

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212099Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212099
Priority or Standard	Priority
Submit Date(s)	February 26, 2019
Received Date(s)	February 26, 2019
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Division/Office	Division of Oncology Products 1/Office of Hematology & Oncology Products
Review Completion Date	
Established/Proper Name	Darolutamide
(Proposed) Trade Name	Nubeqa
Pharmacologic Class	Androgen receptor inhibitor
Code name	427492003 Hormone refractory prostate cancer (disorder)
Applicant	Bayer
Doseage form	300 mg tablets
Applicant proposed Dosing Regimen	NUBEQA 600 mg, (two 300 mg tablets) administered orally twice daily. Swallow tablets whole. Take NUBEQA with food. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.
Applicant Proposed Indication(s)/Population(s)	NUBEQA is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Non-metastatic castration resistant prostate cancer (nmCRPC)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	NUBEQA is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	NUBEQA 600 mg, (two 300 mg tablets) administered orally twice daily.

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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 = Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
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 Harmonisation
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

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OPQ	Office of Pharmaceutical Quality
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 (also known as Patient Information)
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

1 Executive Summary

1.1. Product Introduction

Darolutamide is a small molecule inhibitor of the androgen receptor (AR) and is not approved in any country.

The applicant proposed the following indication for approval of this new drug application:

NUBEQA is indicated for the treatment of patients with nonmetastatic castrate-resistant prostate cancer (NM-CRPC).

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

The recommended dose of NUBEQA is 600 mg (two 300 mg film-coated tablets) taken orally, twice daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The basis of the recommendation for regular approval of darolutamide is a favorable benefit-risk profile in ARAMIS (NCT02200614), a multinational, randomized, double-blind, phase 3 trial of the anti-androgen darolutamide compared with placebo in patients with high-risk nmCRPC conducted under SPA agreement with FDA. Patients were required to have a PSA doubling time of less than 10 months to be eligible for enrollment. A total of 1509 patients were randomized in a 2:1 ratio to darolutamide 600 mg BID versus placebo. Randomization was stratified by PSA doubling time (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no).

The primary endpoint was metastasis-free survival (MFS) defined as the time from randomization to the time of first evidence of confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first, as determined by blinded independent central review (BICR). Distant metastasis was defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation. Secondary endpoints included overall survival (OS), time to pain progression (TTPP), time to first symptomatic skeletal event (SSE), and time to initiation of first cytotoxic chemotherapy. The secondary endpoints were to be tested in the following hierarchical order only if the primary endpoint MFS was significant: OS, TTPP, time to initiation of first cytotoxic chemotherapy for prostate cancer, and time to first SSE. At the time of the primary analysis, there was to be an interim analysis for the secondary endpoints. Based on an assumed 140 OS events at interim and 240 OS events at final analysis, the alpha boundary was set at 0.0005 at interim and 0.0495 at final analysis, respectively. If at any point a secondary endpoint was not significant at the interim analysis, it was to be tested at final analysis, followed by the remaining endpoints in the testing sequence.

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. Patients were to receive darolutamide at 600 mg orally daily. 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. Results were not blinded to subjects, site staff, or applicant.

The trial met its primary efficacy endpoint. With a total of 437 events, the estimated median MFS was 40.4 months for darolutamide vs. 18.4 months for placebo (HR 0.41 [95% CI 0.34, 0.50]; $p < 0.0001$). This magnitude of benefit for MFS provides a positive risk-benefit ratio for this population. This result is supported by multiple sensitivity analyses and the investigator-determined analysis of MFS.

At the data cut-off time for the primary MFS analysis, 136 of the 240 events planned for the final OS analysis had occurred. The HR for the OS analysis was 0.706 (95% CI: [0.501, 0.994]; $p = 0.045$). The median was not reached in either treatment arm. As the pre-specified alpha significance level for this interim analysis of OS was 0.0005, the result is not considered statistically significant. The applicant agreed to a postmarketing commitment to submit the final OS analysis when completed. Although the analyses of additional secondary endpoints were not formally tested due to the hierarchical testing to control overall Type I error, these additional results all tended to favor darolutamide. The TTPP endpoint was described qualitatively in labeling as the data was rigorously collected and thought to be especially relevant to patient care, despite not meeting statistical significance. However, information on time to initiation of first cytotoxic chemotherapy and time to first SSE was not included as data were immature (low event rates) for those endpoints.

Although patients and investigators were not blinded to PSA results and there were more dropouts in patients with rising PSA and no evidence of metastases in the placebo arm (24.5%) compared to darolutamide (9.2%), this did not appear to affect the overall results when adjusting for these dropouts in sensitivity analyses.

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, with 9% of drug discontinuations due to adverse events in both darolutamide and placebo arms. Patient-reported outcome data, although exploratory, appeared supportive of acceptable tolerability compared to placebo. While overall survival data are immature, no decremental OS effect was observed at the interim analysis and the follow-up is ongoing, which increases confidence in the safety of darolutamide. ARAMIS notably enrolled patients with a history of seizure as it is

thought not to cross the blood-brain barrier, unlike other approved agents in this drug class. There were 12 patients enrolled with a seizure history; none had seizures while being treated with darolutamide. Toxicities of darolutamide included fatigue, pain in extremities, and rash. Recommendations for safe and effective use of darolutamide have been 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), and a draft Guidance- "Nonmetastatic, Castration Resistant Prostate Cancer: Considerations for Metastasis-Free Survival Endpoint in Clinical Trials", has been published. In addition, two drugs have previously been approved in this setting based on significant improvement in this endpoint. Thus, the demonstration of a marked improvement in MFS of patients treated with darolutamide compared to placebo, with a HR for OS that currently looks favorable to darolutamide, was considered as evidence of the approvability of darolutamide 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 ARAMIS, it was felt that the relatively arbitrary cutoff of 10 months did not warrant a restricted indication. This efficacy result was bolstered by the overall supportive safety profile of darolutamide.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Patients with castration-resistant prostate cancer with no overt radiographic evidence of metastasis (nmCRPC) are at substantial risk of developing metastatic disease. The FDA's ODAC previously discussed that the use of MFS as a primary efficacy outcome measure for trials in nmCRPC was potentially acceptable if a large magnitude of effect was demonstrated, accompanied by supportive secondary efficacy and safety outcomes. The AR inhibitors apalutamide and enzalutamide were both approved in 2018 for patients with nmCRPC based on large improvements in MFS compared to placebo and consistency among secondary endpoints.

ARAMIS was a multinational trial conducted under SPA agreement that randomized 1509 patients with blinded independent central review (BICR)-confirmed nmCRPC in a 2:1 ratio to treatment with darolutamide vs. placebo and used MFS as its primary efficacy endpoint. Patients were followed by BICR-assessed imaging. The analysis of MFS, as assessed by independent review, showed a statistically significant and clinically meaningful improvement for the darolutamide arm when compared to placebo. Estimated median MFS was 40.4 months (95% CI: 34.3, NE) vs 18.4 months (95% CI: 15.5, 22.3) in the darolutamide and placebo arms respectively (HR 0.413 [95% CI: 0.341, 0.500, $p < 0.0001$]). Investigator analysis was supportive.

While OS data are immature, no decremental OS effect was observed at the interim analysis and follow-up is ongoing. The secondary endpoints time to first symptomatic skeletal event, time to pain progression, and time to cytotoxic chemotherapy were not subjected to formal statistical analysis because the prespecified hierarchical analysis plan did not permit such testing since the interim analysis of OS was not statistically significant. However, the descriptive analyses of these secondary endpoints showed no apparent decrement in the darolutamide arm. The time to pain progression endpoint was described qualitatively in labeling, but information on time to initiation of first cytotoxic chemotherapy and time to first symptomatic skeletal event was not included as data were immature for those endpoints.

The safety profile of darolutamide was generally acceptable in this setting. Overall, 9% of patients on both the darolutamide arm and the placebo arm discontinued treatment due to adverse events. ARAMIS notably enrolled patients with a history of seizure unlike other approved agents in this drug class. There were 12 patients enrolled on the darolutamide arm with a seizure history; none had seizures while being treated with darolutamide. Toxicities of darolutamide included fatigue, pain in extremities, and rash. Patient-reported outcome data, although exploratory, were supportive of an acceptable tolerability compared to placebo.

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 with time 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 premetastatic state is termed non-metastatic castration-resistant prostate cancer (nmCRPC). - Patients with nmCRPC, especially those with a short PSA doubling time (PSADT) (i.e., a PSADT of ≤ 10 months), are at a greater risk for development of metastatic disease and prostate cancer-specific death. - Without treatment, patients with nmCRPC have a median MFS (bone metastases only) of 25 months, which decreases to 22 months for patients with PSADT ≤ 10 months and to 18 months for patients with PSADT ≤ 6 months (MS Smith et al. JCO 2013). - The transition to a metastatic state is clinically significant, and once a patient develops metastatic disease, median overall survival is ~ 11 months without treatment (JS deBono et al. NEJM 2011).	Patients with nmCRPC are at significant risk of disease progression to metastatic disease, with resultant morbidity and mortality. The transition to a metastatic state is considered of clinical importance and delaying that transition via an improvement in MFS is considered clinically meaningful.
Current Treatment Options	- Apalutamide, another AR inhibitor, was approved for the treatment of men with nmCRPC on February 14, 2018 based on an improvement in MFS compared to placebo demonstrated via results from the SPARTAN trial. - Enzalutamide, another AR inhibitor, was approved for the treatment of men with nmCRPC on July 13, 2018 based on an improvement in MFS compared to placebo demonstrated via results of the PROSPER trial.	A similar magnitude of benefit with respect to MFS was demonstrated with darolutamide vs. placebo as compared to apalutamide and enzalutamide in the same disease setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	- Estimated median MFS was 40.37 months (95% CI: 34.33, NE) vs 18.43 months (95% CI: 15.51, 22.34) in the darolutamide and placebo arms respectively with a HR 0.413 (95% CI: 0.341, 0.500, p<0.0001). - With 57% of the OS events the interim analysis of OS was not statistically significant and therefore the secondary endpoints of time to first symptomatic skeletal event, time to pain progression, and time to cytotoxic chemotherapy were not formally tested per the prespecified hierarchical analysis plan. Descriptive analyses of these analyses showed results favorable to the darolutamide arm and were thus considered supportive. - A descriptive analysis of the time to pain progression results were included in labeling as they were considered helpful to inform expected symptomatic outcomes.	The observed hazard ratio and difference in median MFS is substantial and is clinically meaningful. Although the OS analysis is immature, there was no OS decrement observed at the interim analysis and the follow-up is ongoing. Descriptive analyses of other secondary endpoints including time to pain progression, time to initiation of cytotoxic chemotherapy, and time to first SSE showed results favorable to the darolutamide arm and were thus considered supportive.
Risk and Risk Management	- Darolutamide was well-tolerated in most study patients with a low rate of discontinuation due to adverse events. Fatigue, pain in extremities, and rash were among observed toxicities. - Seizure incidence was 0.2% in both arms and no seizures occurred in the 12 enrolled patients with a documented seizure history. Of note, the reported incidence of seizures is similar to ERLEADA (0.2% in SPARTAN) and XTANDI (0.4%) labels. However, ARAMIS is the first completed trial with a marketing intent in the nmCRPC setting to enroll patients with seizures	The safety profile of darolutamide is acceptable in this population. The enrollment of patients with pre-existing seizure history was noted in labeling. The safe use of darolutamide can be managed through accurate labeling and routine pharmacovigilance. No REMS is needed.

1.4. Patient Experience Data

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

☐	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	
☒	Patient reported outcome (PRO)	Section 8.2.6 Section 18.5 Additional Clinical Outcome Assessment Analyses
☐	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 were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

X

Cross Discipline Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Prostate cancer is the second most common form of cancer in men in the United States representing 19% of newly diagnosed cancers and the third leading cause of cancer death responsible for an estimated 39,430 deaths in 2018.¹ Despite high cure rates after prostatectomy and/or radiation therapy, a proportion of patients with prostate cancer will suffer disease relapse. Men who experience rising prostate-specific antigen (PSA) values after therapy for localized prostate cancer are often treated with androgen deprivation therapy (ADT), with either a gonadotropin-releasing hormone (GnRH) analog or surgical orchiectomy. This typically induces PSA declines, but eventually, many patients develop non-metastatic castration-resistant prostate cancer (nmCRPC), which is defined as rising levels of PSA despite castrate levels of testosterone and the absence of radiographic evidence of distant metastatic disease.

While patients with nmCRPC can have an indolent course, a meaningful proportion of men will go on to develop bone metastases, with one series reporting 46% of men with nmCRPC developing a metastasis within 2 years.² A higher PSA and shorter PSA doubling time (PSADT) have each been associated with a shorter time to first bone metastasis and shorter overall survival in patients with nmCRPC, with a notable inflection point at a PSADT of around 8 months.³

The transition to a state of measurable metastatic disease represents a significant event for patients. While early radiographic signs of metastatic disease can be asymptomatic, most patients will eventually develop clinical manifestations, which can include pain, ineffective hematopoiesis, pathologic fracture, spinal cord compression, and interventions such as surgery and radiotherapy.

2.2. Analysis of Current Treatment Options

Two drugs have been approved for the treatment of patients with nmCRPC, apalutamide (ERLEADA) and enzalutamide (XTANDI).

Apalutamide was approved as a new molecular entity in February 2018 for patients with nmCRPC. Approval was supported by a multinational clinical trial (SPARTAN, NCT01946204) that randomized 1207 patients with high-risk ($\text{PSADT} \leq 10$ months) nmCRPC in a 2:1 ratio to apalutamide 250 mg by mouth once daily ($n=806$) vs. placebo ($n=401$). The trial demonstrated an improvement in estimated median MFS of 40.5 months vs. 16.2 months in the apalutamide

and placebo arms, respectively (HR 0.28 [95% CI: 0.23, 0.35]; $p < 0.0001$). The secondary endpoints of time to metastasis, progression-free survival, and symptomatic progression were also statistically significant per their prespecified hierarchical testing analysis plan. OS results were not mature (104 deaths) at the time of the primary efficacy analysis but revealed a favorable trend (HR 0.74 [95% CI: 0.47, 1.04]).

Enzalutamide received supplemental approval in July 2018 for patients with nmCRPC. Enzalutamide had previously been approved for the treatment of patients with metastatic CRPC. Approval in patients with nmCRPC was supported by a multicenter clinical trial (PROSPER, NCT020032924) that randomized 1,401 patients with high-risk nmCRPC (PSADT of ≤ 10 months) in a 2:1 ratio to enzalutamide 160 mg orally once daily (N = 933) vs. placebo (N = 468) orally once daily. The primary efficacy outcome was MFS, defined as the time from randomization to loco-regional and/or distant radiographic progression by blinded independent central review (BICR) or death up to 112 days after treatment discontinuation without radiographic progression. This differed from the definition of MFS in SPARTAN, which included only extra-pelvic (distant) progression and included death at all timepoints. PROSPER demonstrated a statistically significant improvement in MFS for patients receiving enzalutamide compared to those receiving placebo, with median MFS of 36.6 and 14.7 months, respectively (HR 0.29 [95% CI: 0.24, 0.35]; $p < 0.0001$). Analysis of the secondary endpoints of time to first use of new antineoplastic therapy and time to PSA progression also favored the enzalutamide arm. OS results were not mature at the time of the primary efficacy analysis revealed a favorable trend (HR 0.80 [95% CI: 0.58, 1.09]).

Table 1: FDA-Approved therapies in nmCRPC

	SPARTAN (apalutamide)		PROSPER (enzalutamide)	
Date trial initiated	September 19, 2013		November 26, 2013	
Clinical cutoff date	May 19, 2017		June 28, 2017	
Approval date	February 14, 2018		July 13, 2018	
Efficacy endpoint, primary (definition)	Metastasis-Free Survival (Time from randomization to BICR-confirmed radiographic disease progression or death)		Metastasis-Free Survival (Time from randomization to BICR-confirmed radiographic disease progression or death)	
Number of patients enrolled	1207 (apalutamide n=806 vs. placebo n=401)		1401 (enzalutamide n=933 vs placebo n=468)	
Results of MFS analysis	Apalutamide	Placebo	Enzalutamide	Placebo
Median MFS	40.5 months	36.6 months	36.6 months	14.7 months
HR (95% CI)	0.28 (0.23, 0.35)		0.29 (0.24, 0.35)	
P-value	<0.0001		<0.0001	

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Darolutamide has never been marketed in the U.S or in any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

3.2.1. Regulatory history of MFS as a primary efficacy endpoint in nmCRPC

Delaying the morbidity of metastases and toxicities associated with systemic treatments is an important therapeutic goal for men with nmCRPC. This goal is reflected in the use of metastasis-free survival (MFS) as a therapeutic endpoint in this disease setting. Because patients with nmCRPC can have a prolonged disease course and may receive multiple subsequent effective therapies, the use of overall survival (OS) as a primary endpoint has been considered problematic. The FDA engaged the prostate cancer research community to explore challenges in drug development for the nmCRPC population at two meetings of the FDA's Oncology Drugs Advisory Committee (ODAC). FDA published a draft guidance entitled "Nonmetastatic, Castration Resistant Prostate Cancer: Considerations for Metastasis-Free Survival Endpoint in Clinical Trials" in 2018.

3.2.2. Key regulatory history of darolutamide under IND 114769

Oct. 15, 2013: An end-of-phase 2 meeting was held regarding the planned ARAMIS trial. Advice from the clinical review team included the following:

- The trial should be powered for OS, with an interim analysis planned at the time of the final analysis of MFS.
- FDA raised concern that patients might have serum PSA levels checked at their local laboratories and might discontinue study drug based on these results and stated that the extent of patient discontinuation and any resulting imbalances would be a review issue.
- With respect to symptomatic MFS, the applicant was asked to define how a metastasis would be considered symptomatic. FDA recommended anchoring this with adequately captured data on patient reported pain and analgesic use. The FDA Study Endpoints and Labeling Development team discussed issues around the proposed time to pain progression endpoint.

February 21, 2014: The FDA agreed to a Special Protocol Assessment (SPA) for the design of the ARAMIS trial. MFS would be the primary efficacy endpoint, and 1500 enrolled patients would be expected to provide 572 MFS events. Alpha would be adjusted for an interim analysis of OS at the time of the final MFS analysis.

16 Feb 2016: FDA agreed with the proposal to request a waiver for the requirement for pediatric assessments for darolutamide for the treatment of patients with nmCSPC because studies would be impossible or highly impracticable.

Sept. 7, 2016: FDA agreed to a proposed amendment to the ARAMIS Special Protocol Assessment, including the stipulation that new metastases must be confirmed by central reading.

June 29, 2016: FDA designated as a Fast Track development program the investigation of darolutamide for patients with nmCRPC.

November 9, 2017: A Type A meeting was held to discuss the revised statistical analysis plan submitted in Protocol Amendment 3. This revised plan would change the target HR from 0.75 to 0.70, require 370 MFS events instead of 572 MFS events to reach the primary endpoint, while maintaining the type 1 error rate of 0.05 (2-sided) and 90% power; and reduce the number of patients enrolled from approximately 1500 to 1300.

June 28, 2018: FDA agreed to a proposed Special Protocol Assessment amendment changing the target hazard ratio for MFS from 0.75 to 0.65 and thus the targeted number of MFS events from 572 to 385 due to recently published results from SPARTAN and PROSPER that suggested that a target hazard ratio of 0.75 was too conservative.

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

4.1. Office of Scientific Investigations (OSI)

An OSI consult was requested. Three clinical sites were selected for audit. These were Site 6102 (Dr. Neal Shore), Site 5401 (Dr. Teuvo Tammela), and Site 6503 (Dr. Albertas Ulys). The inspectional findings verified the Applicant's reported clinical data with source records at these study sites. No significant GCP compliance deviations were observed at these sites. Based on the inspectional findings, the OSI review team considers the submitted data from this study reliable for this NDA and the respective indication.

4.2. Product Quality

As noted in the OPQ review by Dr Xiao Hong Chen (Technical Lead), darolutamide is a non-steroidal androgen receptor (AR) antagonist with high binding affinity and selectivity to the AR. Darolutamide competitively prevents androgen binding to the AR and inhibits AR nuclear translocation and interaction with DNA. The darolutamide drug substance is a 1:1 mixture of two diastereomers, which are both similarly pharmacologically active. The major metabolite of darolutamide is ketodarolutamide, which has similar high binding affinity for the AR and exhibits comparable activity in *in vitro* assays.

Darolutamide is a filmcoated, immediate-release 300 mg tablet for oral application. Darolutamide is given in doses of 600 mg (2 tablets of 300 mg) twice daily with food, equivalent to a total daily dose of 1200 mg.

The quality review team in the Office of Pharmaceutical Quality reviewed the CMC information in this NDA and found the product quality to be acceptable.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Darolutamide (BAY 1841788, ORM-15674, ODM-201) is a small molecule inhibitor of androgen receptor (AR). Darolutamide is a 1:1 mixture of 2 diastereomers, (S,R)-darolutamide (ORM-16479) and (S,S)-darolutamide (ORM-16555). In humans, the diastereomer ratio of (S,R)-darolutamide to (S,S)-darolutamide was about 1:6 under steady-state conditions. In vitro, darolutamide competitively inhibited AR and transcriptional activation of AR-dependent genes in cells expressing both wild type (WT) and mutant human AR. Darolutamide decreased testosterone-mediated nuclear translocation of AR in vitro. Darolutamide also functioned as a progesterone receptor (PR) antagonist *in vitro* (approximately 1% activity compared to AR). In addition, darolutamide suppressed androgen-induced prostate cancer cell proliferation in vitro. In vivo, darolutamide administration inhibited tumor growth in mouse xenograft models of human prostate cancer and suppressed the relative increase in serum PSA when compared to control group. Based on available pharmacology data with darolutamide, the scientifically valid and clinically relevant Established Pharmacologic Class (EPC) is “androgen receptor inhibitor.”

The metabolic pathways observed across species (rat, mouse, dog and human) involved oxidative and conjugated metabolites (i.e., M1-M40). In humans, the major metabolite was keto-darolutamide (M1). The mean exposure of keto-darolutamide was 1.7-fold higher than parent darolutamide at steady-state in patients administered darolutamide at the recommended dose based on AUC. Following a single oral administration of 300 mg [¹⁴C]-darolutamide to healthy male volunteers, keto-darolutamide was the only major metabolite in plasma, covering about 58.8% of total radioactivity based on AUC. The respective AUC portion of darolutamide was about 28.6% of total radioactivity, summing up to 87.4% of total radioactivity. Given the relative level of keto-darolutamide to darolutamide, the majority of the AR inhibition is likely due to its active keto-darolutamide metabolite. In vitro, pharmacologic activity was comparable between darolutamide and keto-darolutamide, except keto-darolutamide demonstrated approximately 2 to 3-fold greater inhibition of human WT and mutant AR transactivation but was less effective in blocking testosterone-induced nuclear translocation of AR compared to darolutamide (300 nM vs. 100 nM).

