

Appears this way on original

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Data from one clinical trial were submitted to the Agency for the review of efficacy. This trial is summarized in Table 9. The SPARTAN "Selective Prostate AR Targeting with ARN-509" trial ARN-509-003 forms the basis of this application.

Results from an additional clinical study (ARN-509-001) were also discussed in the Summary of Clinical Efficacy (NDA 210951; Module 2.7.3). Cohort 1 (NM-CRPC) of the Phase 2 portion of Study ARN-509-001 (51 patients enrolled; 47 patients included in the efficacy analysis set). The data from the two studies were not integrated due to differences in the efficacy endpoints analyzed and in eligibility criteria. Both populations included patients with NM-CRPC on ADT with castration levels of testosterone (<50 ng/dL; medical or surgical). In Study ARN-509-003, eligibility criteria included patients with a high risk of development of metastasis defined as a PSADT ≤10 months. For Study ARN-509-001, patients enrolled in Cohort 1 had either a PSA value ≥8 ng/mL (obtained within 3 months prior to enrollment) or a PSADT of ≤10 months.

> ***Reviewer's Comment:*** *The applicant's decision not to integrate data from ARN-509-001 with ARN-509-003 is acceptable and is not expected to have a significant impact on the efficacy results, given the small sample size (47 patients) in comparison to the larger sample size of ARN-509-003 (806 patients). The efficacy results of ARN-509-001 were similar to the those of ARN-509-003.*

The applicant submitted a tabular listing of all clinical studies with apalutamide (NDA 210951, Module 5.2) that included 14 clinical studies. Except for the two studies discussed above, the other studies were not appropriate for analysis due to differences in patient population (healthy volunteers) and endpoints (PK, ventricular repolarization). A query of the ClinicalTrials.gov database (http://clinicaltrials.gov) on January 23, 2018, using the search terms, apalutamide, Erleada, JNJ-56021927, or ARN-509 identified 45 clinical studies. The study design and status of these studies were reviewed and excluded from evaluation of efficacy and safety for the following reasons:

- Status was reported as "Active, not yet recruiting" (11)
- Status was reported as "Not yet recruiting" (10)
- Status was reported as "Withdrawn" (1)
- Patient population was healthy volunteers (5)
- Patient population was hepatic impairment (1)
- Neoadjuvant Setting (7)
- Patient population was low risk prostate cancer (2)
- Study treatment was a combination regimen (18)

Reviewer's Comment: *The reviewer agrees with the exclusion of these clinical studies from the efficacy and safety analysis of this NDA.*

Table 9. Listing of Clinical Trials Relevant to the Clinical Review of NDA 210951

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
ARN-509-003 (SPARTAN)	NCT01946204	Multicenter, randomized, double-blind, placebo-controlled study	Apalutamide 240 mg daily orally Placebo	Metastasis-Free Survival	Median treatment duration was estimated to be 16.9 months in the apalutamide arm and 11.2 months in the placebo arm	1207	High risk nonmetastatic castration-resistant prostate cancer	332 Centers 26 Countries
		Studies to Support Safety						
56021927PCR1019	NCT02578797	Open-label Phase 1b QT/QTc study	Apalutamide 240 mg daily orally	Rate of ventricular repolarization (QTcF) by using time-matched electrocardiograms (ECGs)	Unknown	45	Castration-resistant prostate cancer	5 Centers 5 Countries
ARN-509-001	NCT01171898	Open-label, dose-escalation, proof-of-concept study	Starting Dose: apalutamide 30 mg daily orally Highest Dose: apaluatide 480 mg daily orally MTD: 240 mg daily orally	Phase 1: safety and MTD Phase 2: PSA response at 12 weeks according to the Prostate Cancer Working Group 2 (PCWG2) criteria	Unknown	127	Progressive, advanced castration-resistant prostate cancer	18 Centers 1 Country

7.2. Review Strategy

The review included the following:

1. Review of the current literature on prostate cancer and non-metastatic, high-risk castration-resistant prostate cancer, epidemiology, and treatment
2. Review of the current literature on metastasis-free survival, including regulatory history of and the transcripts and meeting minutes of any ODAC meetings related to sBLA 125320/28 for denosumab
3. Review of the applicant-conducted trial ARN-506-003, including the study report, protocol, protocol amendments, Independent Review Committee Charter (b) (4)), statistical analysis plan and amendments, case report forms, and selected datasets
4. Review of the applicant's assessment of their analyses of efficacy and safety for apalutamide
5. Review of datasets and SAS programming algorithms submitted by the applicant
6. Review of patient narratives of serious adverse events and deaths
7. Review of the meeting minutes from meetings conducted during drug development
8. Assessment of Summary of Clinical Safety and the Integrated Summary of Safety
9. Review of consultation reports from the Office of Scientific Investigations
10. Requests for additional information from the applicant and review of applicant responses
11. Formulation of the benefit-risk analysis and recommendations
12. Review and evaluation of proposed labeling
13. Review of ODAC assessment of the benefit-risk profiles of the proposed supplemental indication

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. SPARTAN (ARN-509-003)

This application was part of a pilot program where the applicant agreed to allow FDA to post the clinical study report body, protocol and amendments, and statistical analysis plan from their submission. For full details of these refer to the posted documents. We have summarized relevant information below.

Trial Design

Study SPARTAN was a multinational, randomized (2:1), double-blind, placebo-controlled Phase 3 study of apalutamide (240 mg daily orally) compared with placebo, administered with concurrent gonadotropin-releasing hormone (GNRH) analogs or bilateral orchiectomy in 1207 patients with high risk, non-metastatic, castration-resistant prostate cancer (NM-CRPC), defined as prostate-specific antigen doubling time (PSADT) of ≤ 10 months. The primary objective of this study was to compare metastasis-free survival (MFS) in patients randomized to apalutamide arm or placebo arm. Secondary objectives were to compare time to metastasis (TTM), progression-free survival (PFS), time to symptomatic progression (SymProg), overall survival (OS), and time to initiation of cytotoxic chemotherapy between the two arms.

Patients were centrally randomized in a 2:1 ratio to receive either apalutamide or placebo using the Interactive Voice Response System (IVRS). Randomization was stratified by the following factors:

- PSA doubling time (>6 months vs. ≤ 6 months)
- Use of bone sparing agents (yes vs. no)
- Presence of locoregional disease (N0 vs N1)

The study schema is shown in Figure 2.. The study consisted of three phases: a Screening Phase, a Double-blind Treatment Phase, and a Long-term Follow-up Phase.

Key eligibility criteria included histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features with a PSADT ≤ 10 months; castration-resistant prostate cancer, demonstrated during continuous ADT, defined as three PSA rises at least 1 week apart with the last PSA >2 ng/mL; surgically or medically castrated with testosterone levels of < 50 ng/dL; absence of symptomatic locoregional disease requiring medical intervention, and no prior treatment with next generation anti-androgens. Absence of distant metastases by BICR review of baseline scans was to be confirmed for all patients prior to enrollment.

Reviewer's Comment:
The presence of asymptomatic locoregional disease, defined as pelvic lymph nodes located below the iliac bifurcation whose short axis is > 20 mm (N1 disease), was permitted as per protocol-defined eligibility criteria and in fact was a pre-specified stratification factor. Per Table 17 *, 15% of patients enrolled in SPARTAN had localized disease fulfilling this criterion on enrollment. Additionally, 9/925 patients who were screened for enrollment were found to be ineligible because of symptomatic locoregional disease.*

Absence of metastasis was confirmed for all patients prior to enrollment by BICR review of scans. 24% (511/2132) of patients screened for enrollment were found to be ineligible due to the presence of metastatic disease due to BICR review, when initial investigator review of scans were not read as positive for metastases.

Patients were allowed to be pre-screened by PSADT, calculated by the investigator using the Memorial Sloan-Kettering Cancer Center (MSKCC) PSA Doubling Time prediction tool (http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx). For the Screening phase and stratified randomization, PSADT was calculated by the applicant using a linear regression model of the natural logarithm of PSA and time and using at least three PSA values, and entered by IVRS. These three PSA values were obtained during continuous ADT and within 24 months prior to randomization, and with the first and last PSA values ≥ 8 weeks apart.

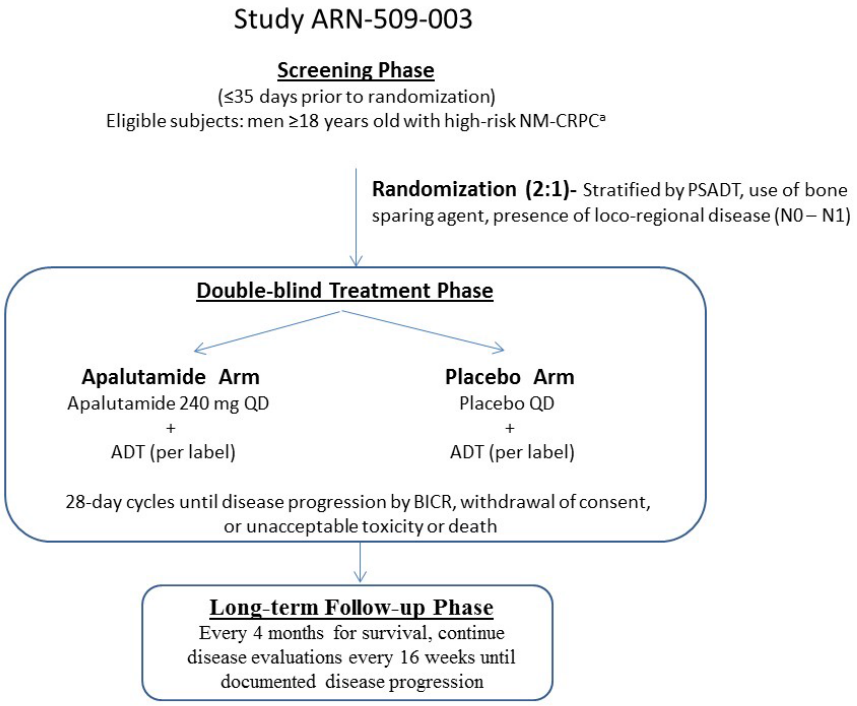
During the Treatment Phase, all patients who were not surgically castrated were to continue ADT to maintain castrate levels of testosterone. Selection of the ADT (gonadotropin releasing hormone [GnRH] agonist or antagonist) was at the investigator's discretion, and dosing was to be consistent with the respective product labelling. Apalutamide or matched placebo was continued until documented radiographic progression (development of distant metastases or locoregional disease progression as assessed by blinded independent central review [BICR]), withdrawal of consent, or the development of unacceptable toxicity. Two dose reduction levels were permitted (240 mg to 180 mg; 180 mg to 120 mg). Re-escalation was not permitted, unless discussed with the applicant. Dose interruptions of > 28 days due to TEAE were allowed.

Tumor measurements (computerized tomography [CT] or magnetic resonance imaging [MRI] and bone scans) were performed by BICR every 16 weeks from Cycle 1 Day 1. Additional scans may have been done at investigator discretion if disease progression was suspected and at the end of treatment. Imaging studies were to include a CT scan or MRI of the chest, abdomen, and pelvis, plus a bone scan. Areas of abnormal uptake on bone scan were confirmed with a correlative CT or MRI by BICR. Serum PSA (by central laboratory) was to be assessed on Day 1, Day 1 of Cycles 1 to 6, then Day 1 of every 2 cycles starting at Cycle 7 to Cycle 13, then Day 1 of every 4 cycles and at end of treatment. Results from the PSA testing done by the central laboratory were blinded to the subjects, site staff, and applicant.

> ***Reviewer's Comment****: Blinding of PSA was an important component of the trial design. Blinding was done to ensure that patients wouldn't discontinue from the trial prematurely due to anxiety about rising PSA in the absence of BICR-confirmed metastatic disease. PSA progression alone was not an indication for discontinuation of study drug.*

Patients who discontinued treatment due to documented radiographic progression were to enter the Follow-up Phase. Per Protocol, the applicant provided abiraterone as a treatment option for subsequent therapy to patients who provided informed consent, were assessed as appropriate for abiraterone as the subsequent therapy, had documented disease progression, lived in a country where abiraterone is indicated for the treatment of metastatic CPRC before chemotherapy, and received no other subsequent therapy. During the Follow-up phase of the study, information regarding survival status, development of symptomatic progression, initiation of subsequent therapy, progression on first subsequent therapy, and medical resource utilization was collected every 4 months. Patients who discontinued treatment without documented radiographic progression also entered the Follow-up Phase but continued scheduled disease assessments every 16 weeks until documented radiographic progression.

Figure 2. Study Schema, SPARTAN



ADT=androgen deprivation therapy; BICR=blinded independent central review; PSADT=prostate-specific antigen doubling time; NM-CRPC=non-metastatic-castration-resistant prostate cancer
[a]high-risk=PSADT ≤10 months

Source: SPARTAN CSR (NDA 210951, Module 5.3.5.1) Figure 1

Radiographic appearance of distant metastasis was based on the development of radiographically detectable bone or soft tissue distant metastasis and assessed by BICR. For new bone lesions detected on bone scans, a second imaging modality (e.g., CT or MRI) was required to confirm metastasis.

While receiving study treatment, if the BICR reported distant metastasis but the investigator provided an alternate explanation for such findings, these patients were permitted to continue receiving study treatment with approval from the applicant. Also, at the investigator's discretion, patients could be removed from study treatment for progressive locoregional disease or new metastasis determined locally but not confirmed by the BICR. However, patients with locoregional-only progression were also allowed to remain on study at the investigator's discretion, even if this progression was symptomatic and/or required intervention.

Study Endpoints

The primary efficacy endpoint of this study was metastasis-free survival. MFS was defined as the time from randomization to the date of first occurrence of BICR-confirmed distant metastasis (i.e., new bone or soft tissue lesions or enlarged lymph nodes outside the pelvis, or death due to any cause, whichever occurred earlier).

Secondary endpoints included time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to cytotoxic chemotherapy.

Time to metastasis was defined as the time from randomization to the date of the first occurrence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis.

Progression-free survival was defined as the time from randomization to the date of first occurrence of BICR-confirmed radiologic progressive disease (including locoregional progression and distant metastasis) or death due to any cause, whichever occurred earlier. Progressive disease (PD) was determined based on RECIST v1.1, and further defined as follows:

- For patients with at least one measurable lesion, PD was defined as at least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must have also demonstrated an absolute increase of at least 5mm. Furthermore, the appearance of one or more new lesions was also considered progression.
- For patients with only non-measurable disease observed on CR or MRI scans, unequivocal progression or the appearance of one or more new lesions were considered progression. For new bone lesions detected on bone scans, a second imaging modality (e.g., CT or MRI) was required to confirm progression.

Time to symptomatic progression was defined as the time from randomization to documentation in the CRF of any of the following (whichever occurred earlier):

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

- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy.
- Development of clinically significant symptoms due to locoregional tumor progression requiring surgical intervention or radiation therapy.

Overall survival was defined as the time from randomization to the date of death due to any cause.

Time to initiation of cytotoxic chemotherapy was defined as the time from randomization to documentation of a new cytotoxic chemotherapy being administered to the patient.

Patient-Reported Outcomes (PRO) were assessed using two instruments: Functional Assessment of Cancer Therapy-Prostate and EuroQOL 5 Dimension (EQ-5D-3L). See Section 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability and Appendix 19.5 for detailed patient-reported outcomes review.

Reviewer's Comment:

The use of metastasis determined by BICR as the primary criteria for study treatment discontinuation led to several scenarios where patients with disease progression could stay on treatment-

1. *If localized-only progression of disease was found by BICR review of imaging but no* ***metastatic*** *disease was found by BICR review, patients were able to continue treatment. Localized progression that would allow patient to remain on treatment, for example, could include new or enlarging pelvic lymph nodes.*
2. *If metastatic disease was determined to be present by investigator but not confirmed by BICR review of scans*
3. *If new bone metastases were suspected based on BICR review of NM bone scan but confirmatory CT, MRI, or X-rays did not show evidence of bony metastases*
4. *If localized disease progression occurred as per the investigator, even if this was symptomatic or required intervention.*

Statistical Analysis Plan

Sample Size Consideration

The study was designed to have 90% power to detect a hazard ratio (HR) of 0.70 for MFS at a two-sided significance level of 5%. With that, approximately 372 MFS events were required for the primary analysis. Based on an assumed median MFS of 25 months in the placebo arm, this targeted treatment effect represents an increase in the median MFS of approximately 11 months (25 months vs. 36 months). Approximately 1200 patients were planned to be randomized.

The study was also designed to have 85% power to detect a HR of 0.75 at a two-sided

significance level of 0.05 for overall survival, based on the assumed median OS of 49 months in the placebo arm. This treatment effect represents an increase in the median OS of approximately 16 months (49 months vs. 65 months). A total of 427 death events would be needed for the final OS analysis. The final analysis of time to symptomatic progression was also planned to be performed with 427 events to have 80% power to detect a HR of 0.75 at a two-sided significance level of 0.05.

> ***Reviewer's Comment:*** *Estimates of MFS and OS used for sample size calculation are similar to those observed on the placebo arm of the previously-published denosumab phase 3 study in NM-CRPC, where MFS on the placebo arm was 25 months. OS for the placebo arm on the denosumab study was 45 months (Lancet. 2012 Jan 7;379(9810):39-46).*

Analysis Populations

The primary analysis population for all efficacy and clinical benefit endpoints was to be the intent-to-treat (ITT) population. All randomized patients were to be included in the ITT population. Patients were to be grouped according to the treatment assigned at randomization.

The primary analysis population for safety and treatment compliance and administration was the safety analysis population. This population included all patients who received at least one dose of study drug, with treatment assignment designated according to actual study treatment received.

Efficacy Analysis Methods

The primary analysis of MFS was based on central blinded assessments and prospectively planned to be performed when approximately 372 MFS events occurred in the ITT population. MFS was to be summarized using Kaplan-Meier plots, and compared between the two treatment arms using a log-rank test stratified by the randomization stratification factors, i.e., PSA doubling time, use of bone sparing agents, and presence of locoregional disease, as collected in the IVRS system. The hazard ratio with a two-sided 95% confidence interval was derived from a stratified Cox proportional hazards model with the same three stratification factors used in the stratified log-rank test.

MFS was to be censored following the rules below in the primary analysis:

1. For patients without metastasis or death: censored on the last date of the last tumor assessment
2. For patients without post-baseline tumor assessment: censored at the date of randomization
3. For patients who were lost to follow-up or whose disease progression or death occurred after 2 or more consecutively missing or unevaluable tumor assessments: censored on the date of the last tumor assessment that the patient was known to be metastasis-free.
4. For patients who received new systemic anti-cancer therapy prior to documented

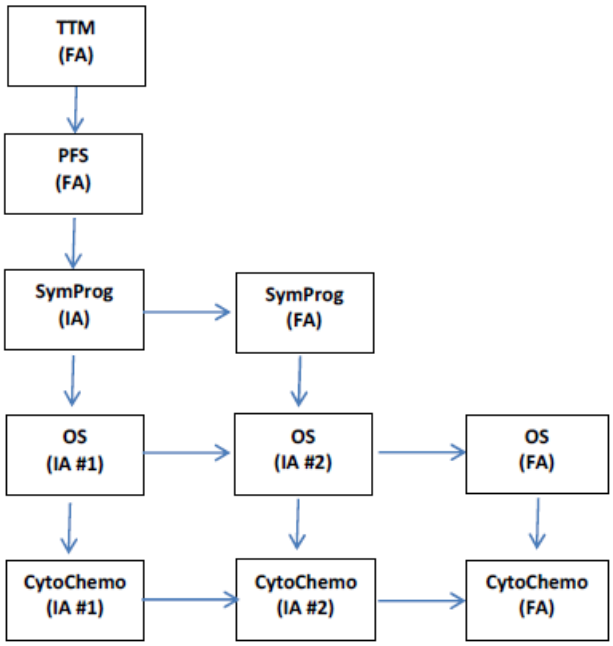
disease progression or death: censored on the date of the last tumor assessment prior to the start of the new systemic anti-cancer therapy,

Secondary endpoints included TTM, PFS, time to symptomatic progression, OS, and time to cytotoxic progression. The overall two-sided type I error rate of the secondary endpoints was controlled at 5% by use of a hierarchical testing procedure. If the primary endpoint MFS reached statistical significance, the secondary endpoints were to be tested in the following order: TTM, PFS, time to symptomatic progression, OS, and time to cytotoxic progression. All the five secondary endpoints were to be analyzed in the same manner as for the primary endpoint MFS, i.e., the two treatment arms were compared using the stratified log-rank test and the hazard ratio was estimated using the stratified Cox proportional hazards model.

Interim Analysis

There was no interim analysis planned for the primary endpoint, MFS, or for the secondary endpoints of TTM and PFS. One interim analysis for time to symptomatic progression and up to 2 interim analyses for OS and time to cytotoxic chemotherapy were planned. The testing of time to symptomatic progression, OS and time to cytotoxic chemotherapy would utilize an adaptive group sequential method, according to the O'Brien-Fleming alpha spending function with possible re-estimation of the required number of events necessary for the next analysis to have a conditional power of 90%. If time to symptomatic progression was statistically significant at the interim analysis, then there would be only one interim analysis for OS and time to cytotoxic chemotherapy; otherwise there would be two interim analyses for OS and time to cytotoxic chemotherapy. As shown in Figure 3., the final analysis of TTM and PFS, interim analysis for time to symptomatic progression, and the first interim analyses of OS and time to cytotoxic chemotherapy would all be conducted at the same time as the primary MFS analysis. The second interim analyses of OS and time to cytotoxic chemotherapy were planned to be conducted at the same time as the final analysis of time to symptomatic progression if it did not cross the efficacy boundary at the interim analysis.

Figure 3. Hierarchical Adaptive Group Sequential Procedure



IA=interim analysis; FA=final analysis
Source: Statistical Analysis Plan, Version 4.0 for ARN-509-003.

Reviewer's Comment.

On March 15, 2017, the Applicant amended their statistical analysis plan to change the multiple testing procedure for secondary endpoints to a hierarchical adaptive group sequential procedure. The method controls the familywise type I error rate for the primary and all secondary endpoints. At the time of the change, the clinical trial was 100% enrolled. This amendment is acceptable.

Protocol and SAP Amendments

There were 8 amendments to Protocol ARN-509-003. The first and second amendments to the protocol were adopted before any study-related procedures had begun. Substantive amendments are included below.

- Amendment 3: addition of 4 secondary endpoints (time to symptomatic progression, time to initiation of cytotoxic chemotherapy, progression-free survival, and time to metastasis); addition of the provision of abiraterone acetate plus prednisolone as a subsequent therapy for eligible subjects (except in Japan).
- Amendment 5: modification of eligibility criteria to clarify the definitions of PSADT (including a 24-month collection period for PSA values) and castration-resistant; addition of an optional prescreening period.
- Amendment 6: formulation changed from softgel capsules to tablet.
- Amendment 8: Clarified that under the hierarchical testing procedure framework, "not tested" means that no statistical significance can be claimed if the endpoint above in the

hierarchy is not found to be positive. Hierarchical testing of secondary endpoints including a provision for re-estimating the timepoints for next analysis of symptomatic progression and other secondary endpoints was enacted; addition of provision for cross-over of the placebo arm, if the study is unblinded; clarification of criteria for disease progression for administration of abiraterone acetate, if the study is unblinded.

Table 10 summarizes the number of patients randomized in each of the arms at the time of the protocol amendments and shows that the proportions randomized are nearly the same on both arms.

Table 10. Patient Randomization per Protocol Amendment, SPARTAN

Protocol Amendment	Amendment Date	Total Patients Randomized in the Apalutamide Arm Prior to Amendment (N=806)	Total Patients Randomized in the Placebo Arm Prior to Amendment (N=401)
1	11 January 2013	0 (0%)	0 (0%)
2	08 May 2013	0 (0%)	0 (0%)
3	11 March 2014	14 (1.7%)	10 (2.5%)
4/5	01 July 2014	54 (6.7%)	31 (7.7%)
6	18 May 2015	353 (44%)	178 (44%)
7	01 June 2016	767 (95%)	381 (95%)
8	15 March 2017	806 (100%)	401 (100%)
Source: adsl.xpt, CSR for ARN-509-003 (Module 5.3.5.1)			

Reviewer's Comment: *At the time of the protocol amendments, the proportion of patients randomized to each arm was balanced.*

The first version of the statistical analysis plan was released on 05 November 2012, and amended six times thereafter. The major changes in each amendment are summarized in Table 11.

Table 11. SAP Amendment Summary

SAP version (stamp date)	Major Changes:
Version 2 (27 February 2014)	• OS was changed from being the only key secondary endpoint to being one of the 5 secondary endpoints including time to symptomatic progression, time to initiation of cytotoxic chemotherapy, PFS, and TTM. The statistical testing of secondary endpoints was to be performed by allocating 0.04 to OS and 0.01 for the rest of the endpoints using Bonferroni method to control the overall family wise type I error rate at 0.05. • The number of deaths required for the OS final analysis was revised to reflect the change of alpha allocated. On additional interim analysis of OS at

	approximately 70% of deaths was added. • The definition and the analysis plan of PFS2 were added.
Version 3 (15 April 2015)	• A new section of Analysis by Formulation was added to include additional analysis plans for patients' distribution, demographic and baseline characteristics, study drug administration, safety, and the primary endpoint.
Version 4 (15 March 2017)	• Changed the multiple testing procedure for the secondary endpoints to a hierarchical testing procedure that also included a sample size re-estimation for the required number of events for time to symptomatic progression and overall survival. • Simplified and removed some sensitivity analyses. • Removed the by-formulation analysis using the arbitrary cutoff of 6 months, added analysis by greater tablet duration or greater capsule duration.
Version 5 (28 March 2017)	• Modified Section 7.5.3 and Appendix 1 to clarify that under the hierarchical testing procedure framework, "not tested" means that no statistical significance can be claimed if the endpoint above in the hierarchy is not found to be positive.
Version 6 (22 June 2017)	• Removed the definition of the PRO population. • Revised the criteria for markedly abnormal vital signs in Section 7.6.3. • Added Appendix 3 "Modified MedDRA queries as search criteria for AE of special interest".
Version 7 (25 June 2017)	• Modified Appendix 1 to clarify the choice of weights in p-value combination methods.
Source: NDA 210951, Module 5.3.5.1: Statistical Methods Interim Analysis Plan.	

8.1.2. Study Results

Data Quality and Integrity

The overall data quality and integrity are acceptable to the reviewers. The submitted datasets are generally consistent and variables are clearly labeled and/or explained. Based on the submitted data and reports, the reviewers believe that the analyses and results are reliable for regulatory decision making.

The electronic submission including Protocols, Statistical Analysis Plan (SAP), Clinical Study Reports (CSRs) and SAS transport datasets for the NDA submission are located in the network path: \\cdsesub1\evsprod\nda210951\0002.

These sources were utilized to perform the clinical and statistical review of this application.

Compliance with Good Clinical Practices

The applicant stated that this study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

In one site in the US and 18 sites in Canada, drug information (Canada: proforma invoices and

packing list; US: packing list) sent to sites had the potential to unblind site staff and/or study monitor to the treatment arm of patients. A total of 47 patients from the sites affected had the potential to be unblinded. Site visits were implemented by applicant personnel not involved in the study to seal documents at potentially affected sites. No site staff were identified as being unblinded. A sensitivity analysis was performed of the MFS with the 47 patients removed (see Table 22).

Financial Disclosure

Please refer to section 19.2 for details.

Patient Disposition

SPARTAN was conducted at 332 centers from 26 countries with 337 patients (28%) accrued in the U.S. The trial was initiated on 19 September 2013 and the clinical data cutoff date was 19 May 2017.

Two thousand one hundred thirty-two (2,132) patients signed the informed consent and were screened; 1207 patients were randomized (Table 12). Of the 925 patients who were ineligible, 517 subjects were ineligible due to the presence of metastatic disease at screening (Table 13). Results of BICR-reviewed screening scans were provided for 385 patients who did not meet eligibility criteria. Of provided scans, 219 patients were found to have bone metastases, 6 patients brain metastases, and 238 patients soft tissue or visceral metastases. Seventy-seven patients had metastases in more than one category (bone, brain, or soft tissue/visceral metastases).

Table 12. Screening Failures, SPARTAN

Disposition	**Number of Patients**
Randomized	1207
Screening Failure	925
Reason for Screening Failure	
Failure to meet randomization criteria	885
Lost to follow-up	2
Missing/incomplete data	1
Withdrawal by subject	26
Other	11
Source: addisp.xpt	

Table 13. Screening Failures by Eligibility Criteria, SPARTAN

Eligibility Criteria Not Met	**Number of Patients**

Exclusion Criteria	
Presence of distant metastases. Pelvic lymph nodes < 2 cm are allowed.	517
History or evidence of any prohibited conditions.	9
Increased seizure risk	16
Concurrent therapy with prohibited medications within four weeks of randomization.	21
Prior treatment for prostate cancer, except if administered in the adjuvant/neoadjuvant setting	33
Symptomatic locoregional disease requiring medical intervention.	48
Inclusion Criteria	
Histologically or cytologically confirmed adenocarcinoma of the prostate with high risk for metastases	125
Testosterone levels of <50 ng/dL	34
Willingness and ability to comply with study procedures.	59
Castration-resistant prostate cancer	3
Prior treatment with first-generation anti-androgen, 5-alpha reductase inhibitor, major surgery or radiation therapy are allowed, if over 4 weeks prior to randomization	36

Source: ie.xpt

Reviewer's Comment: *The presence of metastatic disease (bone, brain, soft tissue/visceral) were identified by BICR in the screening scans submitted for eligibility criteria. Per Independent Review Charter with* (b) (4)*, the independent reviewer was blinded to the following: subject demographics, treatment arm, site assessment of response, site choice of target and non-target lesions and the identification of new lesions, and clinical history. It is unclear whether these independent reviewers were blinded to whether a scan was being reviewed for eligibility criteria or disease progression. A more stringent threshold for the identification of metastases would be important in this clinical study given that the primary efficacy endpoint is MFS. However, this level of scrutiny may not be applied in general medical practice. Consequently, this finding may impact the generalizability of the study results in the real world.*

An Information Request was issued on 02/01/2018 regarding further analysis of the 517 incidences of metastatic disease identified by BICR.

Table 14 provides information on the patient disposition during the Treatment Period. Seventy percent of patients in the placebo arm discontinued study treatment, compared to 39% in the apalutamide arm. The most common reason for treatment discontinuation was progressive disease in both arms (52% in the placebo arm versus 19% in the apalutamide arm).

Reviewer's Comment: *Reasons for Treatment Discontinuation and Reasons for Study Discontinuation that were reported as "Other" in the datasets were further reviewed and reclassified to one of the listed categories. These recategorizations have a minimal impact on the overall observed trend and therefore have not been included in Table 14.*

Table 14. Patient Disposition, ITT Population, SPARTAN

	Placebo N=401 (%)	**Apalutamide N=806 (%)**
Treatment status		
Ongoing	119 (30)	489 (61)
Discontinued	280 (70)	314 (39)
Reason for Treatment Discontinuation		
Progressive disease	210 (52)	155 (19)
Withdrawal by subject	40 (10)	54 (7)
Adverse event	25 (6)	86 (11)
Other	2 (0.5)	9 (1.1)
Protocol violation	2 (0.5)	3 (0.4)
Lost to follow-up	1 (0.2)	1 (0.1)
Noncompliance with study procedures	0 (0)	6 (0.7)
Study status		
Ongoing	316 (79)	687 (85)
Discontinued	85 (21)	119 (15)
Reason for Study Discontinuation		
Withdrawal by subject	37 (9)	50 (6)
Death	38 (9)	59 (7)
Other	7 (1.7)	3 (0.4)
Lost to follow-up	3 (0.7)	7 (0.9)

Source: addisp.xpt

Reviewer's Comment:
We note the discrepancy between the number of MFS events (apalutamide-175/placebo-191) and patients who withdrew for progressive disease. There are several explanations for this discrepancy:

1. *Some patients discontinued treatment due to local PD.*

2. *Some patients discontinued with investigator-determined metastasis but no BICR-metastasis.*
3. *Patients who discontinued treatment due to other reasons than PD could then develop metastasis during follow-up. This explains why the number of discontinuations due to PD in the apalutamide arm (N=155) is smaller than the MFS number (N=175).*

Protocol Violations/Deviations

Approximately 10% of patients had at least one major protocol deviation during the study. There was a similar incidence of protocol deviations in each arm regardless of type. The most common protocol deviation was eligibility criteria not being met, identified for 5% of patients in the apalutamide arm and 4% of patients in the placebo arm. The most common protocol deviation relating to eligibility was exclusion criterion #8: concurrent therapy with any of the following that was not discontinued or substituted at least 4 weeks prior to randomization:

- Medications known to lower the seizure threshold;
- Herbal and non-herbal products that may decrease PSA levels;
- Systemic (Oral/IV/IM) corticosteroids;
- Any other experimental treatment;
- Agents indicated for the prevention of skeletal-related events

Major protocol deviations are summarized in Table 15.

Table 15. Summary of Patients with Major Protocol Deviations

	Apalutamide N=806 n (%)	**Placebo N=401** n (%)	**Total N=1207** n (%)
Patients with major protocol deviations	80 (9.9%)	37 (9.2%)	117 (9.7%)
Patients not meeting inclusion or exclusion criteria	42 (5.2%)	16 (4.0%)	58 (4.8%)
Patients receiving a disallowed concomitant treatment	21 (2.6%)	9 (2.2%)	30 (2.5%)
Patients receiving wrong treatment or incorrect dose	16 (2.0%)	9 (2.2%)	25 (2.1%)
Incorrect study treatment	3 (0.4%)	0	3 (0.2%)
Safety assessment deviation	2 (0.2%)	0	2 (0.2%)
Patients not withdrawing per protocol	0	1 (0.2%)	1 (0.1%)
Other non-compliance	2 (0.2%)	4 (1.0%)	6 (0.5%)

Source: CSR Table 9

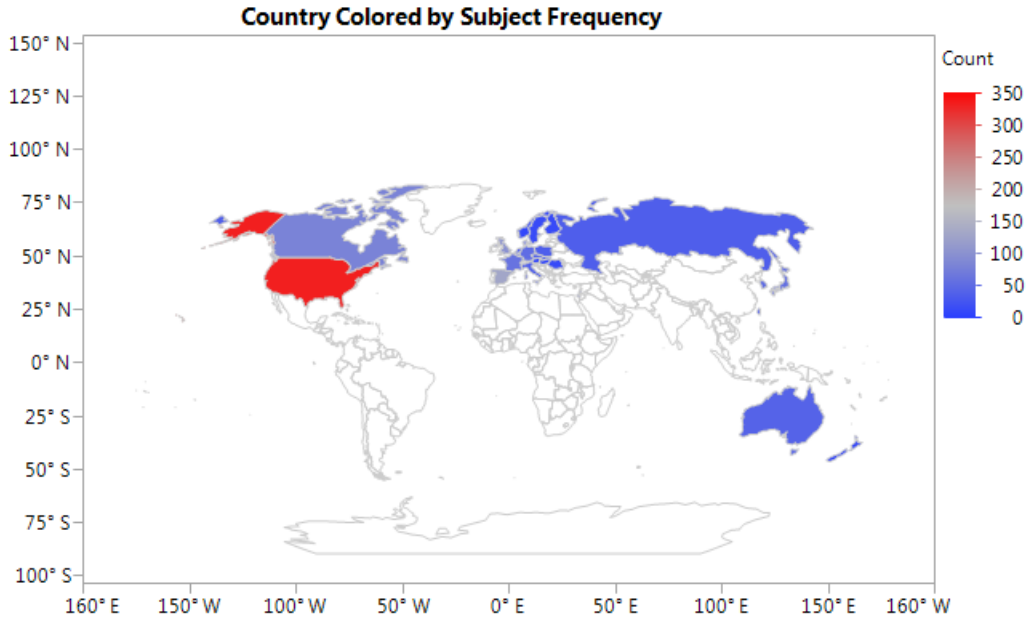
Demographic Characteristics

On SPARTAN, patients 65 and older made up 87% of the apalutamide arm and 11% of the placebo arm. By race, 65% of the patients were white in the apalutamide arm versus 69% in the placebo. Asians represented 12% of patients in both arms, and Black or African American represented 6% and 5% in the apalutamide and placebo arms, respectively. Twenty-eight percent of the patients were enrolled in the US for both arms. Overall, there were no imbalances in the demographics of the study population.

Table 16. Patient Demographics, ITT Population, SPARTAN

	Placebo N=401 (%)	**Apalutamide** (N=806)
Age		
Median (Min, Max)	74 (52 – 97)	74 (48 – 94)
<65	43 (11)	106 (13)
≥ 65	358 (89)	700 (87)
Race		
White	276 (69)	524 (65)
Asian	47 (12)	93 (12)
Black or African American	20 (5)	48 (6)
American Indian or Alaska Native	0 (0)	4 (0.5)
Multiple	0 (0)	1 (0.1)
Other	1 (0.2)	1 (0.1)
Not Reported	57 (14)	135 (17)
Ethnicity		
Hispanic or Latino	5 (1.2)	11 (1.4)
Not Hispanic or Latino	338 (84)	659 (82)
Not Reported	58 (14)	136 (17)
Region		
USA	113 (28)	224 (28)
Rest of the World		
Europe	204 (51)	395 (49)
Asia	43 (11)	83 (10)
Canada	21 (5)	61 (8)
Australia / New Zealand	13 (3.2)	36 (4.5)
Israel	7 (1.7)	7 (0.9)

Data on race and/or ethnicity were not collected in France, Italy, and Spain because of local regulations.
Source: adsl.xpt



Other Baseline Characteristics

Table 17. Baseline Disease Characteristics, ITT Population, SPARTAN

	Placebo N=401 (%)	**Apalutamide** (N=806)
Tumor Stage at Diagnosis		
T1	63 (16)	141 (17)
T2	123 (31)	265 (33)
T3	163 (41)	296 (37)
T4	16 (4)	32 (4)
TX	29 (7)	60 (7)
Lymph Node Stage at Diagnosis		
N0	273 (68)	550 (68)
N1	61 (15)	118 (15)
NX	61 (15)	131 (16)
Metastasis Stage at Diagnosis		
M0	400 (100)	806 (100)
Gleason Score at Diagnosis		
<7	72 (18)	152 (19)
3+4	65 (16)	157 (19)
4+3	77 (19)	125 (16)
>7	169 (42)	341 (42)
PSADT (IVRS)		
<=6 months	284 (71)	576 (71)

>6 months	117 (29)	230 (29)
Locoregional Disease (IVRS)		
N0	336 (84)	673 (83)
N1	65 (16)	133 (17)
Bone-Sparing Agent (IVRS)		
N	362 (90)	724 (90)
Y	39 (10)	82 (10)
ECOG at Baseline		
0	311 (78)	623 (77)
1	89 (22)	183 (23)
Prior definitive therapy for localized prostate cancer		
Y	307 (77)	617 (77)
N	94 (23)	189 (23)
Source: adsl.xpt, adbdc.xpt		

Reviewer's Comment: *SPARTAN was a multi-national study, with North American enrollment representing only 35% of patients overall. Some of the baseline characteristics make this study enrollment less representative of the US population overall, including the fact that only 6% of enrolled patients were African-American. Additionally, we note that 23% of patients did not have definitive local therapy at baseline for their prostate cancer, which is accepted standard of care in the US. This may represent practice norms outside the US regarding treatment of localized prostate cancer. To evaluate whether outcomes differed in patients who did or did not receive definitive local therapy for their disease, an exploratory subgroup analysis was performed. These results will be discussed in Table 24.*

Data of stratification factors were collected in both IVRS and CRF. The concordance and discordance between IVRS and CRF-based stratification data are summarized in Table 18.

Table 18. Concordance and Discordance of Stratification Data between eCRF and IVRS, SPARTAN

	Apalutamide N=806 n (%)	**Placebo N=401 n (%)**
PSA doubling time		
Discordance	13 (1.6)	7 (1.7)
Concordance	793 (98.4)	394 (98.3)
Bone-sparing agent		
Discordance	31 (3.8)	12 (3.0)
Concordance	775 (96.2)	389 (97.0)
Locoregional disease		
Discordance	62 (7.7)	32 (8.0)
Concordance	744 (92.3)	369 (92.0)

Source: datasets ADSTRAT and ADSL

***Reviewer's Comment**:*
There were no notable differences between arms with respect to the IVRS- and the CRF-based stratification data. Following the intent-to-treat rule, the primary efficacy analysis used IVRS-based stratification data. To evaluate the robustness of the results, a sensitivity analysis using CRF-based stratification data was performed and results are shown in the section of efficacy results.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

At each clinic visit, patients were asked to return any remaining study drug from the previous dosing cycle as well as all used and unused study drug containers. The overall treatment compliance was defined as the total dose in mg taken during the study divided by the expected total dose in mg. When patients received softgel capsules, they had a maximum of 8 softgel capsules per day. Once the study drug was switched to tablets, patients had a maximum of 4 tablets per day. An accurate and current accounting of the dispensing and return of study drug for each patient was maintained on an ongoing basis by the Investigator or his/her designated personnel. The number of study drug capsules or tablets dispensed and returned by the patient was recorded on the Investigational Product Accountability Log. Eighty-eight percent (88%) of patients in the apalutamide arm and 93% of patient in the placebo arm had >80% compliance with study drug dosing (Table 19)

Table 19. Treatment Compliance, Exposed Population, SPARTAN

Treatment Compliance	Apalutamide (N=803)	Placebo (n=398)
≤75%	65 (8)	15 (3.8)
>75% - ≤80%	34 (4.2)	12 (3)
>80% - ≤85%	66 (8)	20 (5)
>85% - ≤90%	104 (13)	28 (7)
>90% - ≤95%	149 (19)	57 (14)
>95%	385 (48)	265 (67)
Source: adexsum.xpt		

Efficacy Results – Primary Endpoint

Metastasis-free survival (MFS) by Blinded Independent Central Review (BICR) was the primary efficacy endpoint of the trial. MFS is defined as the time from randomization to first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis or death due to any cause. Per the Statistical Analysis Plan, the primary efficacy analysis was to be performed when approximately 372 MFS events have occurred. At the clinical cutoff date of May 19, 2017, 378 MFS events had occurred (184 patients (22.8%) in the apalutamide arm and 194 patients

(48.4%) in the placebo arm), with a median follow-up time for MFS of approximately 18 months.

Table **20** presents the results of the primary analysis of MFS by BICR assessment in the ITT population. There was a statistically significant improvement in MFS in the apalutamide arm relative to the placebo arm with a hazard ratio of 0.28 (95% CI: 0.23, 0.35). The estimate of median MFS was 40.51 months for the apalutamide arm and 16.20 months for the placebo arm. The Kaplan-Meier curves of MFS are shown in **Figure 4.**

Reviewer's Comment*: Type of metastasis was determined by the BICR-reported location of a new lesion from the first scan showing new distant metastatic lesions.*

Figure 4.

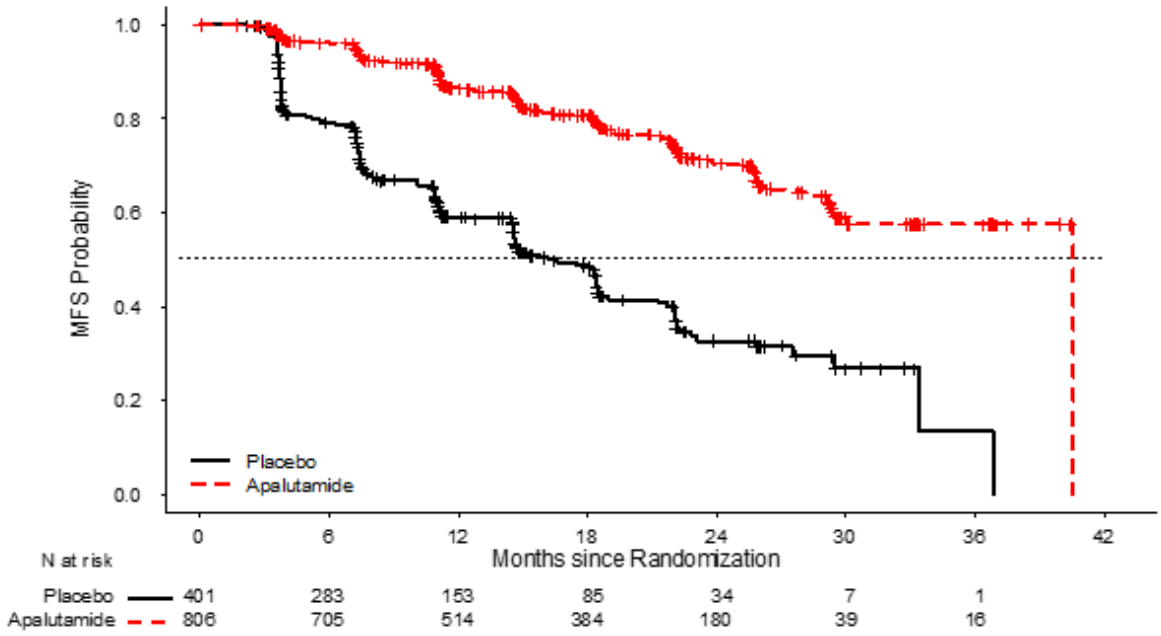
Table 20. Metastasis-Free Survival Analysis per BICR Assessment, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Number of events	184 (22.8%)	194 (48.4%)
Metastasis	175 (21.7%)	191 (47.6%)
Bone only	95 (11.7%)	81 (20.2%)
Soft tissue only	63 (7.8%)	82 (20.4%)
Both bone and soft tissue	17 (2.1%)	28 (7.0%)
Death	9 (1.1%)	3 (0.7%)
Median (95% CI), in months	40.51 (NE, NE)	16.20 (14.59, 18.40)
HR (95% CI)	0.28 (0.23, 0.35)	
P-value	<0.0001	

HR was from a Cox proportional hazards model stratified by PSA doubling time, bone-sparing agent use, and locoregional disease.
P-value was from a log-rank test stratified by PSA doubling time, bone-sparing agent use, and locoregional disease.
NE=Not Estimable
Source: CSR Table 13, adtteef.xpt, tu.xpt

Reviewer's Comment: *Type of metastasis was determined by the BICR-reported location of a new lesion from the first scan showing new distant metastatic lesions.*

Figure 4. Kaplan-Meier Curves for MFS per BICR Assessment, SPARTAN



Source: CSR Figure 2

> ***Reviewer's Comment**: The estimate of MFS median for the apalutamide arm is not reliable as the estimate was driven by one event which occurred in the patient with the longest follow-up.*
>
> *It is also noted that the placebo arm underperformed relative to the assumption that median MFS would be 25 months in this arm. However, as baseline characteristics were balanced between the apalutamide and placebo arms, this does not significantly impact the overall results.*

Per BICR assessments, 622 patients in the apalutamide arm and 207 patients in the placebo arm have been censored. The reasons for censoring are summarized in **Table 21**.

Table 21. Summary of MFS-BICR Censoring Reasons, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Number of patients censored	622 (77.2%)	207 (51.6%)
Reason for censoring, n (%)		
Permanently censored	108 (13.4%)	82 (20.4%)
No post-baseline tumor assessment	25 (3.1%)	13 (3.2%)
Events occurred after 2+ consecutive missing tumor assessments	6 (0.7%)	2 (0.5%)
No BICR- determined metastasis observed prior to any new systemic anti-cancer therapy received	59 (7.3%)	50 (12.5%)

Lost to follow-up	2 (0.2%)	3 (1.4%)
Withdrew consent to remain on study	16 (2.6%)	14 (6.8%)
Still at risk		
On treatment by cutoff	458 (56.8%)	109 (27.2%)
Discontinued treatment by cutoff	56 (6.9%)	16 (4.0%)
Source: Derived from dataset adtteef and adjusted from CSR Table TEFPC03A		

Reviewer's Comment: *The review team noticed that 32 patients (6 placebo patients and 26 apalutamide patients) were censored before January 01, 2017, with the status listed as "Still at risk: on treatment by cutoff" or "Still at risk: discontinued treatment by cutoff.". Per the applicant's response to an information request, for the 27 patients who discontinued study treatment by cutoff, all have declined further on-study imaging, but remained in follow-up for survival; among the 5 patients who were still receiving treatment as of the cutoff date, three patients had no scans performed until after the cutoff date and two patients did not have scans performed due to intercurrent adverse events.*

Of the patients censored due to no BICR-determined metastasis observed prior to any new systemic anti-cancer therapy received, approximately 50% had investigator-determined metastasis but not confirmed by BICR and 7% had locoregional disease progression only before receiving new systemic anti-cancer therapy.

Sensitivity Analyses of MFS

Multiple sensitivity analyses for MFS were conducted by the agency and the applicant to evaluate the robustness of MFS results (**Table 22**).

Table 22. Sensitivity Analysis of MFS, SPARTAN

Sensitivity Analysis	**Apalutamide Events/N (%)**	**Placebo Events/N (%)**	**Median (months) Apalutamide vs. Placebo**	**HR (95% CI)**
1. MFS per INV assessment	189/806 (23%)	219/401 (55%)	41.20 vs. 14.62	0.25 (0.21, 0.31)
2. MFS per BICR, unstratified analysis	184/806 (23%)	194/401 (48%)	40.51 vs. 16.20	0.30 (0.24, 0.36)
3. MFS per BICR, stratification factor data from CRF	184/806 (23%)	194/401 (48%)	40.51 vs. 16.20	0.29 (0.23, 0.35)
4. MFS per BICR, excluding data from 47 patients with potential unblinding status	179/773 (23%)	187/387 (48%)	40.51 vs. 15.70	0.28 (0.23, 0.35)
5. MFS per BICR, applying ex-US censoring rules*	209/806 (26%)	210/401 (52%)	40.51 vs. 15.70	0.30 (0.24, 0.36)

6. MFS per BICR, excluding patients with major protocol deviations	171/726 (24%)	176/364 (48%)	40.51 vs. 15.70	0.30 (0.24, 0.37)
*Ex-US censoring rules: the analysis of MFS did not censor patients with 2+ consecutive missing tumor assessment or patients receiving a new systemic anti-cancer therapy *Source: CSR pages 66-67, datasets adtteef, adstrat and addv*				

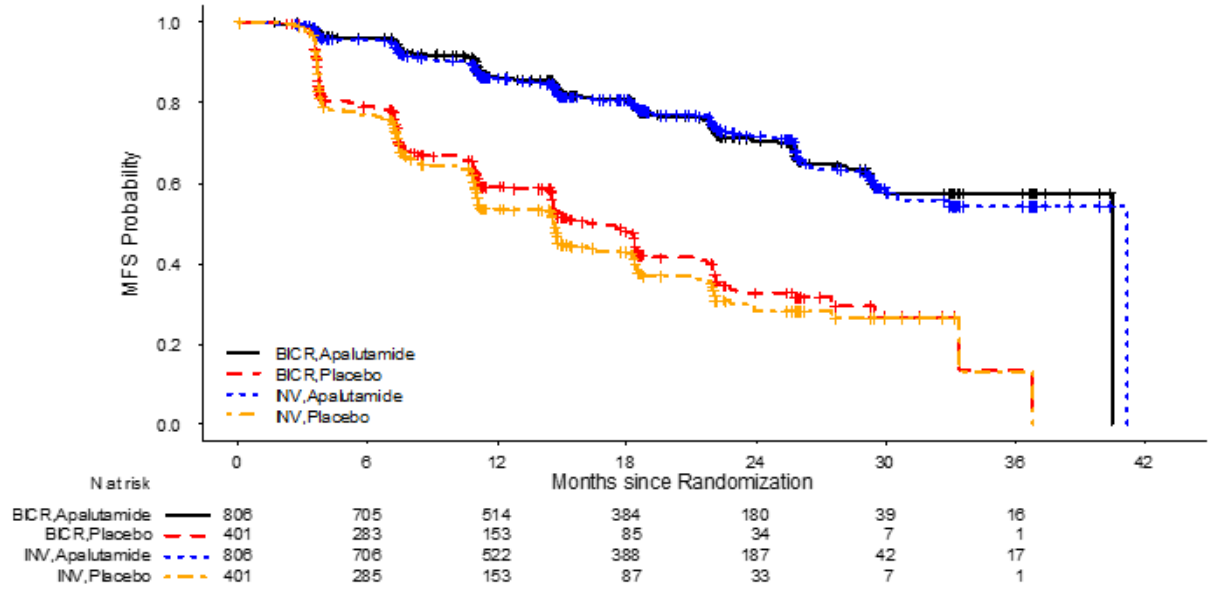
FDA's Analysis of Discordance between BICR and INV Assessment of Metastasis

Per the study design, disease status was assessed by both BICR and INV. The primary MFS analysis was based on the BICR assessment, with the INV-based MFS as a supportive analysis. Discordance rates between BICR and INV assessments are shown in **Table 23**. The discordance rate in terms of MFS status (event vs. censoring) was 9% in the apalutamide arm and 12% in the placebo arm. Relatively more patients in the placebo arm were determined to have metastasis by the investigator but not by the central reviewer. This may cause informative censoring, but indicates that results per BICR are more conservative. The Kaplan-Meier curves of MFS per BICR and INV are shown on the same plot (**Figure 5**). Results are consistent in the two analyses.

Table 23. Discordance and Concordance Rate of MFS Event Status between BICR and INV Assessment, SPARTAN

	Apalutamide (n=806)		**Placebo (n=401)**	
INV	BICR Events	BICR censored	BICR Events	BICR censored
Events	148 (18%)	41 (5%)	181 (45%)	38 (9%)
Censored	36 (4%)	581 (72%)	13 (3%)	169 (42%)

Figure 5. Kaplan-Meier Curves for MFS per BICR and INV Assessment, SPARTAN



Reviewer's Comment: *The sensitivity analysis results were consistent with that of the primary MFS analysis. The results of sensitivity analyses support the primary efficacy findings.*

Exploratory subgroup analyses of MFS by demographics and baseline disease characteristics are presented in Table 24.

Table 24. Subgroup Analyses of MFS-BICR per Baseline Characteristics, SPARTAN

	Number of Events/Total N (% of Patients with Event)		Median (months)		HR (95% CI)[1]
	Apalutamide	Placebo	Apalutamide	Placebo	
Age					
<65	19/106 (18)	25/43 (58)	NE	7.3	0.14 (0.08, 0.27)
65-<75	75/307 (24)	88/169 (52)	NE	14.6	0.25 (0.18, 0.34)
≥75	90/393 (23)	81/189 (43)	40.5	18.5	0.42 (0.31, 0.56)
Race					
White	121/524 (23)	143/276 (52)	40.5	14.6	0.26 (0.21, 0.34)
Black	11/48 (23)	6/20 (30)	25.8	36.8	0.63 (0.23, 1.72)
Asian	14/93 (15)	18/47 (38)	NE	18.5	0.33 (0.16, 0.67)
Others	38/141 (27)	27/58 (47)	30	18.4	0.40 (0.24, 0.65)
Region					
North America	70/285 (25)	67/134 (50)	40.5	15.7	0.30 (0.21, 0.42)
Europe	93/395 (24)	101/204 (50)	NE	14.8	0.29 (0.22, 0.39)

Rest of the world	21/126 (17)	26/63 (41)	NE	18.5	0.30 (0.17, 0.54)
ECOG PS					
0	133/623 (21)	150/311 (48)	40.5	15.7	0.27 (0.21, 0.34)
1	51/183 (28)	44/89 (49)	27.8	18.4	0.40 (0.27, 0.60)
Number of prior hormonal therapy					
1	35/156 (22)	38/84 (45)	NE	16.6	0.34 (0.21, 0.53)
≥2	148/645 (23)	156/316 (49)	40.5	16.2	0.29 (0.23, 0.36)
Prior surgery or radiation therapy					
Yes	138/617 (22)	159/307 (52)	21.88	7.23	0.26 (0.21, 0.33)
No	46/189 (24)	35/94 (37)	21.95	7.39	0.46 (0.29, 0.71)
PSA doubling time (Months)					
≤ 6	147/576 (26)	149/284 (52)	40.5	14.6	0.29 (0.23, 0.36)
> 6	37/230 (16)	45/117 (38)	NE	22.8	0.30 (0.20, 0.47)
≤ 2.9	63/213 (30)	64/103 (62)	14.78	3.94	0.27 (0.19, 0.38)
>2.9 - ≤ 4.4	50/195 (26)	45/95 (48)	19.09	7.20	0.31 (0.21, 0.47)
> 4.4 - ≤ 6.4	40/196 (20)	49/106 (46)	21.75	7.39	0.31 (0.20, 0.48)
> 6.4	31/202 (15)	49/106 (46)	25.89	8.31	0.29 (0.18, 0.48)
Gleason Score					
≤ 7	98/443 (22)	95/218 (44)	22.37	8.28	0.35 (0.27, 0.48)
> 7	79/341 (23)	93/169 (55)	19.55	3.84	0.22 (0.16, 0.30)
Bone sparing agent					
Yes	18/82 (22)	16/39 (41)	NE	22	0.38 (0.19, 0.76)
No	166/724 (23)	178/362 (49)	40.5	14.8	0.29 (0.23, 0.36)
Locoregional disease					
N0	153/673 (23)	155/336 (46)	40.5	18.3	0.33 (0.26, 0.41)
N1	31/133 (23)	39/65 (60)	NE	10.8	0.15 (0.09, 0.25)

[1] HR is estimated from an unstratified Cox proportional hazards model
Source CSR Figure 3, adsl.xpt, adtteef.xpt, Response to Information Request (12/08/2017)

Reviewer's Comment: *All the subgroup analyses are considered exploratory or hypothesis generating and no formal inference may be drawn. No apparent outliers were observed from the subgroup analyses. African-American men were underrepresented in this patient population, comprising 5.6% of the patient population (6.0% in the apalutamide arm vs. 5.0% in the placebo arm). From 2010 to 2012, African-American men had a higher lifetime risk of developing (18.2% vs. 13.3%) and dying from (4.4% vs. 2.4%) prostate cancer compared with Caucasian American men (CE DeSantis et al 2016). Further, SEER data show that from 2008 – 2012, the average annual prostate cancer incidence rate was 208.7 cases per 100,000 black men compared to 123.0 cases per 100,000 white men. This underrepresentation of a group of patients with a worse prognosis and survival rate may affect the generalizability of the results to the African American patients with prostate cancer.*

Additionally, while the trial was conducted in patients with PSADT≤10 months, subgroup analyses for all quartiles of enrolled patients' PSA doubling times showed a consistent effect, with patients in the shortest PSADT group not appearing to drive the overall results. The magnitude of effect was large and appeared to be similarly preserved through all PSADT groups, with no indication of a trend favoring patients in the higher risk PSADT group as deriving proportionally greater benefit from apalutamide. The labeled indication was therefore not restricted to a specific PSADT cutoff, especially in the setting of a supportive safety profile (see section 8.2.11). Given the overall large magnitude of effect demonstrated by SPARTAN, it was felt that the strict cutoff of 10 months would exclude patients in the general population who would be very likely to benefit, for instance those with PSADT slightly higher or those with other poor prognostic features.

Efficacy Results – Secondary and other relevant endpoints

Key secondary endpoints were tested using a hierarchical testing procedure to control the overall alpha level at 0.05, 2-sided, in the order of: TTM, PFS, SymProg, OS, and time to initiation of cytotoxic chemotherapy.

Time to Metastasis

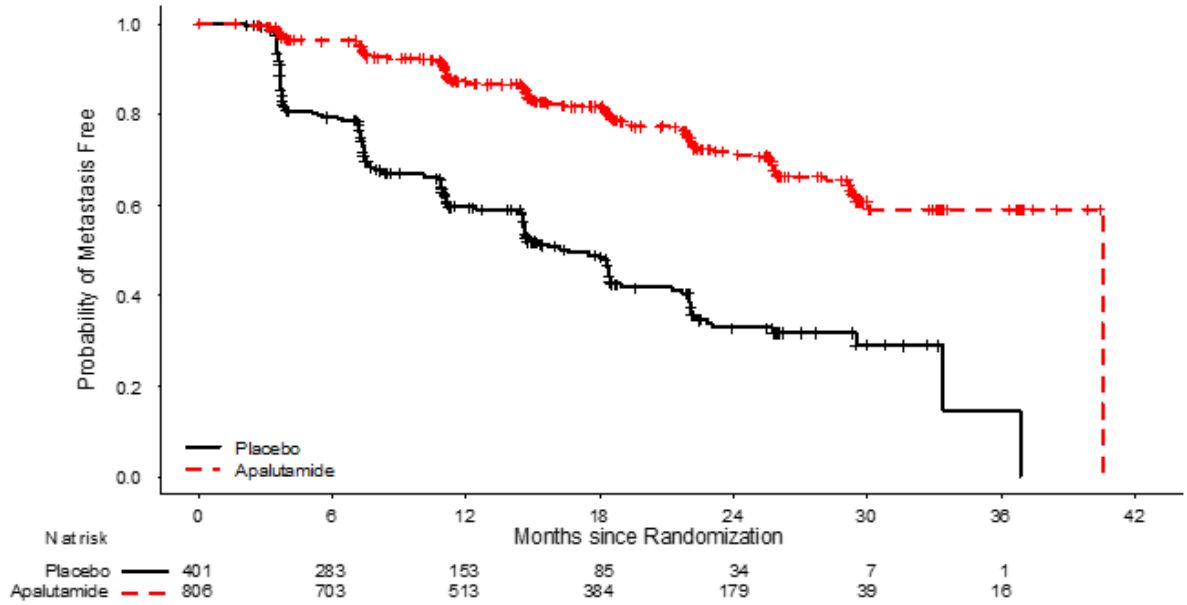
Time to metastasis (TTM) is defined as the time from randomization to BICR-confirmed radiographically detected bone or soft tissue distant metastasis. Only one analysis was planned for TTM and was pre-specified as the final analysis. According to the hierarchical testing procedure, TTM was statistically significant given that the observed p-value is less than 0.05. The median estimate of TTM per BICR assessment was 40.51 months for the apalutamide arm and 16.59 months for the placebo arm, with a hazard ratio of 0.27 (95% CI: 0.22, 0.34), as shown in Table 25. The Kaplan-Meier plot of TTM is presented in **Figure 6.**

Table 25. Analysis of Time to Metastasis per BICR Assessment, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Number of events	175 (21.7%)	191 (47.6%)
Median (95% CI), in months	40.51 (NE, NE)	16.59 (14.59, 18.46)
HR (95% CI)	0.27 (0.22, 0.34)	
P-value	<0.0001	

HR was estimated from a Cox proportional hazards model stratified by PSA doubling time, bone-sparing agent use, and locoregional disease.
P-value was from a log-rank test stratified by PSA doubling time, bone-sparing agent use, and locoregional disease.
NE=Not Estimable
Source: CSR Table 18

Figure 6. Kaplan-Meier Plot of Time to Metastasis, SPARTAN



Source: CSR Figure 5

Progression-Free Survival

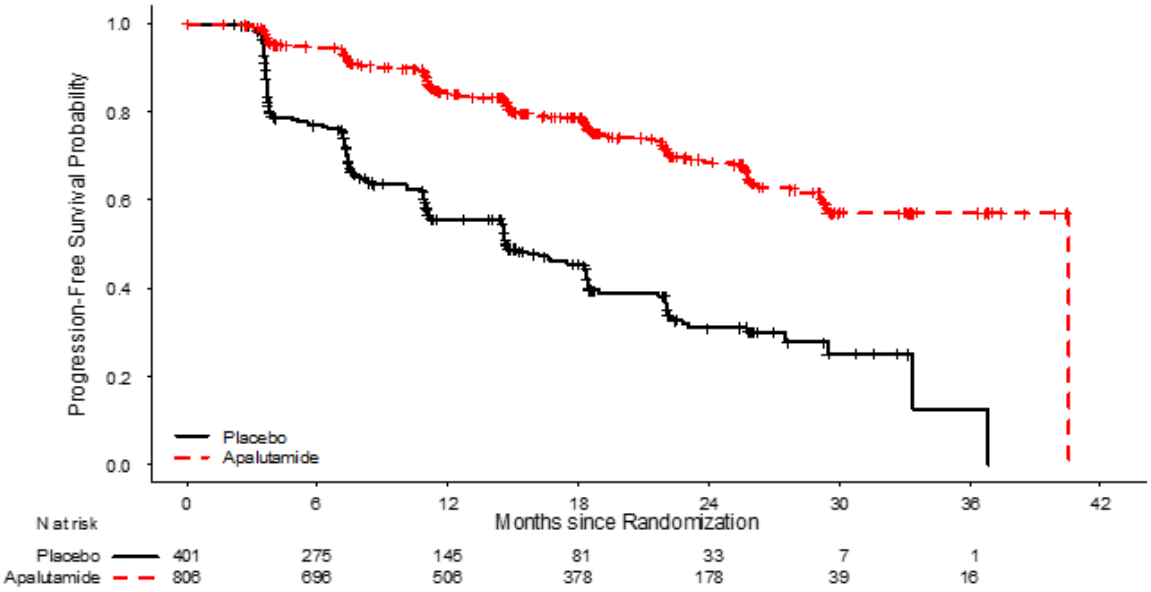
Progression-free survival is defined as the time from randomization to first BICR-confirmed radiographic progressive disease (distant or locoregional) or death due to any cause. As of the clinical cutoff date (05/19/2017), 200 patients (25%) in the apalutamide arm and 204 patients (51%) in the placebo arm were reported with BICR-confirmed disease progression or death. There was no interim analysis planned for PFS, and this was pre-specified as the final analysis. According to the hierarchical testing procedure, the alpha level of PFS was 0.05 (2-sided). A statistically significant improvement in PFS was demonstrated comparing patients randomized to receive apalutamide versus patients randomized to receive placebo, with a hazard ratio of 0.29 (95% CI: 0.24, 0.36). Results are summarized in **Table 26** and the Kaplan-Meier plot is provided in **Figure 7**.

Table 26. Analysis of Progression-Free Survival per BICR Assessment, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Number of events	200 (24.8%)	204 (50.9%)
Median (95% CI), in months	40.51 (NE, NE)	14.72 (14.49, 18.37)
HR (95% CI)	0.29 (0.24, 0.36)	
P-value	<0.0001	
HR was from a Cox proportional hazards model stratified by PSA doubling time, bone-sparing agent use, and		

locoregional disease.
P-value was from a log-rank test stratified by PSA doubling time, bone-sparing agent use, and locoregional disease.
NE=Not Estimable
Source: CSR Table 20

Figure 7. Kaplan-Meier Plot of Progression-Free Survival, SPARTAN



Source: CSR Figure 6

Reviewer's Comment: *The difference between PFS and MFS was that PFS considers locoregional disease progression as events in addition to distant disease progression. Locoregional only progression as per BICR review occurred in approximately 2% of patients in both.*

The use of MFS as a primary endpoint, by definition, does not take locoregional progression events into account. Analysis of SPARTAN revealed little discrepancy overall in apalutamide's effect on MFS and PFS, with a similar magnitude of effect seen on both endpoints. This was partially due to the fact that the overall percentage of patients with locoregional progression was low.

<u>Time to Symptomatic Progression</u>
Time to symptomatic progression is defined as the time from randomization to development of:

- a skeletal-related event (SRE)
- initiation of a new systemic anti-cancer therapy due to pain progression or worsening of disease-related symptoms
- locoregional tumor progression requiring surgery or radiation therapy

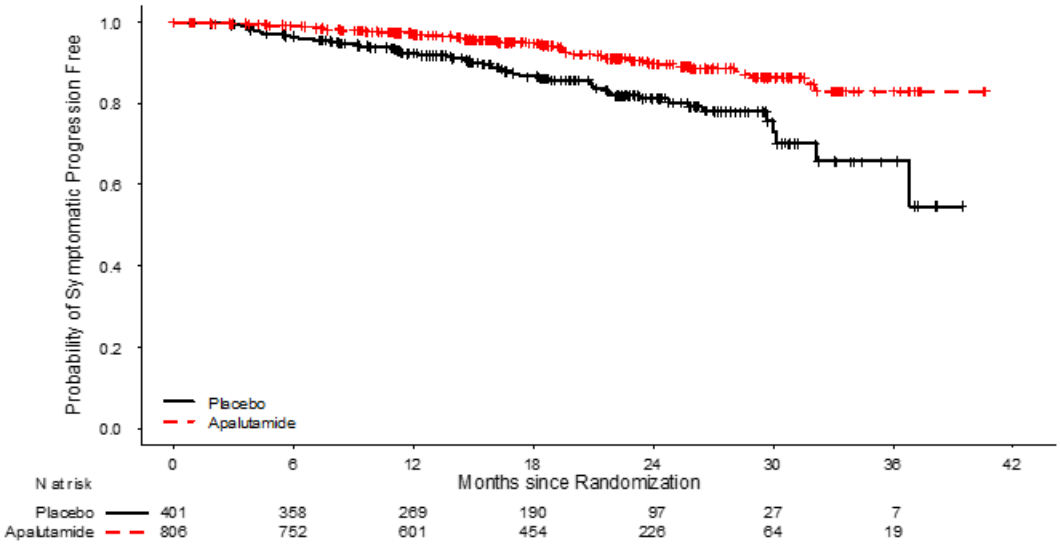
This secondary endpoint was pre-specified to be tested for significance if MFS, TTM and PFS were all statistically significant, according to the hierarchical testing plan. At the time of MFS analysis, an interim analysis of time to symptomatic progression was performed. Using the O'Brien-Fleming type alpha spending function to control the overall type I error rate, the alpha level for this interim test is 0.00008 given that 28% (119/427) of events needed for the planned final analysis were observed. At the interim analysis, a statistically significant improvement in time to symptomatic progression was observed with a p-value of 0.0000074 which has crossed the O'Brien-Fleming efficacy boundary. The results of time to symptomatic progression interim analysis are summarized in Table 27 and the Kaplan-Meier plot is provided in Figure 8.

Table 27. Interim Analysis of Time to Symptomatic Progression, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Number of events	60 (7%)	59 (15%)
Median (95% CI), in months	NE (NE, NE)	NE (36.83, NE)
HR (95% CI)	0.45 (0.31, 0.64)	
P-value	<0.0001	

HR was from a Cox proportional hazards model stratified by PSA doubling time, bone-sparing agent use, and locoregional disease.
P-value was from a log-rank test stratified by PSA doubling time, bone-sparing agent use, and locoregional disease.
NE=Not Estimable
Source: Information request response (dated as of 12/15/2017).

Figure 8. Kaplan-Meier Plot of Time to Symptomatic Progression, SPARTAN



Source: Information request response (dated as of 12/15/2017)

Reviewer's Comment: *The interim analysis p-value crossed the O'Brien-Fleming efficacy boundary and a statistically significant improvement in time to symptomatic progression of apalutamide compared to placebo was demonstrated. However, given that the number of events is small with only 28% of the events needed for the pre-specified final analysis, the estimate of effect size may not be accurate or reproducible. In addition, and importantly, this is a novel composite endpoint and its utility among providers is uncertain. For these reasons, this endpoint was not included in the table describing SPARTAN results in section 14 of the USPI.*

Time to symptomatic progression was a novel composite endpoint which used an aggregate of 3 measures, as described above in section 8.1.1. Table 28 is a description of the number of events in each category that contributed to the final number of events in the composite endpoint:

Table 28. Summary of Symptomatic Progression Type, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Total number of events	60 (7.4%)	59 (14.7%)
Development of SREs	13 (1.6%)	12 (3.0%)
Initiation of new anti-cancer therapy due to worsening pain or symptoms	19 (2.4%)	19 (4.7%)
Locoregional- tumor progression requiring surgery or radiation	12 (1.5%)	17 (4.2%)
SRE and Locoregional tumor progression	1 (<1%)	4 (<1%)
SRE and pain progression	4 (<1%)	1 (<1%)
Pain progression and locoregional tumor progression	2 (1%)	2 (<1%)
SRE, pain progression, and locoregional tumor progression	1 (<1%)	0
Other symptomatic progression[1]	8 (<1%)	4 (<1%)

[1]Specific symptomatic progression type was not recorded in the CRF but with a related intervention (surgical, radiation, or new systemic anti-cancer therapy) documented in the supplemental CRF.
Source: Response to Information Request (dated as of 12/20/2017)

Reviewer's Comment: *In a response to an Information Request, submitted on 12/20/2017 (NDA 210951 SDN 20), the applicant reviewed the data for 127 patients who were reported to have experienced an investigator-assessed symptomatic progression event, to confirm that the event met the definition of a Symptomatic Progression event. The applicant identified eight patients (four in the apalutamide arm and four in the placebo arm) who did not have the supplemental treatment data entered at the time of the clinical data cut-off. The reason for the missing data were:*

- *5 patients died prior to receiving subsequent treatment for symptomatic progression.*

- *1 patient had subsequent treatment, but was not entered at the time of the NDA submission.*
- *2 patients did not have data available.*

The Time to Symptomatic Progression analysis was performed with these eight patients censored. This analysis is shown in Table 27, Table 28, and Figure 8. Kaplan-Meier Plot of Time to Symptomatic Progression. The results from the new analysis were consistent with results from the original investigator-derived analysis as documented in the CSR with HR (95%CI) of 0.447 (0.315,0.634).

Overall Survival

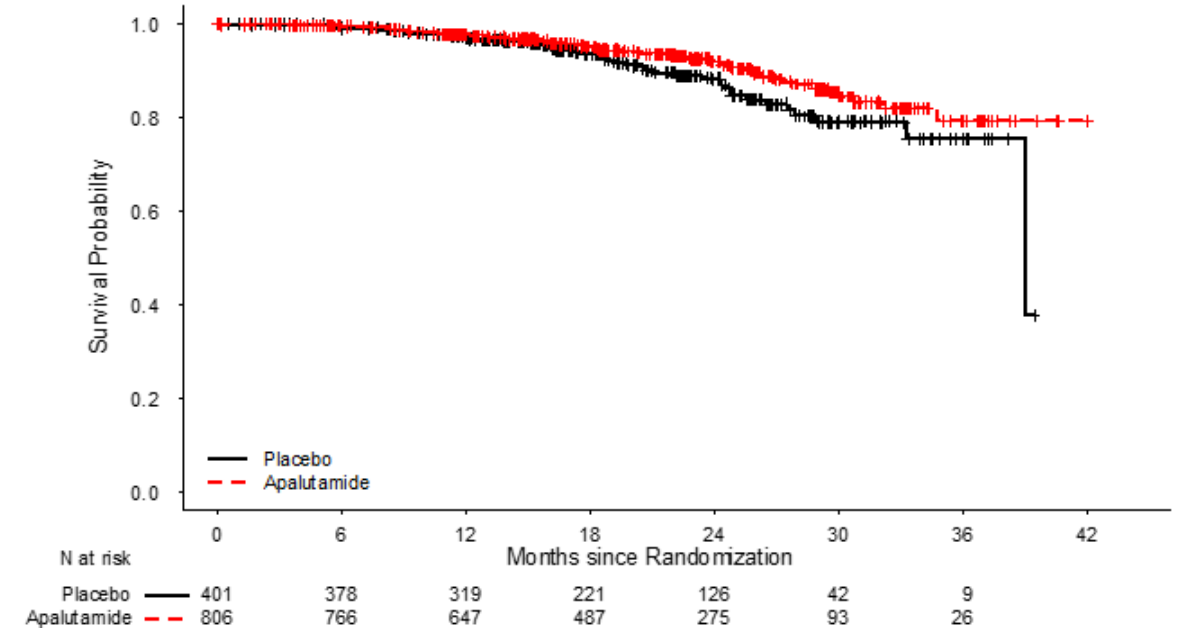
Overall survival was tested since MFS, TTM, PFS, and time to symptomatic progression were all statistically significant. Two interim analyses were planned for overall survival initially; however, per the SAP, if time to symptomatic progression was statistically significant at the interim analysis, the second interim analysis of OS would not be performed. Therefore, this OS interim analysis performed with 24% of events required for the final analysis would be the only interim analysis performed. This interim analysis of OS did not reach the pre-specified statistical significance level based on the O'Brien-Fleming efficacy boundary (i.e., p=0.000012). The results of the OS interim analysis are summarized in Table 29 and the Kaplan-Meier plot is provided in Figure 9. The median survival follow-up was approximately 20 months as of the data cutoff date.

Table 29. Results of Overall Survival Interim Analysis, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Number of events	62 (7.7%)	42 (10.5%)
Median (95% CI), in months	NE (NE, NE)	39.03 (39.03, NE)
HR (95% CI)	0.70 (0.47, 1.04)	
P-value	0.07	

HR was estimated from a Cox proportional hazards model stratified by PSA doubling time, bone-sparing agent use, and locoregional disease.
P-value was from a log-rank test stratified by PSA doubling time, bone-sparing agent use, and locoregional disease.
NE=Not Estimable
Source: CSR Table 23

Figure 9. Kaplan-Meier Plot of Overall Survival Interim Analysis, SPARTAN



Source: CSR Figure 8

> ***Reviewer's Comment:*** *OS data at the interim analysis was immature as only 24% of the events needed for the final analysis have occurred. Results from the interim analysis did not cross the pre-specified efficacy boundary; therefore, no alpha was allocated to the endpoints after OS testing per the hierarchical testing procedure. In a response to an Information Request (NDA 210951 SDN 22), the applicant projects the final analysis to occur in 2022 with a final clinical study report available December 2022. For section 14 of the USPI, the results of the interim analysis for OS were not included. A statement was included that commented on the immaturity of the OS data at the time of MFS analysis.*

Time to Initiation of Cytotoxic Chemotherapy

Time to initiation of cytotoxic chemotherapy is defined as the time from randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer. Per the SAP, a formal statistical assessment of the time to initiation of cytotoxic chemotherapy was to be performed if MFS, TTM, PFS, time to symptomatic progression, and OS were all statistically significant. As the interim OS analysis did not cross the efficacy boundary, no inference could be made for the analysis of time to initiation of cytotoxic chemotherapy. The descriptive results of time to initiation of cytotoxic chemotherapy analysis are summarized in **Table 30**.

The types of subsequent cytotoxic chemotherapy were also reviewed. The majority of patients (46 patients in the apalutamide arm and 40 patients in the placebo arm) received docetaxel as subsequent chemotherapy (**Table 31**).

Table 30. Results of Time to Initiation of Cytotoxic Chemotherapy, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Number of events	46 (5.7%)	44 (11.0%)
Median (95% CI), in months	NE	NE
HR (95% CI)	0.44 (0.29, 0.66)	
HR was from a Cox proportional hazards model stratified by PSA doubling time, bone-sparing agent use, and locoregional disease. NE=Not Estimable *Source: CSR Table TEFPC16*		

Table 31. Subsequent Cytotoxic Chemotherapy, ITT Population, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Docetaxel	46 (6)	40 (10)
Cabazitaxel	4 (0.5)	7 (1.7)
Cyclophosphamide	1 (0.1)	1 (0.2)
Estramustine	0 (0)	1 (0.2)
Source: adsubtx.xpt		

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient reported outcomes were assessed for the SPARTAN study using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) and the EuroQoL (EQ-5D-3L) questionnaires. These data were reviewed and were not considered part of the efficacy analysis but were considered as important data for the review of safety and tolerability. This review is located in Section 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability and Appendix 19.5.

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses of MFS per BICR assessment by formulation

During the conduct of the study, the treatment formulation was switched from capsule to tablet (protocol amendment 6). Newly enrolled patients began treatment using tablets while patients already enrolled and receiving soft-gel capsules made the switch to tablets at the start of a new cycle. Exploratory analyses were performed by formulations received. Two sets of subgroups were used:
Set 1:

- Patients who received capsule only
- Patients who received both capsule and tablet
- Patients who received tablet only

Set 2:

- Patients who had a greater (≥1 days) capsule treatment duration
- Patients who had a greater (≥1 days) tablet treatment duration

The exploratory subgroup analysis results are summarized in Table 32.

Table 32. Subgroup MFS-BICR Analyses per Formulation, SPARTAN

	Number of Events/Total N (%)		Median (months)		HR[1] (95% CI)
	Apalutamide + ADT	Placebo + ADT	Apalutamide + ADT	Placebo + ADT	
Formulation Set 1					
Capsule only	44/100 (44)	70/105 (67)	14.78	6.44	0.30 (0.20, 0.45)
Capsule + Tablet	98/411 (24)	78/157 (50)	40.51	22.05	0.32 (0.24, 0.43)
Tablet only	42/292 (14)	46/136 (34)	19.55	18.50	0.33 (0.22, 0.51)
Formulation Set 2					
Greater capsule treatment duration	85/169 (50)	106/155 (68)	18.43	7.75	0.39 (0.29, 0.53)
Greater tablet treatment duration	99/634 (16)	88/243 (36)	NE	22.28	0.30 (0.23, 0.41)

[1] HR is estimated from an unstratified Cox proportional hazards model
Source: CSR Table 28

***Reviewer's Comment**: The subgroup analyses are considered exploratory or hypothesis generating, and no formal inference may be drawn. No apparent outliers were observed from the subgroup analyses.*

Progression-free Survival During First Subsequent Therapy (PFS2)

PFS2 was defined as the time from randomization to investigator-assessed disease progression (PSA, radiographic, symptomatic, or any combination) during the first subsequent therapy or death prior to start of the second subsequent anti-cancer therapy, whichever occurred first. There was no alpha allocated to the analysis of PFS2. The descriptive results of PFS2 analysis are summarized in Table 33 . A summary of the first subsequent therapy for prostate cancer can be found in Table 34.

Table 33. Results of PFS2 per Investigator Assessment, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Number of events	91 (11.3%)	78 (19.5%)
Median (95% CI), in months	NE	39.03 (30.16, 39.03)
HR (95% CI)	0.49 (0.36, 0.66)	
HR was from a non-stratified Cox proportional hazards NE=Not Estimable *Source: CSR Table 30*		

Table 34. First Subsequent Therapy for Prostate Cancer, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Patients with first subsequent systemic therapy for prostate cancer	175 (21.7%)	222 (55.4%)
Hormonal	**154 (88.0%)**	**193 (86.9%)**
Abiraterone	125 (71.4%)	161 (72.5%)
Enzalutamide	20 (11.4%)	28 (12.6%)
Bicalutamide	8 (4.6%)	3 (1.4%)
Flutamide	1 (0.6%)	1 (0.5%)
Chemotherapy	**15 (8.6%)**	**19 (8.6%)**
Docetaxel	15 (8.6%)	18 (8.1%)
Cabazitaxel	0	1 (0.5%)
Other	**6 (3.4%)**	**10 (4.5%)**
Sipuleucel-T	4 (2.3%)	9 (4.1%)
Investigational Drug	1 (0.6%)	0
Radium Ra 223	1 (0.6%)	0
Dexamethasone	0	1 (0.5%)
Source: absubtx.xpt		

Reviewer's Comment: *This endpoint was incorporated into study design to attempt to gather information about whether initiating treatment with apalutamide in the non-metastatic state, with a therapy that was similar to that available if patients waited until they developed overt metastases, would have a detrimental effect on PFS in the metastatic setting. While the results of the PFS2 analysis are descriptive only, they suggest a reduction in the risk of disease progression during first subsequent therapy or death for patients who receive treatment in the non-metastatic disease state vs. waiting to initiate treatment after confirmation of metastasis in patients with CRPC.*

Time to PSA Progression

The time to PSA progression was defined as the time interval from the date of randomization to the date of PSA progression, according to PCWG2 criteria. PSA progression was documented for 192 patients (24%) in the apalutamide arm and 334 patients (83%) in the placebo arm. The median time to PSA progression was not reached for the apalutamide arm and was 3.7 months in the placebo arm. The descriptive results of time PSA progression are summarized in Table 35.

Table 35. Results of Time to PSA Progression, SPARTAN

	Apalutamide (N=806)	**Placebo (N=401)**
Number of events	192 (23.8%)	334(83.3%)
Median (95% CI), in months	NE	3.71 (3.68, 3.78)
HR (95% CI)	0.06 (0.05, 0.08)	
HR was from a Cox proportional hazards stratified by PSA doubling time, bone-sparing agent use, and locoregional disease. NE=Not Estimable *Source: CSR Table 28*		

Reviewer's Comment: *While the increase in median time to PSA progression is presented as a descriptive result only, we note the low hazard ratio above. From a clinical standpoint, this result may be very relevant to clinicians and patients alike, for whom PSA monitoring (rather than the use of regularly scheduled surveillance imaging, as was the case with SPARTAN, may be the most practical method of screening for recurrent disease in the NM-CRPC setting.*

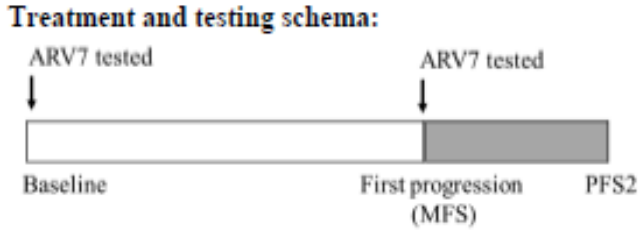
Biomarker Analysis

Exploratory biomarker analysis was performed by the applicant on blood samples collected at the time of progression to identify markers of cross resistance to subsequent therapy. Because the ARV-7 splice variant of the AR is a potential mechanism of resistance for AR directed therapies, samples were collected at the time of disease progression and tested for presence of ARV-7. We describe the applicant's own analyses of these data, as reported in a Biomarker Technical Report TR2017T-018, titled "Analysis of androgen receptor (AR) anomalies using whole blood and plasma samples from Study ARN-509-003" and appended to the SPARTAN CSR.

At the end of first study treatment, a similar percentage of patients who had disease progression and were tested for ARV-7 in both arms was found to express ARV-7, with 9/96 (9.4%) subjects in the apalutamide arm and 13/104 (12.5%) subjects in placebo arm expressing

ARV-7 at end of first treatment. This appears to demonstrate that apalutamide is not inducing ARV-7 expression. Among the subset of subjects who had a PFS2 event, 3 out of 28 (10.7%) subjects in the apalutamide arm and 6 out of 36 (16.7%) subjects in the placebo arm were ARV7 positive. In this population, duration on subsequent therapy in ARV-7 positive subjects was marginally shorter than ARV-7 negative subjects (24.9 months versus 28.5 months; Although there were not enough PFS2 events to make definitive conclusions, these data suggest ARV7 expression does not have substantial impact. Within the apalutamide arm, the estimate of median MFS and PFS2 for ARV7 positive subjects was shorter than that of ARV7 negative subjects (MFS 14.0 months vs. 18.4 months, PFS2 28.5 months vs. 19.7 respectively).
(See also section 6.3.2; Table 6)

Figure 10. Study Schema, ARV Biomarker Analysis, SPARTAN



Analysis	ARV7 status	N	Events	Median	0.95 LCL	0.95UCL
MFS	Negative	87	43	18.37	14.72	22.2
	Positive	9	5	13.96	11.10	NA
PFS2	Negative	87	25	28.5	26.2	NA
	Positive	9	3	19.7	13.2	NA

(Source: SPARTAN CSR Attachment Biomarker Analysis Report)

Integrated Review of Effectiveness

See section 8.1.4 Integrated Assessment of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

Not applicable. In NDA 210951, efficacy was assessed based on data from a single clinical trial (SPARTAN) reviewed in Sections 8.1.1 and 8.1.2.

Primary Endpoints

Not applicable. In NDA 210951, efficacy was assessed based on data from a single clinical trial (SPARTAN) reviewed in Sections 8.1.1 and 8.1.2.

Secondary and Other Endpoints

Not applicable. In NDA 210951, efficacy was assessed based on data from a single clinical trial (SPARTAN) reviewed in Sections 8.1.1 and 8.1.2.

Subpopulations

Not applicable. In NDA 210951, efficacy was assessed based on data from a single clinical trial (SPARTAN) reviewed in Sections 8.1.1 and 8.1.2.

Additional Efficacy Considerations

Not applicable. In NDA 210951, efficacy was assessed based on data from a single clinical trial (SPARTAN) reviewed in Sections 8.1.1 and 8.1.2.

8.1.4. Integrated Assessment of Effectiveness

The efficacy of apalutamide in patients with non-metastatic castration-resistant prostate cancer is supported by a single, multinational, randomized, placebo-controlled, clinical study, SPARTAN. The primary endpoint of BIRC assessed metastasis-free survival (MFS) was prolonged in patients treated with apalutamide (estimated median 40.5 months) when compared to placebo (estimated median 16 months) which is both statically significant (HR 0.28, p<0.0001) and clinically meaningful. BIRC-assessed MFS was analyzed in the following subgroups: stratification factors (PSADT, prior bone-sparing therapy, and loco-regional disease), race, age, gender, region, prior surgery of and radiation therapy. The estimated hazard ratios for these subgroups showed no evidence of a MFS detriment from apalutamide. Although these subgroup analyses are exploratory, the results are supportive.

Patients were required to have castration-resistant prostate cancer (CRPC), an PSADT <10 months by IVRS, an absence of distant metastases confirmed by BIRC. Patients with asymptomatic locoregional disease (N1) were allowed on the study.

Results based on PFS, time to metastasis, time to symptomatic progression also support the primary efficacy endpoint. Overall survival results are not mature; at the time of the clinical cutoff with 24% of deaths were reported. The final OS result for SPARTAN will be submitted when available as part of a post-marketing commitment with this NDA. Per hierarchical testing as specified in the statistical analysis plan, formal assessment of time to initiation of cytotoxic chemotherapy will occur once the other secondary endpoints have achieved statistical significance.

Patient reported outcomes were collected in SPARTAN using Functional Assessment of Cancer Therapy – Prostate (FACT-P) and the EuroQoL (EQ-5D-3L) questionnaires. The FACT-P total score were similar between the treatment arms for the first 13 cycles. Given the relative unresponsiveness of the FACT-P and EQ-5D-3L to drug or disease effects, additional exploratory

analyses were performed with individual items in the questionnaire and were also similar in both arms.