The intended clinical dose of darolutamide in humans is 600 mg administered orally twice daily (1200 mg/day or approximately 750 mg/m²). At steady-state, mean C_{min}, C_{max} and AUC₀₋₁₂ values for darolutamide were 3.78 µg/mL (9.5 µM), 4.79 µg/mL (12 µM) and 52.8 µg•hr/mL, respectively. In addition, mean C_{min}, C_{max} and AUC₀₋₁₂ values of keto-darolutamide were 6.11 µg/mL (15 µM), 8.48 µg/mL (21 µM) and 88.8 µg•hr/mL respectively. In humans, the mean fraction of unbound darolutamide in plasma was 8% for darolutamide and 0.2% for keto-darolutamide, indicating that darolutamide and keto-darolutamide were predominantly distributed in the plasma.

The Applicant conducted an in vitro secondary pharmacology screen to assess the potential for off-target binding to over 100 receptors, enzymes and channels. Darolutamide and keto-darolutamide inhibited binding to human serotonin (5-HT) transporter by 85% and 86%, respectively, at a concentration of 10 μM . In functional in vitro assays using rat brain synaptosomes, darolutamide inhibited 5-HT uptake with IC_{50} values of 3.4 μM , a concentration approximately 4-fold and 6-fold lower than the steady-state C_{max} of darolutamide and keto-darolutamide, respectively, in patients receiving the recommended dose of darolutamide. For some androgen receptor inhibitors, seizures induced through inhibition of GABA_A receptors are a common adverse reaction in humans and animals. To address the potential for GABA_A inhibition, the Applicant assessed the effect of darolutamide and keto-darolutamide on GABA_A receptors in acutely isolated rat striatal neurons using a whole-cell patch-clamp assay. Darolutamide and keto-darolutamide reversibly blocked GABA_A -activated currents with IC_{50} values of 5.5 μM and 3.4 μM , respectively. In male mice, brain/plasma exposure ratios to darolutamide and keto-darolutamide were low (0.02) based on AUC after a 7-day oral administration of darolutamide. In addition, oral doses up to 1000 mg/kg/day in rats and 400 mg/kg/day in dogs did not result in clinical signs indicating effects on CNS at plasma concentrations that were high enough to inhibit 5-HT and GABA_A receptors (C_{max} values up to 18500 ng/mL [46 μM] in rats and up to 13900 ng/mL [35 μM] in dogs). Moreover, there were no remarkable CNS-related adverse reactions observed in patients receiving darolutamide at the recommended dose. Based on available information, the potential for darolutamide to cause CNS effects is low.

In vitro, darolutamide, (S,R)-darolutamide, (S,S)-darolutamide and keto-darolutamide were low-potency hERG channel blockers ($\text{IC}_{50} > 1 \mu\text{M}$). Darolutamide and keto-darolutamide also blocked L-type Ca currents with IC_{50} values that were higher than the C_{min} and C_{max} of darolutamide and keto-darolutamide observed at steady-state in patients receiving the recommended dose of darolutamide. In vitro, keto-darolutamide also inhibited adenosine receptor A3 by 53% at a concentration of 10 μM , which is lower than the steady-state C_{min} and C_{max} of keto-darolutamide in patients receiving the recommended dose of darolutamide. Darolutamide demonstrated little inhibition of adenosine receptor A3 at concentrations up to 10 μM . In vivo safety pharmacology studies revealed that bolus intravenous injection of darolutamide or (S,S)-darolutamide to anaesthetized dogs at 10-20 mg/kg induced a marked vasodilatation, especially at the peripheral level, leading to decreased arterial blood pressure. The decreases in mean systolic and diastolic arterial blood pressure (10-46%) started 1 minute after dosing and only partially recovered 30 minutes after dosing. At doses ≥ 10 mg/kg, C_{max} of darolutamide was 6 to 10-fold higher than the steady-state C_{max} in patients receiving the recommended dose of darolutamide. Based on AUC_{0-24} values in immature male rats, heart/plasma ratio exposure to darolutamide (0.63) and keto-darolutamide (0.16) were low after a 6-day oral administration of darolutamide. In addition, there were no remarkable changes in ECG parameters or arterial blood pressure reported in dogs in repeat-dose toxicity studies following oral administration of darolutamide at doses up to 400 mg/kg/day (2 times the human exposure based on AUC).

In rats, a single oral dose of 1000 mg/kg (6000 mg/m² human equivalent dose [HED]) darolutamide resulted in a decrease in tidal volume up to 32% at 5 hours and 24% at 24 hours. This dose is approximately 8 times the clinical recommended dose based on body surface area (BSA). Toxicokinetics were not assessed in the single dose oral gavage study. In repeat-dose toxicology studies, rats and dogs showed no clinical signs indicating adverse respiratory effects following oral administration of darolutamide. Following repeat doses up to 1000 mg/kg/day darolutamide in rats, exposure to darolutamide was 1.3 to 3 times the human exposure at the recommended dose based on AUC and exposure to keto-darolutamide was 0.8 to 1.4 times the human exposure based on AUC. Therefore, the potential for darolutamide to cause respiratory effects is low, consistent with findings in clinical trials.

The Applicant conducted general toxicology studies to evaluate the effects of daily oral administration of darolutamide in rats for up to 26 weeks and in dogs for up to 39 weeks. There were no early mortalities related to darolutamide treatment. Administration of darolutamide to rats and dogs resulted in changes in male reproductive organs, consistent with the anti-androgenic activity of darolutamide. Toxicities in reproductive organs included atrophy of the male reproductive organs (prostate gland, seminal vesicles, testes, and epididymides), hypospermia, epithelial degeneration of the epididymides and tubular dilation of the testes. Toxicities in male reproductive organs occurred at doses $\geq$ 100 mg/kg/day in male rats (0.6 times the human exposure based on AUC) and $\geq$ 50 mg/kg/day in dogs (1 times the human exposure based on AUC). Toxicities observed in the gastrointestinal tract in rats (minimal erosion and hemorrhage of stomach and minimal inflammation of cecum) and dogs (minimal dilation of cecum) were consistent with the adverse reactions reported in clinical trials including decreased appetite, constipation and diarrhea. Other target organs of toxicity in rats and dogs included the mammary gland (minimal to slight atrophy primarily observed in male rats; slight to moderate decrease in acinar development/secretion in female dogs), adrenal gland (minimal vacuolation in female rats and minimal inflammation in dogs) and thyroid gland (minimal hyperplasia and lymphoid cell infiltration in rats). Findings observed after repeated administration of darolutamide were either completely or partially reversible following a 4-week recovery period in rats and 8-week recovery period in dogs.

Darolutamide was clastogenic in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. However, darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in an in vivo combined bone marrow micronucleus assay and comet assay in the liver and duodenum of the rat. Based on the weight of evidence, the nonclinical data indicate an absence of genotoxic risk. No carcinogenicity studies were conducted or warranted to support this NDA, as the proposed indication was for advanced cancer.

No embryo-fetal development toxicology studies were conducted or warranted to support this NDA submission, as the proposed indication does not include females. The product label states that Nubeqa can cause fetal harm if administered during pregnancy, which is based on inhibition of the androgen receptor, a hormonal signaling pathway critical during development.

The Applicant proposed that male patients with female partners of reproductive potential use effective contraception during treatment and for (b) (4) following the last dose. The current approach in the Office of Hematology and Oncology Products is to recommend patients use effective contraception during treatment and for 5 half-lives (or a minimum of 1 week) following the last dose of a non-genotoxic drug that is expected to be teratogenic based on mechanism of action. The terminal half-life of darolutamide and keto-darolutamide is approximately 20 hours at the recommended clinical dose, and a 1-week duration of contraception covers a washout period of at least 5 half-lives.

Darolutamide may impair fertility in males of reproductive potential based on mechanism of action and findings in animals. In repeat-dose toxicology studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), oral administration of darolutamide resulted in tubular dilatation of testes, hypospermia, and atrophy of seminal vesicles, testes, prostate gland and epididymides at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC). Effects on male reproductive organs were still observed in male rats following 4-week recovery period but were reversible following an 8-week recovery period in dogs.

Recommendations

The nonclinical data submitted in this NDA support approval of Nubeqa for the treatment of patients with non-metastatic, castration-resistant prostate cancer.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

In a competitive androgen receptor (AR) binding assay, binding affinities of ORM-15674 (darolutamide), ORM-15341 (keto-darolutamide), ORM-16497 ([S,R]-darolutamide) and ORM-16555 ([S,S]-darolutamide) were measured in cytosolic lysates obtained from ventral prostates of castrated rats. Cytosolic lysates and 1 nM mibolerone (^3H -17 α -methyl) were incubated with increasing concentrations of test compounds in 100 μL of buffer containing 1% final concentration of DMSO. To determine non-specific binding, parallel incubations were carried out using 1 μM unlabeled testosterone. The K_i values of darolutamide, keto-darolutamide, (S,R)-darolutamide and (S,S)-darolutamide were 9.1 nM, 7.5 nM, 9.3 nM and 18.6 nM, respectively (Study no.10000133) and comparable to the K_i value of 12.1 nM for non-steroidal AR inhibitor bicalutamide.

In a transactivation assay, the Applicant assessed the inhibitory activity of darolutamide, keto-darolutamide, and bicalutamide in human kidney HEK293 cells stably transfected with human AR and an androgen-responsive luciferase reporter gene construct. In the presence of

0.45 nM testosterone to induce AR activation, darolutamide, keto-darolutamide, (S,R)-darolutamide, (S,S)-darolutamide and bicalutamide inhibited human AR with IC₅₀ values of 65 nM, 25 nM, 38 nM, 51 nM and 150 nM, respectively (Study no. 10000134). In another transactivation study, darolutamide, keto-darolutamide, enzalutamide, and apalutamide inhibited testosterone-induced transcriptional activity with IC₅₀ values of 26 nM, 38 nM, 219 nM and 200 nM, respectively (Moilanen, et al., 2015; studies conducted by the Applicant).

The Applicant also evaluated the effect of darolutamide on AR mutants resistant to other AR inhibitors including bicalutamide, enzalutamide and apalutamide (Table 1). Following activation with 0.6 to 1 nM testosterone or 10 nM dihydrotestosterone, darolutamide and keto-darolutamide suppressed transcriptional activities of AR mutants T877A and W741L exogenously expressed in US-OS osteosarcoma cells; bicalutamide showed inhibitory activity against T877A AR mutant but not W741L (Study no. 11000291; Moilanen, et al., 2015). Moreover, darolutamide and keto-darolutamide suppressed testosterone-induced transcriptional activity of missense mutation F876L in the ligand-binding domain of AR; whereas enzalutamide and apalutamide functioned as partial agonists with maximum activity of 43% and 70%, respectively (Table 1; Study no. R140246; Moilanen, et al., 2015).

Table 2 IC₅₀ values for antiandrogen activity in WT and mutant human androgen receptors expressed in osteosarcoma cells

Compounds	IC ₅₀ (nM) in human U2-OS osteosarcoma cells			
	wtAR	AR(F876L)	AR(W741L)	AR (T877A)
Study no. or published literature	Moilanen, et al., 2015	R140246/ Moilanen, et al., 2015	11000291/ Moilanen, et al., 2015	11000291/ Moilanen, et al., 2015
Darolutamide (ORM-15674)	65	85/66	1063/1500	2626/1782
Keto-darolutamide (ORM-15341)	25	47/51	1050/1160	1445/700
Bicalutamide	NA	NA	Agonist/NA	800/NA
Enzalutamide	155	NA/Agonist	NA/>10,000	NA/296
Apalutamide	168	NA/Agonist	NA/>10,000	NA/1130

NA= not available

In the absence of androgen, AR was predominantly cytoplasmic and treatment with testosterone significantly increased nuclear vs. cytoplasmic ratio of AR immunofluorescence, indicating movement of androgen receptor from cytoplasm to nucleus. In HEK293 cells expressing AR, darolutamide and keto-darolutamide decreased testosterone-induced nuclear translocation of AR at ≥ 100 nM and ≥ 300 nM, respectively whereas bicalutamide failed to block testosterone-induced AR nuclear localization at all test concentrations (Study no. 10000162).

In vitro, darolutamide and keto-darolutamide suppressed proliferation of androgen-induced vertebra-derived carcinoma of the prostate (VCaP) cells with IC₅₀ values of 230 nM and 170 nM, respectively (Study no. 10000135). Darolutamide had no effect on the viability of AR-negative cell lines DU-145 prostate cancer cells and H1581 lung cancer cells, suggesting that the anti-tumor activity was specific to AR-dependent prostate cancer cells (Moilanen, et al., 2015).

The in vivo anti-tumor effect of oral darolutamide was evaluated in various mouse xenograft models. In the VCap xenograft model, significant inhibition of tumor growth was observed following oral treatment with 50 mg/kg darolutamide once (46%) or twice daily (67%) for 37 days when compared to untreated orchidectomized (ORX) control mice. In addition, darolutamide delayed VCaP tumor re-growth after orchidectomy in nude immunodeficient mice (Study no. 09000124). In the orthotopic prostate cancer model in male nude mice, oral administration of 50 mg/kg darolutamide twice daily for three weeks significantly decreased prostate cancer tumor volume compared to the vehicle group (124 mm³ vs. 314 mm³) with no effect on the level of serum testosterone (Study no. 0909TM04-R-9760). In the castration-resistant VCaP model, treatment with darolutamide significantly suppressed the relative increase in serum PSA levels at all tested doses (25, 50 and 100 mg/kg twice daily for 28 days). There was a dose-dependent trend for decreased tumor growth when compared to control group, but it was not statistically significant (Study no. 1010TM03).

Secondary Pharmacology

Darolutamide, (S,R)-darolutamide, (S,S)-darolutamide and keto-darolutamide were investigated for in vitro off-target activity at concentrations up to 10 µM in receptor binding and enzyme assays targeting a broad spectrum of over 100 enzymes, receptors and channels. A summary of the results is shown in Table 2.

Table 3 In vitro receptor binding and enzyme assays

Target organ	% Inhibition of control specific binding (concentration of compound)			
	Darolutamide (ORM-15674)	(S,R)-darolutamide (ORM-16497)	(S,S)-darolutamide (ORM-16555)	Keto-darolutamide (ORM-15341)
Study no.	8160217	8160221	8160221	8160205
Progesterone receptor (PR) in human breast cancer cell (T47D)	76% (10 μ M)	Not evaluated	Not evaluated	62% (10 μ M)
Rat central benzodiazepine receptor (rBZD)	58% (10 μ M)	48% (5 μ M)	27% (5 μ M)	Not evaluated
Human serotonin transporter (5-HT)	85% (10 μ M)	56% (5 μ M)	64% (5 μ M)	86% (10 μ M)
Human adenosine receptor A3	Inhibited less than 50% at 10 μ M (3%)	Not evaluated	Not evaluated	53% (10 μ M)
Androgen receptor (AR) in human prostate cancer cell (LNCaP)	80% (10 μ M)	Not evaluated	Not evaluated	68% (10 μ M)

The ability of darolutamide, keto-darolutamide and bicalutamide to affect human progesterone receptor (hPR)-mediated transcriptional activation was studied in human U2-OS osteosarcoma cell line stably transfected with human PR expression plasmid and progesterone-responsive luciferase reporter gene construct. Darolutamide, keto-darolutamide and bicalutamide functioned as PR antagonists with IC_{50} values of 5.1 μ M, 4.5 μ M and 4.1 μ M, respectively, in the presence of 10 nM progesterone, a concentration of progesterone inducing submaximal reporter gene activation (Study no.10000163).

The effect of darolutamide, keto-darolutamide and ORM-16888 (metabolite of darolutamide) on GABA_A receptor was studied in acutely isolated rat striatal neurons using the whole-cell patch-clamp technique. Darolutamide, keto-darolutamide and ORM-16888 reversibly blocked GABA-activated current with IC_{50} values of 5.5 μ M, 3.4 μ M and 6.8 μ M, respectively (Study no. 11000177). In a functional in vitro assay using rat brain synaptosomes, darolutamide and ORM-16888 inhibited 5-HT uptake with IC_{50} values of 3.4 μ M and 3.0 μ M, respectively, whereas imipramine (a known 5-HT uptake inhibitor) had an IC_{50} value of 62 nM (Study no. 8160241).

Safety Pharmacology

Safety pharmacology studies to assess the potential for hERG channel inhibition and cardiovascular and respiratory effects were reviewed previously in the original submission for IND 114769 (Study no. 10000090, 20110265 (b) (4), 20110266 (b) (4) and 610816). In summary, in vitro studies showed that darolutamide blocked hERG current dose-dependently with an extrapolated IC₅₀ value of 87.9 µM. Keto-darolutamide was 11 times more potent with an IC₅₀ value of 8.0 µM. The diastereomers (S,R)-darolutamide and (S,S)-darolutamide dose-dependently inhibited the hERG current with IC₅₀ values of 11.5 µM and 30.2 µM, respectively. Thus, darolutamide, (S,R)-darolutamide, (S,S)-darolutamide and keto-darolutamide were low-potency hERG blockers.

In vivo safety pharmacology studies revealed that bolus intravenous injection of darolutamide or (S,S)-darolutamide to anaesthetized dogs at 10-20 mg/kg induced a marked vasodilatation, especially at the peripheral level, leading to decreased arterial blood pressure. The decreases in mean systolic and diastolic arterial blood pressure (10-46%) started 1 minute after dosing and only partially recovered 30 minutes after dosing (Study no. 20110265 (b) (4)). The maximum concentrations of darolutamide in dog plasma were observed at the first sampling time point (2 min) after each consecutive bolus administration. At 3, 10 and 20 mg/kg, the maximum mean plasma concentrations of darolutamide (sum of [S,R]-darolutamide and [S,S]-darolutamide) were 9.3 µg/mL, 27.3 µg/mL and 46.2 µg/mL in dogs administered IV darolutamide, respectively (Study no. 20110265 (b) (4)). The maximum (30 minutes) mean plasma concentrations of keto-darolutamide were 2.1 µg/mL, 5.6 µg/mL and 8.8 µg/mL in dogs administered IV darolutamide at 3, 10 and 20 mg/kg, respectively (Study no. 20110265 (b) (4)).

In the second safety pharmacology study for cardiovascular effect, one dog displayed a reversible AV nodal abnormality (complete AV block) from approximately 7 minutes to 45 minutes after IV dosing of 10 mg/kg (S,S)-darolutamide. After 45 minutes post-dosing, the arrhythmic episode resolved, but the PQ and PR interval durations remained prolonged (Study no. 20110266 (b) (4)). At 1, 3 and 10 mg/kg, the maximum (2 minutes) mean plasma concentrations of darolutamide were 4 µg/mL, 9.3 µg/mL and 27.3 µg/mL, respectively (Study no. 20110266 (b) (4)). The maximum (30 minutes) mean plasma concentrations of keto-darolutamide were 1.5 µg/mL, 3.6 µg/mL and 8.8 µg/mL in dogs administered IV darolutamide at 1, 3 and 10 mg/kg, respectively (Study no. 20110266 (b) (4)).

The Applicant studied the effects of darolutamide, (S,R)-darolutamide, (S,S)-darolutamide or keto-darolutamide (1, 3, 10, 30 and 100 µM) on L-type calcium channels endogenously expressed by human IMR-32 neuroblastoma cells and measured intracellular calcium changes by fluorometric imaging using fluorescent calcium indicator fluo-4 incubated at 37°C in a 5% CO₂ (n =2-4 replicates/concentrations). The IC₅₀ values for darolutamide, (S,R)-darolutamide, (S,S)-darolutamide and keto-darolutamide were 37.4 µM, 42.5 µM, 46.6 µM, and 22.5 µM, respectively. For comparison, the reference androgen receptor inhibitor bicalutamide inhibited the L-type calcium channel in this study with an IC₅₀ value of 12.9 µM. The known

calcium channel blockers verapamil and 1,4-dihydropyridine had IC₅₀ values of 4.1 μM and 0.6 μM, respectively (Study no. 11000165).

In a GLP-compliant study, the Applicant studied the effect of darolutamide on respiratory parameters in Wistar male rats administered either vehicle control (0.5% methylcellulose with 0.5% tween 80) or 100 to 1000 mg/kg darolutamide as a single oral gavage dose (n=5/group). The results demonstrated a decrease in tidal volume at 2 hours (12%), 5 hours (32%), and 24 hours (24%) in rats administered 1000 mg/kg darolutamide (Study no. 610816).

In two non-GLP studies, the Applicant assessed the effect of darolutamide on gastrointestinal motility and gastric emptying in male Wistar rats using 2 different vehicle controls (Study no. 11000100 and 11000129). Vehicles were 50% macrogol/30% propylene glycol/20% glucose (MPG) (Study no. 11000100) and 0.5% methylcellulose with 0.5% tween 80 (MC) (Study no. 11000129). Rats (n=7-8/group) received single oral doses of 30 and 100 mg/kg darolutamide suspension in the first study (Study no. 11000100) and 30 to 1000 mg/kg in the second study (Study no. 1000129). Four hours after treatment, rats received an oral charcoal suspension. The distance covered by orally administered charcoal was a measure of intestinal transit, and the weight of stomach content was a measure of gastric emptying. When compared to MPG vehicle control, darolutamide decreased % intestinal transit at oral doses of 30 mg/kg (19%) and 100 mg/kg (31%) (Study no. 11000100). In contrast, when compared to MC vehicle control, darolutamide had no gastrointestinal effects in rats when dosed as a single oral dose up to 1000 mg/kg, but darolutamide at a dose of 1000 mg/kg caused slightly shorter intestinal transit compared to MC vehicle control (11%) (Study no. 11000129). In addition, darolutamide induced a dose-dependent increase in the stomach content weight when compared to MPG vehicle control from 30 mg/kg (2-fold above control) and 100 mg/kg (3-fold above control) (Study no. 11000100).

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Study Title/Number: ODM-201, ORM-16497 and ORM-16555: single dose pharmacokinetics after oral and intravenous administration in the male beagle dogs/503175 Dogs were treated with either single IV dose (n=2) or oral administration (n=2) of either darolutamide, (S,R)-	Dog <u>Single IV (S,R)-darolutamide or (S,S)-darolutamide, 3 mg/kg</u> • T_{max} = 0.083-0.25 hours for darolutamide. • (S,R)-darolutamide was eliminated slower (T_{1/2} = 11 hours) than (S,S)-darolutamide (T_{1/2} = 4.5 hours). • Volume of distribution (V_{ss}) = 837 mL/kg for (S,R)-darolutamide and 3780 mL/kg for (S,S)-darolutamide. • The keto-darolutamide metabolite was detected as early as 2 minutes after IV dosing of either diastereomers. Plasma concentrations of keto-darolutamide were higher after dosing (S,S)-darolutamide than (S,R)-darolutamide. The keto-darolutamide/parent darolutamide ratio was 0.21 following

Type of Study	Major Findings															
darolutamide or (S,S)-darolutamide. The IV dose was 3 mg/kg. The oral dose was 300 mg/animal (25.3 mg/kg). There was a one-week washout period between each treatment.	administration of a single IV dose of (S,R)-darolutamide, but 5.3 when dogs were given a single IV dose of (S,S)-darolutamide. <u>Single oral darolutamide, 300 mg/animal (25.3 mg/kg)</u> • T_{max} = 2-12 hours. • $T_{1/2}$ = 17 hours. • Oral bioavailability of (S,R)-darolutamide and (S,S)-darolutamide was 18 to 29% and 29 to 72%, respectively. • The diastereomeric ratio for (S,R)-darolutamide was about 0.9, based on AUC, and the corresponding ratio for (S,S)-darolutamide was 0.1. • The mean keto-metabolite/parent darolutamide ratio based on AUC was about 0.6.															
Distribution																
Study Title/Number: The in vitro plasma protein binding of ORM-15674 and ORM-15341 and blood cell partitioning of ORM-15341 in mouse, rat, dog, human and binding to specific plasma proteins/ 192800 The in vitro plasma protein binding of darolutamide was determined by equilibrium dialysis at concentrations of 20 and 100 ng/mL, and the in vitro plasma protein binding of keto-darolutamide was also determined by equilibrium dialysis at concentrations of 200 to 10000 ng/mL following incubation for 2 hours. The in vitro association of darolutamide with blood cells was determined at concentrations of 200 to 10000 ng/mL following incubation for 1 hour.	• The mean plasma protein binding of darolutamide and keto-darolutamide was similar for all species investigated. <table border="1" data-bbox="652 787 1388 1087"> <thead> <tr> <th>Species</th> <th>Mean % free fraction of darolutamide</th> <th>Mean % free fraction of keto-darolutamide</th> </tr> </thead> <tbody> <tr> <td>Dog</td> <td>0.7-0.8%</td> <td>0.29% at 200 ng/mL 0.39% at 1000 ng/mL 2.3% at 5000 ng/mL 3.4% at 10000 ng/mL</td> </tr> <tr> <td>Human</td> <td>9.1-9.8%</td> <td>0.18-0.20%</td> </tr> <tr> <td>Rat</td> <td>5.5-5.6%</td> <td>0.7-0.8%</td> </tr> <tr> <td>Mouse</td> <td>4.6-4.7% for balb/c 4.1-4.5% for CD-1</td> <td>0.8-1.1% for balb/c 0.6-0.9% for CD-1</td> </tr> </tbody> </table> • Binding of darolutamide to human serum albumin = 84-85% • Binding of keto-darolutamide to human serum albumin = 99.6-99.7% • Binding of darolutamide to α_1-acid glycoprotein = 29-44% • Binding of keto-darolutamide to α_1-acid glycoprotein = 51-66% Binding to α_1-acid glycoprotein decreased as the concentration of keto-darolutamide metabolite increased from 200 ng/mL to 10000 ng/mL.	Species	Mean % free fraction of darolutamide	Mean % free fraction of keto-darolutamide	Dog	0.7-0.8%	0.29% at 200 ng/mL 0.39% at 1000 ng/mL 2.3% at 5000 ng/mL 3.4% at 10000 ng/mL	Human	9.1-9.8%	0.18-0.20%	Rat	5.5-5.6%	0.7-0.8%	Mouse	4.6-4.7% for balb/c 4.1-4.5% for CD-1	0.8-1.1% for balb/c 0.6-0.9% for CD-1
Species	Mean % free fraction of darolutamide	Mean % free fraction of keto-darolutamide														
Dog	0.7-0.8%	0.29% at 200 ng/mL 0.39% at 1000 ng/mL 2.3% at 5000 ng/mL 3.4% at 10000 ng/mL														
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Rat	5.5-5.6%	0.7-0.8%														
Mouse	4.6-4.7% for balb/c 4.1-4.5% for CD-1	0.8-1.1% for balb/c 0.6-0.9% for CD-1														
Study Title/Number: Exposure to ORM-15674 in immature rat plasma and heart after 6-day oral dosing (100 mg/kg/day) /1000152 Immature male rats (18-21	• Darolutamide exposure in the heart was lower than in the plasma. Exposure to the major metabolite keto-darolutamide was lower in the heart than in plasma. • 1/28 rats was found dead after two doses of darolutamide and was replaced with a new rat, which received only 5 doses of darolutamide at 100 mg/kg. The cause of death was not identified.															

Type of Study	Major Findings																																				
days of age; n=7/group) were administered darolutamide, (S,R)-darolutamide, (S,S)-darolutamide, and keto-darolutamide at 100 mg/kg/day by oral gavage once daily for 6 days. Blood and tissue sampling were collected at 0.25, 0.5, 1, 2, 5, 8 and 24 hours.	Sample	Analyte	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₂₄ (h•ng/mL)	Metabolite and diastereomer ratios		Tissue/plasma ratio																													
						C _{max}	AUC ₀₋₂₄																														
	Plasma	Darolutamide	16808	2	194879																																
		(S,R)-darolutamide	9400	2	95749	0.56	0.49																														
		(S,S)-darolutamide	8255	5	99130	0.49	0.51																														
		Keto-darolutamide	17500	5	177964	1.04	0.91																														
	Heart	Darolutamide	10338	2	122901			0.63																													
		(S,R)-darolutamide	4295	2	44847	0.42	0.36	0.47																													
		(S,S)-darolutamide	6043	2	78052	0.58	0.64	0.79																													
		Keto-darolutamide	2625	5	28647	0.25	0.23	0.16																													
Study Title/Number: Pharmacokinetics of ORM-15674 after 7-day oral administration and 14-day subcutaneous administration to male nude mice/10000026	- In all tissues, the C_{max} and AUC₀₋₂₄ values were higher for (S,R)-darolutamide than (S,S)-darolutamide. - Tissue/plasma ratios for all analytes in all tissues were slightly higher after dosing darolutamide 50 mg twice daily compared to once daily dosing. - The results demonstrated that liver and kidney had the highest tissue/plasma ratio while very low brain exposure was observed. Using AUC₀₋₂₄ values, brain exposure to darolutamide was 2.1-3.9% of plasma exposure after a 7-day oral administration of 50 mg/kg darolutamide daily or twice daily. <u>7-Day oral administration, 50 mg/kg/day darolutamide</u> AUC₀₋₂₄ for darolutamide Plasma: 109479 ng•h/mL Brain: 2377 ng•h/mL Kidney: 107248 ng•h/mL Liver: 421294 ng•h/mL Prostate: 44566 ng•h/mL <table border="1" data-bbox="675 1383 1365 1577"> <thead> <tr> <th rowspan="2">Tissue</th> <th colspan="4">Tissue/plasma ratio</th> </tr> <tr> <th>Darolutamide</th> <th>(S,R)-darolutamide</th> <th>(S,S)-darolutamide</th> <th>Keto-darolutamide</th> </tr> </thead> <tbody> <tr> <td>Brain</td> <td>0.02</td> <td>0.02</td> <td>0.04</td> <td>0.02</td> </tr> <tr> <td>Kidney</td> <td>0.98</td> <td>0.95</td> <td>1.1</td> <td>0.30</td> </tr> <tr> <td>Liver</td> <td>3.85</td> <td>3.53</td> <td>5.18</td> <td>0.44</td> </tr> <tr> <td>Prostate</td> <td>0.41</td> <td>0.35</td> <td>0.65</td> <td>0.15</td> </tr> </tbody> </table> <u>7-Day oral administration, 50 mg/kg darolutamide twice daily</u> AUC₀₋₂₄ for darolutamide Plasma: 174807 ng•h/mL Brain: 6819 ng•h/mL Kidney: 288484 ng•h/mL Liver: 748168 ng•h/mL Prostate: 97256 ng•h/mL								Tissue	Tissue/plasma ratio				Darolutamide	(S,R)-darolutamide	(S,S)-darolutamide	Keto-darolutamide	Brain	0.02	0.02	0.04	0.02	Kidney	0.98	0.95	1.1	0.30	Liver	3.85	3.53	5.18	0.44	Prostate	0.41	0.35	0.65	0.15
Tissue	Tissue/plasma ratio																																				
	Darolutamide	(S,R)-darolutamide	(S,S)-darolutamide	Keto-darolutamide																																	
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Brain		0.04	0.03	0.06	0.03																																																					
Kidney		1.65	1.61	1.78	0.35																																																					
Liver		4.28	3.72	6.09	0.54																																																					
Prostate		0.56	0.47	0.83	0.18																																																					
Metabolism																																																										
Study Title/Number: Structure elucidation summary of darolutamide (BAY 1841788) metabolites from in vitro and in vivo/ KINM 170164-BLN	- Minor metabolites M23, M30-M36 are unique to humans and observed in urine, plasma, or the in vitro study. - The major circulating metabolite was M1 metabolite keto-darolutamide. <table border="1" data-bbox="695 646 1349 974"> <thead> <tr> <th colspan="2">Metabolites</th> </tr> </thead> <tbody> <tr> <td>Human</td> <td>M1, M2, M3, M4, M5, M6, M7, M8, M10, M15, M20, M21, M22, M23, M24, M25, M26, M28, M29, M30, M31, M32, M33, M34, M35, M36</td> </tr> <tr> <td>Rat</td> <td>M1, M2, M3, M4, M5, M6, M7, M8, M10, M11, M12, M14, M15, M16, M17, M18, M19, M20, M21, M22, M24, M25, M26, M27, M28, M29, M37, M38, M39, M40</td> </tr> <tr> <td>Dog</td> <td>M1, M2, M3, M4, M5, M6, M7, M8, M9, M10, M11, M12, M13, M22, M26</td> </tr> <tr> <td>Mouse</td> <td>M1, M2, M3, M4, M5, M6, M7, M8</td> </tr> </tbody> </table> M23 = hydroxylated darolutamide conjugated with glucuronic acid identified in human urine; M30 = oxidative cleavage of darolutamide (ORM-31681) which was only detected in the in vitro study when incubated with human liver microsomes; M31 = secondary metabolite of M30, detected in vitro when incubated with human liver microsomes; M32 = product from N-dealkylation of darolutamide, followed by an additional oxidation to the carboxylic acid metabolite detected in human plasma and urine (ORM-33303); M33 = metabolite resulting from an amide cleavage and oxidation of the alcohol to keto in darolutamide detected in human urine (pyrazole keto acid); M34 = pyrazole carboxamide metabolite resulting from oxidative cleavage of the amide and oxidation of the alcohol to keto in darolutamide detected in human urine and plasma (1H-Pyrazole-3-carboxamide,5 acetyl); M35 = pyrazole ketoacid metabolite resulting from an amide cleavage of darolutamide detected in human urine and plasma; M36 = pyrazole carboxamide metabolite, resulting from oxidative amide cleavage of darolutamide detected in human urine and plasma (BAY 2432226).					Metabolites		Human	M1, M2, M3, M4, M5, M6, M7, M8, M10, M15, M20, M21, M22, M23 , M24, M25, M26, M28, M29, M30 , M31 , M32 , M33 , M34 , M35 , M36	Rat	M1, M2, M3, M4, M5, M6, M7, M8, M10, M11, M12, M14, M15, M16, M17, M18, M19, M20, M21, M22, M24, M25, M26, M27, M28, M29, M37, M38, M39, M40	Dog	M1, M2, M3, M4, M5, M6, M7, M8, M9, M10, M11, M12, M13, M22, M26	Mouse	M1, M2, M3, M4, M5, M6, M7, M8																																											
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Study Title/Number: Metabolism of ¹⁴C-ODM-201 in male human and animal cryopreserved hepatocytes/10000142 The in vitro metabolism characteristics of darolutamide were assessed at 5 μM or 20 μM in hepatocytes from human, mouse (CD-1 and balb/c), rat (wistar) and dog using HPLC-RAD and LC-MS method.	No unique metabolites were identified in human hepatocytes. <table border="1" data-bbox="643 1444 1398 1749"> <thead> <tr> <th rowspan="2">Metabolites</th> <th colspan="5">% Fraction of total radioactivity*</th> </tr> <tr> <th>Rat</th> <th>CD-1</th> <th>Balb/c</th> <th>Dog</th> <th>Human</th> </tr> </thead> <tbody> <tr> <td>M1</td> <td>27.4</td> <td>32.1</td> <td>4.2</td> <td>43.6</td> <td>21.5</td> </tr> <tr> <td>M2, M3</td> <td>7.2</td> <td>5.6</td> <td>12.5</td> <td>5.1</td> <td>0.7</td> </tr> <tr> <td>M4</td> <td>10.1</td> <td>10.3</td> <td>20.0</td> <td>7.7</td> <td>2.2</td> </tr> <tr> <td>M5, M6, M7</td> <td>5.3</td> <td>10.8</td> <td>29.6</td> <td>4.6</td> <td>3.7</td> </tr> <tr> <td>M8</td> <td>4.1</td> <td>2.2</td> <td>5.1</td> <td>2.7</td> <td>0.7</td> </tr> <tr> <td>Darolutamide (parent)</td> <td>39.4</td> <td>33.2</td> <td>17.4</td> <td>33.1</td> <td>70.7</td> </tr> <tr> <td>Unknown</td> <td>6.4</td> <td>5.9</td> <td>11.1</td> <td>3.2</td> <td>0.4</td> </tr> </tbody> </table> *5 μM samples following 180-minute incubation					Metabolites	% Fraction of total radioactivity*					Rat	CD-1	Balb/c	Dog	Human	M1	27.4	32.1	4.2	43.6	21.5	M2, M3	7.2	5.6	12.5	5.1	0.7	M4	10.1	10.3	20.0	7.7	2.2	M5, M6, M7	5.3	10.8	29.6	4.6	3.7	M8	4.1	2.2	5.1	2.7	0.7	Darolutamide (parent)	39.4	33.2	17.4	33.1	70.7	Unknown	6.4	5.9	11.1	3.2	0.4
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	Rat	CD-1	Balb/c	Dog	Human																																																					
M1	27.4	32.1	4.2	43.6	21.5																																																					
M2, M3	7.2	5.6	12.5	5.1	0.7																																																					
M4	10.1	10.3	20.0	7.7	2.2																																																					
M5, M6, M7	5.3	10.8	29.6	4.6	3.7																																																					
M8	4.1	2.2	5.1	2.7	0.7																																																					
Darolutamide (parent)	39.4	33.2	17.4	33.1	70.7																																																					
Unknown	6.4	5.9	11.1	3.2	0.4																																																					

Type of Study	Major Findings
Excretion	
Study Title/Number: The mass balance of [¹⁴C]-ORM-15674 in the rat following oral and intravenous administration/192774 The excretion balance of darolutamide and its diastereomers was determined following oral and IV administration of 10 mg/kg [¹⁴C]-darolutamide to male rats.	• Following oral and intravenous administration to male rats, the major route of darolutamide excretion was via the feces. The mean recovery of darolutamide ranged from 61-64% for feces and 30-33% for urine at 168 hours. • (S,R)-darolutamide and (S,S)-darolutamide exhibited comparable systemic exposure (14400 vs. 12700 ng•h/mL based on AUC_{0-t}). Systemic exposure to darolutamide plus keto-darolutamide accounted for approximately 66% of the total radioactivity exposure in plasma. • The time taken to reach the maximum plasma concentration of darolutamide and keto-darolutamide following oral dosing was relatively short (1-2 hours post dose). The mean T_{1/2} for darolutamide, its diastereomers and keto-darolutamide ranged from 3-4 hours.
TK data from general toxicology studies	
Study Title/Number: ODM-201-26-week oral (gavage) toxicity study in the wistar rat followed by a 4-week treatment-free period/AB14461 darolutamide (ODM-201) (S,R)-darolutamide (ORM-16497) (S,S)-darolutamide (ORM-16555) keto-darolutamide (ORM-15341)	Rat T_{1/2} was not determined T_{max}: 0.5-8 hours in Week 26 for darolutamide and (S,S)-darolutamide 0.5-5 hours in Week 26 for (S,R)-darolutamide 2-8 hours in Week 26 for keto-darolutamide Accumulation: No Dose proportionality: increase in systemic exposure was less than dose-proportional. • The systemic exposure (AUC_{0-24 hr}) of diastereomers (S,R)-darolutamide and (S,S)-darolutamide in Week 26 represented on average 57% and 43%, respectively. • The systemic exposure of keto-darolutamide was generally similar to that of darolutamide at all dose levels. • Exposure to darolutamide was higher in females than males.

Type of Study	Major Findings																																																																																																																																																																																																																																																																																											
	<table border="1"> <thead> <tr> <th rowspan="2">Compound</th> <th rowspan="2">Occasion</th> <th rowspan="2">ODM-201 dose level (mg/kg/day)</th> <th colspan="2">C_{max1} (ng/mL)</th> <th colspan="2">C_{max2} (ng/mL)</th> <th colspan="2">AUC_{0-24h} (ng.h/mL)</th> </tr> <tr> <th>Male</th> <th>Female</th> <th>Male</th> <th>Female</th> <th>Male</th> <th>Female</th> </tr> </thead> <tbody> <tr> <td rowspan="6">Diastereomer ORM-16497</td> <td rowspan="3">day 0</td> <td>2x50</td> <td>3010</td> <td>3680</td> <td>3930</td> <td>6820</td> <td>45200</td> <td>64800</td> </tr> <tr> <td>2x150</td> <td>3770</td> <td>4450</td> <td>5110</td> <td>6590</td> <td>60700</td> <td>96300</td> </tr> <tr> <td>2x500</td> <td>6680</td> <td>6230</td> <td>9570</td> <td>7720</td> <td>123000</td> <td>123000</td> </tr> <tr> <td rowspan="3">week 13</td> <td>2x50</td> <td>1850</td> <td>4200</td> <td>2790</td> <td>7270</td> <td>34600</td> <td>76000</td> </tr> <tr> <td>2x150</td> <td>2030</td> <td>4820</td> <td>3970</td> 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C_{max1}: maximum plasma concentration observed after the first daily dosing C_{max2}: maximum plasma concentration observed after the second daily dosing Values were reported to 3 significant figures. (Excerpted from Applicant's submission)	Compound	Occasion	ODM-201 dose level (mg/kg/day)	C _{max1} (ng/mL)		C _{max2} (ng/mL)		AUC _{0-24h} (ng.h/mL)		Male	Female	Male	Female	Male	Female	Diastereomer ORM-16497	day 0	2x50	3010	3680	3930	6820	45200	64800	2x150	3770	4450	5110	6590	60700	96300	2x500	6680	6230	9570	7720	123000	123000	week 13	2x50	1850	4200	2790	7270	34600	76000	2x150	2030	4820	3970	7540	53100	105000	2x500	2840	7030	4890	11500	66700	162000	week 26	2x50	2520	4310	2440	6250	35600	84500	2x150	2690	4810	4270	7960	56500	118000	2x500	3030	8570	4620	11800	69400	177000	Diastereomer ORM-16555	day 0	2x50	1980	1890	2920	3100	34300	35300	2x150	2520	2690	4060	4040	47100	62200	2x500	4440	3260	6930	4230	101000	75500	week 13	2x50	1510	2340	2480	3790	32900	45500	2x150	1630	3210	3570	4720	50700	74100	2x500	2430	4320	4430	7020	66500	112000	week 26	2x50	1400	2060	1960	3150	31100	47800	2x150	2140	3910	3770	4370	48900	75600	2x500	2460	4960	3860	6650	65400	115000	Test item ODM-201	day 0	2x50	4990	5570	6850	9920	79500	100000	2x150	6280	7130	9150	10600	108000	159000	2x500	111000	9500	16500	12000	224000	199000	week 13	2x50	3360	6540	5270	11100	68100	122000	2x150	3660	8030	7530	12200	104000	179000	2x500	5270	11400	9320	18500	133000	274000	week 26	2x50	3930	6370	4410	9400	66800	132000	2x150	4720	8570	8040	12300	105000	193000	2x500	5460	13500	8480	18500	135000	292000	Metabolite ORM-15341	day 0	2x50	4660	3850	6300	6810	70900	71300	2x150	6090	4830	8540	7190	102000	111000	2x500	10100	6770	14600	9360	209000	162000	week 13	2x50	3020	4710	5150	8070	64900	88300	2x150	3690	5140	7250	7510	102000	124000	2x500	4380	8780	8530	14100	124000	222000	week 26	2x50	3590	4850	4820	7510	73200	106000	2x150	4510	6670	7970	8700	114000	146000	2x500	5470	9790	8340	14300	139000	253000
Compound	Occasion				ODM-201 dose level (mg/kg/day)	C _{max1} (ng/mL)		C _{max2} (ng/mL)		AUC _{0-24h} (ng.h/mL)																																																																																																																																																																																																																																																																																		
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Diastereomer ORM-16555	day 0	2x50	1980	1890	2920	3100	34300	35300																																																																																																																																																																																																																																																																																				
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Study Title/Number: ODM-201-39-week oral (gavage) toxicity study in the beagle dog followed by an 8-week treatment-free period. ODM-201 (Darolutamide) ORM-16497 ((S,R)-darolutamide) ORM-16555 ((S,S)-darolutamide) ORM-15341 (keto-darolutamide)	Dog T_{1/2} was not determined T_{max}: 2-11 hours in Week 39 for darolutamide 2-12 hours in Week 39 for (S,S)-darolutamide 1-11 hours in Week 39 for (S,R)-darolutamide 2-12 hours in Week 39 for keto-darolutamide Accumulation: 0.84-1.48 for darolutamide; 0.79-1.52 for keto-darolutamide Dose proportionality: increase in systemic exposure was less than dose-proportional. - The systemic exposure (AUC_{0-24h}) of diastereomers (S, R)-darolutamide and (S, S)-darolutamide represented on average 90% and 10%, respectively, of darolutamide in Week 39. - The systemic exposure of darolutamide and keto-darolutamide were relatively similar. - Exposure to darolutamide was higher in females than males.																																																																																																																																																																																																																																																																																											

Type of Study		Major Findings							
Analyte	Occasion	ODM-201 Dose (mg/kg/day)	C _{max1} (ng/mL)		C _{max2} (ng/mL)		AUC _{0-24h} (ng.h/mL)		
			Male	Female	Male	Female	Male	Female	
Diastereomer	day 0	2x25 (50)	3640	2780	4470	3870	77800	66600	
		2x75 (150)	4390	6440	5340	7670	84800	131000	
		2x200 (400)	6800	8000	10700	11900	168000	190000	
ORM-16497	week 39	2x25 (50)	4510	3940	4610	3800	89000	71500	
		2x75 (150)	4870	6620	5090	7260	93100	132000	
		2x200 (400)	9740	9020	10600	11000	186000	199000	
Diastereomer	day 0	2x25 (50)	470	400	560	460	7300	5570	
		2x75 (150)	670	900	790	960	9890	12800	
		2x200 (400)	1040	1260	1990	2160	24900	25700	
ORM-16555	week 39	2x25 (50)	510	430	520	470	7600	6660	
		2x75 (150)	670	770	750	940	9840	13400	
		2x200 (400)	1280	1150	1450	1450	19200	18700	
Test item	day 0	2x25 (50)	4070	3090	4990	4290	85100	72200	
		2x75 (150)	5030	7150	6120	8610	94700	144000	
		2x200 (400)	7810	9240	12600	13900	193000	215000	
ODM-201	week 39	2x25 (50)	5010	4340	5130	4260	96700	78100	
		2x75 (150)	5490	7370	5800	8190	103000	145000	
		2x200 (400)	11000	10200	12100	12400	206000	217000	
Metabolite	day 0	2x25 (50)	3480	2580	4500	3890	67100	53300	
		2x75 (150)	5700	6430	6620	8860	86700	128000	
		2x200 (400)	7320	9040	13500	13900	175000	188000	
ORM-15341	week 39	2x25 (50)	4060	3890	4440	3780	72600	58400	
		2x75 (150)	4830	7020	5420	8680	75200	135000	
		2x200 (400)	9490	8170	10700	10500	152000	166000	

C_{max1}: maximum plasma concentration observed after the first daily dosing.
C_{max2}: maximum plasma concentration observed after the second daily dosing.
Values were reported to 3 significant figures.