In conclusion, the efficacy of apalutamide administered with continued GnRH analogues for patient who underwent medical castration in patients with NM-CRPC is supported by the result of the primary endpoint, secondary endpoints, subgroup analyses, and sensitivity analyses.

8.2. Review of Safety

The safety of apalutamide was primarily evaluated in the SPARTAN trial. The safety population comprised 1201 men with NM-CRPC. Of these patients, 803 were treated on the apalutamide arm and 398 on the placebo arm and received at least one dose of study therapy. The primary safety population was supplemented with an additional 150 patients treated in two studies at the 240mg daily dose used in SPARTAN.

1. 56021927PCR1019 (An open-label phase 1b QT/QTc study of JNJ-56021927 [ARN-509] in subjects with castration-resistant prostate cancer) (n=45)
2. An open-label phase ½ safety, pharmacokinetic, and proof-of-concept study of ARN-509 in patients with progressive advanced castration-resistant prostate cancer
   - Cohort 1: treatment-naïve NM-CRPC (n=51)
   - Cohort 2: treatment-naïve mCRPC (n=25)
   - Cohort 3: mCRPC with prior abiraterone exposure (n=21)

Adverse events of special interest were closely evaluated due to the class effect of androgen-deprivation-mediated events in anti-androgens.

8.2.1. Safety Review Approach

The safety database included 803 patients treated with apalutamide and 398 patients treated with placebo who received at least one dose of apalutamide at least 28 days prior the NDA DCO of 5-19-2017. The applicant submitted a 120-day safety update to the NDA on 12-15-2017. The safety cutoff date for this update was 9-19-2017. Review of this update did not indicate significant changes to the safety profile of apalutamide compared to the original NDA submission, however the difference in duration of exposure to apalutamide vs placebo was larger. Unless otherwise noted, the review below uses data from the original NDA submission. Additional analysis of AESIs were performed using the 120-day safety update with DCO of 9-19-2017.

The applicant mapped and coded verbatim adverse events (AE) terms for SPARTAN using MedDRA version 19.1.

Reviewer's Comment.

1. *There were no significant discrepancies identified between the dataset and the information provided in the Clinical Study Report.*

2. *The applicant's categorization of data and coding methods were deemed appropriate.*

3. *The clinical review of safety assessed the adequacy of the applicant's mapping of AE verbatim terms to MedDRA preferred terms (PT) for 100% of the SPARTAN raw AE data set. The review used manual matching of all verbatim and MedDRA PTs to assess the acceptability of the applicant mapping from the verbatim term to MedDRA PT. The PTs listed in the dataset adequately represented the investigator-recorded term and did not raise any significant issues.*

4. *A random audit of 5% of the AE case report forms to assess the completeness and verify the accuracy of the raw AE datasets did not raise any significant issues.*

5. *To review the AE datasets, the following terms were pooled:*

Table 36. Pooled Terms

Pooled term	Preferred Terms
Diarrhea	Colitis Diarrhea Frequent bowel movements Colitis microscopic Gastroenteritis Enteritis Enterocolitis
Decreased appetite	Appetite disorder Decreased appetite Early satiety Hypophagia
Hematuria	Haematuria Blood urine present Urinary bladder hemorrhage Cystitis hemorrhagic
Fracture	Rib fracture Lumbar vertebral fracture Spinal compression fracture

	Spinal fracture Facial bones fracture Foot fracture Upper limb fracture Femur fracture Hip fracture Humerus fracture Pubis fracture Thoracic vertebral fracture Costal cartilage fracture Fractured sacrum Hand fracture Acetabulum fracture Ankle fracture Avulsion fracture Compression fracture Lower limb fracture Sternal fracture Wrist fracture Cervical vertebral fracture Fibula fracture Fractured coccyx Pelvic fracture Stress fracture Radius fracture Tibia fracture Traumatic fracture Femoral neck fracture
Syncope	Syncope Presyncope Loss of consciousness
General physical health deterioration	General physical health deterioration Failure to thrive Performance status decreased
Dyspnea	Dyspnea Dyspnea exertional
Abdominal pain	Abdominal pain Abdominal pain upper Abdominal pain lower Flank pain
Fatigue	Asthenia Fatigue Lethargy

	Malaise Sluggishness
Peripheral edema	Oedema Oedema peripheral Localised oedema Lymphoedema Peripheral swelling Scrotal oedema Scrotal swelling
Urinary tract infection	Cystitis Kidney infection Pyelonephritis Urinary tract infection Urinary tract infection bacterial Urinary tract infection pseudomonal Urosepsis
Pyrexia	Pyrexia Tumor-associated fever
Acute kidney injury	Blood creatinine increased Renal failure Glomerular filtration rate decreased Acute kidney injury
Decreased appetite	Decreased appetite Hypophagia
Constipation	Constipation Faecaloma
Anemia	Anaemia Haemoglobin decreased Anaemia of chronic disease
Musculoskeletal pain	Back pain Neck pain Musculoskeletal pain Musculoskeletal discomfort Myalgia Musculoskeletal chest pain
Confusional state	Confusional state Metabolic encephalopathy Mental status changes Delirium
Hypothyroidism	Hypothyroidism Thyroxine decreased Thyroiditis subacute Thyroiditis chronic

Rash	Rash Rash maculopapular Rash generalised Rash macular Rash papular Dermatitis acneiform Dermatitis Psoriasis Dermatitis allergic Rash pruritic Rash papular Rash pustular Skin toxicity Eczema Eczema asteatotic Drug eruption Palmar-plantar erythrodysaesthesia syndrome Dyshidrotic eczema Hand dermatitis Erythema Erythema multiforme Rash erythematous Rosacea Polymorphic light eruption Eczema nummular Parapsoriasis Rash vesicular Acne Lichen planus
Liver injury	Autoimmune hepatitis Hepatic failure Hepatic function abnormal Hepatocellular injury Hyperbilirubinemia Alanine aminotransferase elevated Aspartate aminotransferase elevated Transaminases increased Blood bilirubin increased GGT increased
Cough	Cough Productive cough
Pneumonia	Pneumonia Lower respiratory tract infection

	Lung infection
Intestinal obstruction	Small intestinal obstruction Intestinal obstruction Ileus Subileus Large intestinal obstruction
Urinary obstruction	Ureteric obstruction Hydroureter Obstructive uropathy Bladder outlet obstruction Urinary tract obstruction
Venous thromboembolism	Pulmonary embolism Pelvic vein thrombosis Deep vein thrombosis Embolism
Ischemic heart disease	Angina pectoris Coronary artery disease Myocardial infarction Acute myocardial infarction Angina unstable Arteriosclerosis coronary artery Myocardial ischemia Acute coronary syndrome Coronary artery occlusion Silent myocardial infarction Stress cardiomyopathy
Heart Failure	Cardiac failure congestive Cardiac failure Pulmonary edema Cardiac failure chronic Cardiomegaly Orthopnea Right ventricular dysfunction Cardiac failure acute Nocturnal dyspnea
Source ADAE.xpt	

8.2.2. Review of the Safety Database

Overall Exposure is shown in **Table 37**.

Reference ID: 4221387

Table 37. Overall Exposure

Clinical Trial Arm	Apalutamide (N=803)	Placebo (N=398)
Treatment duration (months)		
Mean (SD)	17.3 (9.5)	12.4 (8.0)
Median (Min, Max)	16.9 (0.1-42.0)	11.2 (0.1-37.1)
Treatment duration (%)		
≥12 months	563 (70%)	178 (45%)
≥24 months	206 (26%)	44 (11%)
≥36 months	21 (3%)	1 (0.3%)
Dose Interruptions/Delays/Reductions		
Any delay	629 (78%)	272 (68%)
Delay due to AE	270 (34%)	77 (19%)
Dose reduction	168 (21%)	49 (15%)
Source ADAE.xpt, ADEXSUM.xpt		

At the time of the database lock for safety, 61% of patients on the apalutamide arm and 30% of patients on the placebo arm were continuing with study treatment. As of the 120-day safety update, the median treatment duration for apalutamide and placebo were 20.2 and 11.5 months respectively, an increase of 3.2 months for apalutamide and 0.3 months for placebo.

> ***Reviewer's Comment.*** *Overall, the size of the safety population and the extent of exposure were adequate and generally allowed sufficient characterization of AEs associated with apalutamide in the target population.*

Relevant characteristics of the safety population:

The safety (n=1201) and efficacy populations (n=1207) were similar. Refer to Section 6.1.2 for additional details regarding the efficacy population. Of note, the trial enrolled a large proportion of geriatric patients (26% were ≥ 80 years). The trial population was largely composed of Caucasian (66%) and Asian (12%) patients.

The trial excluded patients with a history of seizure or conditions that may predispose to seizure, including prior stroke within one year of randomization, brain arteriovenous malformation, other benign CNS or meningeal diseases, and ongoing use of medications known to lower the seizure threshold or induce seizure. Patients with clinically significant cardiovascular disease, including those with myocardial infarction or severe/unstable angina within six months of randomization were excluded. Patients receiving bone-targeted agents (e.g., zolendronate or denosumab) for prevention of skeletal-related events were excluded, although patients receiving these medications at the dose and schedule indicated for bone loss prevention in the setting of osteoporosis were included.

Reviewer's Comment: *The safety database was adequate to represent the expected target population of U.S. patients with NM-CRPC. Of note, as discussed above, this trial did not include those with a history of seizure or who were at risk for seizure, those with a significant history of cardiovascular disease, or those receiving bone-targeting agents at doses and schedules indicated for prevention of skeletal-related events from solid tumors. The trial did not enroll large numbers of non-Caucasian and non-Asian patients. Thus, the safety results may not extend to these populations.*

Adequacy of the safety database:

The size of the safety database and duration of apalutamide exposure were sufficient to characterize the safety of apalutamide for treatment of a serious and life-threatening condition. Of note, two additional large randomized trials of apalutamide in metastatic hormone-sensitive prostate cancer (NCT02489318) and in combination with abiraterone for chemotherapy-naïve metastatic CRPC (NCT02257736) are ongoing and are expected to provide additional data to characterize the safety profile of apalutamide.

Demographics and disease characteristics of the study subjects were adequately representative of the target population of patients with NM-CRPC. The safety database is not yet adequate to evaluate the safety of apalutamide in patients with risk factors for seizure or with a history of significant cardiovascular disease.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Office of Scientific Investigations inspected three clinical sites as well as the applicant. There were no major issues identified at any of the sites. There were no issues regarding submission quality.

Categorization of Adverse Events

Safety and tolerability assessment was based on the frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, select AEs, clinical laboratory assessments (hematology, serum chemistry, and liver and thyroid function tests), and vital sign measurements. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. The MedDRA preferred terms (PT) and the corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding using random audit. Comparison of the applicant's MedDRA PTs to the verbatim terms did not show significant discrepancies. Adverse events and laboratory values were graded for severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

The applicant identified adverse events of special interest (AESIs) based on prior experience with the related compound, enzalutamide, as well as adverse events noted during the earlier phase trials of apalutamide. These events, which included rash, hypothyroidism, falls, fractures, and seizure and the pooled terms used to identify them, were pre-specified in the SAP. Additional detail regarding the assessment of the AESI of rash was requested in the eCRF. See section 8.5 for more details regarding these events.

Safety data was available only for the 28-day post-discontinuation time point.

> ***Reviewer's Comment****: The applicant's definition of AEs of special interest were pre-defined. Other events considered related to androgen deprivation therapy, such as osteopenia/osteoporosis, sarcopenia, new-onset diabetes mellitus, coronary artery disease, and cognitive impairment were not pre-specified, but were analyzed post-hoc. See section 8.1 for terms that were pooled for this review.*

Routine Clinical Test

In SPARTAN, the following assessments were planned starting on Cycle 1 Day 1 and continued on Day 1 of every cycle through Cycle 6, then on Day 1 of every other Cycle until Cycle 14, then on Day 1 of every 4 cycles, unless otherwise specified:

- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also amount of supplemental oxygen if applicable)
- AEs continuously throughout the study.
- Physical examination and physical measurements including weight, and ECOG performance status.
- CBCs with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count.
- Serum chemistry tests (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose and LDH).
- Fasting lipid profile (every 16 weeks).
- Testosterone (every 16 weeks).
- PSA.
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin.
- Coagulation panel.
- Thyroid function testing including TSH with reflex total T3, free T3 and total T4 (every 16 weeks).
- Radiographic disease assessments at 16-week intervals
- FACT-P and EQ-5D questionnaires

All visits had to occur within 2 days of the schedule date. All AEs were collected until 28 days following the last administration of study treatment or until study discontinuation/termination or until initiation of subsequent anti-cancer therapy, whichever occurred first. Patients who discontinued apalutamide were followed in clinic every four months until death, loss of follow-up, or withdrawal of consent, which came first. After this period, investigators reported any death, serious adverse event, or any other adverse event of concern that considered related to prior study treatment.

> ***Reviewer Comments:*** *Routine clinical testing of patients enrolled in the trial, including efforts to elicit adverse event data by monitoring laboratory tests, and vital signs appear to have been adequate. Patients were followed closely for AEs for 28 days, which is likely sufficient to determine late-onset AEs.*

8.2.4. Safety Results

Table 38 presents the overview of safety in SPARTAN.

Table 38. Overview of Safety, SPARTAN

Total number of patients with at least one:	Apalutamide (n = 803) n (%)	Placebo (n = 398) n (%)
Grade 5 AE	10 (1.2%)	1 (0.3%)
Grade 3-4 AE	362 (45%)	136 (34%)
SAE	199 (25%)	92 (23%)
AE leading to treatment discontinuation	85 (11%)	28 (7%)
Source: ADAE dataset		

> ***Reviewer's Comment.*** *There were 20 subjects treated with the drug in the controlled trials who reported a serious adverse event of myocardial infarction. I reviewed all of these narratives and determined that 19 of these subjects did in fact have a myocardial infarction. The remaining subject, who was assigned to drug, appears to have had a pulmonary embolism, not a myocardial infarction. The narrative for that subject is summarized below…*

A 67-year-old man with hypertension and diabetes presented to the hospital with typical symptoms and signs of acute myocardial infarction. The diagnosis was confirmed by serial electrocardiograms and enzyme changes. He underwent coronary stent implantation, had an uncomplicated course, and was discharged.

Reviewer's Comment. *Myocardial infarction is typical in this patient population. Nothing about the case was unusual, and there were no factors suggesting a causal link to the study drug.*

Deaths

Table 39 summarizes total deaths in the safety population of SPARTAN. Listed deaths include deaths during treatment and occurring up to 28 days of the last dose of study drugs as of the database lock date (May 17, 2017). Patient narratives were reviewed for attribution of death to either disease progression or toxicity. Thus, while 10 patients were assessed by the investigator as experiencing Grade 5 adverse events, these included two patients in which the cause of death was assessed by the reviewer as due to disease progression. The reviewer considered eight patients to have experienced death that was reasonably likely to be due to study drug toxicity.

Table 39. Deaths on Study, SPARTAN

	Apalutamide (N = 803) n (%)	**Placebo**
Total deaths	62 (8%)	42 (11%)
Deaths within 28 days of last dose	10 (1.2%)	1 (0.3%)
Death attributed to disease progression	2 (0.2%)	0
Death attributed to other/unknown/toxicity	8 (1.0%)	1 (0.3%)
Source: ADAE dataset		

The applicant considered 10 patients to have TEAEs with an outcome of death. On FDA review, eight of these patients were considered to have died due to apalutamide-related toxicity. These patients died from infection (4), myocardial infarction (3), and cerebral hemorrhage (1), and are discussed in Table 40.

Table 40. Brief Summaries of Related Deaths, SPARTAN

	Adverse event	**Brief case description**	**Days from last dose to death**
Apalutamide-related toxic death	**Myocardial infarction** Patient 2605-027 *Reviewer note: Coronary*	An 83-year-old man with no prior cardiac history experienced a Grade 5 myocardial infarction on Day	**0**

	artery disease and myocardial infarction are known toxicities related to ADT.	323.	
	Myocardial infarction Patient 3107-006 *Reviewer note: Coronary artery disease and myocardial infarction are known toxicities related to ADT.*	An 86-year-old man with prior myocardial infarctions experienced a Grade 5 myocardial infarction on Day 101.	**2**
	Myocardial infarction Patient 3584-012 *Reviewer note: Coronary artery disease and myocardial infarction are known toxicities related to ADT.*	An 82-year-old man with prior transient ischemic attack, coronary artery disease, atrial fibrillation, hypercholesterolemia, and chronic obstructive pulmonary disease was found in cardiac arrest on Day 183. He was suspected to have experienced a myocardial infarction. He was declared dead in the emergency room.	**0**
	Sepsis Patient 3117-009 *Reviewer note: Infection is not a known toxicity related to ADT. The etiology of the patient's intestinal obstruction leading to sepsis is unclear, however occurred while on apalutamide therapy.*	An 84-year-old man with no relevant medical history experienced Grade 4 intestinal obstruction on Day 258 and was hospitalized. He was treated with fluids and antibiotics. He died from sepsis on Day 264.	**6**
	Sepsis Patient 3562-011 *Reviewer note: Infection*	A 78-year-old man with no relevant past medical history experienced disease progression Day 219. On Day	**25**

	is not a known toxicity related to ADT. Although this patient experienced disease progression prior to death, disease progression in the setting of NM-CRPC is not expected to lead to rapid organ dysfunction. Thus, given the proximity of sepsis to apalutamide exposure, a causal relationship is plausible.	255, he experienced Grade 4 sepsis and was treated with antibiotics. He died on Day 256.	
	Sepsis Patient 3121-003 *Reviewer note: Infection is not a known toxicity related to ADT. In this case, skin infection, which lead to hospitalization and sepsis, may be related to the known dermatologic toxicity of apalutamide.*	An 86-year-old man with no relevant medical history experienced Grade 2 xerosis on Day 73, Grade 2 eczema on Day 112. He experienced skin infection on Day 229 and was hospitalized in the setting of renal insufficiency thought related to dehydration. He was discharged on Day 248, however was re-admitted to the hospital on Day 250 with nosocomial pneumonia and died from sepsis on Day 253.	**26**
	Sepsis Patient 3400-011 *Reviewer note: Infection is not a known toxicity related to ADT. It is unclear whether the patient's functional decline prior to experiencing urosepsis may have been related to apalutamide.*	A 77-year-old man with no significant medical history experienced Grade 3 urosepsis on Day 766 in the setting of declining functional status. He was treated with antibiotics, however experienced gradual worsening of his respiratory status. He died from sepsis on Day 796.	**5**
	Cerebral hemorrhage Patient 3531-014	An 80-year-old man with prior pulmonary embolisms and deep	**2**

	Reviewer note: Apalutamide is a weak CYP2C9 inducer, which may result in reduced exposure to warfarin. Falls are increased on apalutamide. It is unknown whether the patient may have experienced a fall prior to cerebral hemorrhage.	vein thrombosis on warfarin anticoagulation therapy presented to the emergency department with a massive cortical hemorrhage on Day 387. He died on Day 388.	
Source: Patient Narratives			

Serious Adverse Events

Non-fatal serious adverse events (SAEs) occurred in 25% of patients on the apalutamide arm and 23% of patients on placebo. Refer to Table 36 for pooled terms. The most frequent SAEs (>2%) of patients were fracture and hematuria. Additionally, pneumonia (1.2% vs 0.5%) and sepsis (1.1% vs 0%) occurred at an incidence >0.5% greater on the apalutamide than the placebo arm. Table 41 summarizes these common SAEs.

Table 41. Serious Adverse Events, SPARTAN

Pooled term	**Apalutamide (n = 803) n (%)**	**Placebo (n=398) n (%)**
SAEs occurring in >2% of patients		
Fracture	27 (3.4%)	3 (0.8%)
Hematuria	14 (1.7%)	9 (2.3%)
Additional SAEs occurring at >0.5% greater frequency in the apalutamide arm		
Urinary tract infection	16 (1.9%)	4 (1.0%)
Pneumonia	10 (1.2%)	2 (0.5%)
Sepsis	9 (1.1%)	0
Source: ADAE dataset		

Reviewer's Comment: *SAEs were relatively uncommon in this asymptomatic patient population. In addition to fracture, infection appeared slightly more common on the apalutamide arm. Hematuria was considered a serious adverse event, but not a serious*

adverse reaction due to a higher incidence on the placebo arm. Additionally, in this clinical context, it is most likely to be due to progression of disease rather than drug toxicity.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 42 below provides information on the 90 (11%) patients on the apalutamide arm and 29 (7%) patients on the placebo arm who permanently discontinued due to adverse events. This includes five patients on the apalutamide arm and one patient on the placebo arm listed as either withdrawal of consent or discontinuation due to patient request who, on review, had actually experienced a discontinuation due to a drug-related adverse event. Overall, in the safety population who had received at least one dose of study drug, 113 patients on the apalutamide arm and 83 patients on the placebo arm discontinued treatment due to withdrawal of consent or other reasons including investigator decision.

Table 42. Adverse Events Resulting in Permanent Discontinuation in >0.5%

	Apalutamide (n = 803) n (%)	**Placebo (n=398) n (%)**
Any Adverse Event Leading to Permanent Discontinuation	90 (11%)	29 (7%)
Rash	21 (2.6%)	0
Fatigue	8 (1.0%)	1 (0.3%)
Decreased appetite/weight decreased	6 (0.7%)	0
Source ADAE dataset		

Reviewer's Comment: *Discontinuation due to adverse event was uncommon with apalutamide and minimally more common than in the placebo arm despite longer duration of exposure. Of note, the most common reasons for discontinuation in the placebo arm were related to disease progression, including hydronephrosis and urinary retention.*

Significant Adverse Events

Adverse events of special interest (AESIs) in SPARTAN were defined as events of scientific and medical interest specific to the apalutamide safety profile and may be serious or non-serious. These included adverse events observed with enzalutamide and in earlier phase trials of apalutamide

1. Rash

2. Seizure
3. Hypothyroidism
4. Falls
5. Fractures

Overall, 338 (42%) patients on the apalutamide arm and 72 (18%) patients on the placebo arm experienced an AESI. Seventy-one (9%) of patients on the apalutamide arm and 5 (1.3%) of patients on the placebo arm experienced a Grade 3 AESI. There were no reported Grade 4 AESIs on either arm. The most common AESI was rash, experienced by 191 (24%) patients on the apalutamide arm and 22 (6%) patients on the placebo arm. See Section 8.4.5 for discussion of severe (Grade 3-4) adverse events and Section 8.5 for further discussion of adverse events by system.

Treatment Emergent Adverse Events and Adverse Reactions

The most common adverse events (>15% of patients) were fatigue, hypertension, rash, diarrhea, nausea, decreased weight, arthralgia, and fall. The most common Grade 3-4 adverse events (>2% of patients) were rash and fracture (Table 43). Note that adverse events based predominantly on laboratory abnormalities, including hypercholesterolemia and hypertriglyceridemia, are excluded from Table 43, but are presented in Table 44. For pooled terms, see Table 36.

Table 43. Grade 1-4 Adverse Events in ≥ 10% or Grade 3-4 Adverse Reactions in ≥ 2% of Patients in SPARTAN

	Apalutamide (n = 803) (%)		**Placebo (n = 398) (%)**	
Adverse Reaction	**Grades 1-4 (%)**	**Grades 3 – 4 (%)**	**Grades 1-4 (%)**	**Grades 3 – 4 (%)**
All Adverse Reactions	97	45	93	34
Gastrointestinal Disorders				
Diarrhea	22	1.1	16	0.7
Nausea	18	0	16	0
Constipation	11	0.1	13	0
Abdominal pain	15	0.4	18	0.5
General Disorders and Administration				
Fatigue	40	1.4	30	0.3
Peripheral edema	11	0	9	0
Metabolism and Nutrition Disorders				
Decreased appetite	12	0.1	9	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	16	0	8	0

Back pain	14	0.8	16	1.5
Vascular disorders				
Hypertension	25	14	20	12
Hot flush	14	0	9	0
Renal and urinary disorders				
Urinary retention	4.4	0.8	8	2.3
Hydronephrosis	1.9	0.9	5	2.8
Injury, poisoning, and procedural complications				
Fracture	12	2.7	7	0.8
Fall	16	1.7	9	0.8
Skin and Subcutaneous Tissue Disorders				
Rash	24	5	6	0.3

Source: ADAE dataset

Laboratory Findings

Laboratory events in the alb.xpt dataset were assessed per CTCAE v4.0 criteria with the additional criterion that a Grade 1 or greater event be aberrant compared to the patient's baseline laboratory value (Table 44). Abnormalities in hematology tests were primarily Grade 1 to 2 in severity. While all-grade anemia, lymphopenia, and leukopenia were increased on the apalutamide relative to the placebo arm, the incidence of Grade 3-4 hematology events was similar between the two arms. The most common chemistry abnormalities were hypertriglyceridemia, hypercholesterolemia, and hyperglycemia, all of which were more common in the apalutamide arm. Hepatic laboratory abnormalities were uncommon. One patient (3106-002) on the apalutamide arm met laboratory criteria for Hy's Law (maximum concomitant hepatic laboratory values: ALT 719 U/L and bilirubin 74 umol/L), however, on review, the patient had experienced disease progression with metastatic liver lesions. The most common Grade 3-4 abnormality was hyperglycemia, which occurred in 6% of patients on the apalutamide arm and 4% of patients on the placebo arm.

Table 44. Laboratory Abnormalities on SPARTAN

	Apalutamide (n = 803) (%)		**Placebo (n = 398) (%)**	
Adverse Reaction	**Grades 1-4 (%)**	**Grades 3 – 4 (%)**	**Grades 1-4 (%)**	**Grades 3 – 4 (%)**
Hematology				
Anemia	70	0.4	64	0.5
Lymphopenia	41	1.8	21	1.6
Leukopenia	47	0.3	29	0
Chemistry				
Hyperkalemia	32	1.9	22	0.5

Hypertriglyceridemia	67	1.6	49	0.8
Hypercholesterolemia	76	0.1	46	0
Hyperglycemia	70	2	59	1
Source: ADLB dataset				

Vital Signs

Based on analyses of mean value and mean change from baseline at each cycle, no clinically meaningful differences in heart rate or temperature were observed during the course of treatment with apalutamide. Elevated systolic blood pressure (>160mmHg and increase from baseline >20 mmHg) was seen in 18% of patients on the apalutamide arm and 15% of patients in the placebo arm. Elevated diastolic blood pressure (>100 mmHg and increase from baseline >10 mmHg) was seen in 5.0% of patients on the apalutamide arm and 4.5% of patients in the placebo arm.

Electrocardiograms (ECGs)

In SPARTAN, ECGs were performed at baseline and as clinically indicated. There were no significant ECG findings noted. An optional sub-study was performed to evaluate the effect of apalutamide on ventricular repolarization, however only 17 out of a planned 100 patients participated, which limited the interpretability.

QT

The QT-IRT team reviewed the data from a dedicated QT study of 42 patients (56021927PCR1019). The reviewers note a QTc interval prolongation when apalutamide was administered as 240mg QD with a largest upper bound of 16 ms observed at one hour post-dose on Cycle 3 Day 1. In an open-label phase 1b study, 45 patients were treated with apalutamide 240mg QD and the maximum upper bound of ΔQTcF was 19.0 ms for apalutamide and 16.2 ms for JNJ-56142060, the active metabolite. An exposure-QT analysis suggested a concentration-dependent increase in QTcF.

Reviewer Comment: *The QTc interval results will be summarized in section 12 of the label. Given that no clinical findings were seen, including no concerning increase in sudden deaths in the treatment arm nor was there increase in QTc >20ms the ability to make strong clinical recommendations based on these findings is not possible.*

Immunogenicity

Not Applicable

8.2.5. Analysis of Submission-Specific Safety Issues

Class effects associated with anti-androgens, including enzalutamide, are primarily related to

the effects of prolonged androgen deprivation and include fatigue, bone density loss, sarcopenia, diabetes mellitus, and coronary artery disease. Seizure was also observed in clinical trials of enzalutamide, which may be due to antagonism of the $GABA_A$ receptor, and was observed at high doses of apalutamide in Beagle dogs in toxicology studies. The applicant further identified rash, fall, fracture, and hypothyroidism as AESIs on an ad hoc basis, subsequent to the clinical study protocol but prior to the database lock.

Rash

Rash (see section Section 8.2 for definition of the grouped term) associated with apalutamide occurred commonly in SPARTAN. Overall, 24% of patients treated with apalutamide experienced rash, compared to 6% of patients treated with placebo. Grade 3 rashes occurred in 5% and 0.3% of patients treated with apalutamide and placebo respectively. There were no reports of Grade 4 rash. Among patients treated with apalutamide, the onset of rash occurred at a median of 82 days. Rash resolved in 81% of patients within a median of 60 days (range: 2-709 days). Among those with skin rash, 9% of patients discontinued apalutamide due to rash, while 28% required dose interruption and 12% required dose reduction. Seventeen percent of patients on apalutamide with rash were treated with topical corticosteroids, 35% with anti-histamines, and 12% with systemic corticosteroids. Fifty-three patients restarted apalutamide after a dose interruption due to rash; twenty-nine (55%) of these patients experienced recurrent rash, including 16/22 (73%) who were rechallenged at a lower dose. No patient who was rechallenged experienced a Grade 3-4 rash.

> ***Reviewer's Comment****: Rash was common among patients treated with apalutamide and was the most common reason for treatment discontinuation due to an adverse event. However, there were relatively few high-grade events and these could be adequately managed with treatment interruption, dose reduction, and supportive medications.*

Seizure

Two patients (0.2%) on SPARTAN experienced seizure on apalutamide while no patients on placebo experienced seizure. One patient (3566-004) was diagnosed with Parkinson's disease while on study and experienced a Grade 3 fall with head trauma on Day 354 with resultant scalp hematoma. A CT did not demonstrate evidence of intracranial hemorrhage. He had a witnessed tonic-clonic seizure (Grade 2) while in the emergency department. He was treated with anti-epileptics. Apalutamide was discontinued. No subsequent seizure was reported. A second patient (1313-002) was reported by his wife to have jerking motions while sleep on Day 475. MRI and EEG were normal. He was not treated, however apalutamide was discontinued on Day 482. He subsequently experienced a Grade 2 seizure approximately 45 days later and was started on anti-epileptics. Other preferred terms potentially associated with seizure were reviewed, including syncope or loss of consciousness leading to hospitalization, coma, epilepsy, convulsion, and myoclonus. No additional likely cases of seizure were identified. There were no cases of seizure identified in patients treated with apalutamide in the earlier phase trials.

Reference ID: 4221387

Reviewer's Comment: *Seizure occurred in 0.2% of patients treated with apalutamide on SPARTAN. In one case, seizure appears to have been induced by head trauma, while in the other a second seizure occurred over five half-lives after discontinuation of apalutamide, suggesting that it is unlikely that apalutamide was the causative factor. Nevertheless, a contribution from apalutamide cannot be ruled out in either case.*

Hypothyroidism

Thyroid-stimulating hormone (TSH) was assessed every 4 months on SPARTAN. Hypothyroidism, occurred in 8% of patients treated with apalutamide compared to 2% of patients treated with placebo, while elevated TSH occurred in 25% and 7% of patients treated with apalutamide and placebo respectively. There were no Grade 3-4 events. The median onset on the apalutamide arm was Day 113. Thyroid replacement therapy was initiated in 7% of patients treated with apalutamide. One patient required dose reduction and no patients discontinued therapy for hypothyroidism. Of the 50 patients treated with apalutamide who experienced an event of hypothyroidism, hypothyroidism was reported as resolved in 15 (30%) patients while an additional seven (14%) patients were reported to have resolving hypothyroidism.

Reviewer's Comment: *Hypothyroidism was reported in 8% of patients treated with apalutamide and occurred after a median of 3.5 months. The mechanism for the toxicity is unclear. The duration of hypothyroidism is unclear, however fewer than half of patients were reported to have resolution or near-resolution of their hypothyroidism. Appropriate measurement of TSH when clinically indicated and treatment of hypothyroidism with thyroid hormone replacement therapy while on apalutamide is appropriate.*

Falls and Fractures

In SPARTAN, falls occurred in 16% of patients treated with apalutamide compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or syncope. The difference in incidence persisted after adjustment for patient-years on study. Fractures (see **Table 36** for pooled terms) were associated with falls and occurred in 12% of patients treated with apalutamide and 7% of patients treated with placebo. Grade 3-4 fractures occurred in 2.7% and 0.8% of patients treated with apalutamide and placebo respectively. After adjustment for patient-years on study, the incidence of fractures per 100 patient-years was 10.5 for apalutamide and 7.8 for placebo. The median time of onset to fracture was 314 days (range: 20-953 days) for patients treated with apalutamide. Fracture was associated with preceding weight loss in patients treated with apalutamide, but not in patients treated with placebo. Approximately 22% of patients with fracture on the apalutamide arm had weight loss of >5% compared to baseline, compared to 6% of patients with fracture on the placebo arm (**Figure**

11). Routine bone density assessment was not performed on SPARTAN and it is unknown whether weight loss may reflect bone density loss, sarcopenia, or a combination of the two, which could have contributed to increased risk for fall and fragility. Weight loss was more common on apalutamide than placebo (16% vs 6%) and appeared to be associated with dysgeusia (7% vs 1.5%); all 13 patients with both dysgeusia and decreased weight were on the apalutamide arm. See **Figure 12** for weight by cycle for each agent.

Patients receiving bone targeted agents (BTA) (e.g. denosumab or zoledronic acid) for prevention of skeletal-related events were excluded from SPARTAN, however patients receiving BTAs at doses and schedules appropriate for an indication of osteoporosis were allowed to continue those agents. There were relatively few patients on SPARTAN receiving a BTA (8% on apalutamide arm and 10% on placebo arm) and few patients who experienced a fracture while receiving a BTA (1% in each arm).

Figure 11. Histogram of Fracture Events by Patient Weight Change, SPARTAN

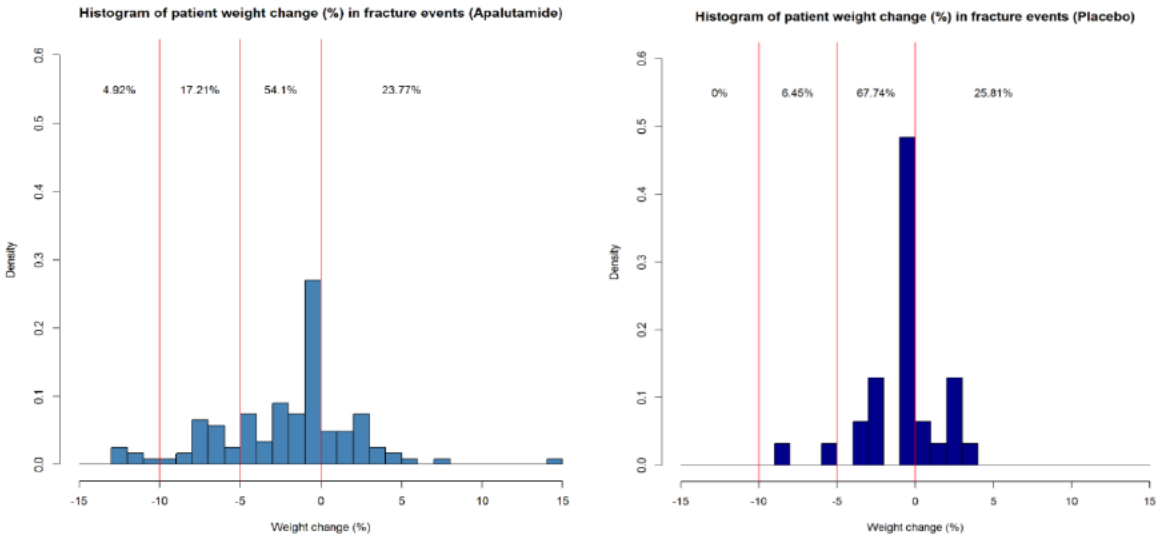
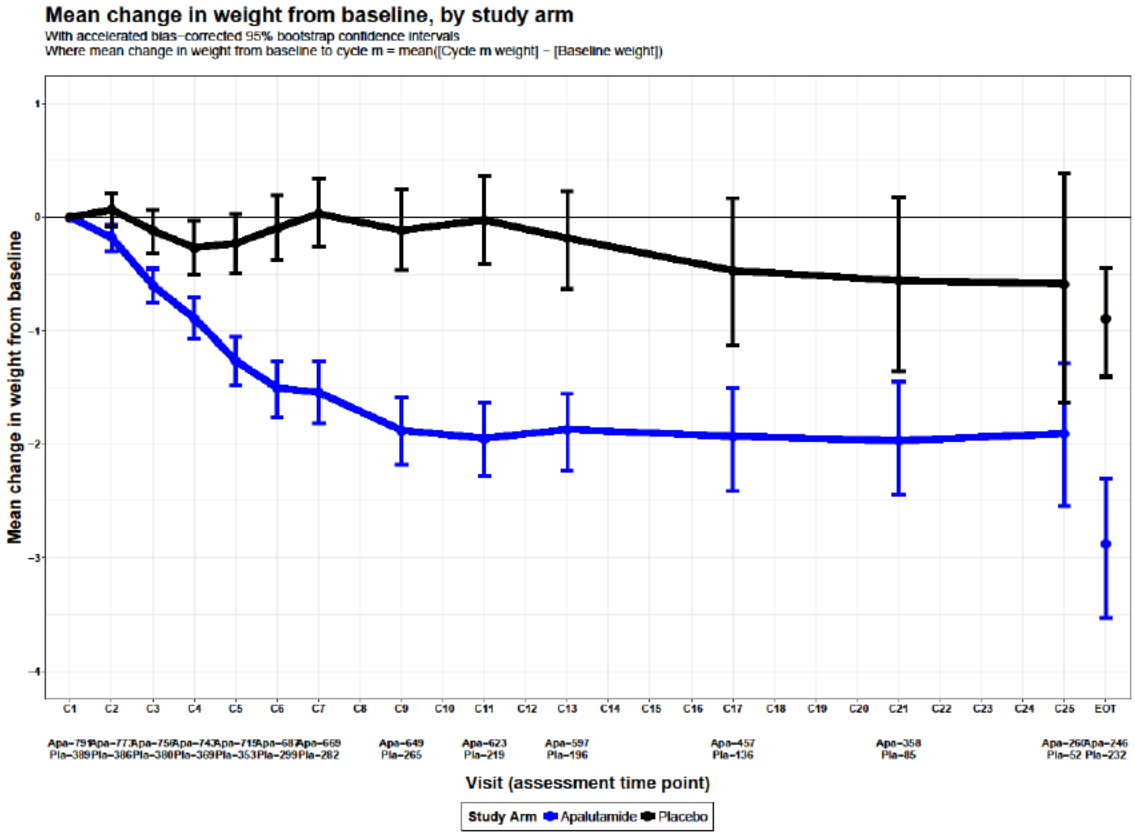


Figure 12. Change in Weight by Cycle



Reviewer's Comment: *Falls and fractures were more common in patients treated with apalutamide. Weight loss was associated with fracture. Sarcopenia and/or bone density loss may have contributed to weight loss. Possible mechanisms may include the effects of more pronounced androgen deprivation than with GnRH agonists/antagonists alone or weight loss due to dysgeusia. It is unclear whether routine assessment of bone density and treatment of osteopenia and osteoporosis or routine initiation of BTAs at doses and schedules indicated for prevention of skeletal events may be of benefit in preventing fracture. In the absence of data, the USPI suggests assessment and treatment of bone density and fracture risk per established guidelines.*

Cardiovascular Disease

Elevated risk for cardiovascular disease is a known toxicity of prolonged androgen deprivation therapy. Several risk factors for cardiovascular disease were elevated in patients on the apalutamide arm. These included hypercholesterolemia (72% all-grade and 0.1% Grade 3-4 vs 36% all-grade and 0% Grade 3-4), hypertriglyceridemia (60% all-grade and 1.6% Grade 3-4 vs 41% all-grade and 0.8% Grade 3-4), hyperglycemia (66% all-grade and 6% Grade 3-4 vs 53% all-grade and 4% Grade 3-4), and hypertension (25% all-grade and 14% Grade 3-4 vs 20% all-grade and 12% Grade 3-4). Ischemic heart disease and heart failure were reviewed as pooled terms (See Table XX for pooled terms). In SPARTAN, patients treated with apalutamide experienced a higher incidence of ischemic heart disease than those treated with placebo (3.7% vs 2.0%). This differences persisted after adjustment for duration of exposure (3.1/100 vs 2.2/100 patient-years). However, the incidence of Grade 3-5 ischemic heart disease was 1.3% in both arms. The incidence of heart failure was also higher in patients treated with apalutamide than placebo (2.2% vs 1.0%) and was higher after adjustment for exposure (1.9/100 vs 1.2/100 patient-years). The incidence of Grade 3-5 heart failure was 0.8% in the apalutamide-treated arm and 0.6% in patients treated with placebo.

Reviewer's Comment*: Severe cardiovascular events were relatively uncommon in this elderly male population with prior androgen deprivation therapy. All-grade events were slightly more common in patients treated with apalutamide compared with patients treated on placebo, however severe events were similar between the two arms.*

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

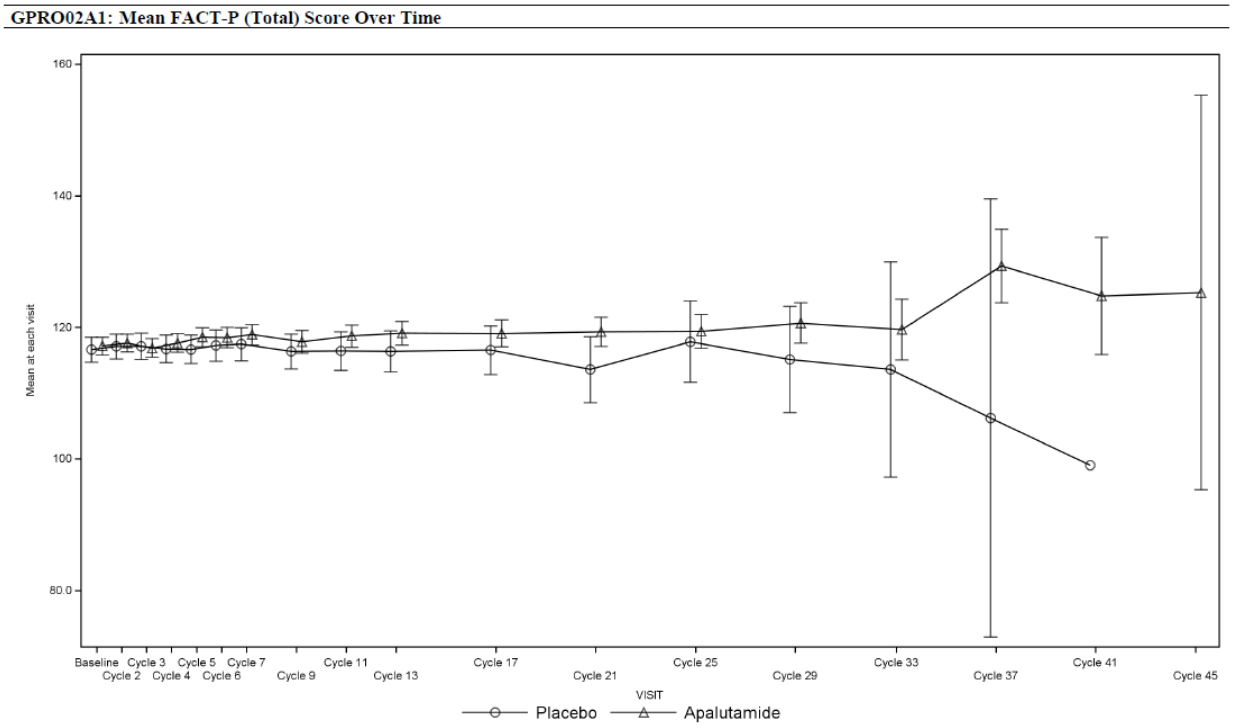
Patient-Reported Outcomes (PRO) were assessed in the SPARTAN Trial using two instruments: FACT-P and EQ-5D-3L. The FACT-G is a generic HRQoL patient-reported outcome instrument and it has four domains: physical, social/family, emotional, and functional. There are a total 27 questions in FACT-G, each of which is answered using a 5-point scale ranging from 0 (Not at all) to 4 (Very much). FACT-P adds an additional 12-item prostate cancer domain to FACT-G. The EQ-5D-3L is a two-part general instrument that captures 5 descriptors of current health status

as well as a general health status as measured by a visual analog scale. This is a generic health assessment tool that is typically used to generate a health utility index for economic analyses and has not been validated as a tool with content validity for use in estimating clinical benefit.

Responses to both instruments were to be collected at Day 1 of Cycle 1 to Cycle 6, Day 1 of every 2 cycles starting at Cycle 7 to Cycle 13, then Day 1 of every 4 cycles during the treatment phase. When the patient discontinued study treatment, PRO assessments should be performed at the end of treatment visit and then every 4 months up to 12 months post progression. The rates of completing at least one item or at least 50% of items of both instruments were greater than 90% for both treatment arms across all on treatment assessments.

Overall FACT-P total score over time was similar during the first 13 cycles (Figure 13).