(Excerpted from Applicant's submission)

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: ODM-201-26-week oral (gavage) toxicity study in the wistar rat followed by a 4-week treatment-free period/Study number AB14461

Key Study Findings

- The major target organs of toxicity included male reproductive organs (prostate gland, seminal vesicle, epididymides), mammary gland, and GI tract.

Conducting laboratory and location:



(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 50, 150, 500 mg/kg/dose twice daily (0, 100, 300, 1000 mg/kg/day)

Route of administration: Oral gavage

Formulation/Vehicle: 0.5% (w/v) methylcellulose with 0.5% (v/v) tween

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80
Species/Strain: Wistar rats
Number/Sex/Group: 10/sex/group (main study), 5/sex/group (recovery for VH and HD)
Age: 8 weeks old
Satellite groups/ unique design: Toxicokinetic group (5/sex/group for VH control; 10/sex/group (LD, MD and HD)
Deviation from study protocol affecting interpretation of results: Yes

Observations and Results: changes from control

Parameters	Major findings																																																							
Mortality	There were no treatment-related deaths during the study.																																																							
Clinical Signs	<u>Terminal sacrifices</u> LD: pale face was observed on Days 133-168 in 8/10 M and 10/10 F. MD: pale face was observed on Days 84-181 in 10/10 M and on Days 133-168 in 10/10 F. HD: pale face was observed on Days 133-168 in 10/15 M and 14/14 F. <u>Recovery</u> All changes in clinical signs were not observed at end of 4-week recovery period.																																																							
Body Weights	Unremarkable																																																							
Food consumption	Unremarkable																																																							
Water consumption	Unremarkable																																																							
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Lung Pigmented macrophages Slight					1				
Prostate gland Atrophy Moderate Marked Corpora amylase Slight Lymphoid cell infiltration Minimal Slight Moderate		4 6	1 9				10 1		
Seminal vesicles Atrophy Marked									
Vagina Inflammation, subacute Moderate									1
Epididymides Epithelium degeneration/regeneration Slight							1		
Extra orbital lacrimal gland (left) Harderian gland changes Minimal							1		
Extra orbital lacrimal gland (right) Harderian gland changes Minimal							1		
<u>Recovery</u> All histopathology findings were reversible at end of recovery period except the following:									
• Minimal necrosis in liver was observed in 1/4 F at HD. • Marked tubular atrophy in testes was observed in 1/5 M at HD. • Minimal to slight lymphoid cell infiltration in prostate gland in 1-2/5 M at HD. • Moderate epithelium cell degeneration/regeneration of epididymides in 1/5 M at HD.									

LD: low dose; MD: mid dose; HD: high dose; M: male; F: female; N=number per group
-: indicates reduction in parameters compared to control.

Study title/ Study number : ODM-201-39-week oral (gavage) toxicity study in the Beagle dog followed by an 8-week treatment-free period/Study number AB19526.

Key Study Findings

- The major target organs of toxicity included male reproductive organs (testes, epididymides, and prostate gland), brain, mammary gland, uterus, lung, GI tract, thymus, mandibular lymph node, kidney, and sublingual gland.

Conducting laboratory and location:



(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 25, 75, 200 mg/kg/dose twice daily (0, 50, 150, 400 mg/kg/day)
 Route of administration: Oral gavage
 Formulation/Vehicle: 0.5% (w/v) aqueous methylcellulose with 0.5% (v/v) tween 80
 Species/Strain: Beagle dogs
 Number/Sex/Group: 4/sex/group (main study); 2/sex/group (recovery study for VH and HD)
 Age: 11 months old
 Satellite groups/ unique design: None
 Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	There were no treatment-related deaths during the study.
Clinical Signs	<u>Terminal sacrifices</u> - Thin appearance was observed in 1/6 M at HD from Days 25-32 and in 1/6 F from Days 19-26. - Liquid feces were observed in 3/6 M at HD on Days 31, 33, 41, 45, 56, 73, 76, 82, 83, 86, 110, 113, 116, 127, 157, 158, 162, 173, 185, 220, 236 and 248. <u>Recovery</u> All changes in clinical signs were reversible at end of recovery period.
Body Weights	<u>Terminal sacrifices</u> - A slight decrease in body weight (10-11%) was observed in M at MD starting from Day 238 to Day 273. - A slight decrease in body weight (10-13%) was observed in M at HD starting on Day 42 until Day 273. <u>Recovery (HD only)</u> - A decrease in body weight was still observed in M at HD during recovery period (11-16%) and at end of recovery period (13%). - A decrease in body weight was observed in F at HD during recovery period (17-19%).
Food consumption	<u>Terminal sacrifices</u> A decrease in food consumption was observed only in F in all dose groups on Days 28, 35, 42, 105, 112-189 with the maximum decreases of 30% at LD, 20% at MD and 25% at HD; however, these changes were not dose-dependent. <u>Recovery (HD only)</u> Mean food consumption normalized to control means during the recovery period.
Ophthalmoscopy	Unremarkable
Arterial blood pressure	Unremarkable
ECG	Unremarkable

Hematology	<u>Terminal sacrifices</u> <table border="1" data-bbox="540 275 1312 636"> <thead> <tr> <th rowspan="2">Parameters</th> <th colspan="6">% Change from control at sacrifices (Day 266)</th> </tr> <tr> <th colspan="3">Males</th> <th colspan="3">Females</th> </tr> <tr> <th>Sex</th> <th>50</th> <th>150</th> <th>400</th> <th>50</th> <th>150</th> <th>400</th> </tr> <tr> <th>Dose levels (mg/kg/day)</th> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <th>Total number of animals</th> <td>4</td> <td>4</td> <td>6</td> <td>4</td> <td>4</td> <td>5</td> </tr> </thead> <tbody> <tr> <td>Red blood cells</td> <td></td> <td></td> <td>-14**</td> <td></td> <td></td> <td>-14*</td> </tr> <tr> <td>% Reticulocytes</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>30</td> </tr> <tr> <td>Absolute eosinophils</td> <td>58*</td> <td>59*</td> <td>64*</td> <td></td> <td></td> <td></td> </tr> <tr> <td>% Eosinophils</td> <td>54</td> <td>28</td> <td>22</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Absolute basophils</td> <td>52</td> <td>40</td> <td>20</td> <td>60</td> <td>60</td> <td>40</td> </tr> </tbody> </table> *p ≤ 0.05; ** p ≤ 0.01 <u>Recovery (Day ; n=2)</u> Changes in hematology parameters were either reversible or trending towards recovery at end of recovery period.	Parameters	% Change from control at sacrifices (Day 266)						Males			Females			Sex	50	150	400	50	150	400	Dose levels (mg/kg/day)							Total number of animals	4	4	6	4	4	5	Red blood cells			-14**			-14*	% Reticulocytes						30	Absolute eosinophils	58*	59*	64*				% Eosinophils	54	28	22				Absolute basophils	52	40	20	60	60	40							
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Clinical Chemistry	<u>Terminal sacrifices</u> <table border="1" data-bbox="505 831 1349 1213"> <thead> <tr> <th rowspan="2">Parameters</th> <th colspan="6">% Change from control at sacrifices (Day 266)</th> </tr> <tr> <th colspan="3">Males</th> <th colspan="3">Females</th> </tr> <tr> <th>Sex</th> <th>50</th> <th>150</th> <th>400</th> <th>50</th> <th>150</th> <th>400</th> </tr> <tr> <th>Dose levels (mg/kg/day)</th> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <th>Total number of animals</th> <td>4</td> <td>4</td> <td>6</td> <td>4</td> <td>4</td> <td>5</td> </tr> </thead> <tbody> <tr> <td>Triglycerides</td> <td></td> <td></td> <td>23</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Alkaline phosphatase</td> <td></td> <td>71</td> <td>57</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Inorganic phosphorus</td> <td></td> <td></td> <td></td> <td></td> <td>-16**</td> <td>-16</td> </tr> <tr> <td>Glucose</td> <td></td> <td></td> <td></td> <td>12*</td> <td>16*</td> <td>32**</td> </tr> <tr> <td>HDL Cholesterol</td> <td></td> <td></td> <td></td> <td></td> <td>-36**</td> <td>-27**</td> </tr> <tr> <td>Glutamate dehydrogenase</td> <td></td> <td></td> <td></td> <td>-61</td> <td>-43</td> <td>-42</td> </tr> </tbody> </table> *p ≤ 0.05; ** p ≤ 0.01 <u>Recovery (Day ; n=2)</u> All changes in clinical chemistry parameters were either reversible or trending towards recovery at end of recovery period except a 22% increase in triglyceride levels in M at HD.	Parameters	% Change from control at sacrifices (Day 266)						Males			Females			Sex	50	150	400	50	150	400	Dose levels (mg/kg/day)							Total number of animals	4	4	6	4	4	5	Triglycerides			23				Alkaline phosphatase		71	57				Inorganic phosphorus					-16**	-16	Glucose				12*	16*	32**	HDL Cholesterol					-36**	-27**	Glutamate dehydrogenase				-61	-43	-42
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Urinalysis	<u>Schedule sacrifices (n=4-6)</u> - A decrease in urine pH was observed in all dose groups in M, but it was not dose-dependent (10% at LD, 14% at MD and 11% at HD). <u>Recovery (n=2; HD only)</u> - A decrease in urine pH was still observed in M at HD (24%).																																																																												
Gross Pathology	<u>Terminal sacrifices</u> - Enlarged thyroid gland in 1/4 M at HD. - Dilated bilateral ventricle in the brain of 1/4 M at HD. - Enlarged liver in 1/4 F at HD. - Enlarged left testes in 1/4 M at HD. - Several cysts were observed in left ovary in 1/4 F at HD. <u>Recovery</u>																																																																												

	All gross pathology findings were not observed at end of recovery period, except the following; • Small thymus was observed in 2/2 M at HD. • Dark testes observed in 1/2 M at HD.																																																																																																			
Organ Weights	<u>Terminal sacrifices</u> <i>Males</i> • A dose-dependent decrease in prostate gland weight relative to body weight was observed from LD to HD and ranged from 78 to 83%. • A dose-dependent decrease in spleen weight relative to body weight was observed from LD to HD and ranged from 30 to 32%. • A decrease in epididymides relative to body weight was observed in all dose groups (31 % at LD, 26% at MD and 31% at HD). • A dose-dependent increase in testes weight relative to body weight was observed from LD to HD and ranged from 10 to 23%. • A 23% increase in adrenal weight relative to body weight was observed in M at HD. • An 11% increase in lung weight relative to body weight was observed in M at HD. <i>Females</i> • A decrease in ovary weight relative to body weight was observed in F in all dose groups, but it was not dose-dependent (18% at LD, 15% at MD and 19% at HD). • A dose-dependent increase in spleen weight relative to body weight was observed in F from LD to HD and ranged from 12 to 38%. <u>Recovery</u> All changes in organ weights were reversible or trending towards recovery except changes adrenal weight (↑67%) and lung weight (↑18%) in M, and spleen weight (↑54%) in F.																																																																																																			
Histopathology Adequate battery: Yes	<u>Terminal sacrifices</u> <table border="1"> <thead> <tr> <th></th> <th colspan="4">Males</th> <th colspan="4">Females</th> </tr> <tr> <th>Dose (mg/kg/day)</th> <th>0</th> <th>50</th> <th>150</th> <th>400</th> <th>0</th> <th>50</th> <th>150</th> <th>400</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>4</td> <td>4</td> <td>4</td> <td>4</td> <td>4</td> <td>4</td> <td>4</td> <td>3</td> </tr> <tr> <td>Brain Ventricular dilation Moderate</td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Eyes Mononuclear cell infiltration, adjacent tissue Slight</td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Pituitary gland Mineralization Minimal</td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Adrenal glands Mononuclear cell infiltration Minimal</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td>1</td> </tr> <tr> <td>Thyroid glands Mineralization, follicular, colloid Minimal</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td>1</td> </tr> <tr> <td>Thymus Atrophy Slight</td> <td></td> <td>1</td> <td></td> <td>2</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Mandibular lymph node (left) Pigment deposit (s) Minimal</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td>1</td> <td>1</td> </tr> <tr> <td>Cecum Dilation; glandular Minimal</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>1</td> </tr> </tbody> </table>		Males				Females				Dose (mg/kg/day)	0	50	150	400	0	50	150	400	N	4	4	4	4	4	4	4	3	Brain Ventricular dilation Moderate				1					Eyes Mononuclear cell infiltration, adjacent tissue Slight				1					Pituitary gland Mineralization Minimal				1					Adrenal glands Mononuclear cell infiltration Minimal						1		1	Thyroid glands Mineralization, follicular, colloid Minimal							1	1	Thymus Atrophy Slight		1		2					Mandibular lymph node (left) Pigment deposit (s) Minimal						1	1	1	Cecum Dilation; glandular Minimal								1
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	Testes							
	Dilation; tubular luminal Minimal		1		3			
	Granulomatous inflammation, tubular							
	Minimal				1			
	Slight				1			
	Degeneration/atrophy; tubular							
	Minimal				1			
	Slight				3			
	Sperm accumulation, tubular luminal							
	Minimal				1			
	Slight				1			
	Epididymides							
	Reduced sperm content							
	Slight	2	3		1			
	Moderate	2						
	Marked		1		3			
	Decreased tubular diameter							
	Minimal		1					
	Slight	4	1		1			
	Moderate		2		3			
Atrophy; epithelial								
Slight	2	2		1				
Moderate	2	2		1				
Marked				2				
Uterus								
Hemorrhage; endometrial								
Minimal							1	
Cyst(s); endometrial								
Moderate						1		
Prostate gland								
Atrophy								
Marked		4	4	4				
Kidneys								
Tubular dilation								
Minimal		1		1				
Gallbladder								
Hyperplasia, mucosal								
Minimal							1	
Rectum								
Cyst(s); muscle layer								
Slight					1		1	
Mammary gland								
Acinar development/secretion; decreased								
Slight						1		
Moderate							1	
Lung								
Alveolar histiocytosis								
Minimal				1				
Hypertrophy; pulmonary artery								
Moderate				1				
Fibrosis, pleural								
Slight							1	
Mononuclear cell infiltration								

	minimal		1	1	2		1	1	
	Lacrimal gland								
	Mononuclear cell infiltrate								
	Minimal			1	1				
	Sublingual gland (left)								
	Mineralization								
	Minimal		1	1	1				
	Urinary bladder								
	Degeneration/regeneration; muscle fiber								
	Minimal								1

Recovery (n=2; only observed at HD)
The following histopathology findings were observed at end of recovery period:

- Moderate hemorrhage of adrenal gland in 1/2 F at HD.
- Slight erosion in rectum in 1/2 F at HD.
- Slight increased pigment deposit in spleen in 1/2 M at HD.
- Minimal mononuclear cell infiltrations in brain, lung, and left parotid gland in 1/2 F at HD.
- Minimal congestion/hemorrhage in mesenteric lymph node in 1/2 F at HD.
- Minimal to moderate atrophy in thymus in 1/2 F at HD.
- Minimal dilation of glandular in esophagus in 1/2 F at HD.
- Minimal decreased acinar development of mammary gland in 1/2 F at HD.

LD: low dose; MD: mid dose; HD: high dose; M: male; F: female; N=number per group
-: indicates reduction in parameters compared to control.

General toxicology; additional studies

Results of one-month general toxicity studies in rats and dogs were reviewed previously in IND 114769.

In the 28-day repeated dose toxicity studies in rats and male dogs, oral administration of darolutamide resulted in dose-dependent decreases in body weight gain associated with reduced food intake in males. Darolutamide was well tolerated in rats at doses up to 1000 mg/kg/day and in dogs at doses up to 800 mg/kg/day when administered orally. In the absence of other signs of toxicity and corresponding findings in female animals, the lower body weight and decreased food consumption in male animals were considered to be related to antiandrogenic effects of darolutamide. At necropsy, lower prostate gland and epididymides weights and higher thymus weights were observed in all male groups treated with darolutamide. The corresponding microscopic findings included reduction of secretion in the prostate gland, vacuolation of the epididymal epithelium and a possible reduction in the normal involution of the thymus. The results from the 28-day repeat-dose toxicity study in rats and dogs showed that darolutamide targets male reproductive organs (epididymides, prostate gland, seminal vesicle and testes) with similar severity when compared to toxicity findings in the 26-week repeat-dose toxicity study in rats and the 39-week repeat-dose toxicity study in dogs.

Study title/number: ODM-210-13-week oral (gavage) toxicity study in the beagle dog followed by a 4-week treatment-free period/AB14462.

Methods: A GLP-compliant 13-week repeat-dose toxicity study with a 4-week recovery period was conducted in male and female beagle dogs. Dogs received twice daily oral darolutamide at doses of 25, 75 or 200 mg/kg/dose (50, 150 or 400 mg/kg/day; n=4/sex/group [main], 2/sex/group [recovery for VH and HD only]). Vehicle control animals received 0.5% (w/v) methylcellulose with 0.5% (v/v) tween 80).

Results: There were no unscheduled deaths in this study or remarkable changes in clinical signs, ophthalmology, body weight, food consumption, arterial blood pressure, and urinalysis. No remarkable changes were observed in ECG parameters, except an increase in RR interval in males administered 150 mg/kg/day (48%) and 400 mg/kg/day (52%) 4 hours post-treatment on Day 84; changes were normalized to control means 2-4 hours following the second treatment on Day 84. One female dog at 150 and 400 mg/kg/day had macroscopic findings of dilation in the right and left cerebral hemisphere. Microscopic findings in the brain were observed in both male and female dogs (minimal ventricles dilation in 1/4 male at 50 mg/kg/day and 400 mg/kg/day and 2/4 females at $\geq$ 150 mg/kg/day). According to the Applicant, similar changes in the brain were observed occasionally in other control dogs from the same breeder with a similar incidence and severity. In another study, 3/12 control dogs had the same change including one with a slight (grade 2) severity. Dogs did not exhibit adverse CNS-related clinical signs in the 13-week or 39-week study. Changes in hematology parameters, clinical chemistry, coagulation and organ weights in the 13-week repeat-dose study were similar to the 39-week study with reduced severity. Microscopic findings were similar between the 13-week and 39-week study. The major target organs were the male reproductive organs (epididymides, prostate gland, and testes). Changes in microscopic findings were trending towards recovery at end of recovery period.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number:ORM-15674: Salmonella typhimurium reverse mutation assay/ 1341900

Key Study Findings:

- Darolutamide was negative in all tester strains in the presence and absence of S9 activation in the bacterial reverse mutation assay.

GLP compliance: Yes

Test system: Salmonella typhimurium strains TA98, TA100, TA102, TA1535 and TA1537; +/-S9 up to 5000 μ g/plate

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number:ODM-201: Chromosome aberration test in human lymphocytes in vitro/ 1487800

Key Study Findings:

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- Darolutamide was positive for the induction of structural chromosome aberrations in human lymphocytes in vitro.

GLP compliance: Yes

Test system: human lymphocytes; +/-S9 up to 400 µg/mL.

Study is valid: Yes

Results:

Table 4 Summary results of in vitro chromosome aberration assay in non-activated and S9 activated cells

Slide no.	Cells scored	% Aberrant cells			Aberrations**											
		incl. gaps*	excl. gaps*	carrying ex-changes	Gaps		Chromatid type				Chromosome type				Other	
					g	ig	b	f	d	ex	ib	if	id	cx	ma	cd
Without S9 mix																
Solvent control: DMSO 1.0 %																
1	100				1	0	2	0	0	0	0	0	0	0	0	0
2	100				0	0	2	0	0	0	0	1	0	0	0	0
1+2	200	3.0	2.5	0.0	1	0	4	0	0	0	0	1	0	0	0	0
Positive control: EMS 825.0 µg / mL																
1	100				3	0	18	2	0	0	0	1	0	0	0	0
2	100				0	0	15	0	0	2	3	1	0	0	0	0
1+2	200	18.0	17.0	1.0	3	0	33	2	0	2	3	2	0	0	0	0
Test item: 130.6 µg / mL																
1	100				0	0	1	0	0	0	0	0	0	0	0	0
2	100				0	0	1	1	0	0	0	0	0	0	0	0
1+2	200	1.5	1.5	0.0	0	0	2	1	0	0	0	0	0	0	0	0
Test item: 228.6 µg / mL***																
1	200				0	0	8	0	0	5	1	1	0	0	0	0
2	200				0	0	4	0	0	5	1	0	0	0	0	0
1+2	400	5.0	5.0	2.3	0	0	12	0	0	10	2	1	0	0	0	0
Test item: 400.0 µg / mL***																
1	200				0	1	7	3	0	1	0	0	0	0	1	1
2	200				1	0	19	3	0	0	1	0	0	0	0	0
1+2	400	6.8	6.3	0.3	1	1	26	6	0	1	1	0	0	0	1	1

* Including cells carrying exchanges

** Note: multiple aberrations may occur in a single cell, therefore, the numbers in these columns may not (nor are they intended to) correlate with the number in the columns of % Aberrant cells.

*** 200 metaphases per culture were evaluated due to inhomogeneous data

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Slide no.	Cells scored	% Aberrant cells			Aberrations**											
		incl. gaps*	excl. gaps*	carrying ex-changes	Gaps		Chromatid type				Chromosome type				Other	
					g	ig	b	f	d	ex	ib	if	id	cx	ma	cd
With S9 mix																
Solvent control: DMSO 1.0 %																
1	100				0	0	1	0	0	0	0	0	0	0	0	
2	100				0	0	0	0	0	0	0	0	0	0	0	
1+2	200	0.5	0.5	0.0	0	0	1	0	0	0	0	0	0	0	0	
Positive control: CPA 15.0 µg / mL																
1	100				0	0	10	0	0	2	0	0	0	0	0	
2	100				0	0	11	0	0	2	0	0	0	0	0	
1+2	200	10.5	10.5	2.0	0	0	21	0	0	4	0	0	0	0	0	
Test item: 200.0 µg / mL																
1	100				0	0	3	0	0	0	0	0	0	0	0	
2	100				0	0	0	0	0	0	0	0	0	0	0	
1+2	200	1.5	1.5	0.0	0	0	3	0	0	0	0	0	0	0	0	
Test item: 240.0 µg / mL***																
1	200				2	0	8	0	0	1	0	0	0	0	0	
2	200				0	0	6	0	0	1	0	0	0	0	0	
1+2	400	4.5	4.0	0.5	2	0	14	0	0	2	0	0	0	0	0	
Test item: 260.0 µg / mL***																
1	200				1	0	9	0	0	2	2	1	0	0	0	
2	200				0	0	1	0	0	3	1	0	0	0	0	
1+2	400	4.8	4.5	1.3	1	0	10	0	0	5	3	1	0	0	0	
Test item: 340.0 µg / mL***																
1	200				2	0	17	1	0	0	0	2	0	0	1	
2	200				0	0	14	1	0	4	1	1	0	0	0	
1+2	400	10.0	9.5	0.8	2	0	31	2	0	4	1	3	0	0	1	

* Including cells carrying exchanges

** Note: multiple aberrations may occur in a single cell, therefore, the numbers in these columns may not (nor are they intended to) correlate with the number in the columns of % Aberrant cells.

*** 200 metaphases per culture were evaluated due to inhomogeneous data

g = gap, ig = iso-gap (gaps are achromatic lesions of chromatid or chromosome type where no or only a minimal misalignment of chromosomal material is visible), b = break, ib = iso-break, f = fragment, if = iso-fragment, d = deletion, id = iso-deletion, ma = multiple aberration (= more than 4 events in one cell [excluding gaps]), ex = chromatid type exchange, cx = chromosome type exchange, cd = chromosomal disintegration (= pulverization)

(Excerpted from Applicant's submission)

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: ODM-201: Combined bone marrow micronucleus test and comet assay in the liver and duodenum in treated male han wistar rats/1841788

Key Study Findings:

- Oral doses up to 1000 mg/kg/day darolutamide did not induce an increase in micronucleated polychromatic erythrocytes in the bone marrow of male rats
- Darolutamide did not induce DNA damage in liver or duodenum cells in the comet assay
- At a dose of 1000 mg/kg/day, C_{max} and AUC of darolutamide on Day 3 were 19700 ng/mL and 311000 ng·h/mL, respectively.

GLP compliance: Yes

Test system:

- Bone marrow from male rats orally administered 0, 100, 500 and 1000 mg/kg darolutamide at 0 (Day 1), 24 (Day 2) and 45 (Day 3) hours (n=3/group).
- In the comet assay, DNA damage was evaluated in liver and duodenum samples collected on Day 3 (48 hours).

Study is valid: Yes

Other Genetic Toxicity Studies

None

5.5.3. Carcinogenicity

Not conducted or warranted to support this NDA submission for a therapeutic intended to treat patients with advanced cancer

5.5.4. Reproductive and Developmental Toxicology

Not conducted or warranted to support this NDA submission for a therapeutic intended to treat male patients with advanced prostate cancer

5.5.5. Other Toxicology Studies

Phototoxicity:

Phototoxicity was evaluated because both darolutamide and keto-darolutamide absorb light in the UVB range from 290 to 320 nm with the highest absorption at 290 nm. The calculated molar absorption coefficients were 23100 and 22500 L mol⁻¹ cm⁻¹, respectively, exceeding the proposed threshold of 1000 L mol⁻¹ cm⁻¹.

Study Title/Number: ODM-201: Neutral red uptake phototoxicity assay in balb/c 3T3 mouse fibroblasts/ 20043930

Method: The objective of this GLP-compliant study was to evaluate the phototoxicity potential of darolutamide (1.78 to 100 mg/L) as measured by the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to darolutamide in the presence or absence of ultraviolet radiation. Promethazine (0.032 to 100 mg/L) was used as the positive control. Promethazine cytotoxicity and phototoxicity criteria were met, indicating that the assays were valid.

Result: Darolutamide demonstrated no phototoxic or cytotoxic potential.

X

Wimolnut Manheng
Primary Reviewer

X

Tiffany K. Ricks
Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

Darolutamide is a nonsteroidal androgen receptor (AR) antagonist that competitively inhibits androgen binding, AR nuclear translocation, and AR mediated transcription. The applicant is seeking approval of darolutamide for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) patients. The proposed dose of darolutamide is a 600 mg orally twice-daily with food. The efficacy and safety of darolutamide in nmCRPC patients was evaluated in a pivotal multinational phase 3 randomized, double blind, placebo-controlled study. In this study, all patients received androgen deprivation therapy (ADT) throughout the studies, i.e. received a gonadotropin-releasing hormone (GnRH) analog concurrently or had bilateral orchiectomy. Darolutamide drug product for commercial use is a 300 mg film-coated tablet.

The key clinical pharmacology review questions focus on appropriateness of darolutamide dose, recommendations for darolutamide dose in patients with hepatic or renal impairment, labeling recommendations for potential drug-drug interactions (DDIs) and the effect of food on darolutamide exposure.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 212099. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in **Table 4**:

Table 5. Key FDA Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of darolutamide in nmCRPC patients was evaluated in a pivotal multinational phase 3 randomized, double blind, placebo-controlled study (17712). In addition, data from Phase 1/2 studies (17829, 18035, 17830 and 17719) in metastatic CRPC (mCRPC) patients was used to support darolutamide efficacy. The proposed dosing regimen is supported by the a statistically significant Metastasis-Free Survival (MFS) improvement in the treatment group (darolutamide in combination with ADT) compared to the placebo group (ADT alone), with a median MFS of 40.4 months vs. 18.4 months, respectively, in patients with nmCRPC (Study 17712).

General dosing instructions	The proposed dose of darolutamide of 600 mg orally twice-daily with food, is acceptable for approval: ▪ This dosing regimen demonstrated a statistically significant MFS improvement in the pivotal phase 3 trial. ▪ This dose appears to have a tolerable safety profile in nmCRPC patients. ▪ Administration with food is acceptable, as both high-fat high-calorie meal and low-fat low-calorie meal boost darolutamide systemic exposure by 2.0-2.5-fold compared to fasting condition.
Dosing in patient subgroups (intrinsic and extrinsic factors)	▪ Hepatic impairment: Reduce darolutamide dose to 300 mg twice-daily in patients with moderate hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment. No data are available in patients with severe hepatic impairment. ▪ Renal impairment: Reduce darolutamide dose to 300 mg twice-daily in patients with severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairments. No data are available in patients with end-stage kidney disease. ▪ Avoid concomitant use with combined P-gp and strong or moderate CYP3A inducers. ▪ (b) (4) for patients concomitantly taking a combined P-gp and strong CYP3A inhibitors. ▪ No dose adjustment is required based on age, weight, or race.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations. Labeling language has been updated according to the guidance of clinical pharmacology section of labeling for human prescription drug and biological products - content and format (published December 2016).
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the Phase 3 Study (17712).

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1 Mechanism of Action

Darolutamide is a nonsteroidal androgen receptor (AR) antagonist that competitively inhibits androgen binding, AR nuclear translocation, and AR mediated transcription. Darolutamide drug substance is a 1:1 mixture of 2 pharmacologically active diastereomers; (S,R)-darolutamide and (S,S)-darolutamide, which show no major differences in pharmacological activity *in vitro*. In addition, the major circulating metabolite; keto-darolutamide shows similar pharmacological activity to darolutamide *in vitro*. However, due to the low unbound fraction of the metabolite (0.2%), the contribution to the overall pharmacological effect *in vivo* is considered minor. In humans, expression of the prostate-specific antigen (PSA) gene is directly regulated by binding of AR. Darolutamide caused a more than 50% decline in the serum level of PSA in 83.6% of the patients in the pivotal phase 3 study (17712). Decreases in serum PSA levels were also seen in the supportive Phase 1/2 studies with the metastatic patient population with the best responses seen in the chemo-/CYP17i naïve subgroup (85.7% and 83.3% of the patients showed a PSA decline of more than 50% in 17829 and 17830 studies, respectively).

6.2.1.2 Clinical Pharmacokinetics

In mCRPC patients, darolutamide and its metabolite, keto-darolutamide, exhibit linear, nearly dose-proportional and time-independent exposure at doses ranging from 100 to 700 mg following single doses and repeated twice-daily doses. At doses higher than 700 mg twice-daily, darolutamide exhibited a saturated absorption, and no further increase in its exposure was observed at 900 mg twice-daily. After single dose administration of darolutamide at 700 mg dose in mCRPC patients, the mean C_{max} is 1.87 $\mu\text{g}/\text{mL}$ (24.8%) and AUC_{12} is 28.9 $\mu\text{g}\cdot\text{h}/\text{mL}$ (38.9%). After administration of darolutamide at dose of 700 mg twice-daily in mCRPC patients, the mean steady state C_{max} is 4.35 $\mu\text{g}/\text{mL}$ (27.5%) and AUC_{12} is 44.7 $\mu\text{g}\cdot\text{h}/\text{mL}$ (31%). In nmCRPC patients, darolutamide has C_{max} of 4.79 $\mu\text{g}/\text{mL}$ (30.9%) and AUC_{12} of 52.82 $\mu\text{g}\cdot\text{h}/\text{mL}$ (33.9%) following a repeated twice-daily administration of 600 mg. Steady-state darolutamide concentrations were achieved by day 2-5 after twice-daily dosing of 600 mg with a mean accumulation index (R_{ac}) of 2.9. In nmCRPC patients, the active metabolite, keto-darolutamide, steady-state total exposure in plasma (C_{max} of 8.5 $\mu\text{g}/\text{mL}$ [35.4%] and AUC_{12} of 87.6 $\mu\text{g}\cdot\text{h}/\text{mL}$ [42.1%]) is 1.7-fold higher compared to darolutamide following a repeated twice-daily administration of 600 mg. Based on comparable values for single dose AUC and multiple dose AUC_{12} , darolutamide exhibited time-independent and predictable pharmacokinetics.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment on pharmacology and clinical pharmacokinetics of darolutamide.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

For the proposed indication of nmCRPC, the applicant proposes a dosing regimen of 600 mg (two 300 mg tablets) to be taken orally twice-daily with food. The proposed darolutamide dosing regimen is based on the results of Phase 1/2 clinical studies 17829, 18035, 17830 and 17719 in mCRPC, and a phase 3 clinical study, 17712 in nmCRPC.

The FDA's Assessment:

The proposed dose of darolutamide of 600 mg orally twice-daily with food is acceptable for approval. For more information, see section 6.3.2.

6.2.2.2. Therapeutic Individualization

Dose adjustment schema

Dose reduction schema: If a patient experiences a greater than or equal to Grade 3 toxicity or an intolerable adverse reaction, withhold dosing or reduce to 300 mg twice-daily until symptoms improve. Then the treatment may be resumed at a dose of 600 mg twice-daily. Dose reduction below 300 mg twice-daily is not recommended.

The FDA's Assessment:

The FDA agrees with the proposed dose reduction schema of darolutamide.

Specific Populations

No dose adjustment is recommended for nmCRPC patients based on demographic characteristics (age, body weight, gender, or race) (b) (4)

The pharmacokinetics of darolutamide has not been studied in patients with end-stage renal disease (eGFR <15 mL/min/1.73 m²) or severe hepatic impairment (Child-Pugh C).

The FDA's Assessment:

The FDA agrees with the Applicant's proposal that no dose adjustment is needed based on demographic characteristics of the patients. (b) (4)

For more information, see section 6.3.2.

Drug-Drug Interactions

Darolutamide is a CYP3A4, P-gp and BCRP substrate. (b) (4) when darolutamide is administered concomitantly with combined P-gp and strong CYP3A4 inhibitors.

The concomitant use of darolutamide with combined P-gp and strong CYP3A inducers should be avoided.

Darolutamide is a weak CYP3A4 inducer and a strong inhibitor of BCRP. (b) (4)

(b) (4) Because co-administration of darolutamide can increase BCRP substrates exposure, (b) (4) when co-administered with darolutamide.

The FDA's Assessment:

The FDA agrees with the applicant's proposal that (b) (4) for darolutamide when it is co-administered with combined P-gp and strong CYP3A4 inhibitors. The FDA agrees with the recommendation to avoid the concomitant use of darolutamide with combined P-gp and strong CYP3A inducers, however, the FDA recommends that the concomitant use of darolutamide with combined P-gp and moderate CYP3A inducers should also be avoided. The FDA (b) (4) recommends that the concomitant use of darolutamide with BCRP substrates should be avoided. For more information, see section 6.3.2.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Absorption: Following a single oral administration of 300 mg darolutamide tablet, peak concentrations are observed at a median T_{max} of ~ 4 hours in healthy volunteers. Absolute bioavailability of darolutamide given as a tablet under fasted condition is 30%. However, absorption of darolutamide from a tablet formulation is improved by 2.0-2.5-fold (corresponding to 60-75% of darolutamide absolute bioavailability) when given together with a high-fat or a low-fat meal. Following repeated oral administration of 600 mg twice-daily together with food to nmCRPC patients, peak plasma concentrations of darolutamide are reached around 4 hours after administration.

Distribution: The apparent volume of distribution of darolutamide in healthy male volunteers after intravenous administration is 119 L. Average total blood-to-plasma ratios are 0.772 for darolutamide and 0.507 for keto-darolutamide. Darolutamide and keto-darolutamide are mainly bound to human serum albumin with mean free fraction of 8% for darolutamide and 0.2% for keto-darolutamide.

Elimination: After a single dose of [^{14}C]-darolutamide, 63.4% of the total administered dose recovered in urine and 32.4% recovered in feces with approximately 7% of the administered dose excreted unchanged in urine. It has a calculated half-life ($T_{1/2}$) of 13 hours with an estimated clearance (CL) of 6.96 L/h. Darolutamide is subject to oxidation as well as to glucuronidation. Oxidative metabolism of darolutamide as well as of its major metabolite keto-darolutamide in human is preferentially catalyzed by CYP3A4 and less pronounced by CYP1A1,

whereas, the reduction of keto-darolutamide is mainly catalyzed by aldo-keto reductase family member 1C3 (AKR1C3). In addition, O-glucuronidation of darolutamide is catalyzed by uridine-5'-diphosphoglucuronosyltransferase UGT1A9, UGT1A1, and UGT1A3. The N-glucuronidation is predominantly mediated by UGT2B10.

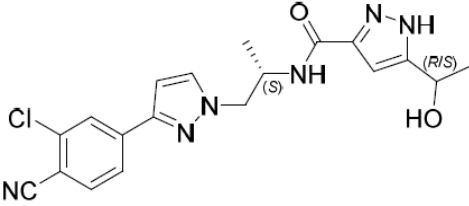
After repeated oral administrations every 12 hours in healthy subjects, plasma darolutamide concentrations declined with an effective $T_{1/2}$ of 13 hours. Accordingly, steady-state should be reached after 2.5 days at the latest. Following repeated oral administration of 600 mg twice-daily together with food to nmCRPC patients, a geometric mean AUC_{12} at steady-state in nmCRPC patients is 1.8-fold higher compared to the AUC_{12} in healthy volunteers. Accordingly, the effective $T_{1/2}$ representing the accumulation of darolutamide increases from 13 hours in healthy volunteers to approximately 20 hours in nmCRPC patients.

Based on AUC_{12} data in healthy subjects at steady-state, the ratio of the two diastereomers, (S,R)-darolutamide and (S,S)-darolutamide, was observed to transition from a 1:1 ratio in the tablet to a 1:6 ratio in plasma. This ratio changed to approximately 1:9 in the plasma of nmCRPC patients at steady-state. The respective $T_{1/2}$ values for (S,R)-darolutamide and (S,S)-darolutamide were 9 and 22 hours, respectively. Due to the different $T_{1/2}$ in nmCRPC patients, steady-state of (S,R)-darolutamide and (S,S)-darolutamide is reached after 2 and 5 days, respectively, following repeated twice-daily dosing.

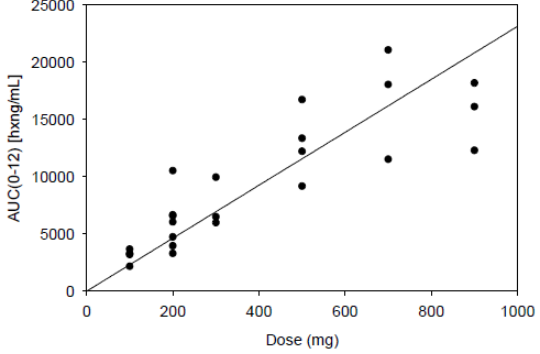
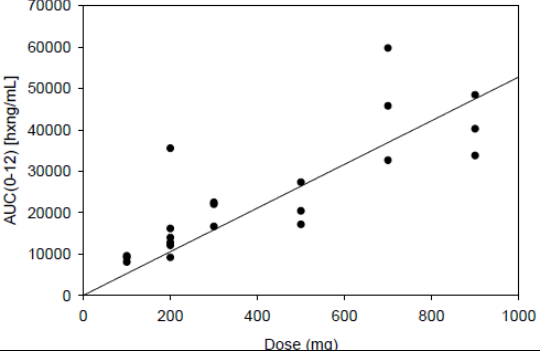
The FDA's Assessment

The FDA generally agrees with the Applicant's position on general pharmacology and pharmacokinetic characteristics. The general overview of darolutamide pharmacology and clinical pharmacokinetics information as assessed by the FDA are presented in **Table 5**.

Table 6. The summary of darolutamide pharmacology and clinical pharmacokinetics information-FDA

Physicochemical characteristics	
Chemical structure	 Molecular formula: C₁₉H₁₉ClN₆O₂ Molecular weight: 398.85 g/mol
Physical properties	Darolutamide appears as a white to greyish- or yellowish white powder that has solubility in aqueous buffer solutions at physiological pH range (pH 1-6.8) of about 14-23 µg/mL. The solubility increases in intestinal fluid simulating solutions such as Fasted-State Simulated Intestinal Fluid (FaSSIF, 30 µg/mL) and Fed-State Simulated Intestinal Fluid (FeSSIF, 108 µg/mL). Darolutamide is a 1:1 mixture of two diastereomers: (S,R)-darolutamide (ORM-16497, BAY 1896951) and (S,S)-darolutamide (ORM-16555, BAY 1896952), which exhibit similar pharmacological activity <i>in vitro</i>.

Pharmacology													
Mechanism of Action	Darolutamide is a nonsteroidal androgen receptor (AR) antagonist developed for the treatment of prostate cancer. It binds to the AR and prevents dihydrotestosterone (DHT) from binding to AR. Darolutamide inhibits androgen-mediated nuclear translocation of AR.												
Active Moieties	(S,S)-Darolutamide, (S,R)-Darolutamide and Keto-Darolutamide												
QT Prolongation	No large QTc prolongation effect (i.e., > 20 ms) of darolutamide (600 mg twice-daily) was observed in phase 3 study. No dose-dependent increases in PR or QTc intervals was observed in the clinical Phase 1/2 studies.												
General Information													
Bioanalysis	Plasma concentrations of darolutamide diastereomers and its metabolite in clinical studies were measured by validated LC-MS/MS following a solid-phase extraction. A summary of the method validation report is included in the Appendix 19.5.1 .												
Healthy volunteers vs. patients	After 600 mg BID administration, darolutamide AUC₁₂ values were slightly higher in nmCRPC patients (study 17712) compared to healthy subjects (study 17723). The slight difference was not considered clinically relevant. <table border="1"> <caption>Approximate data from the scatter plot</caption> <thead> <tr> <th>Study</th> <th>Dose-normalized AUC(0-12) [h/mL]</th> </tr> </thead> <tbody> <tr> <td>Healthy Subjects (Study 17723)</td> <td>0.03 - 0.06</td> </tr> <tr> <td>mCRPC Patients Caucasians (Study 17829)</td> <td>0.04 - 0.18</td> </tr> <tr> <td>mCRPC Patients Japanese (Study 17719)</td> <td>0.04 - 0.17</td> </tr> <tr> <td>nmCRPC Patients (Study 17712)</td> <td>0.07 - 0.16</td> </tr> <tr> <td>17712 5th/95th</td> <td>0.05 - 0.15</td> </tr> </tbody> </table>	Study	Dose-normalized AUC(0-12) [h/mL]	Healthy Subjects (Study 17723)	0.03 - 0.06	mCRPC Patients Caucasians (Study 17829)	0.04 - 0.18	mCRPC Patients Japanese (Study 17719)	0.04 - 0.17	nmCRPC Patients (Study 17712)	0.07 - 0.16	17712 5 th /95 th	0.05 - 0.15
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nmCRPC Patients (Study 17712)	0.07 - 0.16												
17712 5 th /95 th	0.05 - 0.15												
Drug exposure at steady state following the therapeutic dosing regimen	Based on the popPK analysis, darolutamide has steady state C _{max} of 4.79 µg/mL (30.9%) and AUC ₁₂ of 52.82 µg·h/mL (33.9%) following a repeated twice-daily administration of 600 mg in nmCRPC patients.												
Minimal effective dose or exposure	300 mg twice-daily administered orally with food.												
Maximal tolerated dose or exposure	The maximum administered dose of darolutamide in CRPC patients is 900 mg twice-daily. At doses higher than 700 mg twice-daily, darolutamide exhibited a saturated absorption, and no further increase in its exposure was observed at 900 mg twice-daily.												

Dose Proportionality	In patients with mCRPC, the exposure of darolutamide was approximately dose proportional following oral administration at single or multiple dose range of 100-700 mg. ▪ Single-Dose:  <table border="1" data-bbox="1084 424 1427 529"> <thead> <tr> <th></th> <th>Slope (90% CI)</th> </tr> </thead> <tbody> <tr> <td>AUC₁₂</td> <td>0.8 (0.63-0.96)</td> </tr> <tr> <td>C_{max}</td> <td>0.7 (0.54-0.85)</td> </tr> </tbody> </table> ▪ Multiple-Dose:  <table border="1" data-bbox="1084 844 1427 949"> <thead> <tr> <th></th> <th>Slope (90% CI)</th> </tr> </thead> <tbody> <tr> <td>AUC₁₂</td> <td>0.71 (0.51-0.90)</td> </tr> <tr> <td>C_{max}</td> <td>0.66 (0.49-0.84)</td> </tr> </tbody> </table>		Slope (90% CI)	AUC ₁₂	0.8 (0.63-0.96)	C _{max}	0.7 (0.54-0.85)		Slope (90% CI)	AUC ₁₂	0.71 (0.51-0.90)	C _{max}	0.66 (0.49-0.84)
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	Slope (90% CI)												
AUC ₁₂	0.71 (0.51-0.90)												
C _{max}	0.66 (0.49-0.84)												
Accumulation	Based on popPK analysis, 2.9-fold accumulation of darolutamide in nmCRPC patients was calculated following repeated twice ce-daily administration of 600 mg and based on effective T_{1/2} determination.												
Absorption													
Oral Bioavailability	Absolute oral bioavailability of darolutamide is 98.9% (21.3%) as an oral solution and 29.9% (19.4%) as an oral tablet, both at fasted state.												
T_{max} [Oral]	PopPK analysis estimated of darolutamide T_{max} of 3.67 h (2.72-3.92 h) and Keto-darolutamide T_{max} of 2.07 h (1.66-2.18 h) after multiple oral administration of 600 mg twice-daily in nmCRPC patients.												
Food effect	Approximately 2.0-2.5-fold higher exposure (C_{max} and AUC) of darolutamide was observed when darolutamide (600 mg) was administered as tablets and together with food (standardized high-fat, high-calorie meal or typical low-fat, low calorie Japanese breakfast) compared with dosing at the fasted state.												