Figure 13 Mean FACT-P Total Score Over Time



***Reviewer's Comments**: The various composite scores analyzed are problematic from a regulatory perspective because they combine assessments of disease symptoms and treatment side effects with global impacts such as emotional well-being that may be influenced by multiple non-drug factors. Thus, these measures may be stable rather than dynamic and poorly responsive to the effects of the drug in question. The prostate-specific domain of the FACT-P includes items that are more relevant to symptoms associated with the disease and therapy in early-stage prostate cancer, including issues with urination and sexual function, rather than the patients with castration-resistant*

disease.

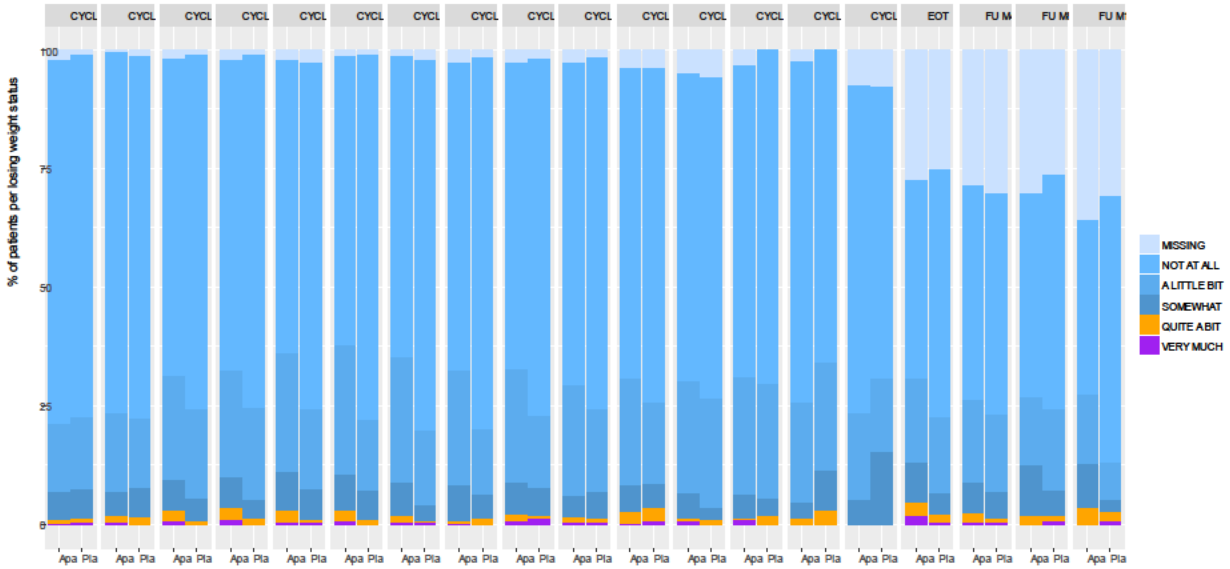
There was a high rate of instrument completion in SPARTAN, which provides an increased level of confidence in the reliability and lack of bias of the results.

Given the relative unresponsiveness of the FACT-P and EQ-5D-3L to drug or disease effects, the Agency identified several items thought potentially more responsive for further descriptive exploratory analysis. These items included the following from FACT-P:

- GP5: "I am bothered by side effects of treatment"
- GP1: "I have a lack of energy"
- GF1: "I am able to work"
- GF7: "I am content with the quality of my life right now"
- GP6: "I feel ill"
- GP7: "I am forced to spend time in bed"
- GP4: "I have pain"
- C6: "I have a good appetite"
- C2: "I am losing weight"

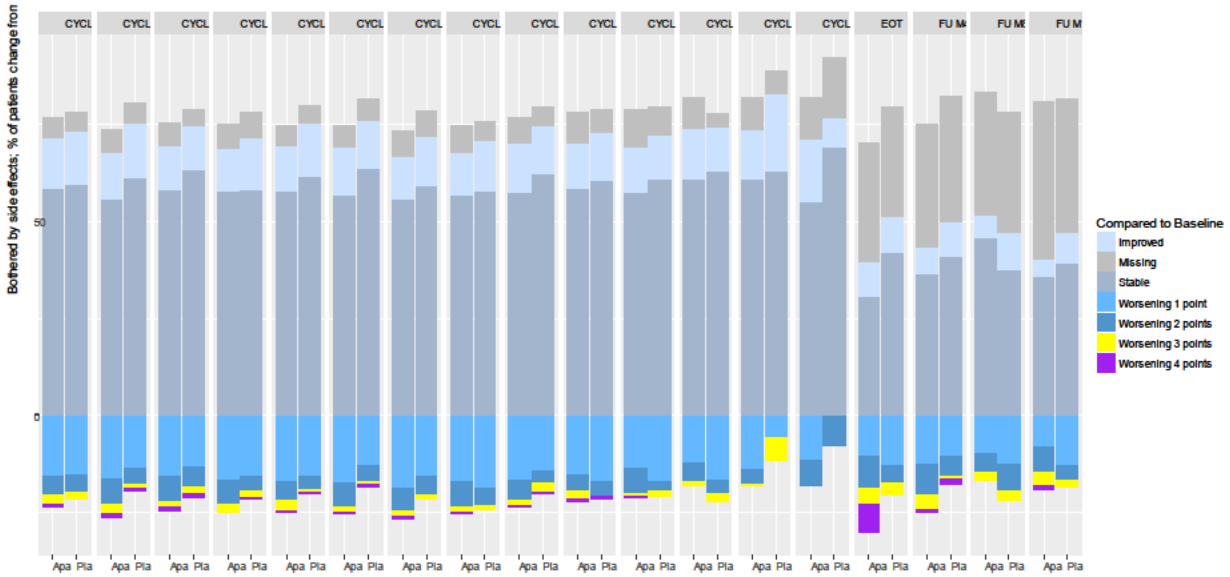
Most individual items had no notable differences in the two arms across on treatment assessments. Item C2 ("I am losing weight") did demonstrate worse outcome over the first twelve cycles (Figure 14) after which the two arms were more similar. Of note, there were not large differences in reported nausea or decrease in appetite.

Figure 14. FACT-P Item C2 "I am losing weight"



There was a small increase from baseline in item GP5 ("I am bothered by side effects of treatment") (Figure 15).

Figure 15. Distribution of Change in Response for FACT-P Item GP5 ("I am bothered by side effects of treatment) by Treatment Arm and Cycle



Reviewer's comment: *Exploratory analyses of PROs indicated that apalutamide did not appear to adversely affect functional outcomes as measured by the FACT-P and appeared well-tolerated over a long duration of therapy compared with placebo. On item level review, weight loss and a small increase in side effect bother were observed.*

8.2.7. Safety Analyses by Demographic Subgroups

Subgroup analyses of SPARTAN based on sex and race were not performed as the study population was entirely male and largely Caucasian. Subgroup analyses based on age are shown below. Of the 803 patients who received apalutamide, 87% were 65 years or older and 44% were 75 years or older. Grade 3-4 adverse events occurred in 46% of patients 65 years or older and 50% of patients 75 years or older compared to 35% (125/358) of patients 65 years or older and 38% (71/189) of patients 75 years or older treated with placebo. All common AEs appear to be similar across ages <65, 65-75, and >75 with the exception of weight decrease and fall, which were more common in the patients >75 years.

Table 45. Grade 1-4 Adverse Reactions in >15% of Patients Treated with Apalutamide by Age

	< 65 years (N = 105) (%)		65-75 years (N =341) (%)		>75 years (N = 357) (%)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
All	103 (98%)	39 (37%)	322 (94%)	145 (43%)	350 (97%)	178 (50%)

Fatigue	43 (41%)	0	135 (40%)	2 (1%)	162 (45%)	9 (3%)
Rash	24 (23%)	6 (6%)	68 (20%)	16 (5%)	97 (27%)	20 (6%)
Arthralgia	16 (15%)	0	59 (17%)	0	62 (17%)	0
Weight decreased	7 (7%)	1 (1%)	50 (15%)	2 (1%)	77 (22%)	6 (2%)
Fall	14 (13%)	2 (2%)	41 (12%)	3 (1%)	74 (21%)	9 (3%)

Source: ADAE dataset

8.2.8. Specific Safety Studies/Clinical Trials

No studies were performed to address specific safety concerns.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The applicant did not conduct carcinogenicity studies.

Human Reproduction and Pregnancy

Apalutamide is contraindicted for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. Apalutamide is not indicated for use in females, so animal embryo-fetal developmental toxicology studies were not conducted with apalutamide. There are no human data on the use of apalutamide in pregnant women.

Pediatrics and Assessment of Effects on Growth

Apalutamide has not been studied in a pediatric population. The applicant has been granted a waiver of pediatric studies based on the low incidence of prostate cancer in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In the phase I/II, the maximum tolerated dose of apalutamide was not reached. One dose-limiting toxicity was observed at 300mg QD. The maximum dose evaluated was 480mg QD, therefore doses greater than 480mg QD should be considered overdose. There was no evidence that suggests a risk for dependence of apalutamide. No cases of withdrawal symptoms were reported during human clinical trials.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Apalutamide has not yet been approved in any market.

Expectations on Safety in the Postmarket Setting

Patients at risk for seizure were excluded from trials evaluating apalutamide. Thus, off-label use in these patients would constitute a safety concern.

8.2.11. Integrated Assessment of Safety

The safety profile of apalutamide in patients with non-metastatic castration-resistant prostate cancer is acceptable. The size of the safety database and duration of apalutamide exposure were sufficient to characterize the safety of apalutamide for treatment of a serious and life-threatening condition. There were relatively few discontinuations due to adverse events compared to placebo. Although overall survival data are immature, there was no decrement in overall survival and a numerical trend to improved overall survival, which increases confidence in the safety of apalutamide. Notable toxicities included rash, weight loss, falls, and fractures. There were rare events of seizure. This reviewer does not recommend a risk evaluation and mitigation strategy (REMS) given the current safety profile of apalutamide. Recommendations for safe and effective use of apalutamide, including recommends to assess and treat patients at risk for fracture, will be made in labeling, including a patient information insert.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

There are no major statistical issues with the efficacy results of the pivotal study SPARTAN. The study met its primary objective of MFS, the results appeared consistent across sensitivity analyses, and no apparent outliers were observed in subgroup analyses.

8.4. Conclusions and Recommendations

The review team recommends regular approval for apalutamide for the following indication:

> Erleada is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

The recommendation is based upon review of the result from the SPARTAN study which was a multinational, randomized, placebo-controlled study in which patients with high-risk, NM-CRPC were randomized (2:1) to receive apalutamide or placebo while maintain castrate testosterone levels (<50 ng/dL) either continuation of GnRH analogues or prior bilateral orchiectomy until radiographically-confirmed distant metastasis. The trial demonstrated a statistically and clinically significant improvement in BIRC-assessed MFS for patients randomized to apalutamide (estimated median MFS 40.5 months) versus placebo (estimated median MFS 16.2 months),

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with a hazard ratio of 0.28 (95%CI: 0.23, 0.35, p<0.0001). Time to metastasis, PFS, time to symptomatic progression, subgroup analyses, and sensitivity analyses all support the primary efficacy endpoint. OS analysis was not mature at the time of the final MFS analysis.

The safety profile of apalutamide in patients with NM-CRPC is acceptable. The size of the safety database and duration of apalutamide exposure were sufficient to characterize the safety of apalutamide for treatment of a serious and life-threatening condition. There were relatively few discontinuations due to adverse events compared to placebo. Notable toxicities included rash, weight loss, falls, and fractures. There were rare events of seizure. All disciplines agreed that apalutamide has a favorable risk-benefit profile, and did not identify any outstanding issues that precluded approval.

{See appended electronic signature page}

Lijun Zhang, PhD
Primary Statistical Reviewer

Jason Schroeder, PhD
Statistical Team Leader

Dow-Chung Chi, MD
Primary Clinical Reviewer (Efficacy)

Daniel L. Suzman, MD
Primary Clinical Reviewer (Safety)

Chana Weinstock, MD
Clinical Team Leader

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9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application.

10 Pediatrics

FDA agreed to the Initial Pediatric Study Plan (iPSP), in which the applicant proposed a full waiver due to the fact that prostate cancer does not occur in children.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling** *(As of February 6, 2018)*
Highlights		
Product Title	Product Title	FDA revised to "ERLEADA® (apalutamide) tablets, for oral use" to be consistent with the FDA Product Title guidance format requirements and recommendations.
Dosage and Administration	Dosage and Administration …	FDA added the following statement: "Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.1)" *See the Full Prescribing Information (FPI), Dosage and Administration (2) for more information.*
Contraindications	Contraindications (b) (4)	FDA revised the contraindications statement in Highlights to "Pregnancy" to be consistent with current labeling practices.
Warnings and Precautions	Warnings and Precautions …	FDA added: • Falls and Fractures occurred in 16% and 12% of patients receiving ERLEADA, respectively. Evaluate patients for fracture and fall risk, and treat patients with bone targeted agents according to established guidelines. (5.1) *See the FPI, Warnings and Precautions (5.1) for more information.*
Adverse Reactions	Adverse Reactions …	FDA reduced the most common adverse reactions statement from an incidence of (b) (4)% to 10% to add clinically relevant verse reactions for hypertension, diarrhea, nausea, hot flush, decreased appetite, fracture, and peripheral edema based on FDA safety review results.

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Use in Specific Populations	Females and Males of Reproductive Potential …	FDA revised this section from (b) (4) [redacted] " to "use effective contraception" to be consistent with current contraception labeling practices and to avoid the use of undefined terminology (i.e., (b) (4) [redacted] ")
Full Prescribing Information (FPI)		
2. Dosage and Administration	2.1 Recommended Dosage …	To identify and describe the recommended concomitant treatment for patients being treated with ERLEADA, FDA added the following statement: "Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.1)"
4. Contraindications	(b) (4) [redacted]	To be consistent with current pregnancy labeling practices, FDA revised the contraindications statement to "Pregnancy ERLEADA can cause fetal harm and potential loss of pregnancy [*see Use in Specific Populations (8.1)*]."
5. Warnings and Precautions	5.1 Falls and Fractures …	FDA added a new Warning and Precaution subsection (5.1) for Falls and Fractures based on the FDA safety review results. *See 8.2.5 Analysis of Submission-Specific Safety Issues, Falls and Fractures for more information.*
	5.2 Seizure …	FDA revised this section to add the following information regarding the risk and management of seizures associated with ERLEADA: "It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others."

		FDA added the onset time for the seizure cases associated with ERLEADA.
6. Adverse Reactions	6.1 Clinical Trial Experience …	For accuracy and to clearly define the concomitant therapies used with ERLEADA, FDA revised [redacted] (b) (4) " to "All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy." FDA added safety results to report the deaths from adverse reactions (ARs) (i.e., infection, myocardial infarction, and cerebral hemorrhage) and added the adverse reactions that lead to treatment discontinuation, dose interruption, or dose reduction. FDA added the serious adverse reactions and incidence rate for fractures for patients treated with ERLEADA. FDA removed [redacted] (b) (4) FDA revised the Adverse Reactions table (Table 1) to include adverse reactions ≥ 10% [redacted] (b) (4) and added ARs for decreased appetite, peripheral edema, hypertension, hot flush, diarrhea, and nausea based on FDA safety analysis. [redacted] (b) (4) was

		removed from the table and retained in a text section to better characterize these ARs. FDA removed the laboratory abnormalities (i.e., (b) (4)) described in text and replaced with a Laboratory Abnormalities table (Table 2) with results from the FDA Safety Review for leukopenia, lymphopenia, anemia, and hyperkalemia laboratory abnormalities elevated on the ERLEADA arm compared to placebo. FDA moved and revised the Fall and Fractures AR information in Section (b) (4) to 5.1 since these events require monitoring and management to mitigate serious adverse reactions.
7. Drug Interactions	7.1 Effect of Other Drugs on ERLEADA … 7.2 Effect of ERLEADA on Other Drugs …	FDA revised the numbered subsections proposed by the Applicant (7.1, 7.2, 7.3, 7.4) (b) (4) to the subsections divided on the effect of other drugs on ERLEADA and the effect of ERLEADA on other drugs. This removed several redundant statements across these subsections and is more consistent with current best labeling practices for drug interactions.
8. Use in Specific Populations	8.1 Pregnancy …	FDA revised the risk summary statement to add information stating that ERLEADA "can cause fetal harm and potential loss of pregnancy" (based on mechanism of action); and added a statement to state that "ERLEADA is not indicated for use in females".
	8.3 Females and Males of Reproductive Potential …	FDA revised this subsection from (b) (4) " to "use effective contraception" to be consistent with current contraception labeling practices and to avoid the use of undefined terminology (i.e., " (b) (4)

	8.5 Geriatric Use …	FDA removed the conclusions that (b) (4) [redacted] FDA added information to provide the number of patients treated with ERLEADA that were 75 years of age or older. FDA added results that show an increase in the incidence of Grade 3-4 ARs in patients 65 years or older (i.e., 46% vs. 35%, respectively), and 75 years or older (51% vs. 37%, respectively), compared to younger patients.
	(b) (4) [redacted]	FDA removed these subsections since there was an absence of specific dose adjustment information for these conditions.
	(b) (4) [redacted]	FDA removed this subsection and moved to 12.2 Pharmacodynamics, Cardiac Electrophysiology to be consistent with best labeling practices for QTc interval study information. *See 8.2.4 ECGs and QT for more information.*
12. Clinical Pharmacology	12.1 Mechanism of Action …	FDA removed unsubstantiated and potentially promotional claims that apalutamide (b) (4) [redacted] and has "(b) (4) [redacted]".
	12.3 Pharmacokinetics …	FDA added the description of the meals administered in the food effects study. In the Specific Populations and the Drug Interactions subsections, FDA removed the (b) (4) [redacted] (b) (4) [redacted] negative PK study information was described in brief text statements in 12.3.
13. Nonclinical Toxicology	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	FDA added the following information based on FDA Nonclinical Review findings: "A reduced number of live fetuses due to

	…	increased pre- and/or post-implantation loss was observed following 4 weeks of 150 mg/kg/day administration (5.7 times the human exposure based on AUC).”
14. Clinical Studies	…	FDA revised the study description to add the study acronym (SPARTAN) and NCT # consistent with current best labeling practices. FDA revised the study treatment regimen from (b) (4) to “All patients in the SPARTAN (b) (4) received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy.” for accuracy and to clearly define the concomitant therapy used with ERLEADA. FDA revised the definition of metastasis-free survival to clarify how enlarged lymph nodes above the iliac bifurcation were considered progression. FDA removed (b) (4) (b) (4) FDA revised Table 3 by adding the number of events for the MFS, Time to Metastasis (TTM), and Progression-Free Survival (PFS) results reported. FDA removed (b) (4) FDA removed the (b) (4) results from Table 3 and replaced the (b) (4)

		text with the following statement: "Overall survival (OS) data were not mature at the time of final MFS analysis (24% of the required number of events)." FDA removed the [redacted] (b) (4) This was replaced with the following text based on clinically relevant subgroup findings: "Consistent results were observed across patient subgroups including PSADT (≤ 6 months or > 6 months), use of a prior bone-sparing agent (yes or no), and locoregional disease (N0 or N1)." FDA removed [redacted] (b) (4) FDA removed [redacted] (b) (4)
17. Patient Counseling Information	…	FDA revised the Patient Counseling Information to provide counseling topic subheadings, provide the required cross references to detailed information in other sections of the FPI, to add new safety information related to FDA-initiated labeling revisions, and to remove inappropriate general counseling advice not related to serious or otherwise clinically significant topics or required for the safe and effective use of ERLEADA.

11.2. Patient Labeling

ERLEADA includes an FDA-approved Patient Package Insert (Patient Information). The FDA DMPP team reviewed the ERLEADA Patient Information and revisions were made to be consistent with the FDA-mandated labeling revisions to the ERLEADA Prescribing Information. *See the FDA DMPP review filed under this NDA for more information.*

12 Risk Evaluation and Mitigation Strategies (REMS)

In the review of NDA 210951, the Division of Risk Management (DRISK) evaluated whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Erleada (apalutamide) is necessary to ensure the benefits outweigh its risks. The risks associated with apalutamide include falls, fractures, and seizures. The applicant did not submit a proposed REMS or risk management plan with this application. Due to the nature of the disease of NM-CRPC, the lack of treatment options available, and the improvement in metastasis-free survival (MFS) compared to placebo in the apalutamide clinical trial, in addition to the likely prescribers will be medical oncologists, this DRISK reviewer's recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks for apalutamide.

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13 Postmarketing Requirements and Commitment

The FDA recommends a PMC for NDA 210951 to require the applicant to submit a final clinical study report for SPARTAN with final OS analysis. This OS analysis is important to confirm the benefit-risk profile of apalutamide, assess based on MFS in this application.

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14 Division Director (DHOT)

{See appended electronic signature page}

John Leighton, PhD
Director, Division of Hematology Oncology Toxicology

15 Division Director (OCP)

{See appended electronic signature page}

Nam Atiqur Rahman, PhD
Director, Division of Clinical Pharmacology V

16 Division Director (OB)

{See appended electronic signature page}

Rajeshwari Sridhara, PhD
Division Director, Division of Biometrics V

17 Division Director (Clinical)

{See appended electronic signature page}

Julia Beaver, MD
Director, Division of Oncology Products 1

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit profile was also assessed by Drs. Beaver, Weinstock, Chi and Suzman who recommend approval. I also recommend approval of this application. My signature below represents an approval recommendation for the clinical portion of this application under the OCE. My signature below also represents the approval decision of this application under CDER.

{See appended electronic signature page}
Gideon Blumenthal, MD
Deputy Director (acting), Office of Hematology Oncology Products

19 Appendices

19.1. References

References are inserted throughout the text.

19.2. Financial Disclosure

Covered Clinical Study: SPARTAN, ARN-509-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3123		
Number of investigators who are applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 14		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 2 Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in applicant of covered study: 3		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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19.3. Nonclinical Pharmacology/Toxicology

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, plasma and urine concentrations of the active parent, apalutamide and the active metabolite, N-desmethyl apalutamide, were measured in the clinical pharmacology and biopharmaceutics studies. Based on the mass-balance trial 006, ^{14}C-radioactivity of apalutamide and N-desmethyl apalutamide accounted for approximately 45 and 44% total ^{14}C-radioactivity AUC_{inf}, respectively. Another in active metabolite M4 was detected in plasma in minor amount (~ 3% of total radioactivity).

Metabolism is the main route of elimination of apalutamide. It is metabolized primarily by CYP2C8 and CYP3A4 to form N-desmethyl apalutamide. Apalutamide and N-desmethyl apalutamide are further metabolized to form the inactive carboxylic acid metabolite by carboxylesterase. The contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but changes to 40% and 37%, respectively at steady-state (See section 19.4.5 for detail).

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentrations of apalutamide and N-desmethyl apalutamide were measured in the clinical trials. This was appropriate due to the constant plasma protein binding of apalutamide and N-desmethyl apalutamide over the clinically relevant concentration range studied. The average fraction unbound (fu) values in human plasma proteins of apalutamide and N-desmethyl apalutamide were 4.2% and 5.1%, respectively. The fu values for apalutamide and N-desmethyl apalutamide were independent of concentrations (0.1 to 30 µg/mL).

What bioanalytical methods are used to assess concentrations?

Five methods for analysis human plasma samples are described below.

<u>Apalutamide and N-desmethyl apalutamide Plasma Assays</u>

Methods (b) (4) and (b) (4): In 2010, at (b) (4), initial LC-MS/MS methods were validated to measure apalutamide (Report Mod5.3.1.4/(b) (4)) and N-desmethyl apalutamide in human plasma (Report Mod5.3.1.4/(b) (4)). In (b) (4), apalutamide concentrations were calculated with a $1/x^2$ linear regression over a concentration range of 20.0 (LLOQ) to 20,000 (ULOQ) ng/mL with 8

calibration standards. In (b) (4), apalutamide concentrations were calculated with a $1/x^2$ quadratic regression with 8 calibration standards over a concentration range of 25.0 (LLOQ) to 25,000 ng/mL(ULOQ) and N-desmethyl apalutamide concentrations were calculated with a $1/x^2$ quadratic regression over a concentration range of 25.0 (LLOQ) to 25,000 (ULOQ) ng/mL with 8 calibration standards. These 2 methods were used in Study 001.

Method (b) (4): In 2013, at (b) (4), an assay was validated for the quantification of apalutamide, N-desmethyl apalutamide, and JNJ-56142021 (ARN000066 or M4) (Report Mod5.3.1.4/ (b) (4)). This method was only used in support of the human mass balance study, Study 006. Calibration ranges were 0.0250 - 25.0 µg/mL with 9 calibration standards for apalutamide and N-desmethyl apalutamide and 0.0150 - 15.0 µg/mL with 9 calibration standards for M4. $1/x^2$ quadratic regressions were used for all calibration curves.

Method BA10609: In 2014, at (b) (4), a new assay was developed for the determination of apalutamide and N-desmethyl apalutamide in human plasma (Mod5.3.1.4/BA10609). This method was optimized from the previous method (b) (4) (optimization of sample processing and chromatography, removal of JNJ-56142021 quantitation) for support of the majority of clinical studies, including the study 003 (SPARTAN). Calibration ranges were 0.0250 - 25.0 µg/mL (with 9 calibration standards) with the extended calibration ranges of 0.125 – 125 ug/mL after 5-fold dilution for apalutamide and N-desmethyl apalutamide.

Method BA10959: In 2 single-dose studies that involved a 60-mg dose (Studies 1015 and 1017), the concentrations of apalutamide in the later portion of the concentration-time profiles were lower than the LLOQ (0.025 µg/mL) of method BA10609. The quantification limit of the assay was lowered to 0.005 µg/mL for both analytes (Mod5.3.1.4/BA10959). Calibration ranges were 0.00500 - 5.00 µg/mL with 9 calibration standards for apalutamide and N-desmethyl apalutamide. In the studies in which both BA10609 and BA10959 were used (Studies 1015 and 1017), a cross-validation for apalutamide and N-desmethyl apalutamide with study samples was performed to demonstrate that both methods have equal performance.

A cross-validation (BA10849) with QC samples was performed to compare the methods of (b) (4) ((b) (4)) and (b) (4)).

<u>Apalutamide and N-desmethyl apalutamide Urine and Feces Assay</u>

Metabolic profiling and identification were performed in urine and feces samples obtained from Study 006. Metabolite profiling work in urine and feces was done using accelerator mass spectrometry. Metabolite identification in urine and feces was done by liquid chromatography with mass spectrometry.

<u>4ß-hydroxycholesterol Plasma Concentrations</u>

Plasma samples obtained in Study 1008 and Study 1010 were analyzed for 4ß-hydroxycholesterol concentrations by (b) (4) using LC-MS/MS in report BTM-1294-R0. The LLOQ was 5.00 ng/mL and the calibration range was appropriate at 5.00 ng/mL to 500 ng/mL. The linearity of this method was evaluated by analyzing 8 calibration standards over the nominal concentration range of 5.00 to 500 ng/mL using a linear regression algorithm.

Prednisone and Prednisolone Plasma Concentrations

Plasma samples obtained in Study 1010 were analyzed for prednisone and prednisolone concentrations by (b) (4) using LC-MS/MS in report P955.00. The LLOQ was 0.500 ng/mL for both prednisone and prednisolone and the calibration range was appropriate at 0.500 ng/mL to 1000 ng/mL. The method was evaluated by analyzing 9 calibration standards over the nominal concentration range of 0.500 ng/mL to 1000 ng/mL using a quadratic regression algorithm.

Abiraterone and Abiraterone Acetate Plasma Concentrations:

Plasma samples obtained in Study 1010 were analyzed for abiraterone and abiraterone acetate concentrations by (b) (4) using LC-MS/MS in report BA10183. The LLOQ was 0.200 ng/mL for both abiraterone and abiraterone acetate. The calibration range was appropriate at 0.200 ng/mL to 500 ng/mL and 0.200 ng/mL to 50.0 ng/mL for abiraterone and abiraterone acetate, respectively. For abiraterone, calibration curves were constructed by plotting the log-transformed peak area ratios (abiraterone/internal standard) against the log-transformed 12 abiraterone standard concentrations. The linearity of the abiraterone acetate method was evaluated by analyzing eight calibration standards over the nominal concentration range of 0.200 to 50.0 ng/mL using a linear regression algorithm.

Itraconazole and 2-Hydroxyitraconazole Plasma Concentrations:

Plasma samples obtained in Study 1012 were analyzed for itraconazole and 2-hydroxyitraconazole concentrations by (b) (4) using LC-MS/MS in report P1079.02. The LLOQ was 0.500 ng/mL and the calibration range was appropriate at 0.500 ng/mL to 500 ng/mL. The linearity of this method was evaluated by analyzing eight calibration standards over the nominal concentration range of 0.500 to 500 ng/mL using a linear regression algorithm.

Gemfibrozil Plasma Concentrations:

Plasma samples obtained in Study 1012 were analyzed for gemfibrozil concentrations by (b) (4) using HPLC with fluorescence detection in report LC 56 V3.02. The LLOQ was 0.0500 µg /mL and the calibration range was appropriate at 0.0500 µg/mL to 25.0 µg/mL. The linearity of this method was evaluated by analyzing nine calibration standards over the nominal concentration range of 0.0500 µg/mL to 25.0 µg/mL using a linear regression algorithm.

Midazolam and 1-OH-midazolam Concentrations:

Plasma samples obtained in Study 1020 were analyzed for midazolam and 1-OH-midazolam concentrations by (b) (4) using HPLC with LC-MS/MS in report P102.02. For both midazolam and 1-OH-midazolam, the LLOQ was 0.100 ng/mL and the calibration range was appropriate at 0.100 ng/mL to 100 ng/mL. The linearity of the methods were evaluated by analyzing eight calibration standards over the nominal concentration range of 0.100 ng/mL to 100 ng/mL using a linear regression algorithm for midazolam and 1-OH-midazolam.

S-warfarin and 7-OH-S-warfarin Plasma Concentrations:

Plasma samples obtained in Study 1020 were analyzed for S-warfarin and 7-OH-S-warfarin concentrations by (b) (4) using HPLC with LC-MS/MS in report P832.00. The LLOQ was 5.00 ng/mL and the calibration range was appropriate at 5.00 ng/mL to 1500 ng/mL for S-warfarin and 7-hydroxy-S-warfarin. The linearity of the methods were evaluated by analyzing eight calibration standards over the nominal concentration range of 5.00 ng/mL to 1500 ng/mL using a linear regression algorithm for S-warfarin and 7-hydroxy-S-warfarin.

Omeprazole and 5-OH-Omeprazole Plasma Concentrations:

Plasma samples obtained in Study 1020 were analyzed for omeprazole and 5-OH-omeprazole concentrations by (b) (4) using HPLC with LC-MS/MS in report P1009.03. The LLOQ was 1.00 ng/mL and the calibration range was appropriate at 1.00 ng/mL to 1000 ng/mL for omeprazole and 5-OH-omeprazole. The linearity of the methods were evaluated by analyzing eight calibration standards over the nominal concentration range of 1.00 ng/mL to 1000 ng/mL using a linear regression algorithm for omeprazole and 5-OH-omeprazole concentrations.

Fexofenadine Plasma Concentrations:

Plasma samples obtained in Study 1020 were analyzed for fexofenadine concentrations by (b) (4) using HPLC with LC-MS/MS in report P1365.00. The LLOQ was 0.500 ng/mL and the calibration range was appropriate at 0.500 ng/mL to 500 ng/mL. The linearity of the methods were evaluated by analyzing eight calibration standards over the nominal concentration range of 0.500 ng/mL to 500 ng/mL using a linear regression algorithm.

Pioglitazone Plasma Concentrations:

Plasma samples obtained in Study 1020 were analyzed for pioglitazone concentrations by (b) (4) using HPLC with LC-MS/MS in report PBRL-RD-1274. The LLOQ was 0.500 ng/mL and the calibration range was appropriate at 0.500 ng/mL to 500 ng/mL. The method was evaluated by analyzing nine calibration standards over the nominal concentration range of 0.500 ng/mL to 500 ng/mL using a quadratic regression algorithm.

Rosuvastatin Plasma Concentrations:

Plasma samples obtained in Study 1020 were analyzed for rosuvastatin concentrations by (b) (4) using HPLC with LC-MS/MS in report P922.07. The LLOQ was 0.100 ng/mL and the calibration

range was appropriate at 0.100 ng/mL to 100 ng/mL. The method was evaluated by analyzing eight calibration standards over the nominal concentration range of 0.100 ng/mL to 100 ng/mL using a quadratic regression algorithm.

19.4.2. Clinical PK

Ten Clinical Pharmacokinetic studies in this submission are summarized in the following Table 46. The to-be-market tablet formulation (G023, 60 mg) and the capsule formulation were used in these studies. There sponsor also reported clinical PK results for other four clinical studies 1007, 1011, 1015 and 1017 (Table 47) to study relatively bioavailability and food effect for other formulations developed during the drug development. In this review, the clinical PK discussion will focus on the to-be-market tablet formulation (G023, 60 mg) and the capsule formulation.

The PK of apalutamide and its major active metabolite N-desmethyl apalutamide can be descripted using a two-compartment model with first-order absorption (Figure 16). Apalutamide showed time dependent PK with the values of apalutamide AUC_{0-24} after multiple once daily dose were lower than that of apalutamide AUC_{inf} after single dose (Table 47). At steady-state in study 1019, mean (CV%) C_{max} and AUC values for apalutamide were 6 µg/mL (28%) and 100 µg.h/mL (32%), respectively, and the mean (CV%) C_{max} and AUC values for N-desmethyl apalutamide were 5.9 µg/mL (18%) and 124 µg.h/mL (19%), respectively. Apalutamide and N-desmethyl apalutamide showed long half-life values after single dose and multiple doses (Table 47). Multiple tablet formulations and a capsule formulation were administrated in the clinical pharmacology and biopharmaceutic studies. Formulation effect, PK dose proportionality, PK time dependency, PK in healthy subjects and PK in patients with CRPC are discussed in this section.

Table 46. Clinical PK Studies in NDA 210951 Submission

Type of Study	Number of Studies	Study ID	Population	Number of Subjects
Phase 1				
Mass-balance	1	Study 006	Healthy subjects	12
Hepatic Impairment	1	Study 1018	Healthy subjects and subjects with mild or moderate hepatic impairment	24
Japanese Subjects	2	Study 1008	Japanese subjects with mCRPC	6
		Study 1021	Healthy Japanese subjects	18
Drug Interaction	3	Study 1012	Healthy subjects	45
		Study 1010	Subjects with CRPC	51
		and 1020		21
Effect on ECG	1	Study 1019	Subjects with CRPC	45
Phase 1/2				
Single-and Multiple-Ascending Dose,	1	Study 001	Subjects with progressive advanced CRPC	30 (Phase 1) 95 [a] (Phase 2)
Food Effect,				12
Effect on ECG				97 [b]
Phase 3				
PK in the target population,	1	Study 003, SPARTAN)	Subjects with NM-CRPC	798 [c]
Exposure-Response,				1,207 [c]
Effect on ECG (substudy)				17
Total				**1,556**

Number of subjects includes only those subjects that were included for the PK analysis presented in this Summary of Clinical Pharmacology.

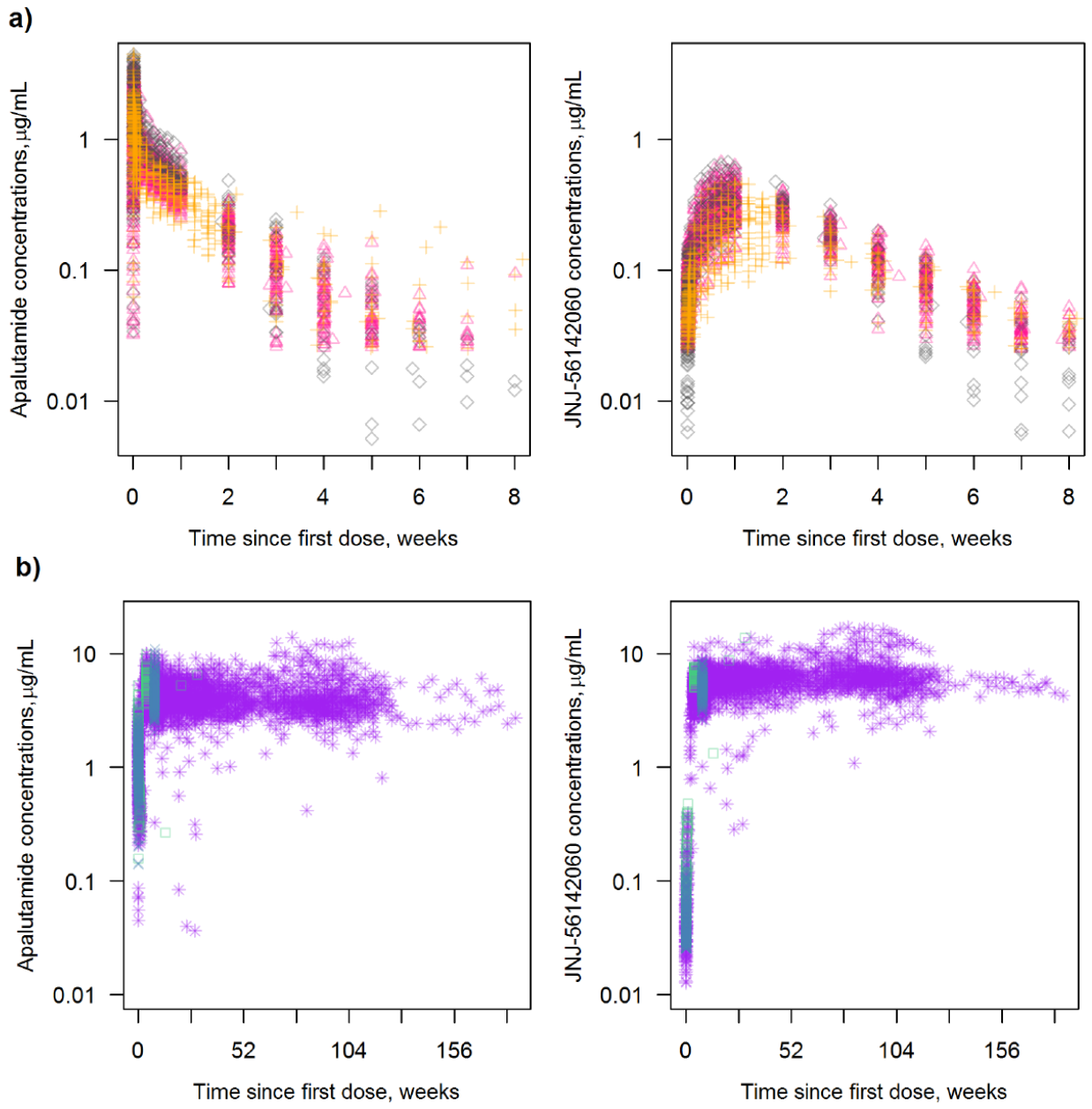
[a] Number of subjects who participated in Phase 2 of the study and were included in the PK analysis. Also includes the 12 subjects from the food effect substudy.

[b] Number of subjects who participated in Phase 2 of the study and were included in the ECG analysis. Also includes the 12 subjects from the food effect substudy.

[c] Total number of subjects in SPARTAN. The analysis dataset for population PK comprised of subjects (n=798) who received apalutamide and for whom there was a sufficient number of quantifiable plasma samples for reliable estimation of PK parameters. For the exposure-response 1,207 subjects were considered. A total of 17 subjects were included in the ECG substudy.

Source: Summary of Clinical Pharmacology Studies Table 2 (Section 2.7.2)

Figure 16. Dose Normalized (to 240 mg) Observed Apalutamide (left) and N-desmethyl apalutamide (right) plasma concentration versus time after single (a) and multiple doses (b)



Symbols represent the observed plasma concentrations of apalutamide and N-desmethyl apalutamide (JNJ-56142060) for the studies 1011 (open triangle), 1018 (plus symbol), 1021 (open diamond), 1008 (open square), 1019 (cross) and 001 (asterisk)

Source: Population Pharmacokinetics Report JNJ-56021927 (ARN-509; Apalutamide) (Section 5.3.3.5) Figure 3.

Formulation Effect

Capsule and tablet formulations have been used over the course of clinical development of apalutamide. Formulations administrated in the clinical pharmacology and biopharmaceutic studies in this NDA submission were summarized in Table 47. In this review, the clinical PK discussion will focus on the to-be-market tablet formulation (G023, 60 mg) and the capsule formulation. The to-be-market 60 mg tablet formulation was used in following studies: registration Phase 3 study 003; DDI studies 1010 and 1020; relatively bioavailability and food effect studies 1007, 1011, 1015 and 1017; dedicated hepatic impairment study 1018; dedicated QT study 1019; Japanese patient with CRPC study 1021. The capsule formulation was used in following studies: Phase 1/2 dose escalation and expansion study 001; study 003; ADME and absolute bioavailability study 006; DDI studies 1010 and 1012; Study 1011; single dose PK study 1008 in Japanese subject.

Those two formulations are almost bioequivalent without clinically relevant exposure difference. In an open-label, randomized, parallel relatively bioavailability study 1011 in healthy subjects, the following GMR (90% CI percentage) values were reported for the to-be-market tablet formulation (N=15) over the capsule formulation (N=15) after a single dose of 240 mg under fasted conditions (Table 48): C_{max} 0.90 (79, 103); AUC_{last} 1.08 (95, 123); AUC_{inf} 1.07 (94, 122). In the same study (Table 7), the to-be-market tablet formulation showed no clinically relevant food effect with the following GMR (90% CI percentage) values for the fasted conditions (≥ 10 hours, N=15) over fed conditions (high-fat breakfast, N=15) after a single 240 mg administration: C_{max} 0.84 (75, 94); AUC_{last} 0.97 (86, 109); AUC_{inf} 0.94 (84, 106). The BE of tablet relative to capsule after repeat dose and single dose apalutamide administrations was also assessed from Monte Carlo simulations using PK parameters and random effects derived from a population model including studies 001, 003, 1008, 1011, 1018, 1019 and 1021. The simulations predicted the tablet and capsule formulations to be bioequivalent with 90% CIs within the 80-125% limit for both C_{max} and AUC after repeat dose administrations to steady-state.

Study 003 was initiated using the capsule formulation and were later switched to the to-be-market 60 mg tablet formulation. The randomization and blinding remained unchanged during the formulation switch. Newly enrolled subjects began treatment using tablets while subjects already enrolled and receiving capsules made the switch to tablets at the start of a new cycle. There were 205 subjects treated with capsule only (100 subjects: apalutamide; 105 subjects: placebo), 428 subjects treated with tablet only (292 subjects: apalutamide; 136 subjects: placebo), and 568 subjects treated with both capsule + tablet (411 subjects: apalutamide; 157 subjects: placebo). There were 324 subjects (169 subjects: apalutamide; 155 subjects: placebo) who had a greater capsule treatment duration than tablet treatment duration, and 877 subjects (634 subjects: apalutamide; 243 subjects: placebo) who had a greater tablet treatment duration than capsule treatment duration. The median duration of follow-up for subjects who received capsule only was 15.1 months, subjects who received capsule + tablet has a median duration of follow-up of 25.6 months, and subjects who received tablet only has a median duration of follow-up of 11.2 months. Subjects who received capsule only were treated at the beginning of the study and hence have been followed up for a longer period of time comparing to that of subjects who received tablet only. An exploratory analyses were performed to assess whether

the capsule and tablet formulations had an impact on key safety and efficacy data. For safety analyses, descriptive analysis by formulation subgroups (capsule only, capsule/tablet, and tablet only) were performed. For efficacy analyses, 2 sets of subgroups were used: set 1 - subjects who received capsule only, subjects who received both capsule and tablet, and subjects who received tablet only, and set 2 - subjects who had a greater (≥1 day) capsule treatment duration and subjects who had a greater tablet treatment duration. The capsule formulation was associated with a higher incidence of TEAEs, Table 49. The treatment effect of apalutamide was similar for MFS and PSA response rate among the 2 sets of formulation subgroups, Table 50. The applicant stated that the estimates for the median MFS should be interpreted with caution for the tablet only (14% event rate) and greater tablet duration (16% event rate) formulation subgroups because of very low event rates.