Bioequivalent (BE) under Fasted Conditions	Darolutamide tablet formulation used in phase 3 clinical trial is the to-be-marketed formulation. However, in early clinical development studies different formulation has been used (capsule). A relative bioavailability study showed no clinically meaningful difference in exposure following the administration of capsule formulation (reference) and two tablet formulations with different drug substance particle size (the to-be-marketed formulation).						
		AUC ₄₈ h×ng/ml			C _{max} ng/ml		
	Formulation	Ratio estimate	Lower 90 %	Upper 90%	Ratio estimate	Lower 90 %	Upper 90%
Tablet A fed/ capsule fed	1.060	0.906	1.241	1.157	0.986	1.357	
Tablet B fed/ capsule fed	0.968	0.824	1.137	0.996	0.860	1.153	
Distribution							
Volume of distribution	Vd = 119 L (28.9%)						
Plasma protein binding	92% and 99.8% darolutamide and keto-darolutamide bound to plasma proteins, respectively, mainly albumin.						
Blood to plasma ratio	0.772 for darolutamide and 0.507 for keto-darolutamide						
Elimination							
Half-life (T_{1/2})	Based on the popPK analysis the effective T _{1/2} of darolutamide and keto-darolutamide in nmCRPC patients after administration of 600 mg twice-daily are 19.6 h (29.7%) and 20.0 h (37.9%), respectively.						
Metabolism	Darolutamide is metabolized via oxidation by CYP3A4 and glucuronidation by UGT1A9, UGT1A1, UGT1A3 and UGT2B10.						
Clearance	Results from mass balance study (study 17831), suggest three equally weighted orthogonal clearance pathways for darolutamide in human; excretion of parent drug, glucuronidation and oxidation. Darolutamide has an estimated clearance of 6.96 L/h (39.7%) in humans.						

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

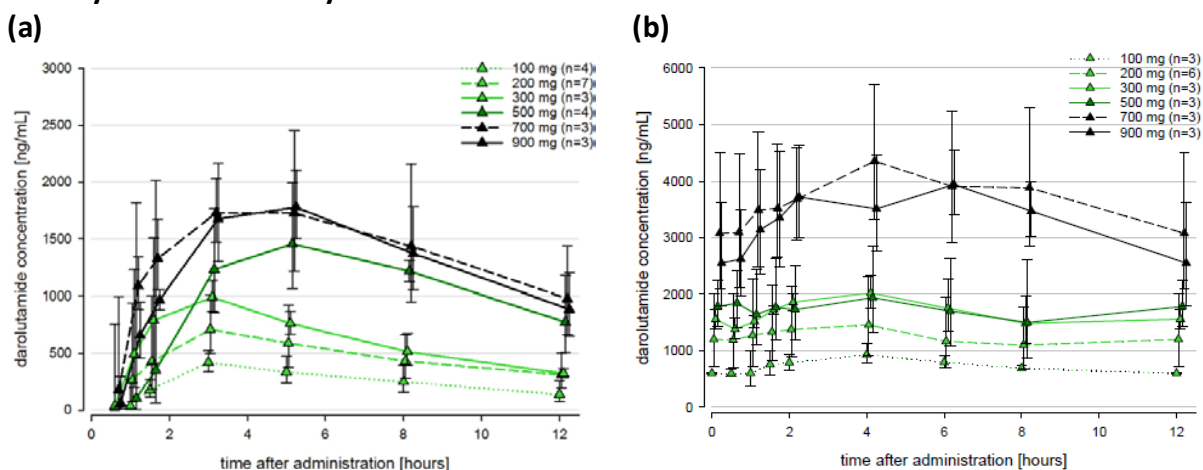
Yes. Darolutamide clinical pharmacology program includes a Phase 1/2 study (17829) and a Phase 1 study (17830) that provided supportive evidence of darolutamide effectiveness in the treatment of CRPC. Also, these studies were used to support the selected darolutamide dose of 600 mg twice-daily. In these two studies, darolutamide treatment decreased the PSA plasma level.

Study 17829:

- In this study, darolutamide has been studied in a dose range of 100 mg to 900 mg twice-daily in mCRPC.
- Dose-linearity of the pharmacokinetic parameters was observed in the dose range of 100 mg and 700 mg. At higher dose (900 mg), no further increase in darolutamide exposure was observed (**Figure 1.**), indicating that saturation of absorption may occur at doses higher

- than 700 mg twice-daily and that there is no benefit to further increase the dose.
- A dose-related response was seen in the chemo-/CYP17i-naïve subgroup, with a higher percentage of patients in the 700 mg twice-daily dose group with a decline in PSA (85.7%) compared to the lower dose levels of 100 (45.5%) and 200 mg twice-daily (69.2%), indicating that the higher dose is more efficacious than the lower doses in this patient population (Table 6 and Figure 2.).

Figure 1. Mean concentration time curves of darolutamide after administration of 100, 200, 300, 500, 700 or 900 mg darolutamide with food: (a) single dose on Day 1 (b) multiple dosing twice-daily with food on Day 7.



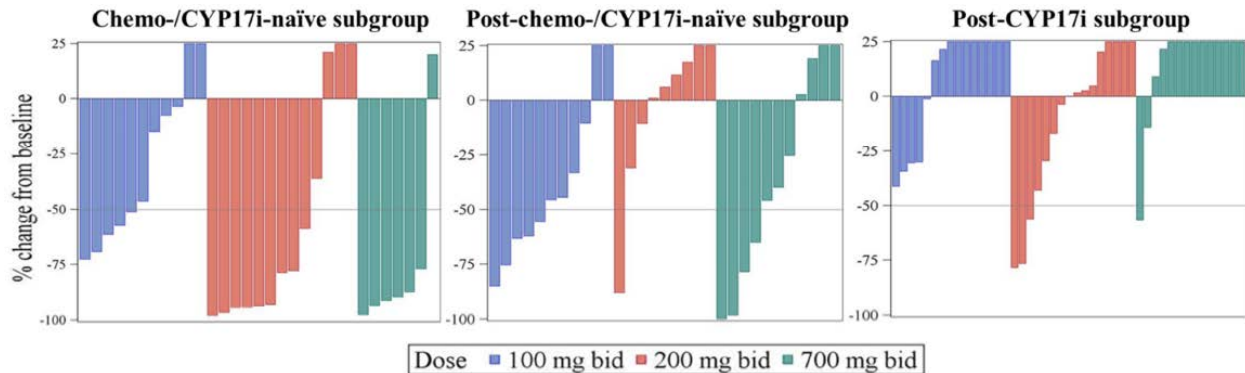
Source: Summary of clinical pharmacology, Figures 2-1 & 2-2, Section 2.2.1.

Table 7. ≥50% decrease in serum PSA from baseline at Week 12 in the combined Phase 1 and 2 components by selected dose levels and by subgroups in study 17829

	100 mg b.i.d. (N=37)	200 mg b.i.d. (N=38)	700 mg b.i.d. (N=33)	Total (all dose groups) ^a (N=117)
All patients, N_e	37	38	33	117
n (%)	10 (27.0%)	13 (34.2%)	11 (33.3%)	40 (34.2%)
Chemo-/CYP17i-naïve subgroup, N_e	11	13	7	36
n (%)	5 (45.5%)	9 (69.2%)	6 (85.7%)	24 (66.7%)
Post-chemo/CYP17i-naïve subgroup, N_e	11	9	11	34
n (%)	5 (45.5%)	1 (11.1%)	4 (36.4%)	12 (35.3%)
Post-CYP17i subgroup, N_e	15	16	15	47
n (%)	0	3 (18.8%)	1 (6.7%)	4 (8.5%)

Source: Summary of clinical efficacy, Table 2-3, Section 2.2.2.1.

Figure 2. PSA waterfall plots of percentage change from baseline at Week 12 by dose for each prior treatment subgroup (Phase 1 and 2) in study 17829

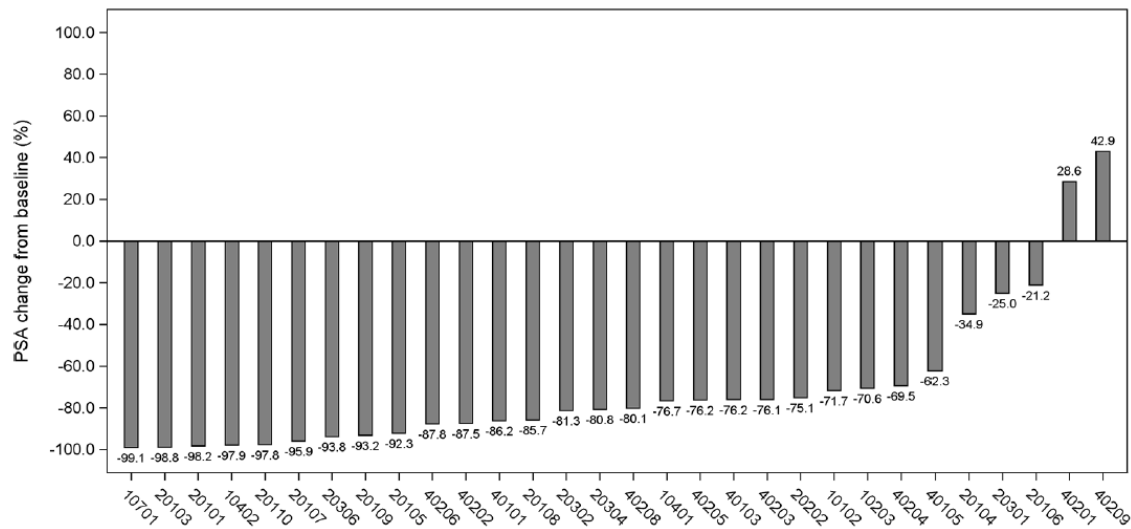


Source: Summary of clinical efficacy, Figure 3-16, Section 3.2.4.1.1.

Study 17830:

- A Phase 1 clinical study of darolutamide in patients with chemotherapy-naïve mCRPC. The study consisted of 2 components: a 3-period crossover PK component with a single dose of 600 mg darolutamide per period at least 7 days apart and a long-term safety and tolerability extension component (repeated dosing) that started on day 4 following the last dose in the PK component with 600 mg darolutamide twice-daily.
- A total of 9 out of 30 patients (30%) showed a $\geq 90\%$ decrease in serum PSA from baseline after 3 months of treatment; 25 patients (83%) showed a $\geq 50\%$ decrease, and 26 patients (87%) showed a $\geq 30\%$ decrease (Figure 3). The median time to PSA progression was 54.4 weeks (95% CI: 23.43-151.3).

Figure 3. Waterfall plot of percentage change in PSA at 12 weeks from baseline in study 17830

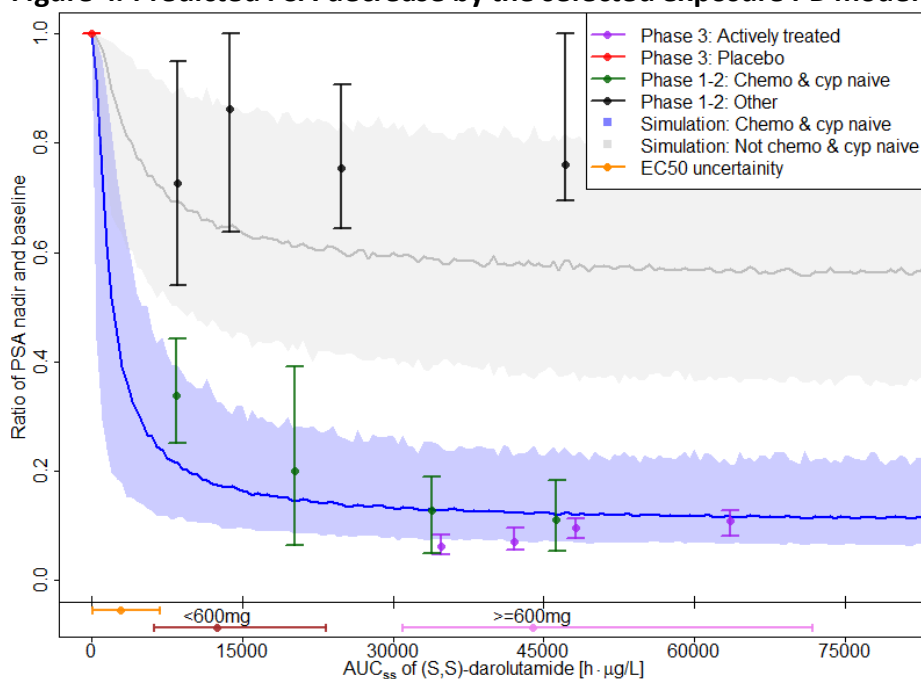


Source: Summary of clinical efficacy, Figure 3-27, Section 3.2.4.3.2.

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

Yes. The proposed darolutamide dosing regimen of 600 mg twice-daily for nmCRPC patient population appears appropriate based on the available efficacy and safety data. In the pivotal phase 3 study in nmCRPC patients, this dosing regimen demonstrated a statistically significant MFS improvement in the treatment group (darolutamide in combination with ADT) compared to the placebo group (ADT alone), with a median MFS of 40.4 months vs. 18.4 months, respectively. The safety analyses of this study showed that dosing darolutamide at 600 mg twice-daily was well-tolerated with comparable incidence of most common TEAEs and similar incidence of permanent discontinuations of treatment between the darolutamide and the placebo arms. The proposed dosing regimen is also supported by exploratory-exposure response analysis. In this analysis, the relationship between darolutamide exposure and change in PSA over time was evaluated based on data from two Phase 1/2 studies in mCRPC patients (17829 and 17830) and data from the Phase 3 study in nmCRPC patients (17712). With increasing darolutamide exposure the PSA level decreased steeply from no decrease at no/zero darolutamide exposure to a maximum of more than 90% PSA response over the exposure range at a dose of 600 mg darolutamide twice-daily in CYP17i therapy naïve mCRPC or nmCRPC patients (Figure 4.)

Figure 4. Predicted PSA decrease by the selected exposure PD model



Source: Summary of clinical pharmacology, Figure 2-9, Section 2.5.2.

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

Yes. FDA agrees with the applicant that no dose adjustment is needed in nmCRPC patients with mild hepatic impairment or mild to moderate renal impairment. The applicant did not conduct any clinical studies to assess the effects of severe hepatic impairment or end-stage kidney disease on darolutamide PK.

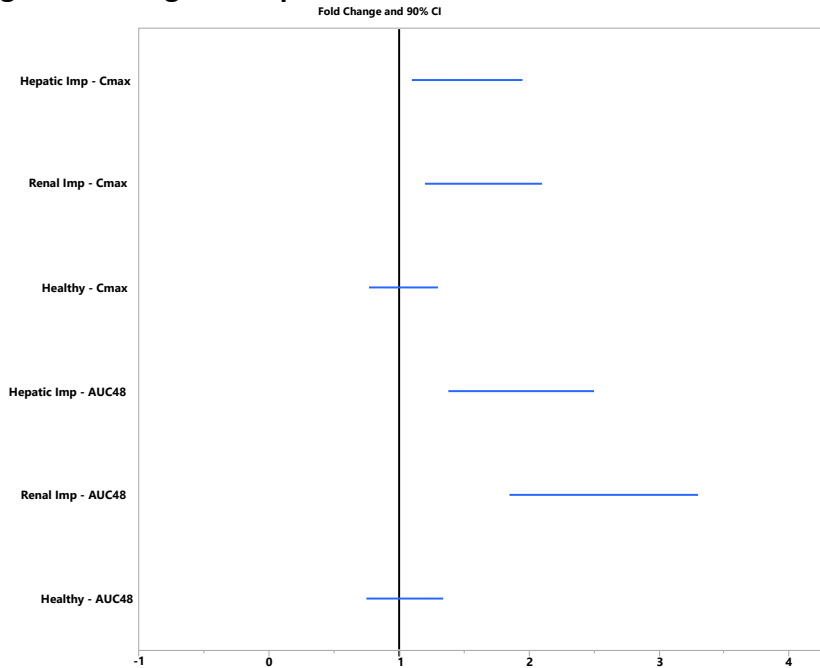
Based on the results from a dedicated organ impairment study (study 17721), darolutamide exposure increased by 1.9-fold and 2.5-fold in non-cancer subjects with moderate hepatic impairment (Child-Pugh Class B) and severe renal impairment (eGFR: 15-29 mL/min/1.73 m²), respectively (**Figure 5**). Given the favorable safety profile of darolutamide observed in patients with normal renal and hepatic functions in the pivotal phase 3 study, the applicant considered the increase of darolutamide exposure in nmCRPC patients with moderate hepatic impairment or severe renal impairment clinically not relevant.

The FDA recommends darolutamide dose reduction to 300 mg twice-daily in nmCRPC patients with moderate hepatic or severe renal impairment to provide exposure that may be comparable to patients with normal hepatic or renal function. The recommended dose is expected to maintain efficacy while avoiding undue AE due to high exposure. The rationale for this recommendation is as follows:

- The lack of safety data in nmCRPC patients with moderate hepatic or severe renal impairment. The phase 3 clinical study protocol allowed enrollment of nmCRPC patients with only normal hepatic and renal functions in the study (only two patients with moderate hepatic impairment and one patient with severe renal impairment were in the safety analysis set of the phase 3 study, 17712). The safety data is mostly contributed by patients with normal or mild organ dysfunction.
- Uncertainty with other potential risk factors for the development of adverse drug reactions in nmCRPC patients with impaired hepatic and renal functions (such as, metabolic abnormalities, or concomitant medications). Additionally, in phase 3 trial, higher incidences of the all grade 5 events, all SAEs and all AEs leading to dose modification were observed in both darolutamide and placebo treatment arms in the moderately or severely impaired renal function group.
- The safety at exposure higher than the exposure achieved after administration of 600 mg twice-daily dose is not established. Results from phase 1/2 study (17829) showed that darolutamide absorption is saturated at doses higher than 700 mg twice-daily, thus darolutamide safety has not been evaluated at higher exposure. However, in case of organ impairments, there is a risk of increased darolutamide exposure beyond the level that has been evaluated in phase 3 study at 600 mg twice-daily.
- Dedicated organ impairment study (17721) showed 1.9-fold increase in the exposure of darolutamide in patients with moderate hepatic impairment (Child Pugh Class B). NCI Organ Dysfunction Working Group (NCI-ODWG) classification criteria identified only 2 patients with mild/moderate hepatic functions with 2.9 and 3.2 fold increase in darolutamide exposure. These findings raise the concern that patients with moderate hepatic impairment might experience higher darolutamide exposure. In this study, single

darolutamide 600 mg dose was well tolerated by all subjects in the hepatic impairment group. However, safety assessment of this study is inconclusive as it assessed the safety of darolutamide after a single dose administration.

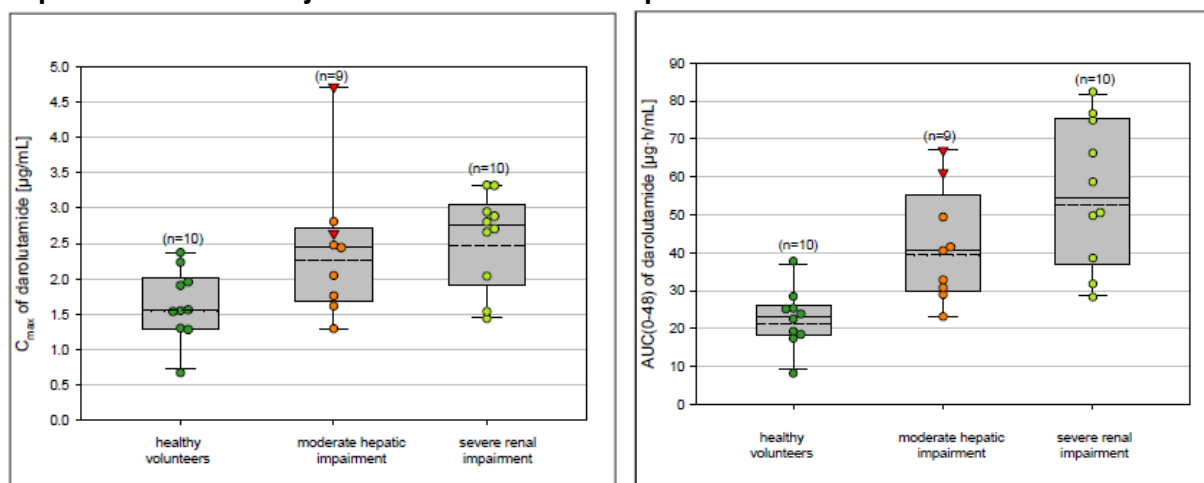
Figure 5. Change of PK parameters of darolutamide based on organ dysfunction



Hepatic and renal impairment study (study 17721):

The applicant conducted an organ impairment clinical study (study 17721) in non-cancer subject to assess the effect of moderate hepatic or severe renal impairment on darolutamide pharmacokinetics. Study 17721 is a phase 1, open-label, single dose study designed to compare the single-dose (600 mg under fed conditions) pharmacokinetics of darolutamide in subjects with moderate hepatic impairment (Class B: Child-Pugh classification score of 7 – 9, groups 2, 9 subjects) or severe renal impairment (eGFR: 15-29 mL/min/1.73 m², groups 2, 10 subjects) to 10 healthy control subjects matched for age and weight (group 3). Results of this study showed a 1.7-2.5-fold and 2-2.6-fold increase in darolutamide diastereomers AUC₄₈ in moderate hepatic and severe renal impairment, respectively (**Table 7 and Figure 6**). AUC₄₈ of the major metabolite, keto-darolutamide increased only in patients with severe renal impairment (1.7-fold higher compared to healthy subjects, **Table 7**).

Figure 6. Box plot of C_{max} and AUC_{48} of darolutamide in plasma after a single oral dose of 600 mg darolutamide in healthy volunteers (control cohort), in subjects with moderate hepatic impairment and in subjects with severe renal impairment



Source: Summary of clinical pharmacology, Figure 2-8, Section 2.4.3.