Table 47. Apalutamide dose, formulation and PK parameters after single and multiple administration in all clinical pharmacology and biopharmaceutic studies

Dose (mg)	Formulation [a]	n	t_{max} (h)		C_{max} (µg/mL)		AUC [b] (µg.h/mL)		$t_{1/2}$ (h)		Study ID
			Median	(Min-Max)	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Single Dose											
30	capsule	3	3.0	(1.0-4.0)	0.268	(0.128)	20.8	(1.99)	205	(89.1)	001
60	capsule	3	1.0	(1.0-1.5)	0.665	(0.104)	50.9	(24.8)	242	(136)	001
90	capsule	3	1.0	(1.0-1.5)	1.14	(0.361)	43.0	(1.16)	135	(44.6)	001
120	capsule	3	1.0	(1.0-1.5)	1.31	(0.237)	214	(170)	486	(499)	001
180	capsule	3	1.0	(1.0-6.0)	2.48	(1.39)	162	(21.1)	206	(123)	001
240	capsule	3	1.0	(1.0-3.0)	2.97	(0.414)	231	(93.2)	218	(128)	001
300	capsule	6	1.5	(1.0-4.0)	2.89	(0.547)	251	(58.5)	173	(68.0)	001
390	capsule	3	1.5	(1.0-2.0)	3.79	(1.01)	285	(87.7)	213	(44.6)	001
480	capsule	3	1.5	(1.0-1.5)	3.56	(0.759)	351	(154)	205	(163)	001
240	capsule	6	1.01	(1.0-1.5)	3.27	(0.400)	201	(29.2)	178	(33.8)	006 (Part A)
240	capsule	6	1.50	(1.0-2.0)	3.21	(0.467)	189	(41.6)	151	(33.2)	006 (Part B)
240	capsule	15	2.00	(1.0-4.0)	2.73	(0.381)	202	(30.0)	167	(48.4)	1007
240	tablet (G010)	15 [c]	2.00	(1.5-4.0)	2.30	(0.580)	202	(36.9)	160	(42.1)	1007
240	tablet (G011)	15 [c]	4.00	(1.5-6.0)	2.04	(0.349)	183	(39.1)	189	(54.6)	1007
240	tablet (G007)	15	4.00	(2.0-6.0)	1.97	(0.408)	192	(35.6)	156	(50.2)	1007
240	tablet (G008)	15 [c]	4.00	(1.0-4.0)	2.01	(0.434)	185	(34.7)	182	(50.7)	1007
240	tablet (G009)	15	4.00	(1.5-8.0)	1.88	(0.542)	193	(38.8)	172	(63.8)	1007
240	tablet (G012)	15 [c]	4.00	(4.0-12.1)	1.75	(0.372)	202	(43.3)	179	(58.4)	1007
240	tablet (G013)	15	4.00	(2.0-4.0)	1.94	(0.541)	194	(30.5)	186	(71.2)	1007
240	capsule	15	2.00	(1.0-3.0)	2.70	(0.493)	212	(42.0)	205	(61.2)	1011
240	tablet	15	3.03	(1.0-5.0)	2.42	(0.381)	225	(33.9)	162	(48.2)	1011
240	tablet (G025)	15	3.00	(2.0-5.0)	2.36	(0.722)	227	(52.8)	184	(67.4)	1011
240	tablet (G024)	15	2.01	(1.5-4.0)	2.58	(0.463)	212	(42.8)	166	(39.7)	1011
240	capsule	15	1.50	(1.0-2.0)	3.40	(0.598)	232	(45.6)	190.9	(73.9)	1012
60	tablet (b) (4)	55 [d]	3.00	(1.0-6.0)	0.624	(0.104)	57.4	(11.3)	179	(52.4)	1015
60	tablet	14	2.50	(1.0-5.0)	0.593	(0.0962)	56.1	(9.45)	193	(55.5)	1015
60	tablet	14	3.00	(1.5-5.0)	0.615	(0.109)	55.9	(9.07)	181	(32.5)	1015
60	tablet	14 [e]	3.00	(2.0-4.0)	0.668	(0.0811)	62.2	(14.0)	183	(39.0)	1015
60	tablet	13 [f]	4.00	(1.5-5.0)	0.573	(0.107)	56.7	(9.83)	163	(48.9)	1015
60	tablet	47 [g]	3.00	(1.5-6.0)	0.633	(0.123)	55.7	(12.7)	188	(60.4)	1017
60	tablet (b) (4)	24 [h]	3.00	(1.0-5.0)	0.628	(0.143)	57.7	(12.6)	214	(86.3)	1017
60	tablet (b) (4)	24	2.00	(1.0-5.0)	0.614	(0.133)	51.6	(12.0)	172	(59.9)	1017

240	tablet	8	3.00	(1.0-3.0)	1.95	(0.428)	203	(37.4)	191	(53.6)	1018
240	tablet	8	1.75	(1.0-3.0)	2.09	(0.948)	196	(56.6)	217	(113.5)	1018 (mild hepatic impairment)
240	tablet	8	1.50	(0.5-3.0)	2.23	(1.17)	253	(134)	236	(123.4)	1018 (moderate hepatic impairment)
240	tablet	45	2.12	(1.1-5.1)	2.06	(0.582)	21.1	(4.93)	-	-	1019
240	capsule	5	1.58	(1.0-2.1)	3.88	(0.793)	33.6	(4.78)	-	-	1008
60	Tablet	6	2.50	(1.5-4.0)	0.870	(0.192)	63.9	(13.1)	138	(62.0)	1021
120	Tablet	6	1.75	(1.0-3.0)	1.73	(0.285)	147	(36.7)	169	(54.0)	1021
240	Tablet	6 [i]	3.50	(2.0-5.0)	3.12	(0.745)	227	(26.6)	130	(36.9)	1021
Single Dose, Fed											
240	tablet	15 [c]	5.05	(2.0-6.0)	2.05	(0.415)	214	(45.9)	165	(57.8)	1011
Multiple Dose											
30	capsule	3	0.5	(0.5-1.0)	0.841	(0.136)	14.7	(2.01)	85.8	(9.27)	001
60	capsule	3	1.0	(1.0-4.0)	1.60	(0.176)	29.7	(6.40)	118	(14.8)	001
90	capsule	3	1.0	(0.5-2.0)	2.53	(0.176)	38.3	(3.75)	93.2	(82.9)	001
120	capsule	3 [j]	2.0	(2.0-24.0)	3.30	(0.542)	59.4	(10.8)	63.8	(11.5)	001
180	capsule	3	1.0	(1.0-1.0)	5.98	(1.24)	93.7	(27.2)	81.3	(45.7)	001
240	capsule	3 [j]	1.5	(1.0-8.0)	7.55	(1.15)	127	(36.3)	106	(8.49)	001
300	capsule	5 [k]	2.0	(1.0-24.0)	7.08	(2.19)	134	(37.3)	2270	(4340)	001
390	capsule	3	1.0	(0.5-1.5)	8.91	(0.995)	140	(22.0)	47.7	(21.9)	001
480	capsule	3	1.5	(0.5-1.5)	11.2	(0.473)	202	(9.70)	153	(111)	001
240	capsule	4	1.50	(0.6-4.0)	6.33	(1.22)	94.4	(9.46)	-	-	1010 (substudy)
240	tablet	4	1.50	(1.0-2.0)	5.85	(1.29)	89.9	(15.8)	-	-	1010 (substudy)
240	capsule	49	0.97	(0.0-2.1)	7.33	(1.65)	108	(22.6)	-	-	1010
240	tablet	43	2.10	(1.0-4.2)	5.95	(1.66)	100	(31.6)	-	-	1019
240	tablet	21	4.05	(0.0-24.0)	6.01	(1.95)	109	(28.6)	-	-	1020
240	capsule	6	1.44	(1.0-4.0)	7.57	(1.19)	122	(17.5)			1008

[a] Tablet refers to the proposed commercial formulation (G023), unless otherwise specified.
[b] AUC_{∞} for single dose, AUC_{0-24} at steady state for multiple dose and Studies 1008 and 1019 single dose.
[c] N=14 for AUC and $t_{1/2}$.
[d] N=53 for AUC.
[e] N=13 for AUC and $t_{1/2}$.
[f] N=12 for AUC.
[g] N=46 for AUC and $t_{1/2}$.
[h] N=22 for AUC.
[i] N=5 for AUC and $t_{1/2}$.
[j] N=2 for $t_{1/2}$.
[k] N=4 for $t_{1/2}$.

Source: Summary of Clinical Pharmacology Studies Appendix 2 (Section 2.7.2)

Table 48. Apalutamide PK Parameters of Capsule (Treatment A) and Tablet (Treatment B) formulation Under Fasted Conditions

Parameter	Treatment Group[a]	N	Geometric Mean	Ratio: Test/Reference (%)	90% Confidence Interval (%)	Total CV (%)
C_{max}(µg/mL)	Treatment A	15	2.66			21.5%
	Treatment B	15	2.40	90.10	(79.15 - 102.56)	
AUC_{last}(µg*hr/mL)	Treatment A	15	198.17			21.7%
	Treatment B	15	213.52	107.75	(94.51 - 122.84)	
AUC_{∞}(µg*hr/mL)	Treatment A	15	207.99			21.0%
	Treatment B	15	222.98	107.20	(94.46 - 121.67)	

[a]Treatment A was used as the reference group

Source: Table 5 of Clinical Study Report 56021927PCR1011 (section 5.3.1.2)

Table 49. Overall Summary of Treatment-emergent Adverse Events by Formulation; Safety Population (Study 003)

	Placebo			Apalutamide		
	Capsule	Tablet	Capsule+Tablet	Capsule	Tablet	Capsule+Tablet
Safety Population	105	136	157	100	292	411
Number of subjects with TEAEs	95 (90.5%)	126 (92.6%)	150 (95.5%)	98 (98.0%)	276 (94.5%)	401 (97.6%)
Drug-related[a]	65 (61.9%)	64 (47.1%)	87 (55.4%)	79 (79.0%)	185 (63.4%)	301 (73.2%)
Number of subjects with grade 3-4 TEAEs	23 (21.9%)	43 (31.6%)	70 (44.6%)	47 (47.0%)	119 (40.8%)	196 (47.7%)
Drug-related[a]	5 (4.8%)	6 (4.4%)	6 (3.8%)	25 (25.0%)	43 (14.7%)	45 (10.9%)
Number of subjects with treatment-emergent SAEs[b]	16 (15.2%)	29 (21.3%)	47 (29.9%)	29 (29.0%)	53 (18.2%)	117 (28.5%)
Drug-related[a]	2 (1.9%)	2 (1.5%)	2 (1.3%)	8 (8.0%)	10 (3.4%)	13 (3.2%)
Grade 3-4	15 (14.3%)	24 (17.6%)	37 (23.6%)	26 (26.0%)	40 (13.7%)	84 (20.4%)
Number of subjects with TEAEs leading to treatment discontinuation	9 (8.6%)	8 (5.9%)	11 (7.0%)	40 (40.0%)	25 (8.6%)	20 (4.9%)
Drug-related[a]	5 (4.8%)	2 (1.5%)	1 (0.6%)	29 (29.0%)	20 (6.8%)	9 (2.2%)
Number of subjects with TEAEs leading to death	0	1 (0.7%)	0	4 (4.0%)	4 (1.4%)	2 (0.5%)
Drug-related[a]	0	0	0	1 (1.0%)	0	0
All deaths within 28 days of last dose	0	1 (0.7%)	0	4 (4.0%)	4 (1.4%)	2 (0.5%)
Adverse event	0	1 (0.7%)	0	1 (1.0%)	4 (1.4%)	2 (0.5%)
Death due to prostate cancer	0	0	0	3 (3.0%)	0	0
Other	0	0	0	0	0	0

Key: TEAE=treatment-emergent adverse event; SAE=serious adverse event.
[a] Adverse events reported as related.
[b] Excludes Grade 5.
Note: Percent is based on the Safety population.
Note: Treatment-emergent adverse events are those that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days. For each category, subjects are counted only once, even if they experienced multiple events in that category.

Source: Table 37 of Clinical Study Report ARN-509-003 (section 5.3.5.1)

Table 50. Summary of Efficacy Analyses by Formulation Subgroups (Study 003)

	Metastasis-free Survival					
	Apalutamide No. of subjects; No. of events (%)	Apalutamide Median months (95% CI)	Placebo No. of subjects; No. of events n (%)	Placebo Median Months (95% CI)	Hazard Ratio (95% CI)	p value
Capsule only	100; 44 (44)	14.78 (11.10, 23.10)	105; 70 (67)	6.44 (3.75, 7.36)	0.300[b] (0.199, 0.452)	<0.0001[a]
Capsule + tablet	411; 98 (24)	40.51 (NE, NE)	157; 78 (50)	22.05 (18.40, 27.50)	0.320[b] (0.237, 0.433)	<0.0001[a]
Tablet only	292; 42 (14)	19.55 (NE, NE)	136; 46 (34)	18.50 (12.45, NE)	0.334[b] (0.219, 0.510)	<0.0001[a]
Greater capsule treatment duration	169; 85 (50)	18.43 (14.78, 22.11)	155; 106 (68)	7.75 (7.26, 10.97)	0.391[b] (0.291, 0.526)	<0.0001[a]
Greater tablet treatment duration	634; 99 (16)	NE (NE, NE)	243; 88 (36)	22.28 (21.22, 33.38)	0.304[b] (0.228, 0.407)	<0.0001[a]

PSA Response Rate

	Apalutamide Number of Subjects	Apalutamide PSA confirmed response n (%)	Placebo number of subjects	Placebo PSA confirmed response n (%)	Relative risk (95% CI)	p value
Capsule only	100	66 (66)	105	0 (0)	-------	<0.0001[c]
Capsule + tablet	411	390 (95)	157	5 (3)	29.796[d] (12.57, 70.61)	<0.0001[c]
Tablet only	292	267 (91)	136	4 (3)	31.089[d] (11.83, 81.69)	<0.0001[c]
Greater capsule treatment duration	169	127 (75)	155	0 (0)	--------	<0.0001[c]
Greater tablet treatment duration	634	596 (94)	243	9 (4)	25.382[d] (13.37, 48.20)	<0.0001[c]

[a] p-value is from a non-stratified log-rank test
[b] Hazard ratio is from a non-stratified proportional hazards model with a single factor of treatment group
[c] p-value is based on confirmed response from the non-stratified Chi-square test
[d] Relative risk is based on confirmed response
NE= not estimable

Source: Table 38 of Clinical Study Report ARN-509-003 (section 5.3.5.1)

PK Dose Proportionality

Dose proportionality of apalutamide PK using PK data from study 001 with single and repeat doses ranging from 30 to 480 mg. In study 001, patients with NM-CRPC or mCRPC received a single administration of the assigned dose (30, 60, 90, 120, 180, 240, 300, 390, or 480 mg) on Week 0 Day 1. One week later, subjects began once daily administration of the same dose.

In Study 001, power models using Week 0 Day 1 (after single dose) and Week 4 (after multiple dose) AUC_{0-24} and C_{max} values suggested approximately dose-proportional PK for apalutamide 30 to 480 mg after single dose (Figure 17) and multiple doses (Figure 18). The slopes of the power model on logarithmic scale were close to unity after single dose (C_{max}: 0.9645 (95% CI: 0.83, 1.12); AUC_{0-24} 1.035 (95% CI: 0.92, 1.15)) and multiple doses (C_{max}: 0.9335 (90% CI: 0.86, 1.01); AUC_{0-24} 0.9344 (90% CI: 0.86, 1.01)).

In Study 001, pair-wise comparisons of the dose-normalized AUC_{0-24} and C_{max} on Week 4 between individual doses and the reference dose (30 mg) were performed. A mixed-effect ANOVA model that included treatment as fixed effect was used to estimate the least squares means. Ratios of the geometric means and 90% CIs for each of the pairs were calculated to estimate the deviation from dose proportionality. The results indicated approximately dose-proportional PK of the daily dose range for 30 to 480 mg apalutamide (Table 51). The 90% CIs included unity for both AUC0-24 and C_{max} at all dose levels, including the clinically relevant dose range of 120, 180, and 240 mg, with the only exception of AUC_{0-24} at the dose of 390 mg.

Following multiple dose administration of 240-, 300-, 390-, and 480-mg apalutamide, N-desmethyl apalutamide C_{max} and AUC seems generally increased with increasing dose (Figure 19). Statistical analysis of dose proportionality of N-desmethyl apalutamide PK was not performed due to the limited amount of data.

The dose proportionality was also supported by the PopPK analysis.

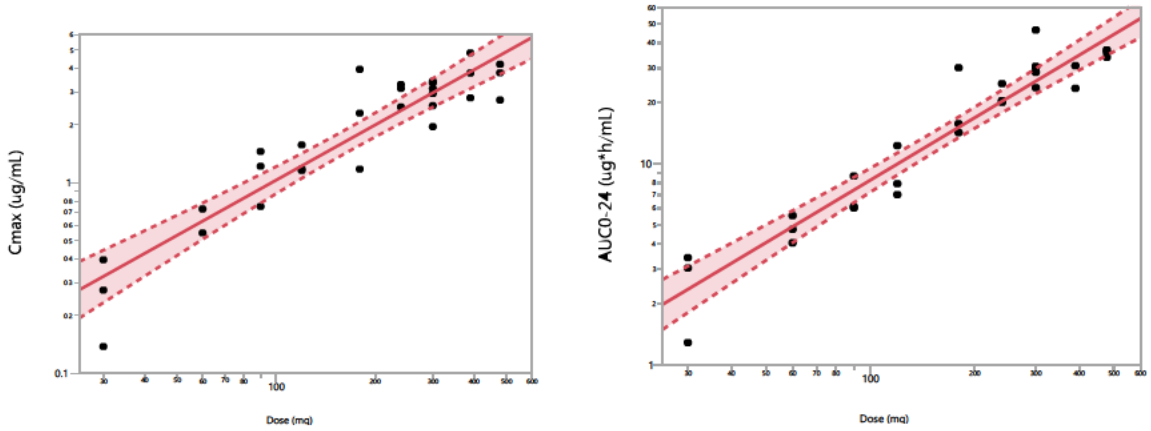
Table 51. Statistical Analysis of Apalutamide PK Dose Proportionality at Steady State (Week 4)

PK parameter	Dose (mg)	N	Dose-Normalized Geometric Mean [a]	GMR (%)	90% CI (%)
AUC_{0-24} (µg.h/mL)	30	3	14.64	-	-
	60	3	14.63	99.90	74.73, 133.56
	90	3	12.74	86.98	65.06, 116.29
	120	3	14.70	100.36	75.07, 134.16
	180	3	15.21	103.84	77.68, 138.83
	240	3	15.38	105.05	78.58, 140.44
	300	5	12.97	88.60	68.34, 114.87
	390	3	10.71	73.11	54.69, 97.74
	480	3	12.64	86.29	64.55, 115.36
C_{max} (µg/mL)	30	3	0.83	-	-
	60	3	0.80	95.38	73.10, 124.44
	90	3	0.84	101.00	77.41, 131.78
	120	3	0.82	98.02	75.12, 127.88
	180	3	0.98	118.03	90.46, 153.99
	240	3	0.94	112.31	86.08, 146.54
	300	5	0.68	81.52	64.26, 103.41
	390	3	0.68	81.86	62.74, 106.81
	480	3	0.70	84.16	64.51, 109.81

[a] Parameters were normalized to the reference dose of 30 mg.

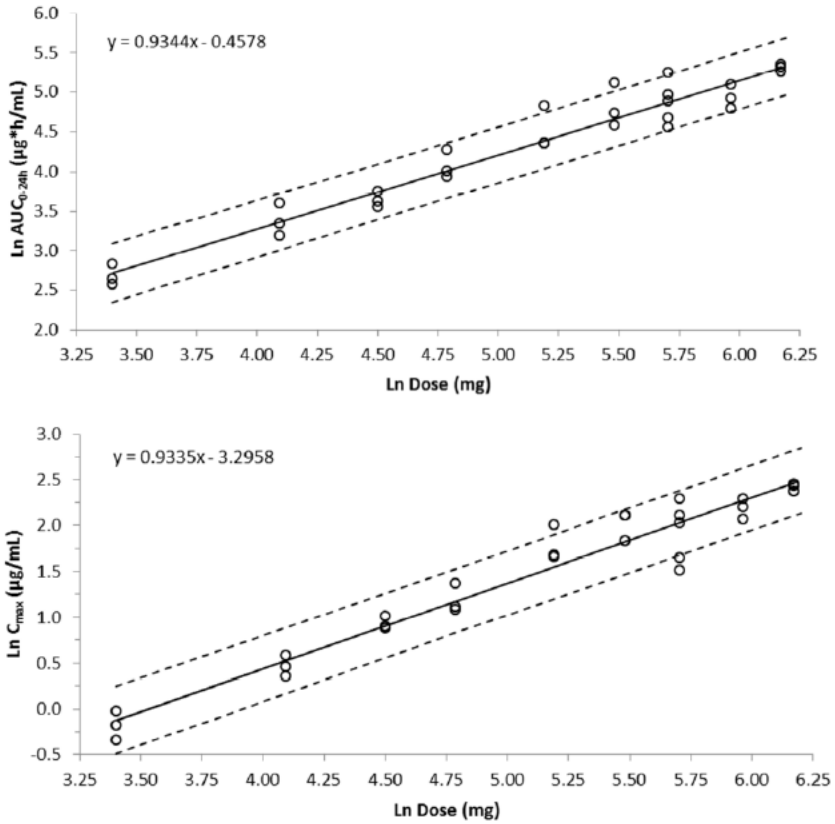
Source: Summary of Clinical Pharmacology Studies Table 39 (Section 2.7.2)

Figure 17. Dose Proportionality for Apalutamide C_{max} and AUC_{0-24h} After Single Dose



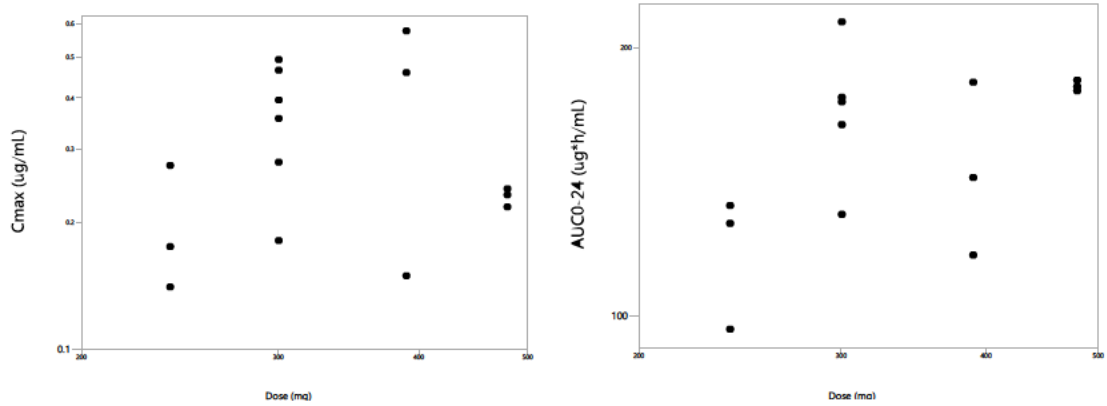
The shaded area is the 95% confidence interval of the slope. The dots represent the observed C_{max} and AUC_{0-24} from 30 patients in Study 001.

Figure 18. Dose Proportionality for Apalutamide C_{max} and AUC_{0-24h} at Steady State (Week 4)



Source: Summary of Clinical Pharmacology Studies Figure 15 (Section 2.7.2)

Figure 19. N-desmethyl Apalutamide C_{max} and AUC_{0-24h} After Mulitple Apalutamide Dose (Week 4)



Time Dependency

The values of apalutamide AUC_{0-24} after multiple once daily dose were lower than that of apalutamide AUC_{inf} after single dose (Table 47). In the popPK analysis the apalutamide total apparent oral clearance increased from 1.31 L/h to 2.04 L/h between single and repeat dosing at steady-state.

In vitro, apalutamide was identified as a CYP3A4 inducer. The apalutamide as a strong CYP3A4 inducer was confirmed in an in vivo study 1020, in which apalutamide 200 mg daily dose decreased midazolam (a CYP3A4 substrate) C_{max} and AUC by 77% and 92%, respectively. In vitro and in vivo (study 006), apalutamide was identified to be metabolized by CYP3A4 to form N-desmethyl apalutamide. The in vitro and in vivo results suggested that apalutamide is a strong inducer of CYP3A4 and induces its own metabolism (ie, auto-induction) upon repeated dosing, which explained the increase in oral clearance at steady state and less accumulation as predicted by single-dose data.

PK in Healthy Subjects and in Patients with CRPC

Only single dose was administered in healthy subjects studies. Comparisons was made using dose-normalized data from the studies 1011, 1015, and 1017 in healthy subjects and Cycle 1 Day 1 data from the standalone QT study 1019 in subjects with CRPC (Table 52). To-be-market tablet formulation was used in these studies. Mean C_{max} and AUC_{0-24} of apalutamide appeared to be slightly higher in healthy subjects by about 17% to 23% and 30% to 47%, respectively, compared to subjects with CRPC. Median t_{max} was comparable between healthy subjects and subjects with CRPC. Comparison of N-desmethyl apalutamide PK between healthy subjects and subjects with CRPC after a single dose of apalutamide was not done because characterization of the N-desmethyl apalutamide PK profile requires serial PK sampling for at least 816 hours, which couldn't be practically achieved in Studies 001 and 1019 in subjects with CRPC.
In population PK analysis, healthy subjects (n=117) showed higher apalutamide ($AUC_{0-24,ss}$ GMR 1.47 (90% CI 1.40 to 1.55)) and N-desmethyl apalutamide ($AUC_{0-24,ss}$ GMR 1.30 (90% CI 1.26 to 1.35)) exposure comparing to these of CRPC patients (N=975) at steady-state.

Table 52. Apalutamide PK Parameters Following Single-Dose of 240-mg Apalutamide in Healthy Subjects and Subjects With CRPC

Study ID	N	Population	Mean (SD)		Median (Range)
			C_{max} (µg/mL)	AUC_{0-24} (µg.h/mL)	t_{max} (h)
1011 [a]	15	Healthy subjects	2.42 (0.381)	31.1 (6.86)	3.03 (1.00-5.00)
1015 [b]	55	Healthy subjects	2.50 (0.42)	28.0 (4.12)	3.00 (1.00-6.00)
1017 [c]	47	Healthy subjects	2.53 (0.492)	27.4 (5.84)	3.00 (1.50-6.00)
1019 [d]	45	Subjects with CRPC	2.06 (0.582)	21.1 (4.93)	2.12 (1.08-5.10)

N=number of subjects in the dose group with estimable PK parameters.
[a] Treatment B (tablet).
[b] Treatment A (tablet), dose-normalized to 240 mg.
[c] Treatment A (tablet) only, dose-normalized to 240 mg.
[d] Cycle 1 Day 1 (tablet).

Source: Summary of Clinical Pharmacology Studies Table 38 (Section 2.7.2)

19.4.3. Population PK and/or PD Analyses

Applicant conducted population pharmacokinetic (PK) analysis of apalutamide and its active metabolite JNJ-56142060 (N-desmethyl-apalutamide, M3) to describe the PK of apalutamide and JNJ-56142060 after oral dosing. The objectives were:

- To obtain estimates of typical PK parameters and quantify their related inter- and intra-individual variability for apalutamide and JNJ-56142060 in subjects with prostate cancer,
- To provide a quantitative assessment of the potential effect of the intrinsic and extrinsic factors on apalutamide and JNJ-56142060 exposure to consider the need for apalutamide dose adjustments in special subpopulations,
- To derive individual exposure metrics [area under the curve at steady-state ($AUC_{0-24,ss}$), pre-dose concentration at steady-state ($C_{0h,ss}$) and possibly maximum concentration at steady-state ($C_{max,ss}$)] for apalutamide and its JNJ-56142060 metabolite for subjects in study ARN-509-003 (SPARTAN).

Datasets

Rich and sparse plasma concentration data of apalutamide and JNJ-56142060 obtained from 7 clinical studies [ARN-509-001, 56021927PCR1008, 56021927PCR1011, 56021927PCR1018, 56021927PCR1019, 56021927PCR1021 and ARN-509-003 (SPARTAN)] were pooled for the population PK analysis. The clinical studies were selected according to the following criteria:

- the availability of PK data in subjects with NM-CRPC or metastatic CRPC (mCRPC),
- characterization of the full PK profile, including administration of tablets and softgel capsules,
- the clinical studies performed in Japanese subjects to allow proper assessment of the race effect.

A list of the studies included in the population PK analysis is provided below and Table 53 in results section provides a summary of the key characteristics for each study.

- Study ARN-509-001: a multi-center, first in man, Phase 1/2, dose-escalation and proof-of-concept study, in which eligible subjects with progressive advanced CRPC received oral doses of apalutamide to determine the safety, PK and preliminary evidence of the anti-tumor effects of apalutamide. The objective of this study was to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose,
- Study 56021927PCR1008: an open-label, multicenter, Phase I study conducted in Japanese subjects with mCRPC. The primary objective of this study was to determine the tolerability, safety, PK and preliminary evidence of the anti-tumor effects of apalutamide after the administration of an oral dose of apalutamide at 240 mg
- Study 56021927PCR1011: the primary objective of this Phase 1 randomized, openlabel, single-center study was to evaluate the PK and relative bioavailability of apalutamide

when administered as 3 different tablet formulations compared with the softgel capsule formulation used before in healthy male subjects at a single dose of 240 mg. Only data from relevant tablet formulation was included in the analysis. The secondary objectives are to explore the potential effects of concomitant food intake on the single-dose PK of the final selected tablet formulation and, also to assess the safety and tolerability of the apalutamide tablet formulations and softgel capsule,

- Study 56021927PCR1018: a single-dose (240 mg), open-label study to evaluate the pharmacokinetics of apalutamide in subjects with mild or moderate hepatic impairment compared with subjects with normal hepatic function,
- Study 56021927PCR1019: an open-label Phase 1b QT/QTc study of apalutamide conducted in subjects with CRPC. The main objectives of this study were to investigate the effects of apalutamide and its active metabolite, on ventricular repolarization (QTcF) and other electrocardiogram (ECG) parameters at a dose level of 240 mg daily. This study evaluates the PK profile of apalutamide and its relationship with QTcF interval,
- Study 56021927PCR1021: a single-dose (60, 120 and 240 mg), open-label, randomized, parallel-group study to assess the pharmacokinetic profile of apalutamide when administered as the tablet formulation in healthy male Japanese subjects.

All plasma samples with quantifiable plasma apalutamide and JNJ-56142060 concentrations, with available date and time, as well as apalutamide dose administration were used for the population PK analyses. A number of samples were not included in the analysis due to quantifiable concentrations measured before the first dose, concentrations with incomplete dosing history or with values that are inconsistent with the sampling time. No records were deleted from the dataset, but records that, for any reason, were excluded from the analysis were marked.

Population PK analysis

The applicant performed the population PK analysis using a nonlinear mixed effects modeling approach where the typical value of model parameters, their variances, and residual noise in apalutamide and JNJ-56142060 plasma concentrations were estimated. The plasma concentration-time data were used for non-linear mixed effect modeling using NONMEM® version 7.1.0 or higher (ICON plc)24 in a validated environment, Navigator 9.1.5146, based on Good Automated Manufacturing Practice (GAMP) and in accordance with 21 CFR Part 11 and good clinical practice (GCP) regulations. The Fortran compiler was Intel(R) Fortran 64 Compiler Professional, Version 11.1. The first-order conditional estimation method (FOCE) estimation method with INTERACTION was used. The exploratory analysis, diagnostic graphics and postprocessing of NONMEM® analysis results were carried out in R version 3.2.3.
The applicant conducted the analysis in the following steps:

1. Exploratory analysis: An initial exploratory analysis on plasma concentrations of apalutamide and JNJ-56142060, as well as on the subject covariates was performed.

2. Model development: Dataset A was used to develop the reference population PK model for apalutamide and JNJ-56142060
3. Model evaluation: The reference model was internally evaluated using dataset A. In addition, an external evaluation on Dataset B was performed to assess the predictability of the reference population PK model in subjects from study ARN-509-003. Visual predictive check (VPC), prediction corrected VPC (pcVPC) and goodness-of-fit (GOF) plots on the data from the Dataset A and B were used as evaluation methods.
4. Covariate analysis and Potential refinements in the model developed were evaluated to adequately describe the available data in the combined dataset and to obtain the final model.

Model development

The structural model was developed using data from study ARN-509-001 to describe the pharmacokinetics of apalutamide. The analysis did not include the description of the metabolite. The population PK analysis of apalutamide pharmacokinetics was initially described by an open linear two-compartment disposition model with time-dependent CL and apparent firstorder absorption, quantified by the apparent absorption rate constant (ka) after a lag-time (tlag). Both softgel capsule and tablet formulations have been used during the clinical development program of apalutamide, and provided comparable exposure following a single dose 240 mg. A different ka for each formulation was estimated separately to account for the small difference in peak concentrations. The population PK model was parameterized in terms of apparent volumes of distribution of the central (Vc/F) and peripheral (Vp/F) compartment, apparent intercompartmental clearance (Q/F) and apparent total clearance (CLt/F). The CLt/F was composed of a constant, not inducible, clearance (CLni/F) and inducible clearance (CLi0/F) that increased over time until achieving steady state (CLiss/F) after the continuous once daily dosing. The inducible clearance was concentration-independent and the time to achieve steady state was driven by a first-order turnover rate constant (kenz) after a lag-time needed to initiate the enzyme induction (tenz). The base population PK model also accounted for the JNJ-56142060 formation, disposition and elimination. Given the absence of plasma concentration of JNJ-56142060 following the intravenous administration of JNJ-56142060, it is not possible to simultaneously determine the fraction of apalutamide converted to JNJ-56142060 and the volume of distribution of JNJ-56142060 from plasma concentration of apalutamide and JNJ 56142060 obtained after oral administration of apalutamide. Therefore, it was assumed that the apalutamide elimination is equivalent to the JNJ-56142060 formation, thus the PK model parameters estimated for JNJ-56142060 become apparent. The disposition of JNJ-56142060 was initially described by an open one-compartment disposition model, which was parameterized in terms of apparent clearance (CLm/F), apparent volume of distribution of the central (Vcm/F) compartment. During the model development, it was investigated whether the formation of JNJ-56142060 was driven by the total apalutamide clearance, or just the inducible or non-inducible clearance. In addition, the inclusion of a peripheral compartment to describe

the JNJ-56142060 disposition was assessed. Between subjects (or inter-individual) variability (IIV) in PK parameters were included in the model and assumed to be log-normally distributed according to the following equation:

$$Pj= P^* \times \varepsilon^{\eta pj}$$

where P_j is the PK parameter for the j_{th} individual, P* is the typical value of the PK parameter, *ηpj* (IIV) is an independent and normally distributed random between subject variable with zero mean and variance ω_P^2. Inclusion of IIV on PK parameters was evaluated and the magnitudes of IIV were expressed as coefficients of variations (CVs). However, the long half-life of apalutamide and the sampling scheme implemented in the clinical studies included in the analyses dataset precluded the evaluation of inter-occasion variability.

Residual unknown variability (RUV) was evaluated by using an additive error model after natural logarithmic transformation of the measured plasma concentrations and model predictions. The same error model was used to describe the JNJ-56142060 RUV in plasma concentration. The shrinkage obtained by NONMEM® for those parameters for which an IIV was estimated was also assessed. Small values of shrinkage i.e. 20% or less, indicate good individual estimates of a PK parameter of interest, while larger values i.e. 30% or more, indicate poor individual estimates of a PK parameter of interest or that the values estimated are "shrunk" towards the population mean values.

The covariates such as age, body weight, race, AST, ALT, ALP, TB, TP, serum albumin, eGFR-MDRD, health status (healthy subjects vs subjects with CRPC and further subcategorizing subjects with CRPC with ECOG=0 and ECOG=1) at baseline, co-medication with cytochrome inhibitors (CYP2C8) and inducers (CYP3A4) were included in the stepwise covariate model (SCM) approach. Height, body surface area (BSA), body mass index (BMI) and lean body (LBM) mass were not tested as covariate because of its correlation with body weight. If after the covariates analysis, body weight was identified as a significant covariate, then the other body size metrics described above would be evaluated to investigate whether any of these covariates improve the fit relative to the body weight. Serum creatinine (CREA) and creatinine clearance (CRCL) were neither tested as covariates due to their correlation with eGFR-MDRD. In addition, if the exploratory covariate analysis identifies any correlation among the covariates that may cause collinearity if both covariates are present in the model, only the most relevant covariate will be included in the SCM approach. The EBE's of the individual model parameters from the reference model were computed using NONMEM, to screen the influence of subject covariates on model parameters. The covariate screening was based on visual graphical inspection and stepwise linear regression of the relationships between the EBE and the continuous covariates and analysis of variance (ANOVA) for the categorical covariates. Only covariates that were statistically significant ($p < 0.001$) and had a coefficient of determination $r^2 > 0.15$ with model parameters were considered as potentially clinically relevant and were further tested one by one in NONMEM to be incorporated in the population model. Categorical covariates were incorporated into the model as index variables, whereas continuous covariates were included through the centering on the median (or a rounded value around the median) and power equations. Missing values for the quantitative covariates were imputed using the median value

in each data set, and missing values for categorical covariates were analyzed as an independent category, if feasible. For categorical covariates, if less than 30 subjects were present in a category, the effect of that category was not independently assessed. The resulting minimum value of objective function (MVOF) after fitting the reference model was considered as a starting value to test the significance of the covariates in NONMEM. The inclusion of one covariate in the population model was considered if a decrease in the MVOF of greater than 7.88 (χ^2 test, df: 1, $p < 0.005$) was obtained during the univariate analysis. After the univariate analysis in NONMEM, the covariates with a statistically significant effect on pharmacokinetic parameters were incorporated into the population model, all at one time to get the intermediate population pharmacokinetic model. A full model was determined when no additional covariates could improve the model fit. Then, the relative contribution of each covariate to the goodness-of-fit was re-evaluated by deleting it from the full model. If the exclusion of a fixed effect resulted in an increase in MVOF less than 10.83 (df = 1, $p < 0.001$), the covariate was dropped out of the model. With this methodology, only covariates showing significant contributions were conserved in the population pharmacokinetic model. The population predicted parameter-covariate relationships together with the 95% prediction interval (PI), computed based on the IIV on the PK parameter of interest, were compared with the observed individual relationships. Furthermore, the final model was used to evaluate the magnitude of the covariate effects on the exposure of apalutamide and JNJ-56142060.

Results

The analysis datasets were categorized as follows:

1) Dataset A comprised a total of 6 studies (ARN-509-001, 56021927PCR1008, 56021927PCR1011, 56021927PCR1018, 56021927PCR1019 and 56021927PCR1021), which were included for the development of the population PK model.
2) Dataset B consisted of the pivotal Phase III study ARN-509-003 (SPARTAN) and was used as an external evaluation of the population PK model developed from Dataset A.
3) Dataset C combined the Dataset A and Dataset B, and was used for updating the population PK model parameters and conducting the covariate analysis.

The summary of subject's demographic and baseline characteristics stratified by dataset used in the development of the population PK model are shown in Table 53 below. The final model describing the PK of apalutamide and JNJ-56142060 is shown in Table 54. Apalutamide PK were described with an open linear two-compartment disposition model with a time-dependent apparent clearance and apparent first-order absorption. The JNJ-56142060 pharmacokinetics were described with an open linear two-compartment disposition model with linear elimination from the central compartment. IIV in model parameters was quantified on ka, Vc, CLt (sum of inducible and not inducible clearance), Vp, Q, F, Vcm, CLm, Vpm and Qm without quantifying correlations between IIV's. An additive error model was used to quantify the residual unexplained variability after natural logarithmic transformation of the measured plasma

concentrations of apalutamide and JNJ-56142060 with a separate estimate of the variance for each compound. The parameter-covariate relationships included in the final model are body weight on Vp/F and F, albumin on F and health status on Qm/F and F. The final model parameters are shown in Table 54, and were estimated with adequate precision with a RSE <35.2% for the fixed effects and RSE<30% for the random effects. The condition number was 127. In addition, the residual error was 22.6% for apalutamide and 14.9% for JNJ-56142060.