Table 8. Point estimates and two-sided exploratory 90% CIs for the ratios ‘moderate hepatic impairment / healthy volunteers’ and ‘severe renal impairment / healthy volunteers’ of PK parameters of darolutamide, its major metabolite and diastereomers in plasma

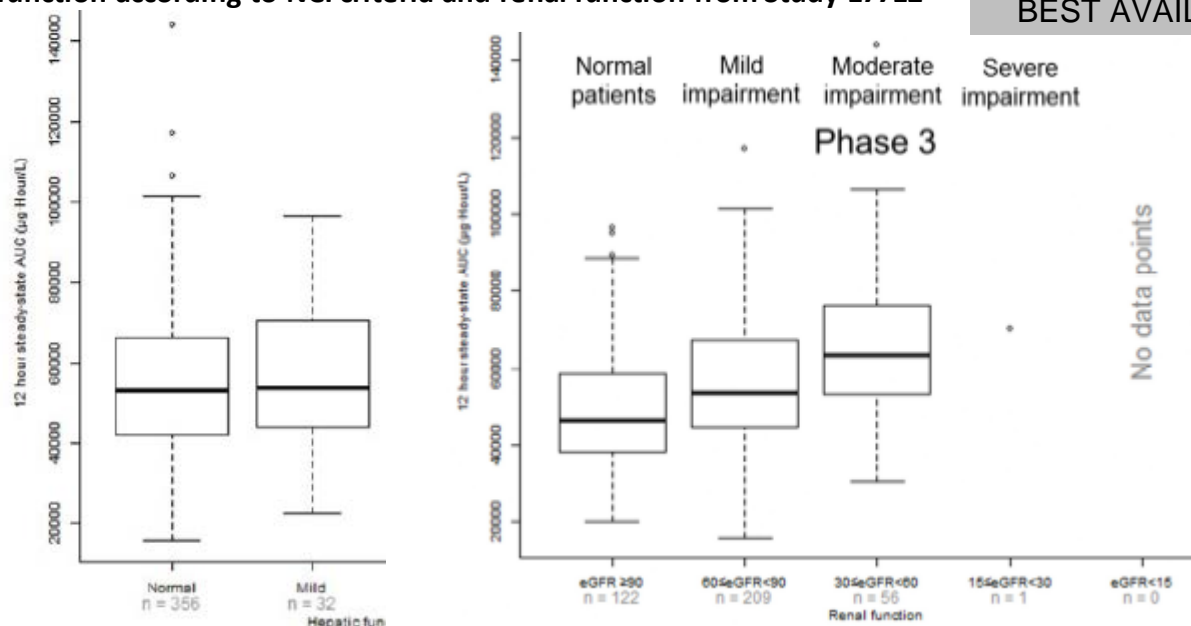
Ratio	Parameter	AUC(0-48)	C_{max}
		Estimated ratio [90% CI]	Estimated ratio [90% CI]
Moderate hepatic impairment (N=9) / Healthy volunteers (N=10)	Darolutamide	1.8540 [1.3684 ; 2.5118]	1.4587 [1.0879 ; 1.9558]
	(S,R)-darolutamide	2.4517 [1.6825 ; 3.5725]	1.8381 [1.3078 ; 2.5835]
	(S,S)-darolutamide	1.7250 [1.2819 ; 2.3214]	1.2901 [0.9884 ; 1.6839]
	Keto-darolutamide	1.1907 [0.8399 ; 1.6878]	0.9297 [0.6860 ; 1.2599]
Severe renal impairment (N=10) / Healthy volunteers (N=10)	Darolutamide	2.4704 [1.8270 ; 3.3404]	1.5888 [1.2283 ; 2.0553]
	(S,R)-darolutamide	1.9999 [1.4240 ; 2.8087]	1.5932 [1.1838 ; 2.1442]
	(S,S)-darolutamide	2.5597 [1.8981 ; 3.4519]	1.6284 [1.2690 ; 2.0896]
	Keto-darolutamide	1.6965 [1.2000 ; 2.3986]	1.2024 [0.9253 ; 1.5626]

Source: Study 17712, Study synopsis, Table 2-2.

PopPK analysis from phase 3 study 17712:

The impact of hepatic and renal impairment was investigated in nmCRPC patient using a popPK analysis of the data from the pivotal phase 3 study. Using NCI-ODWG criteria for categorization in the popPK analysis, a comparable mean $AUC_{12, ss}$ of darolutamide was observed in nmCRPC patients with mild hepatic impairment (N=356) and those with normal liver function (N=32). Similarly, a 1.1- and 1.3-fold higher $AUC_{12, ss}$ was observed in nmCRPC patients with mild and moderate renal impairment compared to nmCRPC patients with normal kidney function after repeated administration of darolutamide 600 mg twice-daily (**Figure 7.**). Based on the safety subgroup analyses of nmCRPC patients in the Phase 3 study, the overall incidence of TEAEs was consistent across hepatic function groups (normal and mild) and renal function groups (normal, mild and moderate) and comparable between darolutamide and placebo arms. However, the limited data available in phase 3 study from patients with moderate hepatic impairment (2 patients) or severe renal impairment (1 patient) preclude safety conclusion of darolutamide in these patient subpopulations.

Figure 7. Box Comparison of steady-state $AUC_{12, ss}$ in nmCRPC patients stratified by hepatic function according to NCI criteria and renal function from Study 17712



Source: Summary of clinical pharmacology, Figure 3-19 & 3-21, Section 3.3.5 & 3.3.6

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

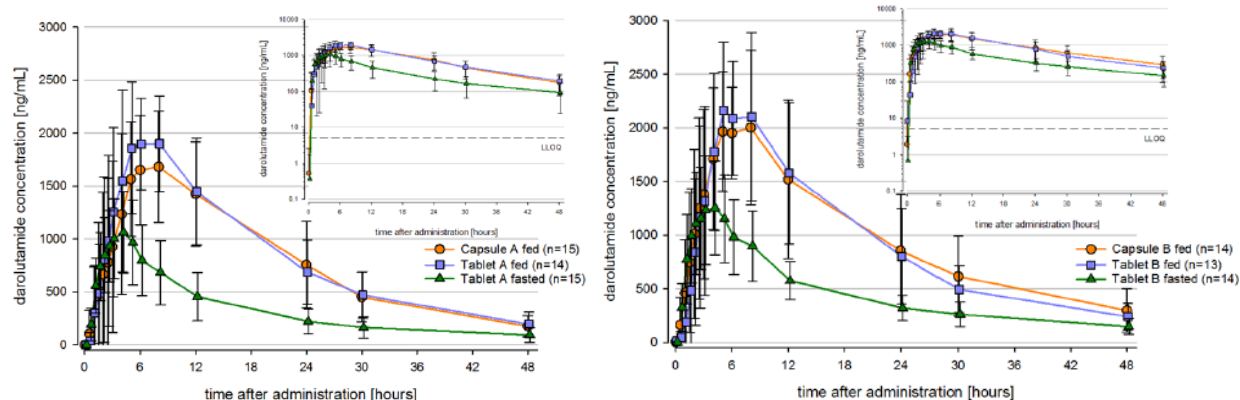
Yes. The clinically relevant food and drug interactions of darolutamide are summarized below with the respective labeling recommendations for appropriate management strategy.

Food Effect:

The effect of food on bioavailability of darolutamide was determined in two clinical studies (17830 and 17719). In study 17830, mCRPC patients received two types of tablet formulation each with and without food. When administered under fed conditions, patients consumed a standardized high fat (~50% of total caloric content of the meal) and high calorie (~800 to 1000 calories) meal 60 minutes prior to administration of darolutamide. In Study 17719, food effect assessments were performed in Japanese mCRPC patients with fed (typical Japanese breakfast with a total caloric content of approximately 500 calories and approximately 22% fat). Administration of darolutamide under fed conditions resulted in higher exposures in both studies (2.0-2.5-fold higher bioavailability corresponding to 60-75% of darolutamide absorbed when given together with food) (**Figure 8.**, **Figure 9.**, and **Table 8**). Therefore, it is recommended that darolutamide is taken together with food. Efficacy and safety of darolutamide have been established in the fed state in nmCRPC patients in the pivotal phase 3 study (17712). Thus, the applicant's proposal to administer darolutamide with food is acceptable.

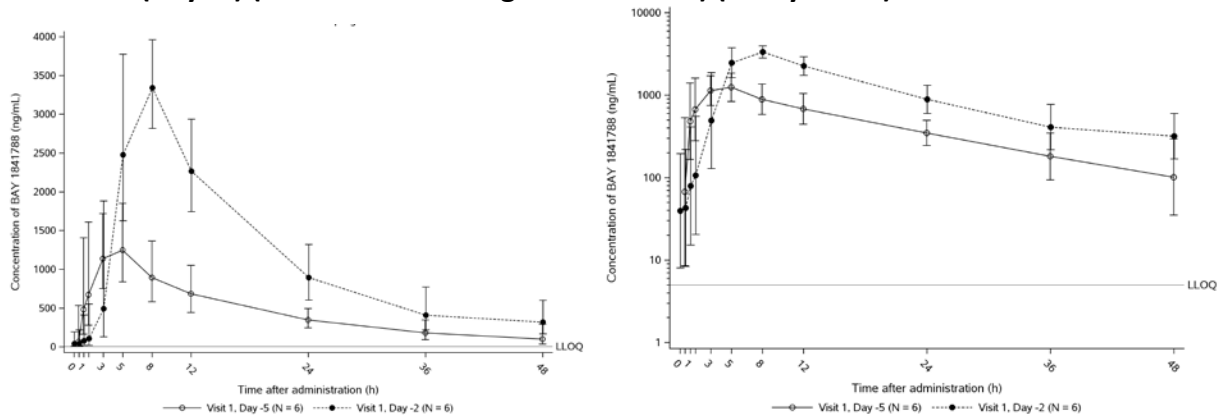
Figure 8. Darolutamide concentration-time curves after a single oral 600 mg dose given as 300 mg tablets (Tablet A or Tablet B) in both the fed and fasted states or as 100 mg capsules under fed conditions, linear and semilogarithmic figures (Study 17830)

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Source: Summary of clinical pharmacology, Figure 2-3, Section 2.2.3

Figure 9. Geometric mean/STD for concentrations of ODM-201 (ug/L) in plasma after a single oral (tablet) dose of ODM-201 600 mg (Cohort 2) under fasting condition (Day -5) and fed condition (Day -2) (linear and semi-logarithmic scale) (Study 17119)



Source: Study 17719, Clinical study report, Figure 9-12, Section 9.4.3.1.

Table 9. Darolutamide PK parameters after administration of 600 mg darolutamide tablet formulations at fed or fasted state, (Study 17830 and Study 17719)

	Study 17830				Study 17719	
	Tablet A Fed	Tablet A Fasted	Tablet B Fed	Tablet B Fasted	Fed	Fasted
Type of meal	High-fat, high-calorie		High-fat, high-calorie		Japanese breakfast	
Dose	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg
n	14	15	13	14	6	6
C _{max} ^a , ng/mL	2265 (16.77)	1071 (35.34)	2311 (30.72)	1272 (34.55)	3498 (12.1)	1258 (41.3)
t _{max} ^b , h	5.0 (2.0-8.2)	4.0 (1.5-5.0)	5.0 (3.9-12.0)	4.0 (2.0-5.1)	6.29 (4.93-7.90)	4.85 (3.05-4.92)
AUC(0-48) ^a , h×ng/mL	37625 (32.29)	14832 (45.06)	40739 (32.11)	20462 (35.34)	55635 ^d (24.0)	22024 ^d (41.4)
Half-life ^c , h	12.1 (2.5)	16.1 (5.6)	15.4 (5.8) ^e	18.9 (7.2)	14.1 (36.7) ^f	10.1 (21.2) ^f

Source: Summary of clinical pharmacology, Table 3-6, Section 3.2.1.3

Drug-Drug interactions:

In-vitro studies:

- Darolutamide is a substrate for CYP3A4, UGT1A9, UGT1A1, UGT1A8, UGT2B17, and UGT1A3. Furthermore, darolutamide was identified as a substrate of both P-gp and BCRP, with a higher sensitivity for P-gp.
- Darolutamide is not a CYP enzymes inhibitor but it is a CYP3A4 inducer. It is not an inhibitor for most of the efflux and uptake transporters, however, it is an inhibitor of BCRP, OAT3, MATE2K, P-gp, OATP1B1, MATE1 and OATP1B3 in decreasing order of relevance (Table 9).

Table 10. Inhibitory effects of darolutamide and metabolite keto-darolutamide on formation of metabolites from standard probes mediated by transporters

Transporter	Substrate	IC ₅₀ [μM]	
		Darolutamide	metabolite keto-darolutamide
P-gp	Digoxin	16.4	2.57
BCRP	Cladibrine	1.33	0.567
OATP1B1	Atorvastatin	16.8	>10
OATP1B3	Atorvastatin	39.3	>10
OAT1	PAH	>50	>2
OAT3	Furosemide	4.46	>2
OCT1	MPP+	>50	>10
OCT2	MPP+	>50	>2
BSEP	Taurocholic acid	>60	>300*
MRP2	CDCF	>50	>10
MATE1	Metformin	32.3	>10
MATE2K	Metformin	9.50	2.96
OATP2B1	Estrone 3-sulfate	>50	>10
NTCP	Estrone 3-sulfate	>50	>10

Source: Summary of clinical pharmacology, Table 3-15, Section 3.4.2.4.

Clinical studies:

- *Darolutamide as a victim of DDIs*

Darolutamide is metabolized by CYP3A4, therefore, inhibitors and inducers of CYP3A4 could clinically affect its exposure. The Applicant conducted a clinical study (17726) to assess the effect of concomitant use of a combined P-gp and strong CYP3A4 inducer (rifampin) and a combined P-gp and strong CYP3A4 inhibitor (itraconazole) on darolutamide exposure. The results of this study showed significant reduction in darolutamide exposure (72% reduction in darolutamide AUC₇₂, **Figure 10.**) when it is concomitantly used with rifampin. Accordingly, the applicant recommended that the concomitant use of combined P-gp and strong CYP3A4 inducers with darolutamide should be avoided. Given the potential loss of darolutamide activity when it is coadministered with a combined P-gp and moderate CYP3A4 inducer (the Applicant provided analysis that predicted 32%-58% reduction in darolutamide exposure with moderate inducers), the FDA changed the label recommendation to include both strong and moderate CYP3A4 inducers.

Inhibition of CYP3A4 and P-gp by itraconazole increased darolutamide exposure (AUC₇₂) by 1.7-fold (**Figure 10.**). This raises the concern that the exposure increase due to CYP3A4 and P-gp inhibition may lead to increased incidence and severity of TEAEs.

FDA recommends that label includes a recommendation to frequently monitor patients for darolutamide toxicity when it is concomitantly used with combined P-gp and strong CYP3A4 inhibitors. The rationale for the recommendation is as follows:

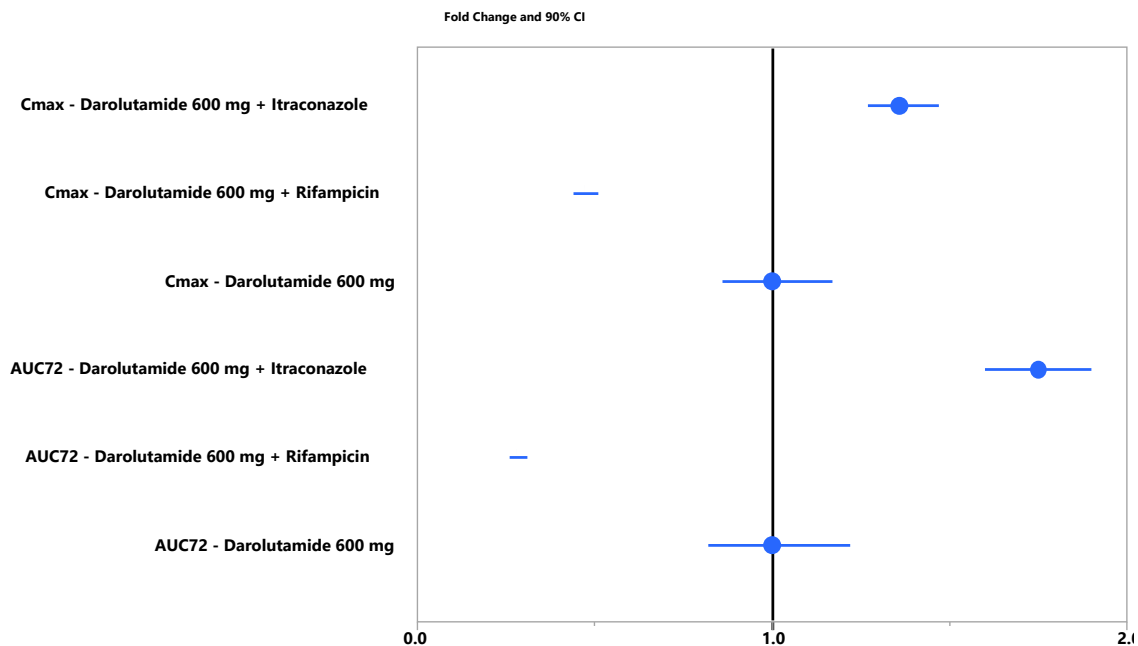
- The Protocol of the phase 3 trial allowed the concomitant use of CYP3A4 inhibitors. The PopPK analysis of the pharmacokinetic subset of the data of phase 3 trial (n=388) showed that darolutamide AUC₅₅ for patients who used CYP3A4 inhibitors at any time during PK sampling (n=84) is 1.1-fold higher than patients who did not receive CYP3A4 inhibitor during the PK sampling period. The absence of increase in darolutamide exposure in this analysis might be explained carefully because factors, such as the type of inhibitor, time of its dosing, and the length of coadministration, have not been considered in this analysis. The safety profile of the 84 (21.3%) patients who used CYP3A4 inhibitors concomitantly with darolutamide were similar to the patients without the inhibitors (TEAEs observed in 33%

and 30% of patients with and without concomitant use of CYP3A4 inhibitor, respectively. Fatigue occurred in 7% and 10.8% of patients with and without concomitant use of CYP3A4 inhibitor, respectively).

- In the safety analysis set of phase 3 trial, 23 patients received a strong CYP3A4 inhibitor, ketoconazole, itraconazole, clarithrymycin or diltiazem, concomitantly with darolutamide. No concerning safety signals were reported in these patients during the concomitant treatment with CYP3A4 strong inhibitors. The duration of concomitant treatment with these agents ranged from less than a week for ketoconazole, itraconazole, and clarithrymycin to more than a year for diltiazem.
- The coadministration of commonly used strong CYP3A4 inhibitors is typical of genral practice. However, these drugs are used episodically, and would not be used for prolonged periods of time in most cases, hence, the risk of DDI-based AEs with these drugs is low. For instance itraconazole and clarithromycin are commonly used anti-infective agents, however, their use in nmCRPC will be short (1-2 weeks) and it might not increase darolutamide AEs as supported by the safety data of phase 3 trial.
- The labeling will include a provision for lowering the dose for any grade 3 or 4 toxicity.

The patients will have the option to switch to drugs that are not inhibitors of CYP3A4 and P-gp. Although UGTs enzymes (UGT1A9, UGT1A1, UGT1A8, and UGT2B17) contribute to the metabolism of darolutamide, the clinical significance of the effect of UGT inhibitors on darolutamide was not further investigated due to the contribution of several clearance pathways to the overall clearance of darolutamide.

Figure 10. Change of darolutamide PK parameters based on CYP3A4/P-gp modulators



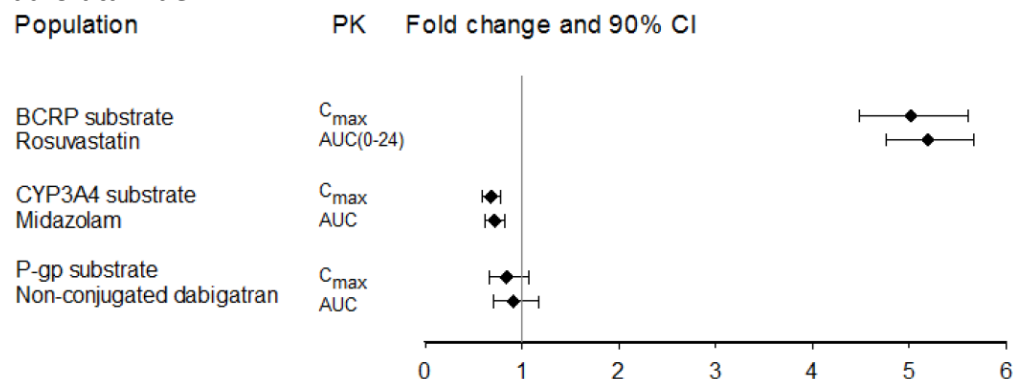
Darolutamide as a perpetrator of DDIs

In vitro, darolutamide is a CYP3A4 inducer and a P-gp and BCRP inhibitor. To assess the effect of darolutamide on the exposure of CYP3A4 and P-gp substrates, the applicant conducted a clinical study (17726). Administration of darolutamide (600 mg twice daily for 9 days) prior to co-administration of a single dose of the CYP3A4 substrate (midazolam, 1 mg) together with food, decreased the mean exposure (AUC) and C_{max} of midazolam by 29% and 32%, respectively (**Figure 11.**), indicating a weak inducing effect of darolutamide on CYP3A4 substrates. In the same study, administration of darolutamide (600 mg twice-daily for 9 days) prior to co-administration of a single dose of both darolutamide (600 mg) and the sensitive P-gp substrate dabigatran etexilate (75 mg given either simultaneously together with food or slightly separated under fasted conditions), did not show any increase but a mean decrease of less than 20% in the mean exposure (AUC) and C_{max} of non-conjugated or total dabigatran (**Figure 11.**). FDA agrees that darolutamide is unlikely to clinically affect pharmacokinetics of CYP3A and P-gp substrates. No specific recommendations were included in the label for CYP3A and P-gp substrates.

Clinical drug interaction study (study 17723) to assess the effect of darolutamide on rosuvastatin (a BCRP, OATP1B1, OATP1B3 and OAT3 substrate) showed a 5.2-fold increase in AUC and a 4.9-fold increase in C_{max} of rosuvastatin (**Figure 11.**). This effect is mainly attributed to inhibition of intestinal and hepatic BCRP. The contribution of OATP1B1, OATP1B3 and OAT3 inhibition by darolutamide is unlikely because there is no change in the total and renal clearance of rosuvastatin by darolutamide. This conclusion is supported by *in vitro* studies that showed low darolutamide IC_{50} for BCRP inhibition compared to the high *in vitro* darolutamide IC_{50} values for uptake transporters. In the label, the Applicant proposed a recommendation to (b) (4) BCRP substrate when co-administered with darolutamide. However, the FDA recommends that the concomitant use of darolutamide with BCRP substrates should be avoided or its dose should be adjusted in accordance with the approved product labeling. These recommendations based on the following observations:

- In a dedicated study, darolutamide increased BCRP substrate (rosuvastatin) exposure by 5-fold
- Subgroup safety analysis of the data from phase 3 study for patients who concomitantly used statins (that are BCRP substrates) with darolutamide showed an increase in the risk of pre-defined TEAEs that reflect frequent undesirable effects of statins (hyperbilirubinaemia, blood creatinine increased, AST and ALT elevations).
- Similar toxicity profiles between darolutamide and statins (muscle weakness, ALT and AST elevation, and serum creatinine increase).
- The risk of increased toxicity of BCRP substrates other than statins.

Figure 11. Change of PK parameters of other substances administered together with darolutamide

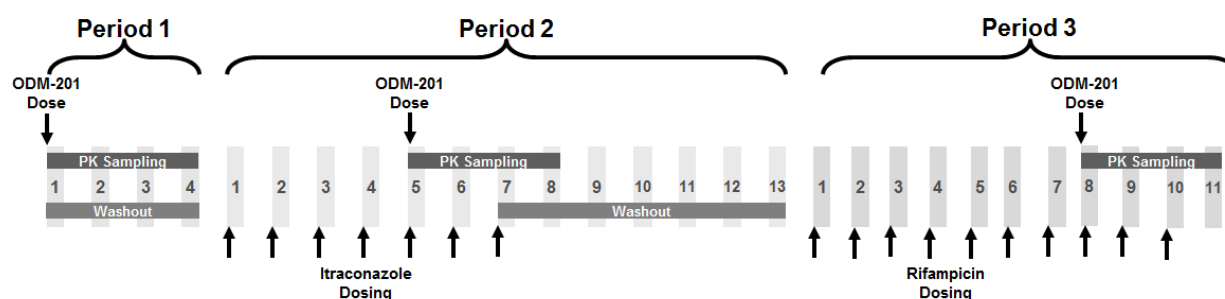


Source: Summary of clinical pharmacology, Figure 1-4, Section 1.3.3.2.