Table 53. summary of subject's demographic and baseline characteristics stratified by dataset used in the development of the population PK model (Source: Applicant's population PK report, Table 5, page 52)

Subject Characteristics	Dataset A (N=294)	Missing data in dataset A	Dataset B (N=798)	Missing data in dataset B	Dataset C (N=1092)	Missing data in dataset C
Age (y)	61.0 [18, 91]	0 (0.0)	74.0 [48, 94]	0 (0.0)	72.0 [18, 94]	0 (0.0)
Body weight (kg)	81.7 [49.8, 154.0]	9 (3.1)	85.0 [45.0, 182.1]	5 (0.6)	84.1 [45.0, 182.1]	14 (1.3)
Race[b]		0 (0.0)		133 (16.7)		133 (12.2)
White	241 (82.0)		520 (65.2)		761 (69.7)	
Caucasian	193 (80.1)		511 (98.3)		704 (92.5)	
Hispanic	48 (19.9)		9 (1.7)		57 (7.5)	
Black	24 (8.2)		47 (5.9)		71 (6.5)	
Asian	25 (8.5)		91 (11.4)		116 (10.6)	
Japanese	24 (96.0)		34 (37.4)		58 (50.0)	
Non-Japanese	1 (4.0)		57 (62.6)		58 (50.0)	
Other[c]	4 (1.4)		7 (0.9)		11 (1.0)	
Health status		0 (0.0)		0 (0.0)		0 (0.0)
Healthy subjects	117 (39.8)		0 (0.0)		117 (10.7)	
CRPC[d]	177 (60.2)		798 (100.0)		975 (89.3)	
ECOG=0	123 (69.5)		619 (77.6)		742 (76.1)	
ECOG=1	54 (30.5)		179 (22.4)		233 (23.9)	
AST (U/L)	22 [9, 190]	2 (0.7)	24 [12, 101]	0 (0.0)	24 [9, 190]	2 (0.2)
ALT (U/L)	20 [3, 170]	2 (0.7)	22 [6, 107]	0 (0.0)	22 [3, 170]	2 (0.2)
ALP (U/L)	80 [33, 802]	2 (0.7)	77 [30, 353]	0 (0.0)	78 [30, 802]	3 (0.3)
Total bilirubin (μmol/L)	8.6 [1.7, 37.6]	2 (0.7)	8.6 [1.7, 30.8]	1 (0.1)	8.6 [1.7, 37.6]	3 (0.3)
Hepatic impairment[e]		0 (0.0)		0 (0.0)		0 (0.0)
Normal	255 (86.7)		719 (90.1)		974 (89.2)	
Mild[f]	39 (13.3)		79 (9.9)		118 (10.8)	
Serum albumin (g/L)	43 [26, 51]	2 (0.7)	44 [35, 52]	0 (0.0)	44 [26, 52]	2 (0.1)
Total protein (g/L)	70 [55, 90]	127 (43.2)	70 [58, 81]	651 (81.6)	70 [55, 90]	778 (71.3)
eGFR (mL/min)[g]	102.3 [32.9, 150.0]	2 (0.7)	97.6 [21, 150]	133 (16.7)	100 [21, 150.0]	135 (12.4)
Renal impairment[h]		2 (0.7)		133 (16.7)		135 (12.4)
Normal	147 (50.0)		225 (28.2)		372 (34.1)	
Mild	106 (36.0)		347 (43.5)		453 (41.5)	
Moderate[i]	39 (13.3)		93 (11.7)		132 (12.1)	
Subjects with						
CYP Inhibitors	5 (1.7)	0 (0.0)	27 (3.4)	0 (0.0)	32 (2.9)	0 (0.0)
CYP Inducers	4 (1.4)	262 (89.1)	15 (1.9)	0 (0.0)	19 (1.7)	262 (24.0)

Continuous variables are expressed as median (range), whereas categorical variables are expressed as counts (%). AST, Aspartate transaminase; ALT, Alanine transaminase; ALP, Alkaline phosphatase; eGFR, Estimated glomerular filtration rate; CYP, cytochrome P450. [a]Studies 56021927PCR1011, 56021927PCR1018 and 56021927PCR1021 were conducted in healthy subjects, defined as non-cancer subjects. [b]Ethnicity (Caucasian, Hispanic, Japanese, Non-Japanese) is expressed as percentage of race classification (White, Asian). [c]Native Hawaiian, pacific islander, American Indian or Alaskan native,

Table 54. Population PK parameter estimates (RSE, %) for the base, reference and final population PK model for apalutamide and JNJ-56142060 (Source: Applicant's population PK report, Table 7, page 55)

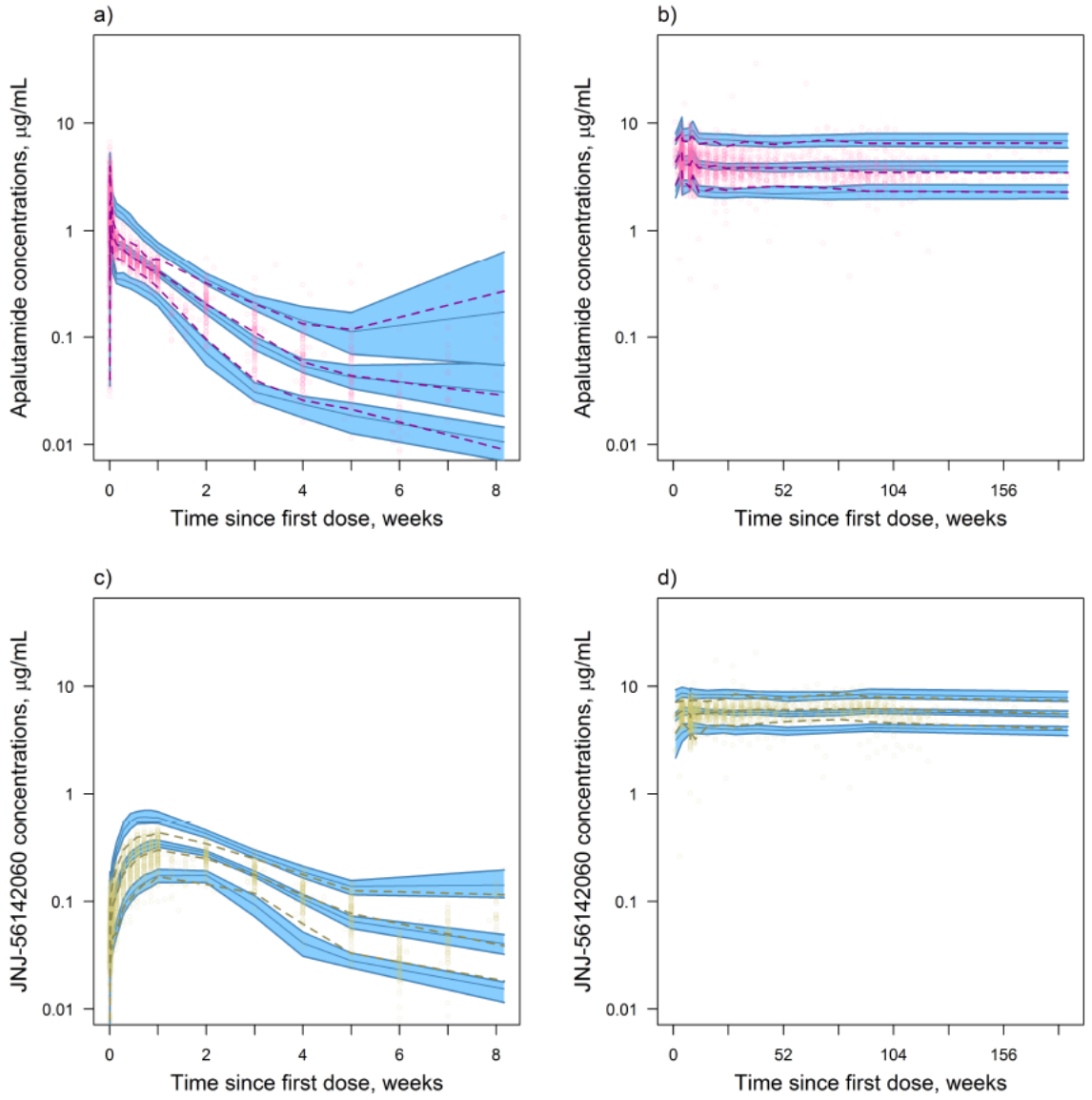
Pharmacokinetic Parameters[a]	Reference Model (Dataset A; Run003.mod)	Reference Model (Dataset C; Run004.mod)	Final Model (Dataset C; Run041.mod)
	Estimate (RSE%)	Estimate (RSE%)	Estimate (RSE%)
Apalutamide			
t_{lag} (h)	0.417 (0.3)	0.417 (0.3)	0.418 (0.3)
$k_{a,tablet}$ (1/h)	0.223 (7.0)	0.212 (6.8)	0.216 (6.7)
$\Theta_{capsule}$[b]	0.977 (9.8)	0.861 (8.8)	0.851 (8.6)
V_c/F (L)	16.1 (11.6)	16.4 (10.7)	14.5 (9.7)
CL_{ni}/F (L/h)	1.10 (5.4)	1.16 (3.8)	1.17 (4.4)
CL_{i0}/F (L/h)	0.222 (22.1)	0.182 (20.9)	0.141 (35.2)
CL_{iss}/F (L/h)	0.904 (6.0)	0.972 (4.6)	0.869 (6.0)
k_{enz} (1/h)	0.0015 (6.3)	0.0016 (4.1)	0.0016 (4.0)
t_{enz} (h)	49.5 (22.6)	57.7 (20.6)	57.7 (fixed)
V_p/F (L)	313 (4.3)	299 (4.5)	261 (4.3)
Θ_{WT}[c]	-	-	0.882 (12.7)
Q/F (L/h)	21.2 (4.2)	22.9 (3.5)	22.6 (3.5)
F_{CRPC}[f]	-	1 (fixed)	1 (fixed)
Θ_{weight}[d]	-	-	-0.519 (5.2)
$\Theta_{Albumin}$[d]	-	-	0.545 (13.0)
$\Theta_{healthy\ subjects}$[d]	-	-	0.27 (10.6)
JNJ-56142060			
V_{cm}/F (L)	26.9 (7.3)	26.3 (7.1)	26.3 (6.9)
CL_m/F (L/h)	1.51 (1.9)	1.6 (0.8)	1.53 (0.8)
V_{pm}/F (L)	242 (3.9)	223 (4.6)	212 (4.6)
$Q_{m,CRPC}/F$ (L/h)	50.5 (5.0)	53.1 (4.4)	67.3 (4.8)
$\Theta_{healthy\ subjects}$[e,f]	-	-	-0.355 (10.7)
Inter-individual variability (CV %)			
Apalutamide			
$\omega\ k_a$	47.3 (16.8)	59.0 (12.4)	60.7 (11.8)
$\omega\ V_c$	231.5 (12.5)	230.1 (14.6)	230.1 (14.9)
ω CL	23.8 (9.2)	19.1 (5.3)	19.1 (4.8)
$\omega\ V_p$	37.1 (13.5)	54.5 (8.5)	46.1 (8.1)
ω Q	34.1 (15.8)	35.2 (15.9)	34.6 (17.0)
ω F	26.5 (6.7)	22.7 (4.7)	15.0 (4.6)
JNJ-56142060			
$\omega\ V_{cm}$	56.8 (23.0)	58.2 (23.9)	56.8 (25.3)
$\omega\ CL_m$	8.3 (41.1)	4.6 (52.1)	7.3 (16.2)
$\omega\ V_{pm}$	32.8 (14.1)	47.1 (10.2)	47.3 (10.9)
$\omega\ Q_m$	30.6 (19.1)	31.0 (10.2)	22.6 (29.2)
Residual variability (CV %)			
σ_1 (Apalutamide)	22.4 (0.4)	22.6 (0.3)	22.6 (0.3)
σ_2 (JNJ-56142060)	13.7 (0.3)	14.9 (0.2)	15.0 (0.2)
Objection function value	-21334.332	-31011.378	-31703.204

RSE, relative standard error; CV, coefficient of variation; t_{lag} is the lag-time after which apalutamide absorption begins; $k_{a,tablet}$, apalutamide apparent first-order absorption rate constant for tablet formulation; *capsule* is the formulation effect of apalutamide capsule being $k_{a,capsule} = k_{a,tablet}/F \times \Theta_{capsule}$; V_c/F, apalutamide apparent volume of distribution of the central compartment; CL_{ni}/F, apalutamide apparent not inducible clearance; CL_{i0}/F, apalutamide apparent inducible clearance at baseline; CL_{iss}/F, apalutamide apparent induced clearance at steady state; CL, apalutamide total clearance; k_{enz}, enzyme inducible first-order turnover rate; t_{enz}, lag time after which the induction begins; V_p/F, apalutamide apparent volume of distribution of the peripheral compartment; Q/F, apalutamide apparent inter-compartmental clearance; V_{cm}/F, JNJ-56142060 apparent volume of distribution; CL_m/F, JNJ-56142060 apparent clearance; V_{pm}/F, JNJ-56142060 apparent volume of distribution of the peripheral compartment; Q_m/F, JNJ-56142060 apparent inter-compartmental clearance; F, relative biovailability. [a]Typical PK parameters reported are apparent since the absolute bioavailability and the fraction of apalutamide converted to JNJ-56142060 are unknown and not estimable from the available datasets. [b]$k_{a,capsule} = k_{a,tablet} x \Theta_{capsule}$. [c] $V_p/F = \Theta_{VP/f}\ x(WT/75)^{\Theta WT}$. [d]$F = 1x(AGE/75)^{\Theta WT} x(WT/75)^{\Theta WT} x(ALB/44)^{\Theta WT} x(1+\Theta_{HLTH})$. [e] $Q_m/F = \Theta_{Qm/F} x(1+\Theta_{healthy\ subjects})$. [f]CRPC castrate resistant prostate cancer subjects

The prediction corrected VPC in Figure 20 shows that the final model adequately described the time course of both apalutamide and JNJ-56142060 plasma concentrations following single and multiple dose administrations. Both the general trend in the data and the observed variability are well captured by the population PK model. There were no further covariates identified after both the stepwise covariate modelling and as shown in forest plots. The forest plot in Figure 21 show that the $AUC_{0\text{-}24,ss}$ across different subgroups, based on age, body weight, race, hepatic impairment, renal impairment, albumin and co-medication with CYP2C8 inhibitors and CYP3A4 inducers, had relatively small observed differences which fall within the 80-125% interval. Only for health status a marked difference could be observed with a geometric mean ratio of 1.42 and 1.29 for the $AUC_{0\text{-}24,ss}$ of apalutamide and JNJ-56142060, respectively and a geometric mean ratio of 1.39 and 1.29 for the $C_{max,ss}$ of apalutamide and JNJ-56142060, respectively. These updated plots were based on response which was requested by the Agency (EDMS-ERI-154336810, 1.0).

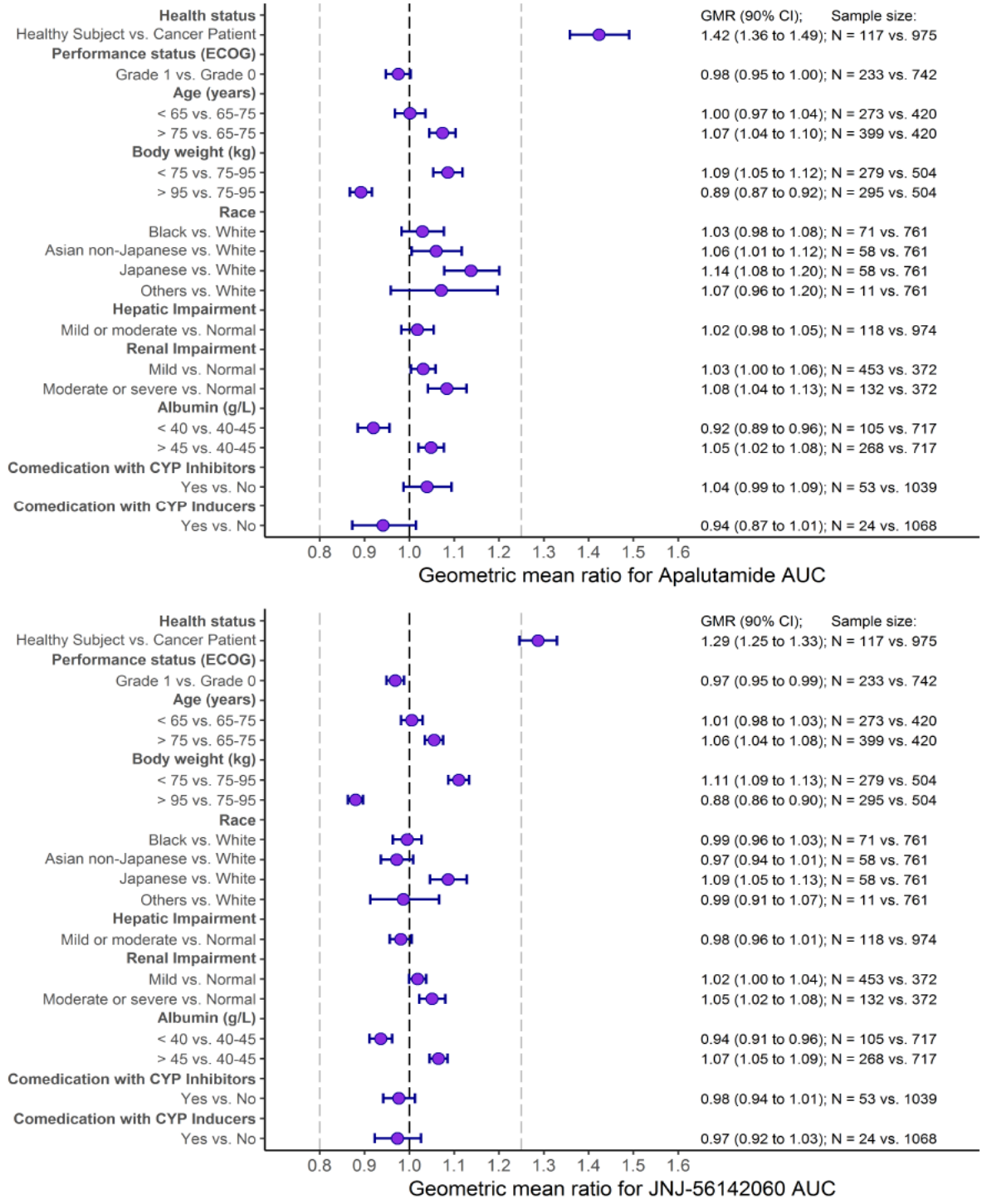
During covariate analysis by the applicant, the following covariate-parameter relationships with r^2 above 0.15 and p-value below 0.001 were selected for the univariate analysis: body weight on Vp/F and F, age and albumin on F, and health status on Qm/F and F. The applicant investigated if the other body size parameters BSA, BMI and LBM could potentially be better predictors for the covariate relationships instead of body weight. The linear regression analysis showed that BSA, BMI and LBM had a lower or comparable correlation with both Vp/F and F. Therefore, body weight was carried forward for further investigation. In addition, it was observed that there was no difference in Qm/F or F between cancer subjects with an ECOG score of 0 and 1. The difference in Qm/F or F was mainly driven by the health status (healthy vs cancer subjects). Hence, health status was considered for the univariate analysis without further differentiating in cancer subjects according to their ECOG score. There was no significant difference in individual parameter estimates between White, Black and Asian subjects. Because 24 out of 25 Asians were Japanese in Dataset A and because of the low number of Japanese and Black subjects in this data, the difference between races and between Japanese and non-Japanese cannot be investigated with only Dataset A. In addition, because of the low number of subjects taking concomitant Cytochrome (CYP3A4) inducers (5 subjects; 1.7%) and CYP2C8 inhibitors (4 subjects; 1.4%), the effect of concomitant administration of CYP3A4 inducers and CYP2C8 inhibitors should be evaluated with caution in this graphical analysis.

Figure 20. pcVPC applying the final model for apalutamide (panels a and b) and JNJ-56142060 (panels b and d) for single and multiple doses (Source: Applicant's population PK report, Figure 22, page 109)



Upper panels (a and b): pcVPC of apalutamide; lower panels (c and d): pcVPC of JNJ-56142060; left panels (a and c): single dose; right panels (b and d): multiple dose.
Blue solid lines: median, 5th and 95th percentiles of the simulated data with its 95% confidence interval (blue shaded area); purple and green dashed lines: median, 5th and 95th percentiles of the observed data for apalutamide (a, b) and JNJ-56142060 (c, d) respectively

Figure 21. Forest plot ($AUC_{0-24,ss}$) for the Covariate Evaluation for Apalutamide (upper panel) and Ndesmethyl apalutamide (lower panel), using Dataset C (Source: Applicant's Health Authority response, Figure 2. EDMS number: EDMS-ERI-154336810, 1.0)



GMR: geometric mean ratio; CI: confidence interval; AUC: area under the curve at steady state ($AUC_{0-24,ss}$)

Reviewers comments
The model was appropriate for characterizing the PK profile of apalutamide and JNJ-56142060. A linear, two-compartment disposition model with first-order absorption and time dependent clearance was suitable to describe the plasma pharmacokinetic profiles of apalutamide while the profile of JNJ-56142060 plasma concentrations was also characterized by a linear, two-compartment disposition model with first-order formation from apalutamide, as shown in pcVPC. The parameters were well estimated with good precision. The reviewer agrees with the identified covariates. The applicant updated population PK analysis in Health Authority response (EDMS-ERI-154336810, 1.0). For CYP3A4 population PK analysis, the applicant initially did not account for 5 subjects in Study ARN-509-001 who had some PK samples collected during dexamethasone co-administration. In Studies 56021927PCR1008, 56021927PCR1019, and ARN-509-003 (SPARTAN), 1 subject in each study (3 subjects total) received topical or ophthalmic administration of dexamethasone. Hence, these subjects were correctly labeled as not receiving systemic CYP3A4 inducers. Finally, in Study ARN-509-003 (SPARTAN), 3 subjects, who received the salt form of dexamethasone (dexamethasone sodium phosphate) were later labeled accordingly in the population PK dataset, making a total of 24 subjects are now identified as those who have received apalutamide co-administered with CYP3A4 inducers at any time during the treatment. Further corrections to update population PK analysis were done on CYP2C8. In total, 53 subjects (6 from Study ARN-509-001 and 47 from Study ARN-509-003 [SPARTAN]) were now identified as subjects who received apalutamide co-administered with CYP2C8 inhibitors. The geometric mean ratios for $AUC_{0-24,ss}$ and $C_{max,ss}$ after corrections in the dataset fell within 80-125% interval, and supports the applicant's claim that no dose adjustments will be necessary when CYP3A inducers and CYP2C8 inhibitors are co-administered with apalutamide.

19.4.4. Exposure-Response Analyses

<u>Exposure efficacy</u>

The primary objective of the study was to evaluate the efficacy of apalutamide compared to placebo in patients with high risk NM-CRPC as measured by metastasis-free survival (MFS), based on BICR of tumor assessments. The applicant performed efficacy analyses for the ITT population, using the randomization stratification factors as documented in the IVRS, unless otherwise specified. The ITT included 1207 randomized subjects (806 subjects in the apalutamide arm and 401 subjects in the placebo arm). As of the clinical cut-off date (19 May 2017), the median survival follow-up time for all subjects was 20.3 months. Analyses were performed for MFS, TTM, and PFS using both US censoring and ex-US censoring rules

· Methods

The applicant firstly used univariate Kaplan–Meier analyses to explore the influence of the treatment, prognostic factors as well as the exposure metrics on MFS. The apalutamide exposure metrics were sorted by rank order and classified into four approximately equal size groups based on the quartiles of exposure. An additional category was included for the subjects

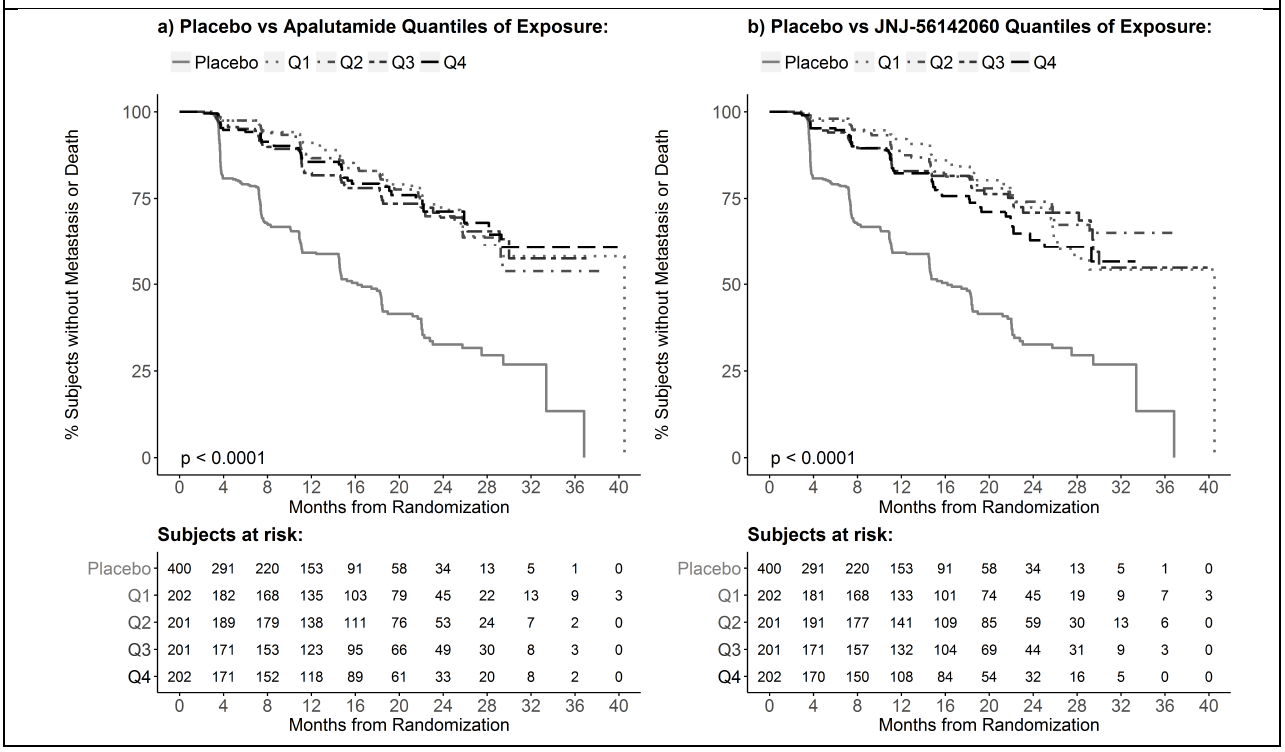
randomized to placebo arm. Log-rank tests for homogeneity assessed differences between the Kaplan–Meier curves for exposure categories, and pairwise log-rank tests compared exposure categories with one another, in presence and absence of placebo. If the correlation between the exposure metrics of apalutamide and JNJ-56142060 was lower than 0.80, the analysis described above for apalutamide was also conducted for JNJ-56142060.

Secondly, the applicant used multivariate Cox regression analysis was conducted in a step-wise manner. Initially, the treatment effect and the prognostic factors identified were incorporated into the model (Model A) and the relative contribution of each of them was evaluated. In a next step, the exposure metrics of apalutamide (and JNJ-56142060, if the correlation between the exposure of apalutamide and was lower than $r^2 = 0.80$), were incorporated into the previous model as continuous variables (Model B). Subjects randomized to placebo arm had apalutamide and JNJ-56142060 exposure metric assigned to zero. If Model B shows that the treatment effect is not statistically significant (p-values > 0.05). after the simultaneous inclusion of the apalutamide and JNJ-56142060 exposures, then the treatment effect was removed from the model (Model C). The impact of apalutamide and JNJ-56142060 exposure on MFS, after adjusting for the prognostic factors, was assessed by the hazard ratio and its 95% confidence interval (CI). The p-values as well as the change in -2 loglikelihood (LL) after the inclusion of each exposure metric was used for model comparison. Furthermore, if the apalutamide and JNJ-56142060 exposure metrics were found to be statistically significant variables, the proportion of treatment effect that can be explained by apalutamide and JNJ-56142060 exposures was calculated using Li's method.

· Results

The exposure-efficacy results are shown in Figure 22 below. Apalutamide 240 mg/day has been proven to be efficacious in extending the MFS in subjects with NM-CRPC. No statistically significant exposure-MFS relationship was found for apalutamide and N-desmethyl apalutamide when categorized by quartiles of exposure (Figure 22) or when used as a continuous variable in the univariate and multivariate Cox regression models. Therefore, differences in apalutamide and N-desmethyl apalutamide exposure when 240 mg/day is administered are not expected to be associated with clinically relevant differences in MFS in subjects with NM-CRPC. These results support that a 240 mg once daily dose of apalutamide provides efficacious exposure in most subjects with NM-CRPC with similar efficacy across the exposure range.

Figure 22. Kaplan Meier Plot for MFS as a function of Placebo and the Lowest Exposure Quartile (Q1) to Highest Exposure Quartile (Q4) of Apalutamide (Left Panel) and N-Desmethyl Apalutamide (Right Panel) Plasma Steady-State AUC_{0-24} (Source: Applicant's exposure-response report (Efficacy and Safety), Figure 6, page 42)



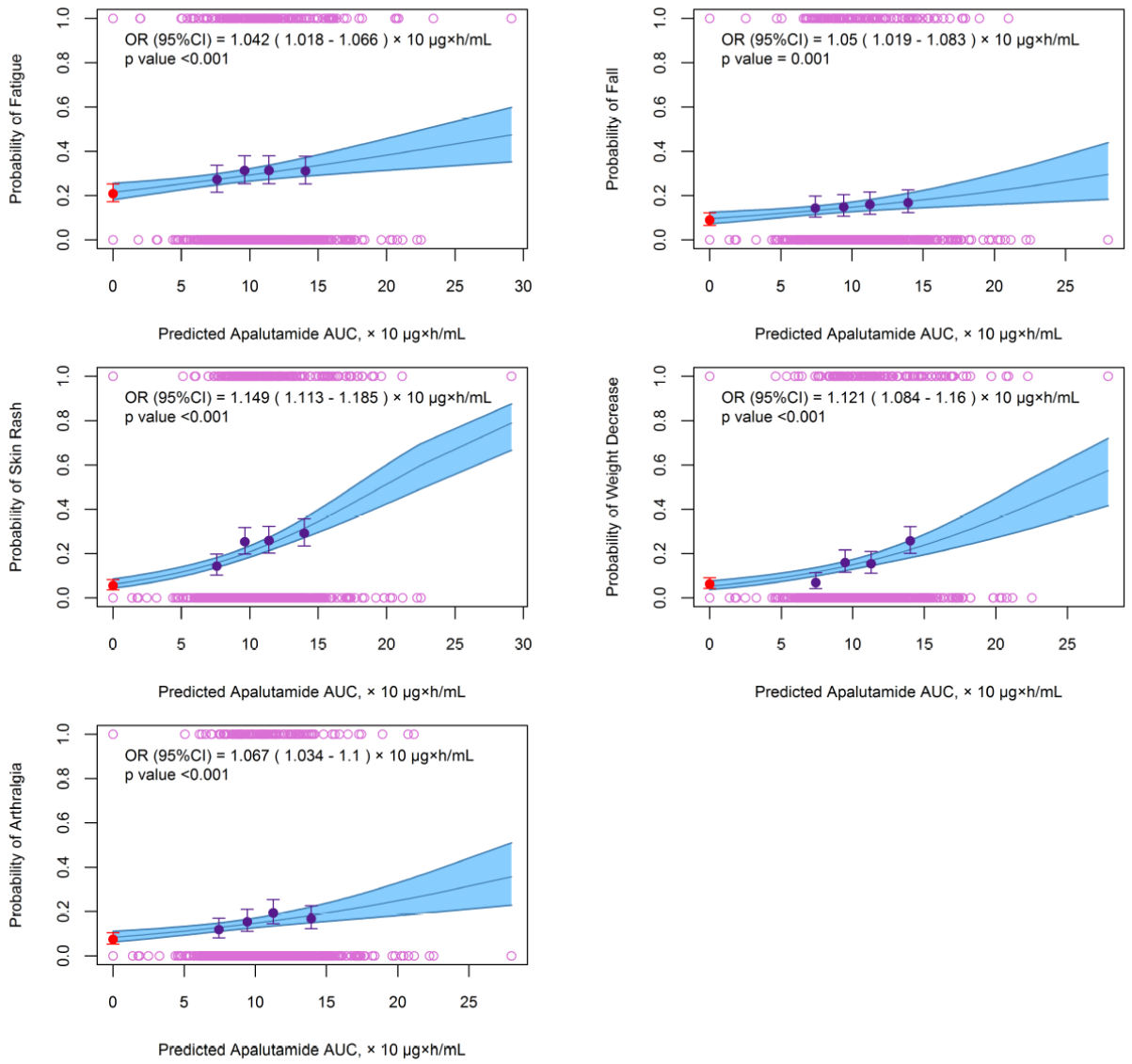
Exposure safety

The applicant evaluated the relationship between exposure to apalutamide, its active metabolite JNJ-56142060, and selected clinical safety endpoints including fatigue, fall, skin rash, weight decreased, and arthralgia was explored. The AEs were selected based on clinical relevance with incidence higher than 10%, at any grade. Data from Study ARN-509-003 with 1,201 treated subjects (803 subjects receiving apalutamide and 398 subjects receiving placebo) were included in the exposure-response analysis. A similar approach as for exposure-efficacy was used.

· Results

Fatigue, fall, skin rash, weight decrease and arthralgia are apalutamide-related toxicities affecting to more than 10% of the NM-CRPC subjects. The univariate logistic regression analysis for the apalutamide AUC0-24h (Figure 23) showed that the probability of experiencing one of the described AE significantly increases as apalutamide AUC0-24h increases.

Figure 23. Logistic regression representing the probability of experiencing fatigue, fall, skin rash, weight decrease and arthralgia as function of apalutamide steady-state $AUC_{0\text{-}24h}$ (Source: Applicant's exposure-response report (Efficacy and Safety), Figure 7, page 43)



The upper and lower open circles represent the presence or absence of a given treatment-emergent event across the range of the predicted apalutamide $AUC_{0\text{-}24h}$ exposure respectively. The dots depict the observed incidence for the placebo and the quartiles of exposure for the apalutamide arm respectively whereas the corresponding vertical bars represent the exact 95% CI calculated using Wilson's method.[16] Finally, the middle line and its corresponding shaded area represent model-based exposure–safety relationship and the 95% CI respectively.

Based on the exposure-AE relationships observed, the incidence of each AE was predicted for typical exposures observed at doses of 240, 180 and 120 mg once daily using the logistic regression model. As expected, the predicted incidence was lower with lower doses with some

of these differences being small (<5% difference between 240 and 120 mg) especially for fatigue, fall, and arthralgia, regardless of whether placebo subjects were included or not. The impact of a lower dose on the incidence of skin rash and weight decrease was more significant, as predicted by the stronger relationship observed with exposure.

Reviewer's comments
The analysis performed by the applicant is appropriate for this analysis. The ER analysis for efficacy showed no significant relationship between exposure and efficacy, which could suggest that the efficacy of apalutamide could have reached a plateau. Also, even though apalutamide is well tolerated, there was a significant relationship between exposure and fatigue, fall, skin rash, weight decrease and arthralgia, at any grade, have a positive and statistically significant relationship with apalutamide average exposure expressed as predicted steady-state $AUC_{0\text{-}24h}$ *for the average dose from Day 1 up to time of AE.*

19.4.5. PBPK Analyses- enzyme mediated DDIs

Objective
The objectives of this review are to evaluate the adequacy of the physiologically-based pharmacokinetic (PBPK) modeling submitted by the applicant to support dosing recommendations of apalutamide concomitant administration with CYP inhibitors or inducers. The following PBPK reports were submitted in this NDA:

- Study FK10644 : Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-56021927 and inhibitors/inducers of CYP2C8 and CYP3A4 in Human Subjects
- Study FK13005: A physiology based pharmacokinetic approach to assess potential transporter mediated drug-drug interactions with JNJ-56021927 (Apalutamide) as perpetrator in human

Background
Apalutamide is an orally administered, selective androgen receptor (AR) inhibitor for the treatment of men with non-metastatic castration-resistant prostate cancer. The recommended dose is 240 mg (4×60-mg tablets) once daily (qd), administered with or without food. Apalutamide is metabolized by cytochrome P450 (CYP) 2C8 and CYP3A4 to form an active metabolite, N-desmethyl apalutamide (M3). The applicant reported that M3 is 3 times less potent compared to apalutamide. M3 is further metabolized to the inactive carboxylic acid metabolite. Apalutamide and M3 exhibit multiple CYP-based interaction mechanisms in vitro, including time-dependent inhibition (TDI) and mixed inhibition/induction. In addition, apalutamide and M3 are inhibitors of the renal transporters OCT2, MATEs, and OAT3 in vitro. Given the complex pharmacokinetic (PK) properties of apalutamide and M3, the applicant conducted eight clinical DDI studies. Table 55 summarizes the ratios of maximum observed plasma concentration (Cmax) and area under curve (AUC) of test substrates with and without co-administration with a perpetrator compound in these studies.

Table 55. Summary of Clinical and Simulated DDI studies

Drug name	Description	Observed* Parent AUCR (single dose)	Simulated Parent AUCR (steady-state)	Analysis
Apalutamide and M3 as Victim for CYP3A modulator				
Itraconazole	Strong CYP3A4 Inhibitor	0.99		Pred-vs-Obs
Gemfibrozil	Strong CYP2C8 Inhibitor	1.68	1.23[1]	Pred-vs-Obs
Ketoconazole	Strong CYP3A4 Inhibitor	1.17[1]	1.06[1]	Pred.only
Rifampicin	CYP3A4 and 2C8 inducer	0.51[1]	0.66 or 0.78[2]	Pred.only
Apalutamide and M3 as Perpetrator for CYP enzyme				
Midazolam	CYP3A substrate	0.08		Pred-vs-Obs
S-warfarin	CYP2C9 substrate	0.51		Obs.only
Omeprazole	CYP2C19 substrate	0.16		Pred-vs-Obs
Pioglitazone	CYP2C8 substrate	0.82		Pred-vs-Obs
Apalutamide and M3 as Perpetrator for transporters				
Rosuvastatin	BCRP substrate	0.43		Obs.only
Fexofenadine	P-gp substrate	0.68		Obs.only
Metformin	OCT2/MATEs substrate	1.18 or 1.28[3]		Pred.only
Benzylpenicillin	OAT3 substrate	1.05 or 1.09[3]		Pred.only

*DDI data reported in Study 56021927PCR1012 (Itraconazole or Gemfibrozil); 56021927PCR1012 (CYP and transporter substrate)
[1] Simulated AUCinf for total unbound active moieties (PBPK report FK10644)
[2] Simulated AUCinf ratio using multiplicative or additive induction
[3] Simulated AUCinf ratio of substrate with assumed IC50 as IC50 or Ki/2 (PBPK report FK13005)

PBPK models were developed to investigate the DDI potential of a strong CYP3A4 inhibitor (ketoconazole), a strong CYP2C8 inhibitor (gemfibrozil) and a CYP3A4/CYP2C8 inducer (rifampicin) on the steady-state PKs of apalutamide. The total unbound plasma active compounds (apalutamide+M3) was proposed by the applicant as the dosing metric for dosing recommendation. Based on the simulation results, the applicant proposed no initial dose adjustment for apalutamide concomitant administration with strong CYP3A or CYP2C8 inhibitors and no dose adjustment when used with CYP3A/CYP2C8 inducers.
This review evaluates the adequacy of the applicant's conclusions regarding the ability of its PBPK models to 1) describe the PK profiles for apalutamide and M3; and 2) predict DDI potential of strong CYP3A4 and CYP2C8 inhibitors and inducers on the steady state pharmacokinetics of apalutamide and M3. Section 19.4.6 is the PBPK review that evaluates the adequacy of the applicant's PBPK model to predict effect of the steady-state pharmacokinetics of apalutamide on OCT2, MATE and OAT3 transporter substrates in human.

Method
PBPK development for apalutamide and M3

The applicant developed a full PBPK models for apalutamide and M3 using SimCYP (a Certara company, Sheffield, UK, version 16) based on available physicochemical properties, in vitro experiments and clinical study data. The model assumed no renal elimination, since less than 3% of unchanged apalutamide and M3 were recovered in urine. The total clearances were reported to be 1.2 and 1.37 L/hr following a single dose of 240 mg apalutamide via oral or iv administration, respectively. Thus, the applicant assumed there was a minimal first pass effect. The contributions of CYP2C8 and CYP3A4 in the metabolism of apalutamide following a single-dose administration were set to be 58% (fmcyp2C8) and 13% (fmcyp3A4), respectively, based on the clinical DDI study data with the CYP3A4 inhibitor itraconazole and the CYP2C8 inhibitor gemfibrozil. The applicant then applied the retrograde method to calculate CYP-specific clearance. The applicant assigned the clearance of M3 at a rate of 1 L/hour, compared to 1.5 L/hour reported clinically. Parameters and their sources for apalutamide and M3 are summarized in PBPK Appendix Table A1.
In-vitro half maximal inhibition concentrations, IC50, of apalutamide and M3 on multiple CYP enzymes were used by the applicant to derive the inhibition constant, Ki, in the PBPK model, except the Ki of apalutamide on CYP2C8. By fitting to data observed in DDI study with pioglitazone (a CYP2C8 substrate), the applicant set the Ki of apalutamide on CYP2C8 at 0.3 uM, approximately 10 times lower than the in-vitro IC50 (2.6 uM).
In-vitro half maximal induction parameters, Ind50, of apalutamide and M3 on CYP2C19 and CYP3A were used in the PBPK model. Results of the interaction studies with midazolam (CYP3A substrate) and omeprazole (CYP2C19) were used to set the maximal induction potential, Indmax, of apalutamide and M3 on CYP3A4 and CYP2C19 respectively.
DDI studies from published literatures were also used to support the development of additional PBPK models used in this PBPK analysis (see 'Development of additional PBPK models' section below). For example, trimethoprim PBPK model was developed to verify the CYP2C8 contribution of pioglitazone PBPK model which was also developed by the applicant as a CYP2C8 substrate model. Table 56 listed the DDI mechanisms of the drugs used in these DDI studies.

Table 56. Summary of DDI mechanisms of the compounds used to verify DDI potential of apalutamide and M3

	S	S	S	S	I	I	I	U	U	U	U
	2C8	2C9	2C19	3A4	2C8	2C9	3A4	2C8	2C9	2C19	3A4
Apalutamide	√			√	√	√	√			√	√
M3					√	√	√			√	√
Itraconazole				√			√				
Ketoconazole				√			√				
Rifampin								√	√	√	√
S-Warfarin		√									
Midazolam				√							
Gemfibrozil		√			√						

Omeprazole			√	√							
Pioglitazone	√		√	√							
Enzalutamide	√	√									
Trimethoprim					√						

*S: as substrate. I: as inhibitor. U: as inducer

Development of additional PBPK models
In addition to apalutamide, nine PBPK models were used by the applicant for DDI simulations. The applicant first verified these PBPK models by reproducing the time-plasma profiles from clinical PK studies. The ability of these models to be used as a substrate or perpetrator model of a target DDI mechanism was then verified by comparing the predicted DDI effects with observed data. Five of the nine PBPK models from SimCYP built-in library were modified by the applicant (see Table 57 for details), and then used for DDI simulations. The PBPK model of itraconazole, pioglitazone, enzalutamide and trimethoprim were either adapted from the previously published PBPK model or created by the applicant based on in vitro, in vivo and in silico data. Table 57 summarized the published literature and clinical DDI data used to develop and verify these PBPK models.

Table 57. Summary of additional PBPK models used to verify DDI potential of apalutamide and M3

		PK verification		DDI potency verification
	Model description	Single dosing PK	Multi-dosing PK	Interacting drugs
Itraconazole	New PBPK model. Adapted from Chen et al.		√	Midazolam*
Ketoconazole	Modify the default Simcyp file by incorporating the CYP3A mediated clearance		√	Rifampin Rilpivirine
Rifampin	Modify the default Simcyp file by including CYP2C8 induction effects		√	Midazolam Omeprazole Pioglitazone
Midazolam	Modify the default Simcyp file by increasing midazolam metabolism in gut	√		Ketoconazole Clarithromycin Erythromycin Itraconazole Verapamil Diltiazem Grapefruit Juice Fluconazole Rifampin
Gemfibrozil	Default compound file from Simcyp library		√	Pioglitazone
Omeprazole	Modify the default Simcyp file by adjusting CYP2C19 contribution	√		Fluconazole Rifampin

Pioglitazone	New PBPK model. Adapted from Varma et al.	√		Gemfibrozil Itraconazole Rifampin
Enzalutamide	New PBPK model developed in house by the applicant	√		Gemfibrozil Itraconazole Rifampin
Trimethoprim	New PBPK model. Adapted from Yeo et al.		√	Pioglitazone

*The reviewer performed additional analysis to confirm the model can describe the published DDIs with midazolam. Reference: Chen et al.; Clin Pharmacokinet. 2016; 55: 735. Varma et al.; Drug Metab Dispos. 20 Eur J. Yeo et al. ; Clin Pharmacol (2013) 69:1311 15; 43:1108

Model Application

The applicant used the final apalutamide PBPK model to simulate three unknown DDI scenarios. First, the model was used to predict the DDI effects of ketoconazole (strong CYP3A inhibitor) on the PKs of apalutamide at steady state with concomitant administration of multiple-dose of ketoconazole (400 mg qd, day 1-49) and multiple-dose of apalutamide (240 mg qd, day 4-49). Second, the model was used to predict the DDI effects of gemfibrozil (strong CYP2C8 inhibitor) on the PKs of apalutamide with concomitant administration of multiple-dose gemfibrozil (600 mg twice daily, day 1-49) and multiple-dose of apalutamide (240 mg qd, day 6-49). Third, the model was used to predict the DDI effects of rifampin (dual CYP3A/2C8 inducer) on the PKs of apalutamide with concomitant administration of multiple-dose of rifampin (600 mg qd, day 1-49) and multiple-dose of apalutamide (240 mg qd, day 6-49). PBPK simulations were conducted in 100 subjects (10 trials with 10 subjects) using the Simcyp virtual populations for healthy subjects.

Results

Q1: Can PBPK model provide a reasonable description of the PK of apalutamide?

Yes, the apalutamide PBPK model was verified with the observed apalutamide PK following a single and repeat doses of 240 mg apalutamide once daily.

For apalutamide, the simulated median and geometric mean values for Cmax and AUC of apalutamide (21 subjects in each of 5 virtual trials) were in agreement with those observed following a single dose of 240 mg apalutamide. Reviewer noted that the model under-predicted the Cmax and AUC for M3. Table 58 shows the comparison of the simulated and observed PK parameters for apalutamide and M3 following a single dose of 240 mg apalutamide.

Table 58. Comparison of the simulated and observed PK profiles of apalutamide and M3 following a single dose of 240 mg apalutamide

	Simulated (5x21 (105) subjects)			Observed (6 from study ARN-509-006/15 subjects from study 56021927PCR1012)		
	Tmax (h)	Cmax (µg/mL)	AUCinf (µg.h/mL)	Tmax (h)	Cmax (µg/mL)	AUCinf (µg.h/mL)
	apalutamide					

G.M.	0.82	2.38	189	NR/ 1.4	3.25/3.35	200/228
Median	0.81	2.48	199	1.01/1.5	3.38/3.24	202/240
	M3					
G.M.	151	0.265	134	NR/ 174	0.302/0.335	199/206
Median	152	0.276	136	266/168	0.289/0.321	198/209

Source: Study FK10644 Table 1. G.M.: geometric mean

The contributions of the elimination pathways were estimated by comparing the simulated and observed ratio of PK of apalutamide and M3 alone or with co-administration of itraconazole (a strong CYP3A inhibitor) and gemfibrozil (a strong CYP2C8 inhibitor). As shown in Table 59, the model reasonably described the observed DDI effects of itraconazole and gemfibrozil on PKs of apalutamide and M3. The contributions of CYP2C8 and CYP3A4 in the metabolism of apalutamide at single dose were set as 58% and 13% respectively.

Table 59. Comparison of the simulated and observed PK parameter ratios of apalutamide and M3 with co-administration of itraconazole

	Itraconazole 200 mg bid for 32 days				Gemfibrozil 600 mg bid for 32 day			
	Observed		Simulated		Observed		Simulated	
	AUC ratio	Cmax ratio	AUC ratio	Cmax ratio	AUC ratio	Cmax ratio	AUC ratio	Cmax ratio
	apalutamide							
Geo. mean	0.99	0.78	1.10	1.00	1.53	0.79	1.58	1.01
90% CI	0.9-1.09	0.71-0.86	1.09-1.1	1.0-1.0	1.39-1.69	0.72-0.87	1.50-1.66	1.01-1.01
	M3							
Geo. mean	0.91	0.85	0.86	0.83	0.57	0.55	0.46	0.39
90% CI	0.81-1.03	0.71-1.02	0.84-0.88	0.66-0.96	0.51-0.65	0.46-0.66	0.29-0.66	0.22-0.64

Source: 20170703-apalutamide-itraconazole.xls, 20170703-apalutamide-gemfibrozil.xls and PBPK report Table 3-4 (Study FK10644). bid: twice daily

As shown in Table 60, the applicant's PBPK models reasonably described the DDI between several CYP substrates after repeated doses of 240 mg apalutamide qd for 29 or 38 days.

Table 60. Comparison of the simulated and observed PK parameter ratios of midazolam, omeprazole and pioglitazone when co-administration with apalutamide

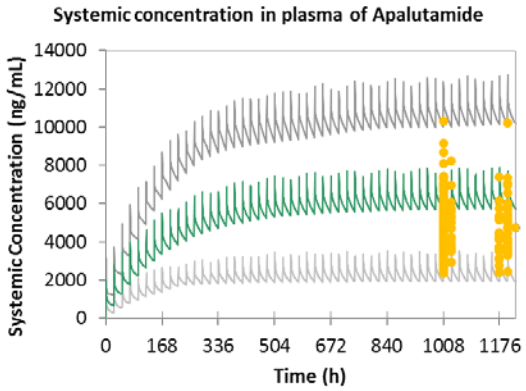
	Observed Geo. Mean		Simulated Geo.Mean	
	AUC ratio	Cmax ratio	AUC ratio	Cmax ratio
Midazolam, 2mg single dose on day 29	0.083	0.23	0.09	0.13
Omeprazole, 40 mg, single dose on day 36	0.15	0.33	0.23	0.28
Pioglitazone, 15 mg, single does on day 36	0.82	0.91	0.87	0.96

Source: Study FK10644 Table 5-7

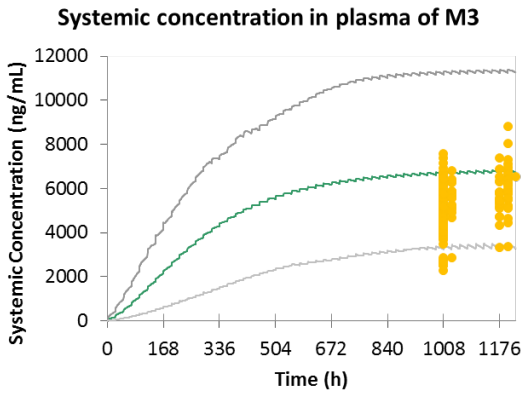
By quantifying contributions of CYP2C8 and CYP3A4 clearance and the inhibition/induction properties of apalutamide and M3 on its own metabolism pathways (CYP2C8 and CYP3A4), the applicant's PBPK models reasonably described the observed PK profiles of apalutamide and M3 after repeated administration of apalutamide.
Figure 24 shows the overlay of simulated and observed apalutamide (left) and M3 (right) plasma concentration-time profiles following repeated doses of 240 mg qd for 48 days. The model predicts that, at steady state, the contribution of CYP3A4 increases from 13% to 37%, and the contribution of CYP2C8 decreases from 58% to 40%.

Figure 24. Comparison of the simulated (line) and observed (points) apalutamide (left) and M3 (right) plasma concentration-time profiles following repeated doses of 240 mg apalutamide qd for 48 days

(a) Apalutamide



(b) M3



The lines represents the 95th , mean, and 5th of simulated results
Source: Modified from applicant's simulation output "20170703-apalutamide-qd-PCR1020.xls"

Reviewer noted that these DDI datasets, where apalutamide was used as CYP substrate or perpetrator, were used to optimize, but not verify, the PBPK model parameter (such as fmcyp and Indmax). However, given the complex DDI mechanism exhibited for both apalutamide and M3, the adequacy of the applicant's PBPK model to predict the PK of apalutamide alone or with other CYP modulators was demonstrated by simultaneously describing the PK of apalutamide and M3 following a single or repeated apalutamide dosing, as well as the DDI effects with other compounds.

Q2: Can PBPK model predict the effects of CYP2C8 inhibitor and CYP3A modulators on PK of apalutamide?
Yes, the applicant's apalutamide PBPK model is adequate to predict the effects of strong CYP3A4 and/or CYP2C8 inhibitors and inducers on the steady state pharmacokinetics of apalutamide and M3.

Given the apalutamide and M3 could induce and inhibit its own clearance pathway (mediated by CYP2C8 and 3A4), the compositions of parent and active metabolites are likely changed during the DDI scenario. Therefore, the PK parameters (such as Cmax and AUC) in the form of total unbound active compounds are the most relevant metric to describe the DDI effects of a CYP modulator on apalutamide. The ratio of PK of total unbound active compounds (parent and M3) with and without a CYP modulator is calculated as below[1].

$$\frac{(\text{parameterunbound, parent, after inhib} + 1/3 * \text{parameterunbound, metabolite, after inhib})}{(\text{parameterunbound, parent} + 1/3 * \text{parameterunbound, metabolite})}$$

Ketoconazole: Strong CYP3A4 inhibitor

Following a repeat administration of ketoconazole 400mg qd for 50 days in combination with repeated 240 mg apalutamide qd dosing from day 4 to 50, the simulations shows a minimal changes (less than 12%) in the predicted geometric mean Cmax and AUC for apalutamide and M3 compared to those for apalutamide alone. As shown in Table 61, the ratios of the AUC and Cmax of the total unbound active compounds with and without administration of ketoconazole were 1.06 and 1.05, respectively. The applicant also simulated a worst-case scenario by removing the CYP3A induction of apalutamide on ketoconazole. The geometric mean ratios of the AUC and Cmax of the unbound total active compounds with and without administration of ketoconazole were 1.28 and 1.23, respectively.

Table 61. Simulated PK profiles of apalutamide and M3 after co-administration of 400 mg qd ketoconazole

	Induction of ketoconazole incorporated		No induction of ketoconazole incorporated	
	AUC ratio	Cmax ratio	AUC ratio	Cmax ratio
apalutamide				
Median	1.11	1.08	1.46	1.34
Geo. mean	1.11	1.09	1.51	1.38
M3				
Median	0.97	0.97	0.79	0.81
Geo. mean	0.96	0.96	0.75	0.76
Total unbound active compounds (parent and M3)				
Median	1.06	1.05	1.25	1.21
Geo. mean	1.06	1.05	1.28	1.23

Source: Modified from Study FK10644 Table 9

Gemfibrozil: Strong CYP2C8 inhibitor

Following a repeated administration of gemfibrozil 600 mg b.i.d.for 50 days in combination with repeated doing of 240 mg apalutamide qd from day 4 to 50, the model predicted the AUC ratio

[1] The unbound fraction in plasma, fup, for AA and M3 are 0.04 and 0.05 respectively.

of the total unbound active compounds with and without administration of gemfibrozil were 1.23 and 1.19, respectively (Table 62).

Table 62. Simulated PK profiles of apalutamide and M3 after co-administration of 600 mg bid gemfibrozil

	AUC ratio	Cmax ratio
	apalutamide	
Median	1.32	1.25
Geo. mean	1.44	1.32
	M3	
Median	0.89	0.89
Geo. mean	0.87	0.87
	Total unbound active compound (parent and M3)	
Median	1.17	1.14
Geo. mean	1.23	1.19

Source: Study FK10644 Table 10

Rifampin: Strong CYP3A inducer/moderate CYP2C8 inducer

Table 63 showed the effects of repeated doses of rifampin on PKs of apalutamide and M3 following a single or repeated doses of 240 mg apalutamide once per day. When co-admistration with repeated rifampin 600 mg qd doses for 50 days, the model predicted that the AUC of apalutamide changed by 0.5 with a single dose of apalutamide (given on day 4), and 0.66 with repeated doses of apalutamide (given on day 6-50). The applicant explained that the smaller decrease in the AUC of apalutamide following repeated doses of apalutamide could be attributed to the already induced metabolism of apalutamide in a repeat dosing scenario. Additionally, the simulated changes in the AUC of total unbound active compounds were always smaller than those simulated for apalutamide. That was due to that coadministration of rifampin with apalutamide decreased apalutamide exposure, but increased the active metabolite, M3, exposure. When rifampin was coadministered with a single 240 mg apalutamide, the model predicted the AUC and Cmax of the total unbound active compounds (parent and M3) changed by 0.67-fold and 1.02-fold, respectively.

Table 63. Simulated PK profiles of apalutamide and M3 after co-administration of 600 mg qd rifampin

	A single dose of 240 mg apalutamide on day 4		Multiple doses of 240 mg apalutamide qd on day 6-50					
	default		default		additive		multiplicative	
	AUCR	CmaxR	AUCR	CmaxR	AUCR	CmaxR	AUCR	CmaxR
	apalutamide							
Median	0.49	0.98	0.66	0.75	0.62	0.72	0.32	0.47
Geo. mean	0.50	0.98	0.66	0.75	0.62	0.73	0.31	0.46
	M3							

Median	1.21	1.72	1.08	1.08	1.09	1.08	1.1	1.15
Geo. mean	1.23	1.78	1.1	1.1	1.1	1.1	1.12	1.17
	Total unbound active compound (parent and M3)							
Median	0.68	1.01	0.82	0.85	0.8	0.84	0.67	0.72
Geo. mean	0.67	1.02	0.81	0.85	0.78	0.83	0.66	0.71

Souce: Study FK10644 Table 11-12

Through choosing the three induction mechanisms provided in Simcyp (default, additive and multiplicative), the applicant conducted three DDI simulations to investigate the DDI effects of rifampin on the PKs of apalutamide with a repeat doses of apalutamide. The model predicted a 68% decrease in AUC of apalutamide when the model assumed the multiplicative induction mechanism, in comparison to a 34% decrease in AUC of apalutamide with default induction mechanism. However, the effects of rifampin on the PKs of total unbound active compounds at steady state were similar across the three mechanisms of induction. The model predicted the geometric mean ratios of the AUC and Cmax of the total unbound active compounds (parent and M3) ranged from 0.66-0.81 and 0.71-0.85-fold respectively, across the three mechanisms of induction. Reviewer concludes a less than 35% decrease in the AUC of the steady-state total unbound active compounds.

Conclusion

The apalutamide PBPK models are adequate to predict the PK of apalutamide and it's active metabolite, M3 with strong CYP3A and CYP2C8 inhibitors and dual CYP3A/2C8 inducers. The simulation results predicted less than 1.3-fold increase in the steady-state exposure of total unbound active compounds (apalutamide and M3) when the drug is co-administered with a strong CYP3A inhibitor (i.e. ketoconazole) and a strong CYP2C8 inhibitor (i.e. gemfibrozil). The simulation results also indicate less than 35% decrease in steady-state exposure of total unbound active compound when the drug is co-administered with a CYP3A/2C8 inducer (i.e. rifampin). These analyses are determined to be adequate to support applicant's conclusion that "the no initial dose adjustment with concomitant administration of apalutamide with strong CYP3A or CYP2C8 inhibitors and no dose adjustment when used with CYP3A/CYP2C8 inducers".

PBPK Appendix

PBPK Table A 1. Input parameters for apalutaminde model

Input parameter	Value	Unit	Comment/source
MW	477.44	g/mol	ADMET predictor
logP	2.89		in house data
Compound type	Monoproticacid		in house data
pKa	9.7		in house data
B/P	0.79		in-vitro
fu,p	0.0418	fraction	in-vitro
Absorption	1st order		

Fa	1		Assumed based on clinical observation
Ka	3	h-1	Fitted
Lag time	0.5	hour	Fitted
Caco-2 Papp	42.3	10-6 cm/s	Reference compound propranolol
fugut	1		Assumed
Qgut	17.8	L/h	Predicted
Distribution	FullPBPK		Vss=3.9L/kg
Elimination	Enzymekinetics		
CL iv	1.2	L/h	Absorption complete with negligible first pass due to very slow clearance
Fm CYP3A4	13	%	Estimated, Clint CYP3A4=0.007ul/min/pmol
Fm CYP2C8	58	%	Estimated, Clint CYP2C8=0.18ul/min/pmol
additional	29	%	Estimated, Clint additional=2.15 ul/min/mg
Interaction			
CYP2C8 Ki	0.3	uM	Fitted based on pioglitazone DDI data
CYP2C9 Ki	28	uM	IC50 = 56 uM, in-vitro study
CYP2C19Ki	33.5	uM	IC50 = 67 uM, in-vitro study
CYP3A4 Ki	27	uM	IC50 = 54 uM, in-vitro data
CYP3A4 Indmax	16		By compared with in-vitro rifampicin data
CYP3A4Ind50	2	uM	Fitted based on midazolam DDI data
CYP2C19Indmax	3.5	-	Fitted based on omeprazole DDI data

PBPK Table A 2. Input parameters for the M3 model

Input parameter	**Value**	**Unit**	**Comment/source**
MW	463.42	g/mol	ADMET predictor
logP	2.82		ADMET predictor
Compound type	Neutral		ADMET predictor
B/P	0.78		in-vitro
fu,p	0.0511	fraction	in-vitro
Distribution	Full PBPK		
Elimination	Enzyme kinetics		
CL iv	1	L/hour	Assumed
Interaction			
CYP2C8 Ki	23.5	uM	IC50 = 47 uM, in-vitro study
CYP2C9 Ki	19	uM	IC50 = 38 uM, in-vitro study
CYP3A4 Ki	34.5	uM	IC50 = 69 uM, in-vitro study
CYP3A4 Indmax	11.2		70% of rifampicin data
CYP3A4 ind50	7	uM	Fitted based on midazolam DDI data
CYP2C19 Indmax	2.45		Fitted based on omeprazole DDI data

19.4.6. PBPK Analyses-transporter mediated DDIs

Objective
The objectives of this review are to evaluate the adequacy of the modeling to predict DDI potential of the steady-state pharmacokinetics of JNJ-56021927 on OCT2, MATE and OAT3 transporter substrates in human. The following PBPK reports were submitted to the NDA:

- Study FK10644 : Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-56021927 and inhibitors/inducers of CYP2C8 and CYP3A4 in Human Subjects
- Study FK13005: A physiology based pharmacokinetic approach to assess potential transporter mediated drug-drug interactions with JNJ-56021927 (Apalutamide) as perpetrator in human

Background
Apalutamide is primary metabolized by CYP2C8 and CYP3A4 to form an active metabolite, N-desmethyl apalutamide (M3). Both apalutamide and M3 are slowly cleared at a rate of 2.04 and 1.5 L/hr following multiple dosing to steady state. Apalutamide and M3 exhibit complex DDI profiles. Clinically, apalutamide (and/or M3) was shown to be a strong inducer of CYP3A and CYP2C19, a weak inducer of CYP2C9, and a weak inducer of P-gp and BCRP/OATP1B1 transporter. Applicant has used the PBPK modeling approaches to predict the DDI potential of apalutamide as a substrate and a modulator regarding multiple CYP enzymes. Please section 19.4.5 for more detail.

Based on in-vitro studies, apalutamide is also an inhibitor of the renal transporters OCT2, MATEs, and OAT3. There is no clinical study to evaluate the effects of apalutamide on a substrate of these transporters. By using the in-vitro inhibition parameters (such as IC50), the applicant used the PBPK modeling approach to investigate the effect of apalutamide on the pharmacokinetics of transporter substrates metformin (OCT2 and MATEs) and benzylpenicillin (OAT2/3) at steady state. Table 64 listed the reported IC50 values of apalutamide and M3 for these renal transporters.

Table 64. In-vitro inhibitory parameters of apalutamide and M3 for OCT2, OAT3, MATE-1, and MATE-2K

	IC50 values for apalutamide and M3 inhibition			
	OCT2 (µM)	OAT3 (µM)	MATE-1 (µM)	MATE-2K (µM)
Apalutamide	27.2±1.7	12.0±1.0	13.8±0.8	37.9±2.6
M3	4.8±0.2	7.6±1.3	17.6±0.8	50*

Data: Applicant's PBPK modeling report for transporter (Study FK13005) * M3 inhibited 32.3% of MATE-2K activity at 50µM

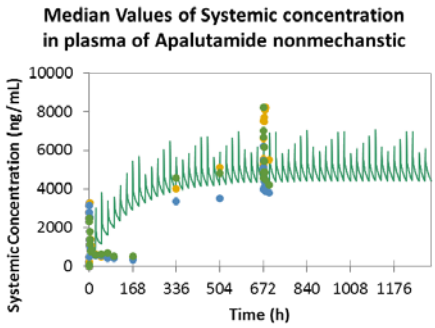
Based on the basic model recommended in the draft guidance published in October 2017[2] , the R1 values of apalutamide and M3 calculated for OAT3 were less than the predefined cutoff value of 0.1. This result suggests that co-administration of apalutamide would not significantly increase the exposure of OAT substrates (such as benzylpenicillin). Thus, this review only evaluates the adequacy of the applicant's conclusions regarding the ability of its PBPK models to predict potential DDI potential of apalutamide on the exposure of OCT2/MATEs substrates (such as metformin).

PBPK model development

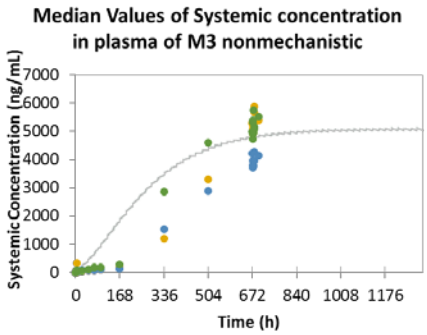
The model and simulation results described here were performed using the Simcyp software (version 16; Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). A full apalutamide PBPK model was developed by the applicant based on in-vitro and in-vivo dataset. As showed in Figure 25, the model reasonable described the PK profiles of apalutamide and M3 following repeat doses of 240 mg oral dose once daily. Different from the apalutamide PBPK model used in the Study FK10644, the applicant did not include the inhibition/induction parameters of apalutamide and M3 on the CYP enzymes in the PBPK model used in this analysis (Study FK13005). Thus, this PBPK model does not describe the time dependent effects in the pharmacokinetics of apalutamide, and is only suitable as perpetrator model.

Figure 25. Compare observed (points) and simulated (line) time-plasma profiles of apalutamide and M3 following repeat dosing of 240 mg oral dose for 28 days

(a) apalutamide



(b) M3 (active metabolite)



Source: extracted from the simulation results "20170727 apalutamide nonmechanistic.xls"

The applicant developed three additional PBPK models to support the verification of the inhibition of OCT2 and MATEs by apalutamide. The PBPK models for metformin (substrate for OCT2 and MATE) and cimetidine (inhibitor of OCT2 and MATE) from Simcyp library were used by the applicant with some adjustments. For example, the reviewer noted that the applicant adjusted the hepatic clearance of metformin (within 10% of that used by Simcyp) to fit the observed metformin plasma concentration-time profiles following a single 500 mg dose. In

[2] Draft guidance for industry (2017) In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies Guidance for Industry

addition, the applicant adjusted the relative activity factor (RAF) of metformin for OCT2 and MATEs mediated clearance from 3 to 1. The applicant also developed and verified the pyrimethamine (inhibitor of MATE) PBPK model using the data reported in the published literatures.

The applicant conducted in-vitro analysis to measure the inhibition potential of cimetidine and pyrimethamine on OCT2 and MATE transporters by using the same cell lines as the ones used for apalutamide and M3. To verify the adequacy of using in-vitro derived inhibition (IC50 or IC50/2) for OCT2 and MATEs to predict in vivo DDI potential, the applicant simulated the effect of cimetidine and pyrimethamine on the PK of metformin (OCT2 and MATEs substrate) and compared the simulated effects with the observed DDI studies.

Model application
DDI between apalutamide and metformin were then simulated using the in-vitro derived IC50 and PBPK models described above. Table 65 summarized the observed and simulated DDI effects of OCT2/MATEs inhibitors on metformin.

Table 65. Comparison of observed and simulated DDI effects of multiple OCT2/MATEs inhibitors on AUC of metformin

	In-vitro MATE IC50 (µM)	In-vitro OCT2 IC50 (µM)	Observed AUC ratio	Simulated AUC ratio with Ki as	
Metformin 250 qd				IC50	IC50/2
+Cimetidine 400 mg twice daily, 5-day	1.4	52.4	1.46	1.31	1.41
+Pyrimethamine single 50 mg dosing	0.01	1.4	1.35	1.59	1.71
+Apalutamide/M3 240 mg qd for 45 day	13.8/17.6	27.2/4.8	NA	1.18	1.28

Data source: Table 2, 4, 5, 7, 8 of Study FK13005

Review question:
Can the apalutamide PBPK model be used to predict inhibition of OCT2 and MATEs?
Reviewer noticed that, despite the low in-vitro IC50 value reported for pyrimethamine, a less than 2-fold increase in AUC of metformin was predicted when co-administration metformin with pyrimethamine. Reviewer searched the Metabolism and Transport drug interaction database[3] to investigate the magnitude of clinical DDI effects between OCT2/MATEs inhibitors and metformin. As shown in Table 66, Oh et. al reported a 2.58 fold increase in metformin AUC when co-administration with a single dose of 50mg pyrimethamine. Thus, reviewer was concerned about a possible under-estimated MATE-mediated clearance used in the applicant's

[3] Metabolism and Transport Drug Interaction Database (http://www.druginteractioninfo.org)

metformin model, and consequently, the ability of the applicant's PBPK models to predict the DDI effects of MATE inhibitors on metformin.

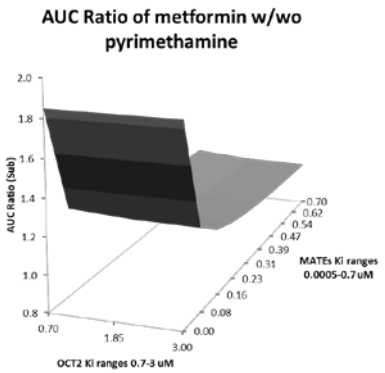
Table 66. Clinical DDI effects of OCT2/MATEs inhibitors on AUC of metformin

No. of subjects	Object drug	Precipitant drug	AUC ratio	Reference
7 HV	metformin 250 mg	cimetidine 400 mg bid for 5 days	1.46	Somogyi A., et al., Br J Clin Pharmacol. 1987 May;23(5):545-51.
15 HV	metformin 500 mg	cimetidine 400 mg bid for 6.5 day	1.54	Wang ZJ., et al., Pharmacogenet Genomics. 2008 Jul;18(7):637-45
8 HV	metformin 250 mg	pyrimethamine single 50 mg	1.35	Kusuhara, H., et al. CPT 89.6 (2011): 837-844.
20 HV	metformin 700/500 mg	pyrimethamine single 50 mg	2.58	Oh, J., et al. Diabetes, Obesity and Metabolism 18.1 (2016): 104-108.

Data source: Metabolism and Transport Drug Interaction Database[3]; HV: healthy subjects; bid: twice daily

The reviewer conducted a sensitivity analysis by varying the Ki of pyrimethamine (0.7 →0.0001 µM to investigate the maximum increase of metformin exposure when co-administrated a single dose of 500 mg metformin with a single dose 50 mg pyrimethamine as shown in Figure 26. The simulated AUC ratio is 1.8 when the Ki of MATE was 0.0001 µM. This result indicated that there is an upper ceiling of the simulated AUC ratio of metformin with or without co-administration of pyrimethamine. In addition, by using the applicant's metformin model, the reviewer simulated the metformin exposure by setting the both MATEs and OCT2 clearance, Clint,t at zero. The model predicted an approximate, but less than, 2-fold increase in the AUC of metformin following a single dose of 500 mg compared to those simulated with the applicant's original model, confirmed that there is an upper ceiling of the simulated AUC ratio of metformin with/without a MATE/OCT inhibitor using the applicant's metformin PBPK model. Thus, until the MATE/OCT-mediated clearance of metformin can be further verified with additional data, there is uncertainty associated with the predicted DDI effects of apalutamide on metformin.

Figure 26. AUC ratios of metformin after a single dose of 500mg with or without co-administration of a single dose of 50 mg of pyrimethamine using 100-fold lower in vitro IC50 value for MATEs



Conclusion
The applicant's apalutamide PBPK model did not fully describe the observed increases in metformin exposure with concomitant use with a single oral dose of 50mg pyrimethamine. The adequacy of the applicant's apalutamide PBPK model to predict the DDI effects of MATE inhibitor (such as pyrimethamine) on an OCT2/MATE substrate (such as metformin) has not been demonstrated. FDA's basic model suggested that that co-administration of apalutamide would not significantly increase the exposure of OAT3 substrates (such as benzylpenicillin).

19.5. Additional Clinical Outcome Assessment Analyses

Patient reported outcomes (PRO) data were collected in the SPARTAN study. The applicant used two instruments, i.e., FACT-P and EQ-5D-3L, to assess the impact of addition of apalutamide to ADT on patients' health-related quality of life and worsening of prostate cancer symptoms in this largely asymptomatic population of men with NM-CRPC.

Instruments

FACT-P

FACT-G is a generic HRQoL patient-reported outcome instrument and it has four domains: physical, social/family, emotional, and functional. There are a total of 27 questions in FACT-G, each of which is answered using a 5-point scale ranging from 0 (Not at all) to 4 (Very much). FACT-P adds an additional 12-item prostate cancer subscale. Scoring of the FACT is performed through a simple sum of item scores.

Reviewer Comments: *Although the FACT questionnaire is a widely-used PRO instrument in oncology clinical trials, it is challenging to interpret because it combines disease-related symptoms, treatment-related symptoms, and disease impacts into its summary and domain scores.*

EQ-5D-3L

The EQ-5D-3L instrument is self-administered and consists of 2 parts. The first part is comprised of 5 descriptors of current health state including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The patient rates each state on a 3-level scale (1=no problem, 2=some problem, 3=extreme problem). Published weights are used to create a single summary score from these responses, which is called the EQ-5D index. Lower scores in this index represent a higher level of dysfunction and 1 is assigned as a score for perfect health.

The second part of this instrument assesses general health status, and is measured by a visual analog scale called the EQ-5D VAS. This scale measures the patient's self-rated health status on a scale from 0 (worse imaginable health state) to 100 (best imaginable health state).

Reviewer Comments: *The EQ-5D-3L is a composite that incorporates self-reported ability to function, pain, and general health status as filled out by the patient. This instrument is a generic*

Reference ID: 4221387

preference based measure intended to provide a health utility index value for use in economic analyses and lacks content validity for use in estimating clinical benefit for the purposes of labeling claims, though we acknowledge that this instrument is often used by other regulatory authorities and/or payers.

Schedule of Assessments

Patients were to complete the PRO assessments at Day 1 of Cycle 1 to Cycle 6, Day 1 of every 2 cycles starting at Cycle 7 to Cycle 13, then Day 1 of every 4 cycles during the treatment phase. When the patient discontinued study treatment, PRO assessments should be performed at the end of treatment visit and then every 4 months up to 12 months post progression. Patients would complete the assessments at the clinic during the Treatment Phase prior to any other clinical activity. During Long-term Follow-up contact every 4 months via clinic visit or an alternative contact method per institution policy/practice up to 12 months post progression.

Statistical Analysis Plan

Patient reported outcomes were exploratory endpoints of the SPARTAN study. There was no specific hypothesis testing plan, nor were there type I error adjustments for multiple comparisons. The purpose of these analyses was descriptive.

The completion rate for each PRO assessment was defined as the number of patients who completed the questionnaires at that time point, divided by the number of patients expected to be assessed for that study visit.

The analysis of the PRO endpoints was based on the intent to treat population. Summary statistics of absolute scores at each scheduled visit were to be calculated by treatment group for each FACT-P domain. The applicant also planned to perform time to degradation analyses for each domain of FACT-P and the FACT-P total score using threshold values specified in Table 65 to define clinically meaningful deterioration. EQ-5D-3L data was planned to be used for pharmaco-economic modeling purposes and is not covered in this review.

Table 67. Time to Deterioration Thresholds for FACT-P

Scale/Sub-Scale	Threshold for definition of progression/deterioration
Physical Well-Being (PWB)	3
Social/Family Well-Being (SFWB)	3
Emotional Well-Being (EWB)	3
Functional Well-Being (FWB)	3
FACT-G (General) Scale	9
Prostate Cancer Subscale (PCS)	3
Trial Outcome Index (TOI)	9
FACT-P Total Scale	10
FACT-P Pain Scale	2
FAPSI-8	3

Source: Study PRO-SAP Table 2

Reviewer's Comments.

As the PRO analyses were not controlled for multiple comparisons, these analyses are considered exploratory.

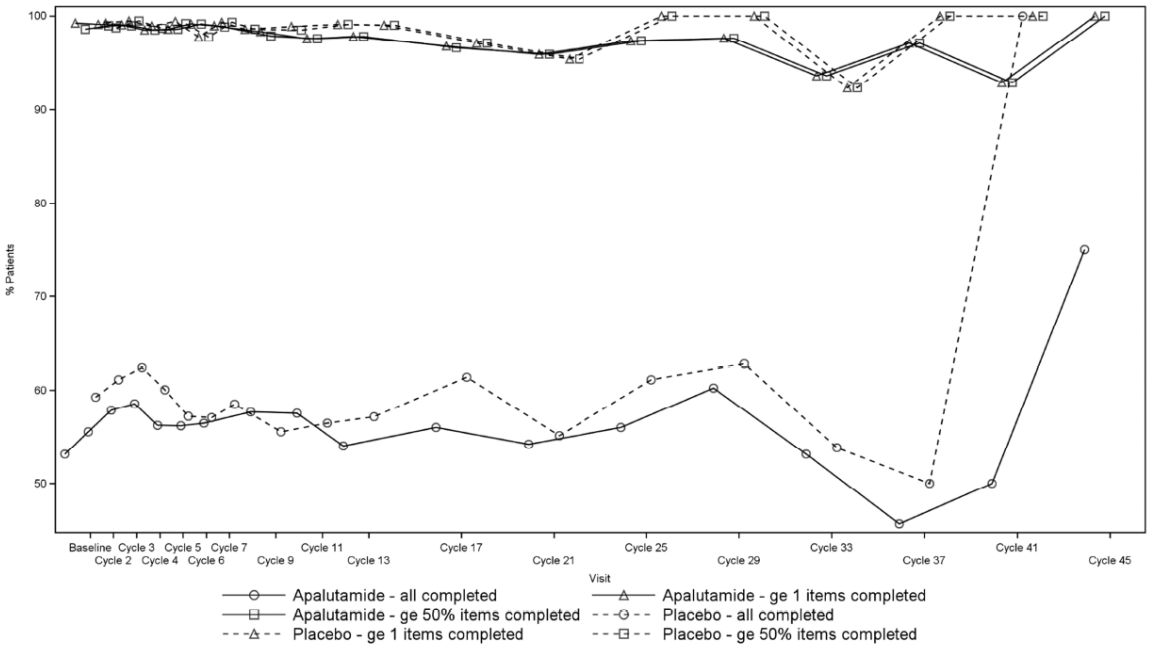
The applicant pre-specified thresholds to define clinically meaningful deterioration for the FACT-P total score and domains. However, there is insufficient evidence to support those thresholds.

Patient-Reported Outcome Results

PRO Completion Rates

Completion rates of FACT-P are summarized in Figure 23. The completion rates were calculated based on the completion of (1) at least one item; (2) at least 50% of items; and (3) all items. As shown in Figure 23, the completion rates of at least one item as well as at least 50% of items were high for both arms; however, the rates of completing all items were decreased to approximately 50% to 60% in both arms. Overall the completion rates were similar between treatment arms.

Figure 27 FACT-P Completion Rates at Each Assessment

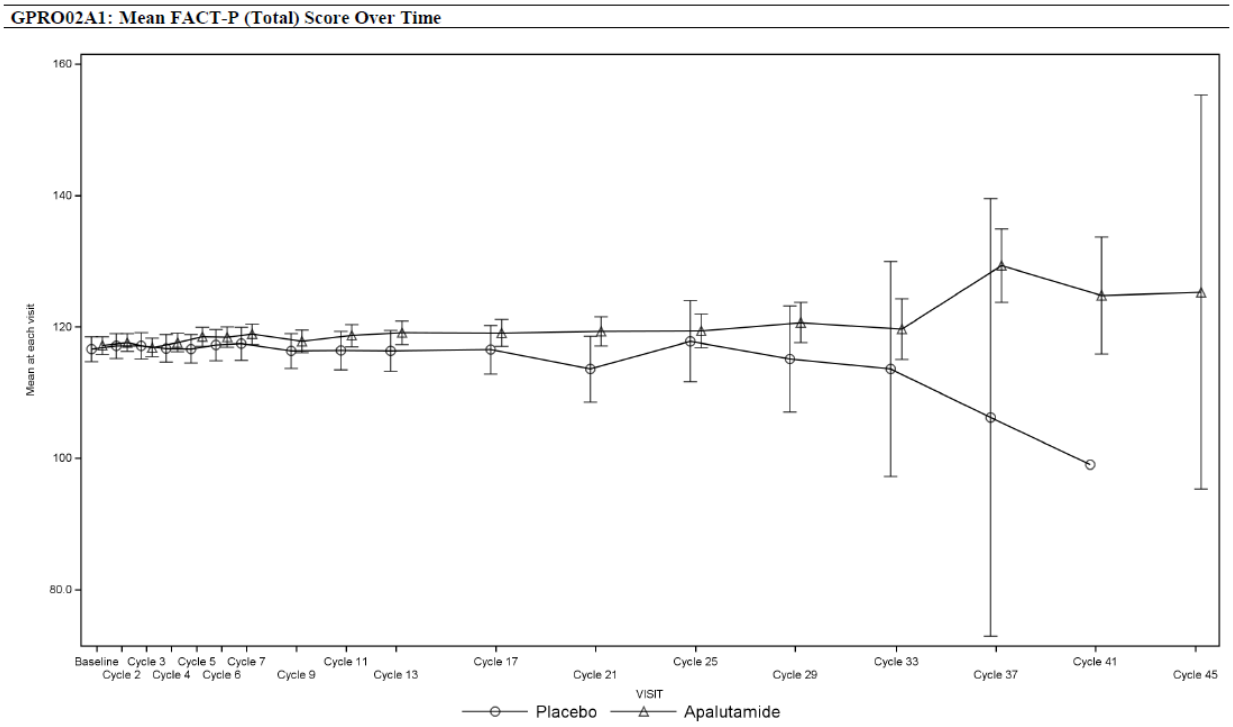


Source: Response to Information Request (dated as of 12/4/2017) Figure GPRO01E

<u>Analysis of FACT-P</u>

Mean of the FACT-P total score over time was similar during the first 13 cycles (Figure 24).

Figure 28. Mean FACT-P Total Score Over Time



Source: Response to Information Request (dated as of 12/4/2017) Figure GPRO02A1

> ***Reviewer's Comment****. The various composite scores analyzed are problematic from a regulatory perspective because they combine assessments of disease symptoms and treatment side effects with global impacts such as emotional well-being that may be influenced by multiple non-drug factors. Thus, these measures may be stable rather than dynamic and poorly responsive to the effects of the drug in question. The prostate-specific domain of the FACT-P includes items that are more relevant to symptoms associated with the disease and therapy in early-stage prostate cancer, including issues with urination and sexual function, rather than the patients with castration-resistant disease.*

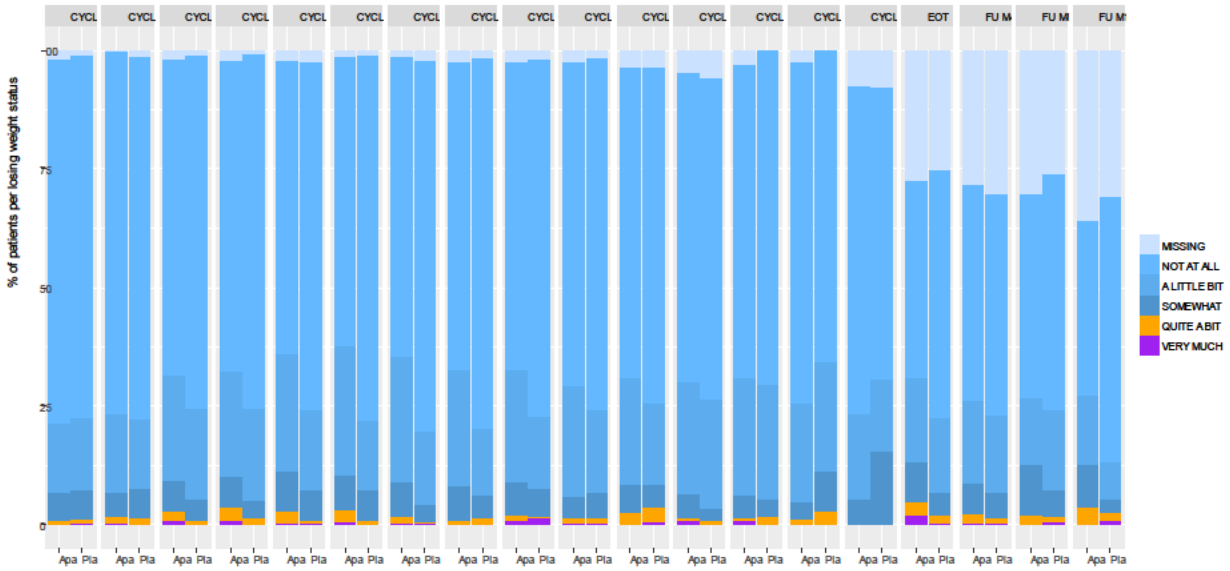
Given the relative unresponsiveness of the FACT-P to drug or disease effects, the review team identified several items thought potentially more responsive for further descriptive exploratory analysis. These items included the following from FACT-P:

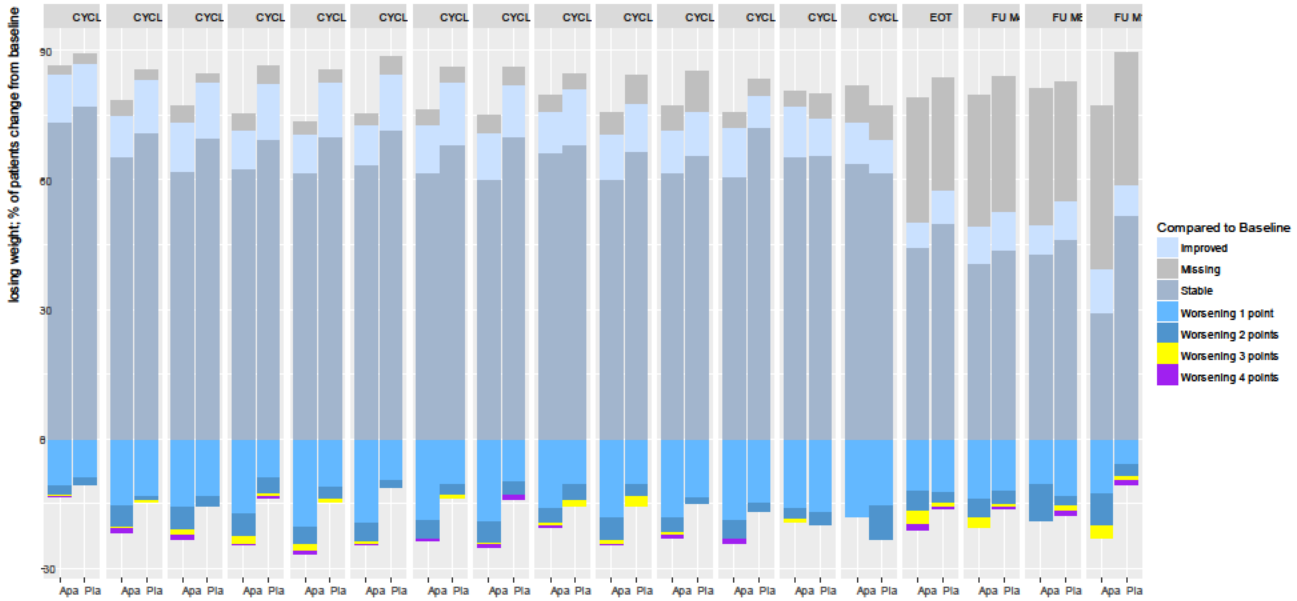
- GP5: "I am bothered by side effects of treatment"
- GP1: "I have a lack of energy"
- GF1: "I am able to work"
- GF7: "I am content with the quality of my life right now"
- GP6: "I feel ill"
- GP7: "I am forced to spend time in bed"

- GP4: “I have pain”
- C6: “I have a good appetite”
- C2: “I am losing weight”

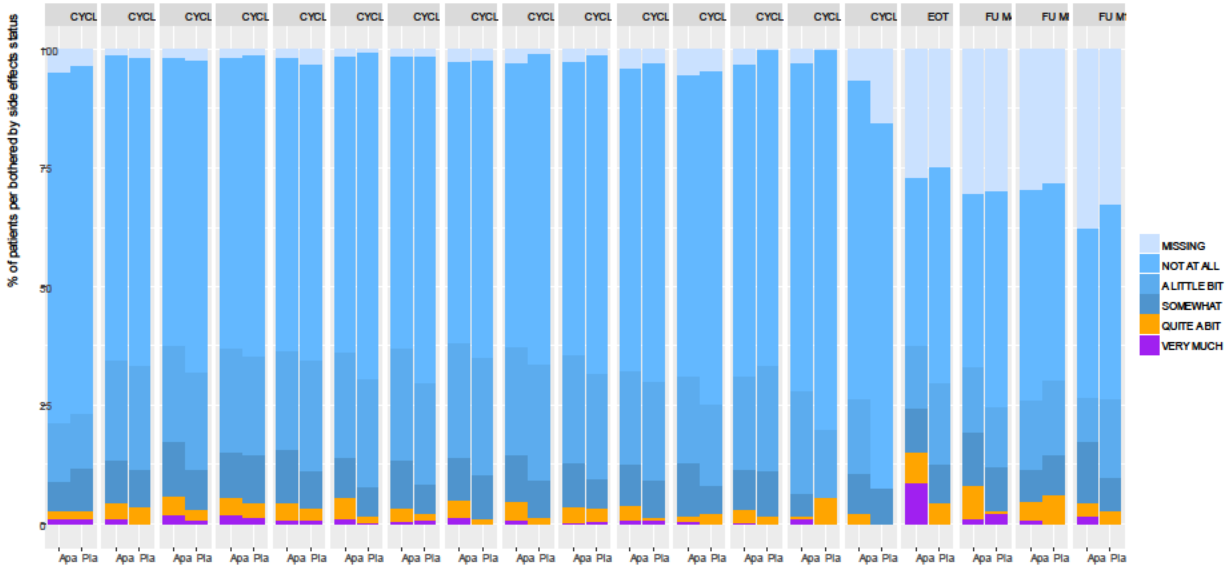
Most individual items had no notable differences in the two arms across assessments on treatment. Item C2 (“I am losing weight”) did demonstrate worse outcome over the first twelve cycles after which the two arms were more similar. Of note, there were not large differences in reported nausea or decrease in appetite. There was a small increase from baseline in item GP5 (“I am bothered by side effects of treatment”).

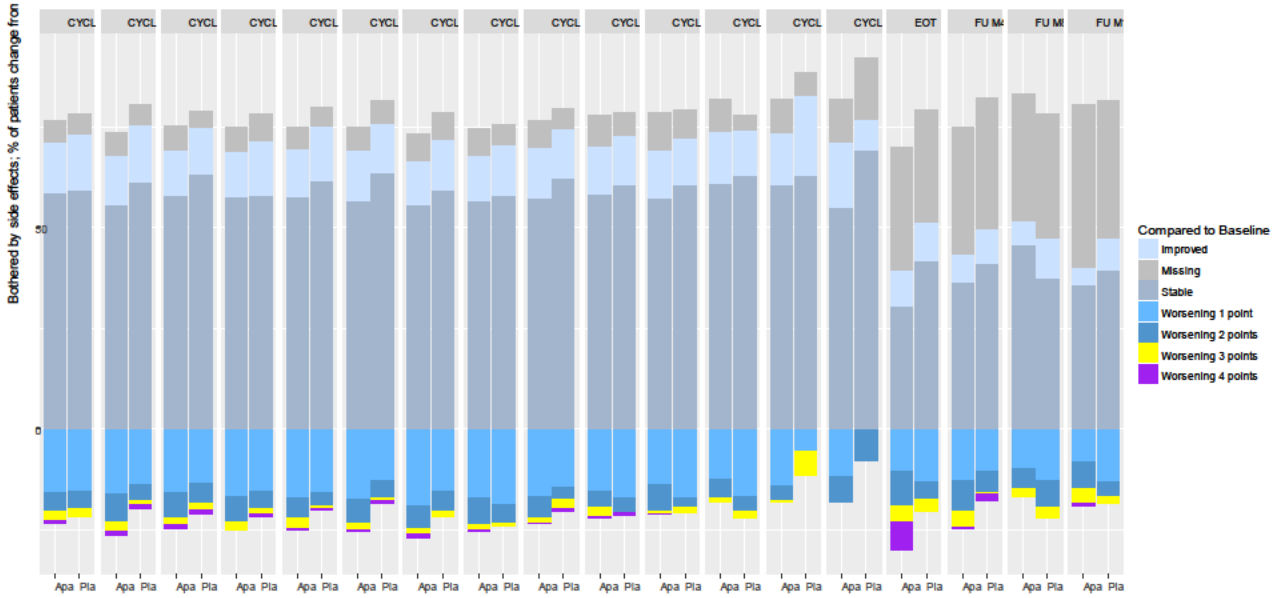
FACT-P Item C2 "I am losing weight"



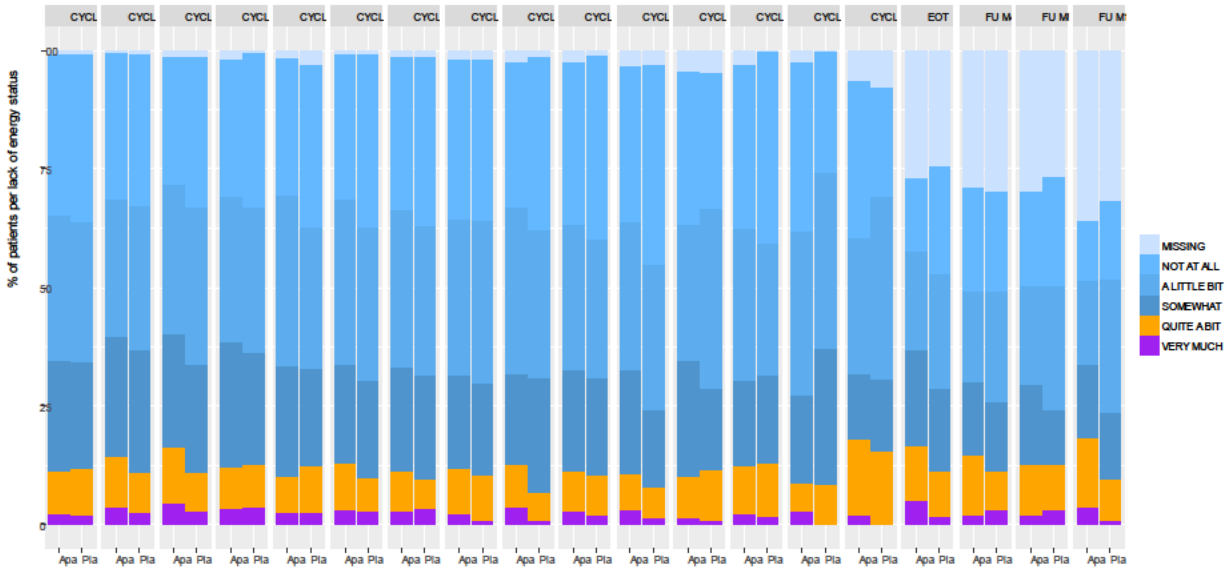


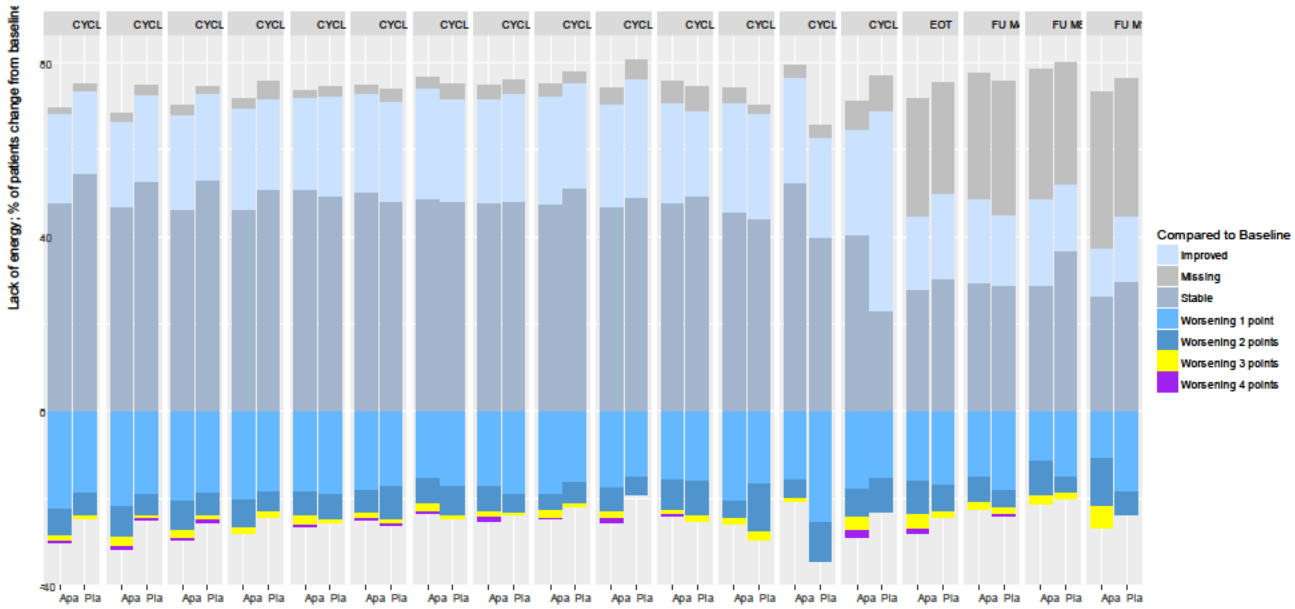
FACT-P Item GP5 ("I am bothered by side effects of treatment")



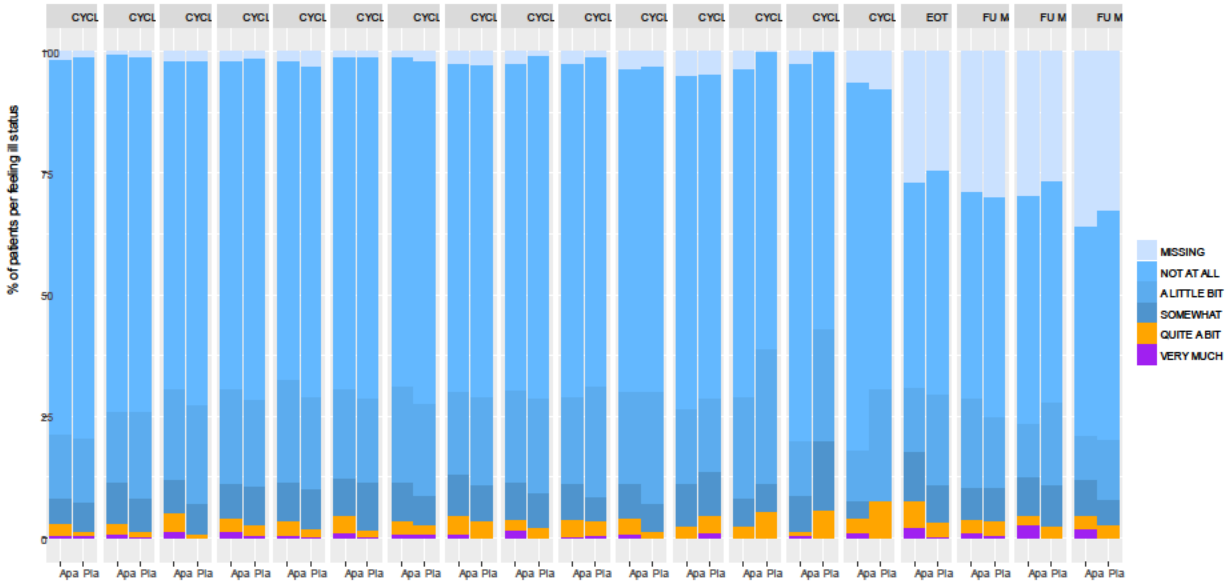


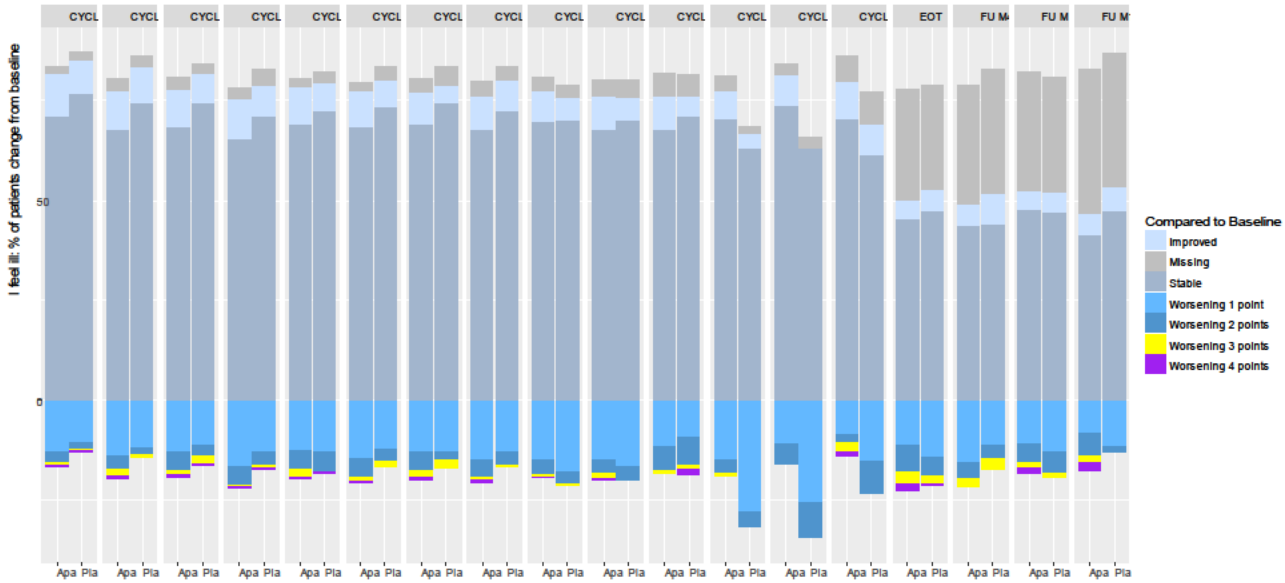
FACT-P Item GP1: "I have a lack of energy"



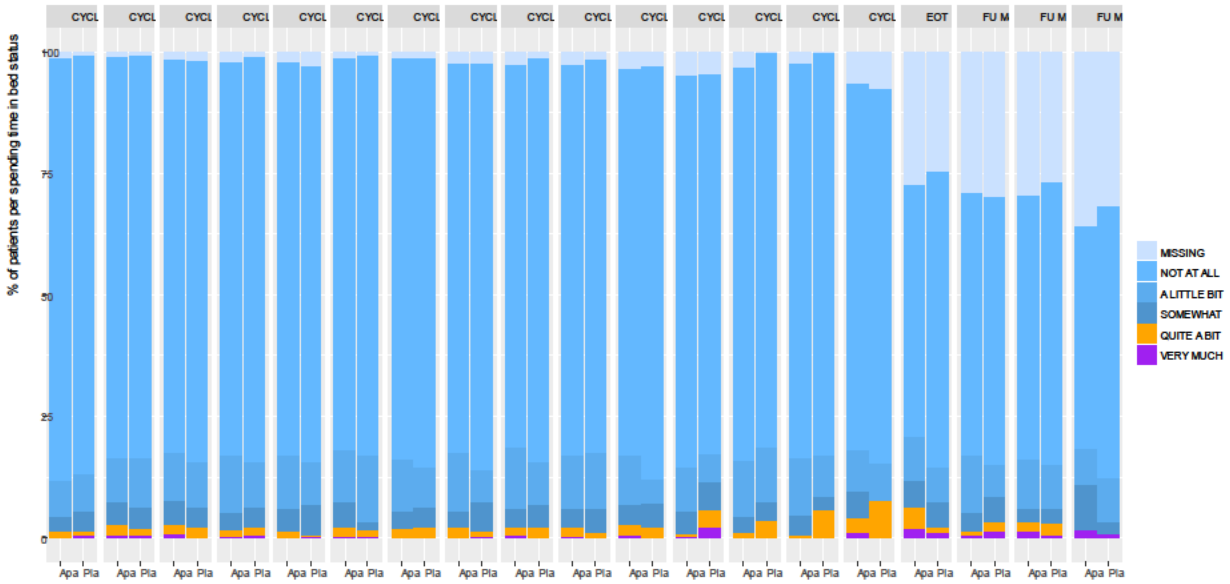


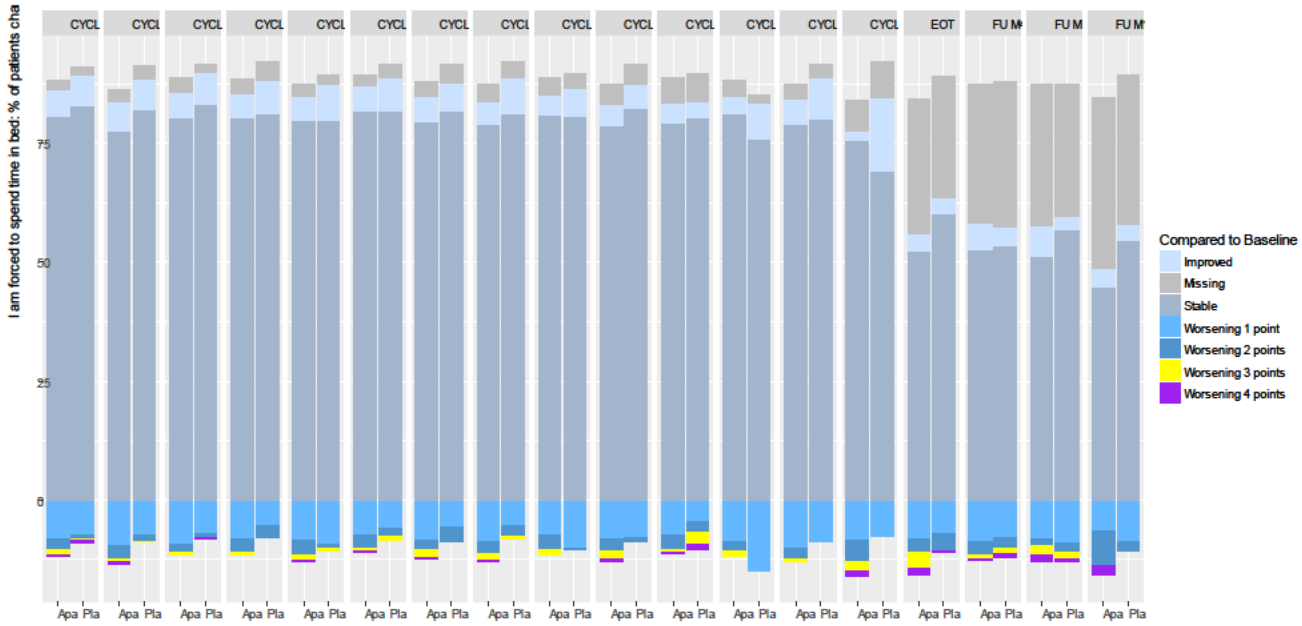
FACT-P Item GP6: "I feel ill"



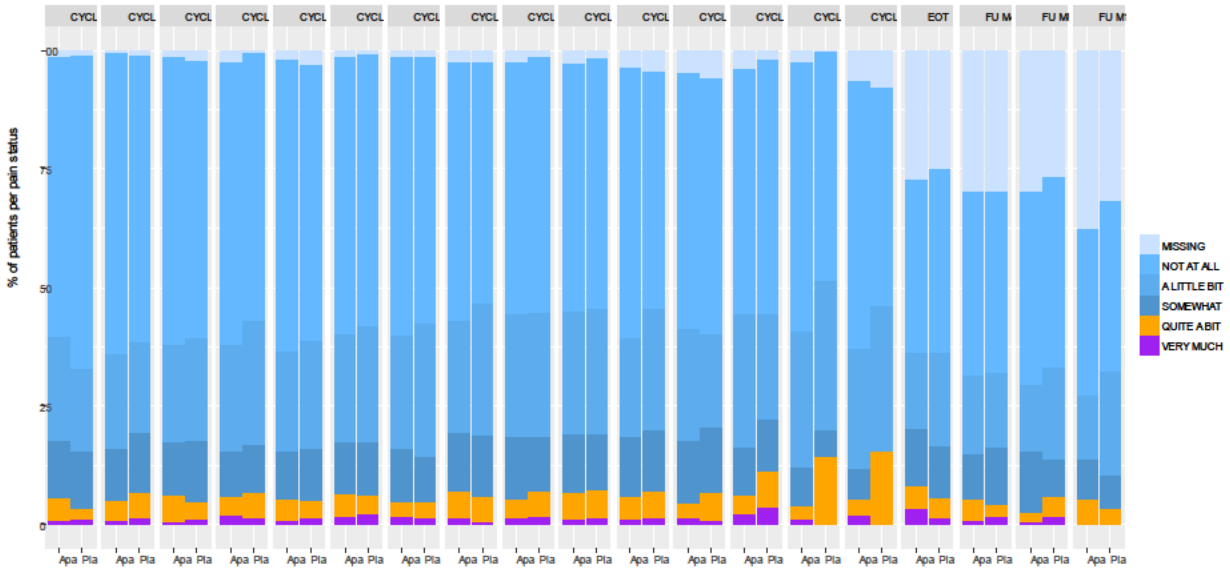


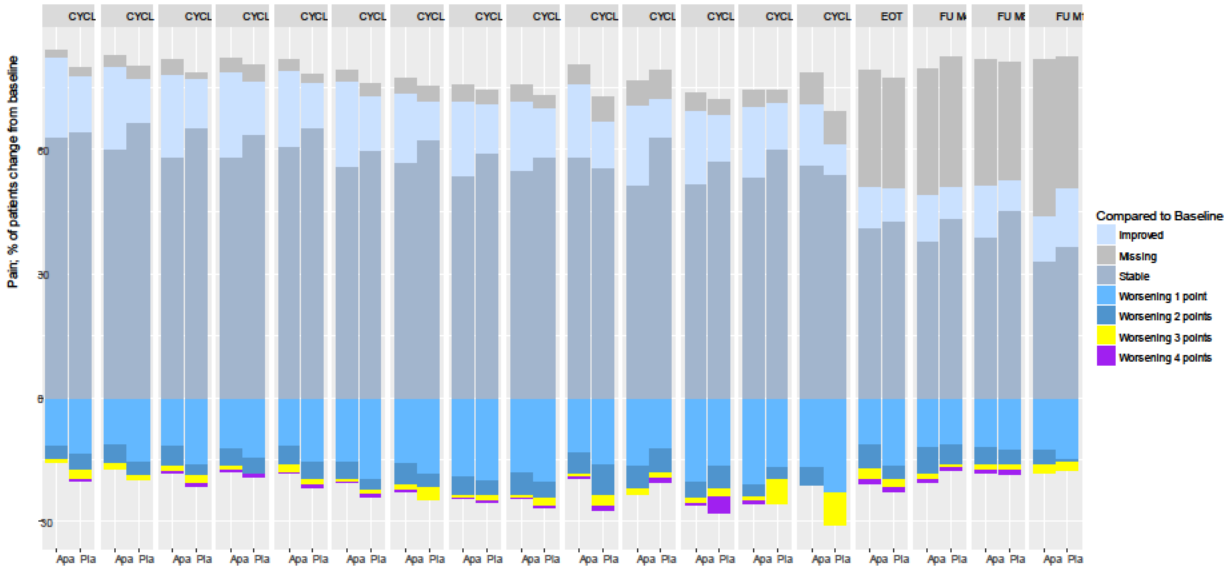
FACT-P Item GP7: "I am forced to spend time in bed"



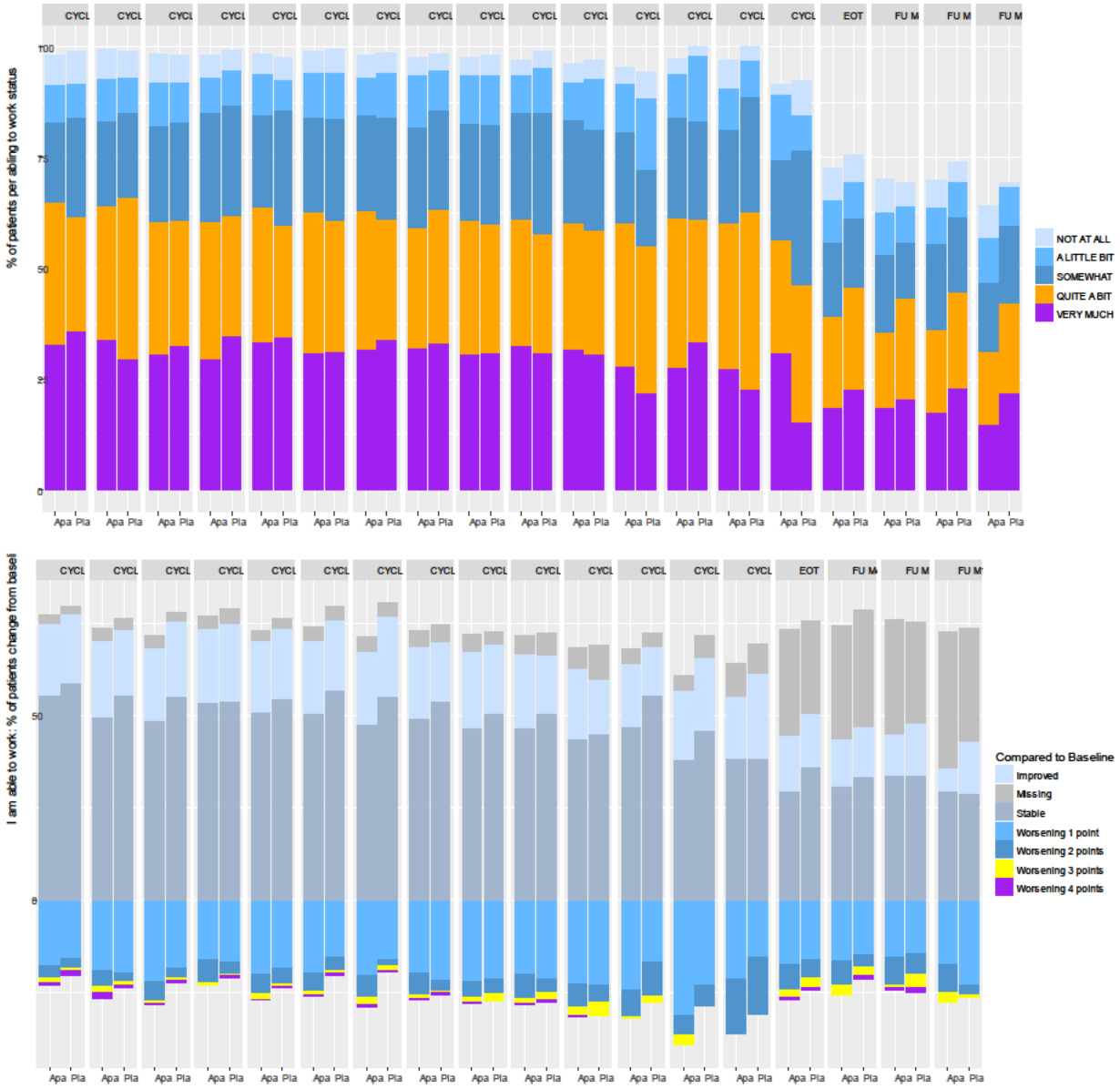


FACT-P Item GP4: "I have pain"

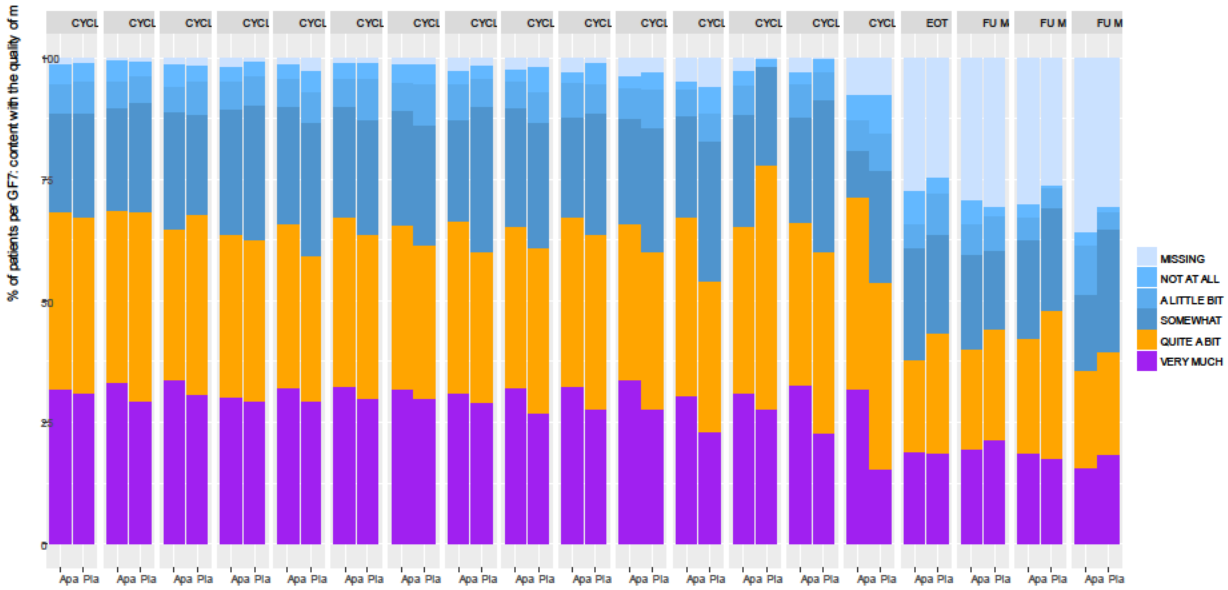


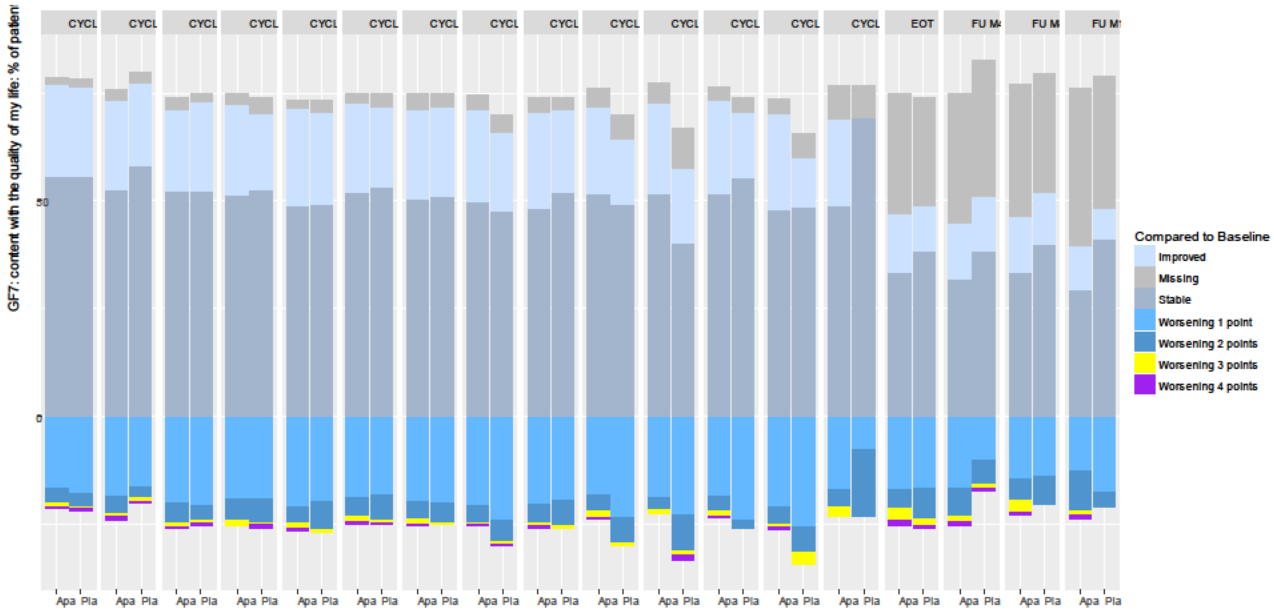


FACT-P Item GF1: "I am able to work"

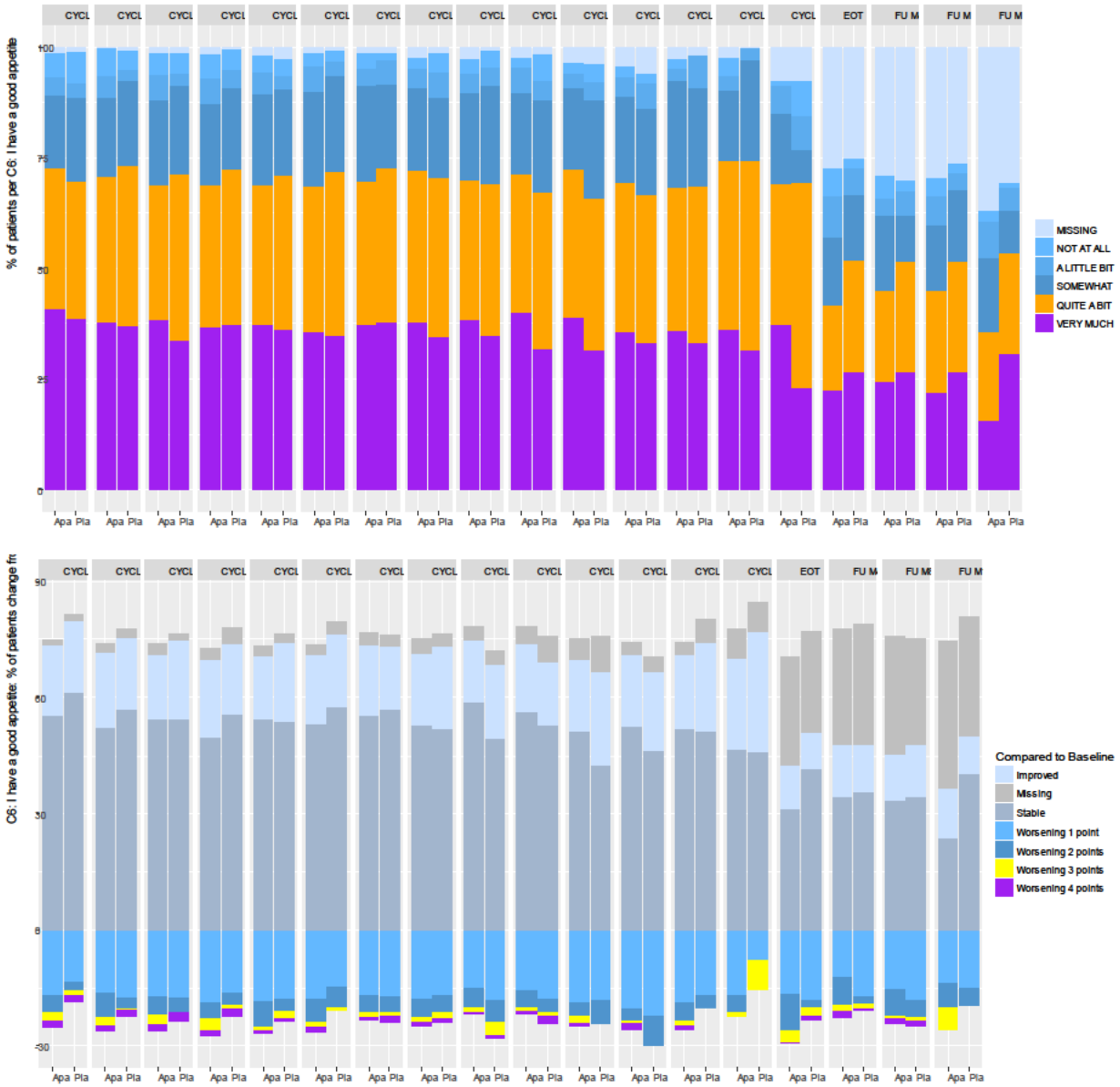


FACT-P Item GF7: "I am content with the quality of my life right now"





FACT-P Item C6: "I have a good appetite"



***Reviewer's Comment**. Exploratory analyses of PROs indicated that apalutamide did not appear to adversely affect functional outcomes as measured by the FACT-P and appeared well-tolerated over a long duration of therapy compared with placebo. On item level review, weight loss and a small increase in side effect bother were observed.*

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/s/

CHRISTY L COTTRELL
02/13/2018

WEI CHEN
02/13/2018

HALEH SABER
02/14/2018

JOHN K LEIGHTON
02/14/2018

WENTAO FU
02/14/2018

SIMBARASHE P ZVADA
02/14/2018

NAN ZHENG on behalf of JINGYU YU
02/14/2018

YUCHING N YANG
02/14/2018

XINYUAN ZHANG
02/14/2018

JIELIN J SUN
02/14/2018

ROSANE CHARLAB ORBACH
02/14/2018

QI LIU
02/14/2018

NAM ATIQUR RAHMAN
02/14/2018
I agree with the review team's recommendation.

LIJUN ZHANG
02/14/2018

RAJESHWARI SRIDHARA on behalf of ROBERT J SCHROEDER
02/14/2018
Signed for Schroeder

WILLIAM F PIERCE
02/14/2018

DANIEL L SUZMAN
02/14/2018

DOW-CHUNG CHI
02/14/2018

CHANA WEINSTOCK
02/14/2018

RAJESHWARI SRIDHARA
02/14/2018

JULIA A BEAVER
02/14/2018

GIDEON M BLUMENTHAL
02/14/2018

Division Director review is complete and has been added to the NDA Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

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

/s/

JULIA A BEAVER
02/13/2018

NDA 210951 Review

Clinical review is complete and has been added to the NDA Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

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/s/

DANIEL L SUZMAN
02/13/2018

NDA 210951 / SDN 01
Clinical Review Memo
02/12/2018

The Clinical review for NDA 210951 is complete, and has been added to the NDA 210951 Multidisciplinary Review and Evaluation. The clinical team recommendation for this application is approval.

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/s/

DOW-CHUNG CHI
02/12/2018

MEMORANDUM

From: Wentao Fu, PhD; Qi Liu PhD;
Division of Clinical Pharmacology V
To: File for NDA 210951 Erleada (apalutamide)

The Clinical Pharmacology review is complete and has been added to the NDA 210951 Multidisciplinary Review and Evaluation. Our recommendation for this application is approval.

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/s/

WENTAO FU
02/08/2018

QI LIU
02/08/2018

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 210951 | **Applicant: Aragon Pharmaceuticals, Inc., represented by Janssen Research & Development, LLC.** | **Stamp Date: October 10, 2017**

Drug Name: Apalutamide | **NDA/BLA Type: Original**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	x			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159 htm	x			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
10.	Has the applicant submitted a benefit-risk analysis for the product?	x			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	505 (b) (1)			
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?				
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?				
14.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)?	x			

Reference ID: 4218181

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Number: ARN-509-001 Study Title: Open-label, dose-escalation, proof-of-concept study Sample Size: 127 Treatment Arms: Phase 1: safety and MTD Phase 2: PSA response at 12 weeks according to the Prostate Cancer Working Group 2 (PCWG2) criteria Location in submission: 5.3.3.2				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 SPARTAN Indication: Non-metastatic castration-resistant prostate cancer Pivotal Study #2 Indication:	x			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

Reference ID: 4218181

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?			x	
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
37.	Are all datasets to support the critical safety analyses	x			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	available and complete?				
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___x_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Chana Weinstock 2//7/2018

Clinical Team Leader Date

Reference ID: 4218181

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/s/

CHANA WEINSTOCK
02/07/2018

Statistical Reviewer Memo

NDA 210951

Statistical Review is complete, and has been added to the NDA Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

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/s/

LIJUN ZHANG
02/07/2018

ROBERT J SCHROEDER
02/07/2018

MEMORANDUM

Date: February 5, 2018
From: Todd Palmby, PhD
Division of Hematology Oncology Toxicology for Division of Oncology Products 1
To: File for NDA 210951 Erleada (apalutamide)

The nonclinical secondary review is complete. My recommendation for this application is approval.

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/s/

TODD R PALMBY
02/05/2018

MEMORANDUM

Date: January 31, 2018
From: Wei Chen, PhD
Division of Hematology Oncology Toxicology for Division of Oncology Products 1
To: File for NDA 210951 Erleada (apalutamide)

The nonclinical review is complete and has been added to the NDA 210951 Multidisciplinary Review and Evaluation. My recommendation for this application is approval.

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/s/

TODD R PALMBY on behalf of WEI CHEN
02/01/2018

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NSA Number: 210951 **Applicant:** Janssen Research & Development **Stamp Date:** 10/10/2017

Drug Name: Apalutamide **NDA/BLA Type:** NME NDA

Indication: non-metastatic castration-resistant prostate cancer

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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/s/

LIJUN ZHANG
01/25/2018

ROBERT J SCHROEDER
01/25/2018

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NSA Number: 210951 **Applicant:** Janssen Research & Development **Stamp Date:** 10/10/2017

Drug Name: Apalutamide **NDA/BLA Type:** NME NDA

Indication: non-metastatic castration-resistant prostate cancer

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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/s/

LIJUN ZHANG
11/28/2017

ROBERT J SCHROEDER
11/29/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	210951	**SDN**	SDN 4
Applicant	Janssen Biotech	**Submission Date**	10/10/2017
Generic Name	Apalutamide	**Brand Name**	ERLEADA®
Drug Class	Androgen receptor inhibitor		
Indication	For the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC).		
Dosage Regimen	240 mg (four 60 mg tablets) administered orally once daily with or without food.		
Dosage Form	60 mg Tablets	**Route of Administration**	Orally
OCP Division	DCP V	**OND Division**	DOP1

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Wentao Fu, Ph.D.	Qi Liu, Ph.D.
Pharmacometrics	Simbarashe Zvada, Ph.D.	Jingyu (Jerry) Yu, Ph.D.
PBPK	Yuching Yang, Ph.D.	Xinyuan Zhang, Ph.D. and Yaning Wang, Ph.D.
Genomics	Jielin (Jillian) Sun, Ph.D.	Rosane Charlab Orbach, Ph.D.

Review Classification	☐ Standard ☐ Priority ☑ Expedited		
Filing Date	12/9/2017	**74-Day Letter Date**	12/23/2017
Review Due Date	1/31/2018	**PDUFA Goal Date**	4/10/2018

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s):

The followingis IR comment was sent to the Applicant on 10/30/2017 by the PBPK reviewer. The complete model files, dataset and worksheet were received on 11/06/2017 in CD format.

Submit model files used to generate final PBPK simulations in your PBPK reports (FK13005 and FK10644) including drug model files, population files, and workspace files (.cmp, .lbr, and .wks).

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

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

The following IR was sent to the Applicant on 11/03/2017 by the Genomics reviewer. The complete dataset and the justification for the threshold used to evaluate *ARV7 expression were received on 11/13/2017 (SN: 0010)*

Reference ID: 4185214

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

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☑ Metabolism Characterization	11	• 301091248: Evaluation of Induction Potential of Cytochrome P450 Isoforms by ARN-509 and ARN000308 in Cultured Human Hepatocytes. • FK10955: Induction of CYP1A2 in cryopreserved human hepatocytes following incubation with JNJ-56021927 and JNJ-56142060. • FK10651: An In Vitro Investigation of the Potential of JNJ-56021927 (ARN-509) to Inhibit the Major CYP450 Isoforms in Human Liver Microsomes. • CYP361_R6: Study to Investigate the Potential for Reversible and/or Time Dependent Inhibition of Human Cytochrome P450 by ARN-509 and ARN000308. • FK10660: An In Vitro Investigation of the Potential of JNJ-56142060 (ARN000308) to Inhibit the Major CYP450 Isoforms in Human Liver Microsomes. • DR-10-007-DSD: In Vitro and In Vivo Metabolite Profiles of ARN-509 in Rat, Dog and Human Liver Microsomes and Rat and Dog Plasma. • FK10596: The in vitro phenotyping of JNJ-56021927-AAA in human liver hepatocytes. • FK10924: The in vitro phenotyping of JNJ-56142060-AAA in human liver hepatocytes. • FQA0001: [14C]ARN-509: Absorption, Distribution, Metabolism and Excretion Studies in the Male Rat after Single Oral Dosing man liver hepatocytes. • FK10704: The metabolism and excretion of 14C-JNJ-56021927 in male beagle dog after a single oral administration of 14C-JNJ-56021927 at 10 mg/kg. • FK10840: The analysis of the radioactivity levels and metabolite profiling and identification in biological samples collected during clinical trial ARN-509-006, part B, investigating the absorption, metabolism and excretion of 14C-JNJ-56021927 after a single oral dose of 240 mg (37 kBq, 1000 nCi) in healthy male subjects.
☑ Transporter Characterization	2	• 12ARAGP1R1: Bidirectional Permeability Through Caco-2 Monolayers. • FK11028: Study on the inhibition potential of JNJ-56021927 and JNJ-56142060 on OCT2 (SLC22A2), OAT1 (SLC22A6), OAT3 (SLC22A8), MATE-1 (SLC47A1) and MATE 2K (SLC47A2) in cell lines overexpressing these transporters.

Reference ID: 4185214

☑ Distribution		4	• 301010034: Plasma Protein Binding Determination by Rapid Equilibrium Dialysis. • 301093931: Protein Binding Determination of ARN000308 in Mouse, Rat, Dog and Human Plasma by Rapid Equilibrium Dialysis. • DR-12-014-DSD: Assessment of In Vitro Protein Binding of ARN-509 in Male SHO Mouse Plasma by Equilibrium Dialysis. • FK10658: The distribution of 14C-JNJ-56021927 and 14C-JNJ-56142060 in blood. The protein binding of JNJ-56021927 and JNJ-56142060 in plasma from mouse, rat, dog, rabbit and human and the binding to human α1-acid glycoprotein and albumin.
☑ Drug-Drug Interaction		2	• FK10661: An in vitro study on the transport of JNJ-56021927 by ABCB1 and ABCG2 efflux proteins. • FK10693: Study on OATP1B1- and OATP1B3-mediated transport of 14CJNJ-56021927 and on the inhibition potential of JNJ-56021927 on OATP1B1 and OATP1B3 transport in HEK293 cell lines overexpressing OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3).
In Vivo Studies			
Biopharmaceutics			
☑ Absolute Bioavailability		1	• 006: 30 mg softgel capsules (oral) plus 14C-labeled apalutamide solution for injection (intravenous) or 14C-labeled apalutamide softgel capsule (oral); To determine the rate and routes of excretion of apalutamide and the mass balance in urine, feces and expired air; PK of total radioactivity in plasma and whole blood; determine the PK of apalutamide and metabolite(s) in plasma; determine the absolute oral bioavailability of apalutamide capsules
☑ Relative Bioavailability		4	• 1007: 30 mg softgel capsules, 60 mg tablets, (b) (4) (oral); To evaluate the pharmacokinetic (PK) and relative bioavailability of apalutamide from 7 different tablet formulations compared with the softgel capsule formulation • 1011: 30 mg softgel capsules or 60 mg tablets (oral); To evaluate the PK and relative bioavailability of apalutamide from 3 different tablet formulations compared with the softgel capsule formulation • 1015: 60 mg tablets (oral); To evaluate the effect of varying particle size distribution (PSD) on the bioavailability of apalutamide from tablet formulations manufactured from different batches of (b) (4). • 1017: 60 mg tablets (oral); To evaluate the bioavailability of apalutamide from tablet formulations manufactured at different sites
☐ Bioequivalence			
☑ Food Effect		1	1011
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	6	• 006, 1007, 1011, 1015, 1017 • 1021: To assess the PK profile of apalutamide and its active metabolite JNJ-56142060 after single-dose administration of 60 mg, 120 mg, or 240 mg of apalutamide in healthy male Japanese subjects (JAPAN)
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	3	• 001: Phase ½ Open-label, dose escalation, proof-of concept, multicenter study • 1008: Phase 1 Open-label, multicenter study (JAPAN) • 003: Phase3 Randomized, doubleblind, placebo-controlled, multicenter study
☑ Mass Balance Study		1	006
☐ Other (e.g. dose proportionality)			

Reference ID: 4185214

Intrinsic Factors		
☑ Race	1	003
☑ Sex	1	003
☑ Geriatrics	1	003
☐ Pediatrics		
☑ Hepatic Impairment	1	• 1018: PK in subjects with mild and moderate hepatic impairment
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☑ Effects on Primary Drug	1	• 1012: As CYP3A4 (itraconazole as an inhibitor) or 2C8 (gemfibrozil as an inhibitor) substrate
☑ Effects of Primary Drug	2	• 1020: repeat dosing of apalutamide on the single dose PK of multiple CYP450 enzymes (CYP3A4, CYP2C9, CYP2C19, CYP2C8) and transporter (P-gp and BRCP) substrates • 1010: To evaluate the effect of apalutamide on steady state PK of abiraterone acetate and prednisone (AA-P) in men with mCRPC during combination treatment of apalutamide with AA-P
Pharmacodynamics		
☐ Healthy Subjects		
☑ Patients	1	1019: QTcF
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☑ QT	1	1019
Pharmacometrics		
☑ Population Pharmacokinetics	7	001,1008,1011,1018,1019, 1021, 003
☑ Exposure-Efficacy	1	003
☑ Exposure-Safety	1	003

Total Number of Studies	**In Vitro**	19	**In Vivo**	14
Total Number of Studies to be Reviewed		19		14

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	The commercial drug product formulation is the same as those used for the Phase 3 clinical trial.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	

Reference ID: 4185214

5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☑Yes ☐No ☐N/A	Dataset received on 11/13/2017 in response to IR.
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted	☑Yes ☐No ☐N/A	

and submitted as described in the Exposure-Response guidance?		
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

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/s/

WENTAO FU
11/22/2017

SIMBARASHE P ZVADA
11/22/2017

YUCHING N YANG
11/22/2017

JIELIN J SUN
11/22/2017

XINYUAN ZHANG
11/22/2017

ROSANE CHARLAB ORBACH
11/22/2017

JINGYU YU
11/22/2017

QI LIU
11/22/2017

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 210951 **Applicant:** Janssen Biotech Inc **Stamp Date:** October 10, 2017

Drug Name: ERLEADA® (apalutamide) **NDA Type:** 505(b)(1)

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	s the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	s the pharmacology/toxicology section ndexed and paginated in a manner allowing substantive review to begin?	x		
3	s the pharmacology/toxicology section egible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 ncluding referenced literature) completed and submitted carcinogenicity, mutagenicity, teratogenicity, effects on fertility, uvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	f the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted ith appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			n/a
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed n accordance with the GLP regulations 21 CFR 58) or an explanation for any	x		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
	significant deviations?			
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			n/a
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and n accordance with 201.57?	x*		* No human dose multiples were used in the proposed label as no reproduction and carcinogenicity studies have been conducted.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	*x		* Issues generally identified during review
11	Has the applicant addressed any abuse potential issues in the submission?			n/a
12	f this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			n/a

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____yes____

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

WEI CHEN
11/20/2017

TODD R PALMBY
11/20/2017