Study 17726: Effect of CYP3A and P-gp modulators on darolutamide pharmacokinetics:

This is an open-label, phase 1, three-period drug-drug interaction study that assessed the effect of combined P-gp and strong CYP3A4 inhibitor (itraconazole) and combined P-gp and strong CYP3A4 inducer (rifampin) on darolutamide exposure. In this study, 15 healthy adult males were assigned for the treatment (**Figure 12.**).

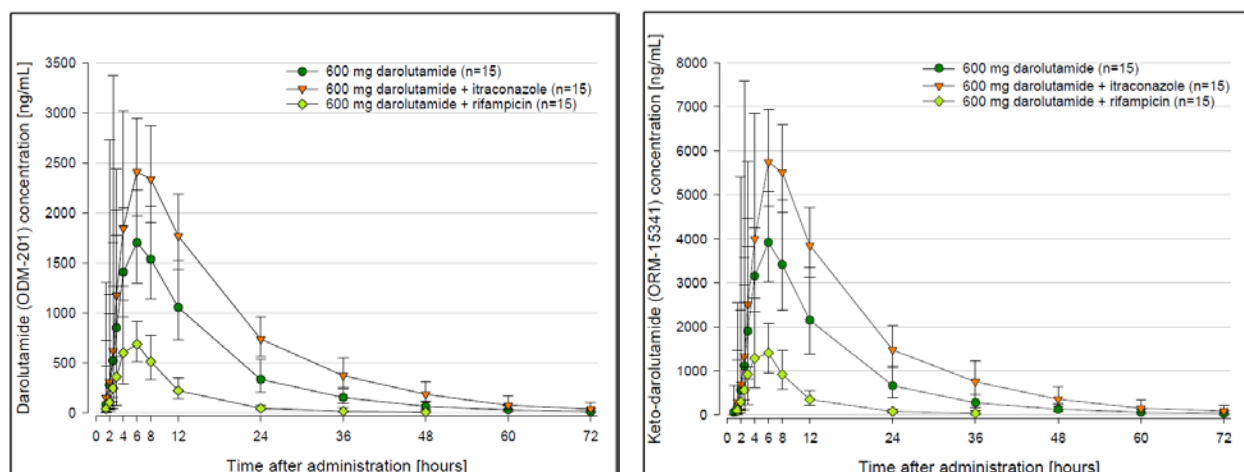
Figure 12. Study Scheme for the assessment of CYP3A and P-gp modulators effect on darolutamide pharmacokinetics.



Source: Study 17726, Clinical study report, Figure 7-1, Section 7.1.1.

Co-administration of itraconazole (a combined P-gp and strong CYP3A4 inhibitor) with darolutamide resulted in 1.75-, 1.70-, 1.76- and 1.80-fold higher mean AUC₇₂ and in 1.36, 1.50, 1.38- and 1.39-fold higher mean maximum plasma concentrations of darolutamide, (S,R)-, (S,S)- and keto-darolutamide (**Figure 13.** and **Table 10**). Concomitant administration of rifampicin led to a decrease to 28, 24, 29 and 25% of mean AUC₇₂ and a decrease to 48, 37, 51 and 47% of mean maximum plasma concentrations of darolutamide, (S,R)-, (S,S)- and keto-darolutamide, respectively, compared to darolutamide alone.

Figure 13. Concentration time profiles of darolutamide (ng/mL) and keto-darolutamide (ng/mL) in plasma after a single oral dose of 600 mg darolutamide alone (Period 1), with itraconazole (Period 2) or with rifampicin (Period 3).



Source: Summary of clinical pharmacology, Figure 2-6 & 2-7, Section 2.4.2.2.

Table 11. PK parameters of darolutamide in plasma following a single oral dose of 600 mg darolutamide alone (Period 1), with itraconazole (Period 2) and with rifampicin (Period 3).

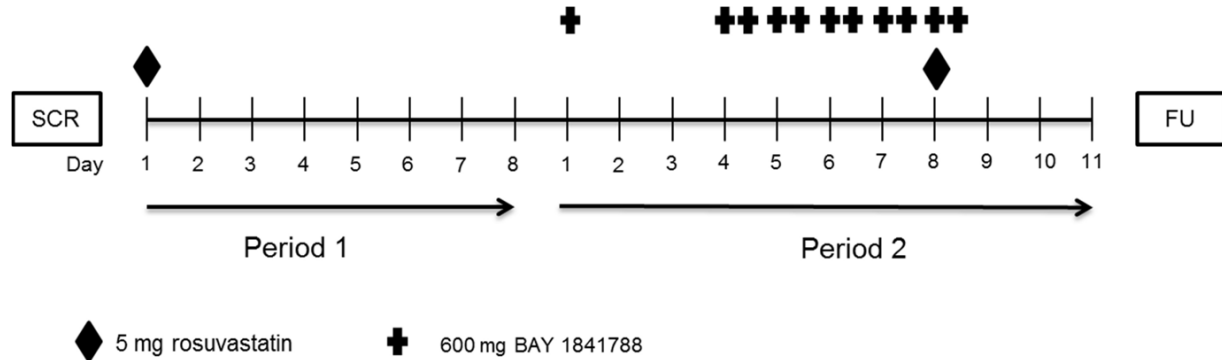
Parameter	Unit	geometric mean/CV% (range)		
		Darolutamide alone Period 1 n=15	Darolutamide + itraconazole Period 2 n=15	Darolutamide + rifampicin Period 3 n=15
C_{max}	µg/mL	1.86/25.1 (1.07-2.63)	2.53/19.6 (1.66-3.53)	0.883/27.8 (0.514-1.48)
AUC(0-72)	µg·h/mL	26.9/32.3 (15.2-52.1)	47.1/23.7 (29.2-63.4)	7.61/30.9 (3.44-13.7)
AUC(0- t_{last})	µg·h/mL	26.9/32.4 (15.2-52.1)	47.1/23.6 (29.2-63.3)	7.52/31.7 (3.30-13.7)
AUC	µg·h/mL	27.4/32.5 (15.8-52.6)	48.6/25.8 (29.8-69.0)	7.69/30.8 (3.44-13.7)
AUC(0-12)	µg·h/mL	14.1/29.5 (7.41-22.0)	20.7/24.1 (12.1-27.7)	5.42/31.7 (2.51-9.23)
$t_{1/2}$	h	11.4/35.9 (5.58-18.2)	12.1/41.1 (7.66-31.9)	9.13/58.1 (3.96-22.3)
			Median (range)	
t_{max}	h	6.00 (1.48-8.02)	5.98 (2.98-8.02)	4.00 (1.48-7.98)

Source: Summary of clinical pharmacology, Table 2-21, Section 2.4.2.2.

Study 17723: Effect of darolutamide on rosuvastatin pharmacokinetics:

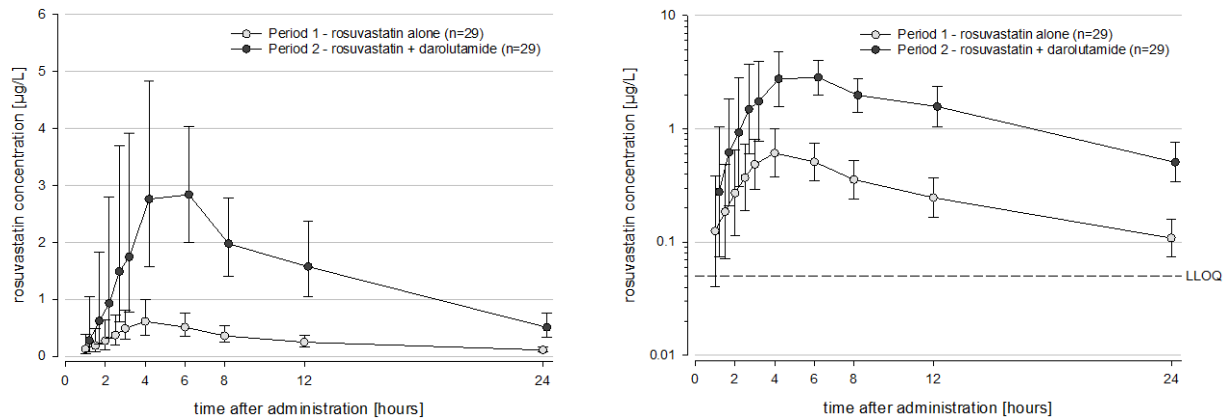
This is an open-label, phase 1, two-period drug-drug interaction study that assessed the effect of darolutamide on drug transporters using rosuvastatin as probe substrate. In this study, 30 healthy adult male (n = 15) and female (n = 15) subjects were assigned to treatment (Figure 14.). The results from this study showed that AUC₂₄ and C_{max} of rosuvastatin given in combination with darolutamide under steady state conditions and in the fed state were approximately 5-fold higher compared to those parameters of rosuvastatin given alone. (Figure 15. and Table 11).

Figure 14. Study Scheme for the assessment of darolutamide effect on rosuvastatin pharmacokinetics.



Source: Study 17723, Clinical study report, Figure 7-1, Section 7.1.1.

Figure 15. Concentration time profiles of rosuvastatin ($\mu\text{g/L}$) in plasma, geometric mean/StD, linear and semi-logarithmic scale.



Source: Summary of clinical pharmacology, Figure 2-5, Section 2.4.2.1.

Table 12. Point estimates, two-sided exploratory 90% CIs and 95% prediction intervals for the ratio “rosuvastatin + darolutamide (Period 2) / rosuvastatin alone (Period 1)” of selected PK parameters of rosuvastatin

Parameter	n	Estimated Ratio	90% Confidence Interval	95% Prediction Interval	Geom. CV (%)
AUC(0-24)	29	5.1897	[4.7577, 5.6608]	[2.9258, 9.2052]	19.6
C_{max}	29	5.0142	[4.4782, 5.6143]	[2.3789, 10.5687]	25.7
CL_R	29	0.9745	[0.8941, 1.0620]	[0.5524, 1.7189]	19.4

Source: Summary of clinical pharmacology, Table 2-18, Section 2.4.2.1.

Study 18860: Effect of darolutamide on CYP3A and P-gp substrates:

An open-label, two-period, Phase 1 study of darolutamide in healthy male subjects to determine the effect of darolutamide on the PK of the probe CYP3A4 substrate midazolam and the probe P-gp substrate dabigatran etexilate. 15 subjects were assigned to treatment. Concomitant dosing of midazolam with 600 mg twice-daily darolutamide on day 9 of twice-daily darolutamide treatment led to a decrease of approximately 29% and 22% in AUC of midazolam and 1-OH midazolam, respectively. Likewise, maximum plasma concentrations decreased by approximately 32% for both midazolam and 1-OH midazolam when compared to dosing of midazolam without darolutamide (**Table 12**).

Table 13. Point estimates and two-sided 90% CIs for the ratios “Period 2 Day 3” / “Period 1 Day 1” and “Period 2 Day 9” / “Period 1 Day 1” of main PK parameters of non-conjugated and total dabigatran, MDZ and 1-OH midazolam

Parameter	Geometric CV (%)	Ratio	Estimated Ratio	90% CI (2-sided)
Non-conjugated dabigatran				
AUC	37.51	B/A	0.7558	[0.5920; 0.9649]
		C/A	0.9108	[0.7086; 1.1706]
C _{max}	37.79	B/A	0.8684	[0.6796; 1.1097]
		C/A	0.8396	[0.6570; 1.0729]
Total dabigatran				
AUC	33.56	B/A	0.7869	[0.6259; 0.9895]
		C/A	0.8777	[0.6981; 1.1036]
C _{max}	38.59	B/A	0.8845	[0.6888; 1.1358]
		C/A	0.8272	[0.6442; 1.0621]
Midazolam				
AUC	21.28	C/A	0.7138	[0.6161; 0.8269]
C _{max}	19.12	C/A	0.6779	[0.5938; 0.7740]
1-OH midazolam				
AUC	11.01	C/A	0.7796	[0.7162; 0.8486]
C _{max}	19.32	C/A	0.6744	[0.5899; 0.7710]

Source: Summary of clinical pharmacology, Table 2-25, Section 2.4.2.3.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 14. Clinical Studies Relevant to the Clinical Review of NDA 212099

Trial ID	Design	Population	N	Treatment	Primary Objective	Region
ARAMIS	Randomized, double-blind	nmCRPC	1509	Darolutamide 600 mg BID vs. placebo	Efficacy, safety	N. America, Asia Pacific, ROWd
ARADES phase 1 portion	Open label, dose-escalation	mCRPC	24	Darolutamide 100-900 mg BID	Safety, PK	Europe, US
ARADES phase 2 portion	Open-label, randomized, uncontrolled	mCRPC	110	Darolutamide 100, 200, or 700 mg BID	Safety, efficacy	Europe, US
ARADES extension	Extension of ARADES phase 1/2	mCRPC	76	Continuation of ARADES phase 1/2	Safety, activity	Europe, US
ARAFOR	Open-label, randomized, uncontrolled	mCRPC	30	Darolutamide 600 mg BID	Safety, PK	Europe
ARASENS	Ongoing placebo-controlled	mHSPC	1303	ADT/docetaxel ± darolutamide	Efficacy	Europe, N. America, Asia Pacific

7.2. Review Strategy

The clinical and statistical reviewers reviewed the following:

1. Published literature on the epidemiology, biology, and treatment of high-risk nmCRPC.
2. Relevant meeting minutes from IND 114769
3. Transcripts of relevant ODAC meetings.
4. The ARAMIS trial study report, protocol, protocol amendments, Independent Review Committee Charter, statistical analysis plan and amendments, select case report forms, patient narratives, datasets and SAS programming algorithms.
5. The applicant's Summary of Clinical Safety and the Integrated Summary of Safety.
6. Consultation reports from the Office of Scientific Investigations.
7. The applicant's responses to FDA requests for additional information.
8. The regulatory history of other drugs approved for nmCRPC.

The efficacy of darolutamide in the proposed indication was based primarily on a randomized, double blind, placebo-controlled, multicenter, phase 3 trial study (ARAMIS) of darolutamide in patients with high-risk nmCRPC, with additional supporting data from single-arm Phase 1 and Phase 2 studies (ARADES, ARAFOR) in patients with mCRPC. Because of differences in trial design and patient populations, data from ARAMIS were not pooled with data from the single-arm trials.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. ARAMIS

Trial Design

ARAMIS was a multinational, randomized (2:1), double-blind, placebo-controlled trial evaluating darolutamide (600 mg BID orally), administered with concurrent ADT (GnRH analogue or bilateral orchiectomy) in 1509 patients with high-risk nmCRPC. Key eligibility criteria included histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features; castrate level of serum testosterone (< 50 ng/dL) on GnRH agonist or antagonist or after bilateral orchiectomy; a PSA doubling time $\leq$ 10 months and PSA $\geq$ 2 ng/mL at screening. Disease was required to be asymptomatic and not requiring medical intervention (e.g., moderate or severe urinary obstruction or hydronephrosis due to local-regional prostate cancer would be an exclusion criteria).

For each patient, the study might involve 1 to 2 variable length periods: a study treatment period (a double-blind part for darolutamide or placebo arms and an open-label darolutamide treatment phase) and a follow-up period.

The double-blind treatment was planned to be continued until the total number of events for the MFS analysis had been reached. During this part the treatment code would remain blinded.

Once the study results were available, and if they supported a positive benefit/risk assessment for darolutamide in the study by judgement of the Applicant, those patients who were on placebo were to be offered the opportunity to receive darolutamide through open-label treatment in this study.

During treatment, all patients who were not surgically castrated were to continue ADT to maintain castrate levels of testosterone. Darolutamide or placebo was continued until radiographic progression as assessed by the investigator and blinded independent central review (BICR); initiation of cytotoxic chemotherapy, androgen receptor inhibitors, or other investigational agents; withdrawal of consent, or unacceptable toxicity.

Patients who experienced a treatment-related Grade 3 or higher toxicity that could not be ameliorated with medical intervention were to interrupt treatment with blinded study drug for 1 week or until the toxicity grade improved to Grade 2 or lower, at which time blinded study drug could then be resumed at 300 mg BID. Any patient who required dose interruption for 28 consecutive days or who experienced a Grade 3 or higher treatment-related AE on 300 mg BID was to permanently discontinue study treatment.

Tumor measurements (CT or MRI of the chest, abdomen and pelvis and whole-body radionuclide bone scans) were to be performed every 16 weeks from Cycle 1 Day 1 until confirmed metastasis. Additional scans may have been done at investigator discretion if disease progression was suspected and at the end of treatment. Radiographic progression for bone disease was defined as the appearance of 1 or more metastatic lesions on bone scan. Confirmation with a second imaging modality (plain film, CT, or MRI) was required when bone lesions were found in a single region on the bone scan. The appearance of metastatic lesions in 2 or more of the 5 regions on a bone scan did not require confirmation with a second imaging modality. Radiographic progression for soft tissue disease was defined by RECIST 1.1 with the exception of asymptomatic progression in pelvic lymph nodes. Serum PSA (by central laboratory) was to be assessed on Day 1 of Cycles 1 to 6, on Day 1 every 2 cycles starting from Cycle 7 to Cycle 13, and at the end of treatment.

All radiographic and clinical information collected on study to assess the primary MFS endpoint underwent blinded independent central review (BICR). All patients required an independent evaluation of radiological images for metastases at baseline to be eligible for randomization (eligibility review by reader pool 1). The radiology charter stipulated that if the Site Radiologist and Independent Reviewer 1 agreed that the patient had no evidence of distant metastases at baseline, the patient could enter the trial. Likewise, if the Site Radiologist and Independent Reviewer 1 agreed that the patient had evidence of metastases, the patient would be considered to have an event. If the two disagreed, Independent Reviewer 2 would evaluate the scans and the patient's status would be based on Reviewers 2's agreement with the Site Radiologist or Reviewer 1. All patients also had an independent central imaging review performed during the study where all images (including baseline images) were assessed for metastasis (efficacy review by reader pool 2). Results per the efficacy review by reader pool 2 were the basis of the primary efficacy analysis.

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. Patients in whom the BICR reported metastasis during study treatment but the investigator provided an alternate explanation for the findings were permitted to continue study treatment. Conversely, at the investigator's discretion, patients could discontinue study treatment for progressive locoregional or metastatic disease not confirmed by the BICR.

Reviewer comments:

- 1. Selection of the darolutamide oral dose of 600 mg BID was based on clinical experience. In the phase 1 trial ARADES, C_{max} and AUC were dose-proportional in the dose range of 100 mg to 700 mg darolutamide BID. At 900 mg BID, C_{max} and AUC plateaued, indicating saturation of absorption. The results of the extension part of ARADES suggested that the 700 mg BID dose was as safe as 100 and 200 mg BID and led to greater PSA decline. The phase 2 ARAFOR trial showed promising clinical activity at a dose of 600 BID.*
- 2. The applicant calculated PSA doubling times for subject screening and randomization using a linear regression model of the natural logarithm of PSA and time, using at least*

three PSA values measured over the 12 months before randomization, separated by at least four weeks, where all values are >0.2 ng/mL. This was consistent with the Agency's EOP2 and SPA recommendations.

- 3. PSA values were not blinded during the trial.*
- 4. The protocol defined the date of metastasis as the first appearance of one or more lesions by bone scan, or anatomic imaging (CT, MRI, or X-ray), confirmed by a central reading. New bone scan findings required confirmation by anatomic imaging (performed up to 2 weeks prior to the bone scan or later). This was consistent with the Agency's EOP2 and SPA recommendations.*
- 5. The decision to allow enrollment of patient with asymptomatic disease in pelvic lymph nodes was consistent with the Agency's EOP2 and SPA recommendation that this is considered loco-regional rather than metastatic disease.*
- 6. No standardized monitoring for and management of bone density loss was required for patients on the trial. It is unknown whether adherence to guidelines on bone density loss and fracture risk may have mitigated the increased incidence of fractures seen on the darolutamide arm.*
- 7. Per the Applicant, the open-label part of the study started officially on October 30, 2018. This date is after the study data cutoff date (03 September 2018), so the study efficacy results presented here are less likely to be affected by the open-label darolutamide use.*

Study Endpoints

The primary objective was to demonstrate the superiority of darolutamide over placebo in MFS per BICR in this patient population. Key secondary objectives were to demonstrate superiority in terms of OS, time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, and time to first symptomatic skeletal event (SSE).

MFS was defined as the time from randomization to confirmed evidence of metastasis or death from any cause within 32(+1) weeks after the last evaluable scan, whichever occurred first. OS was defined as the time from randomization to death due to any cause. Time to pain progression was defined as time from randomization to pain progression, where progression was defined as an increase of 2 or more points from baseline in question 3 of the Brief Pain Inventory-Short Form questionnaire (BPI-SF) related to the worst pain in the last 24 hours taken as a 7-day average for post-baseline scores, or initiation of short- or long-acting opioids for pain, whichever came first. A minimum of 4 completed daily reports out of the 7 days required per protocol were needed at each time point to consider the assessment valid. The time to initiation of first cytotoxic chemotherapy was defined as time from randomization to the start of the first cytotoxic chemotherapy cycle. Time to first symptomatic skeletal event was defined as the time from randomization to the occurrence of the first external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention. The censoring rules for each of these endpoints are shown in Table 15.

Table 15. Censoring Rules for Primary and Secondary Efficacy Analyses

NDA 212099 Multi-disciplinary Review and Evaluation
Darolutamide/NUBEQA

Situation	End Date on or prior to cut-off date	Censored
Metastasis-Free-Survival		
Documented metastasis	Date of documented metastasis	No
Documented metastasis at baseline	Date of randomization	No
Documented metastasis after two or more consecutively missed tumor assessments, i.e. metastasis later than last evaluable scan + (32+1) weeks	Date of last tumor assessment that the patient was known to be metastasis-free	Yes
Death before documented metastasis and not later than last evaluable scan + (32+1) weeks	Date of death	No
Death before documented metastasis and after two or more consecutively missed tumor assessments, i.e. death later than last evaluable scan + (32+1) weeks	Date of last tumor assessment that the patient was known to be metastasis-free	Yes
Discontinued the study before any post-baseline tumor assessments	Date of randomization	Yes
Discontinued the study before any postbaseline tumor assessments and died within (32+1) weeks after randomization	Date of death	No
Discontinued the study before any postbaseline tumor assessments and died later than (32+1) weeks after randomization	Date of randomization	Yes
Discontinued the study, but no documented metastasis	Date of last tumor assessment before discontinuation	Yes
Prohibited new anticancer treatment started prior to documented metastasis	Date of last tumor assessment before start of prohibited new treatment	Yes
Patients still on treatment without documented metastasis as of data cut-off	Date of last tumor assessment	Yes
Overall Survival		
Death during study	Date of death	No
Patient still alive at data cutoff	Date of data cut-off	Yes
Patient lost to follow-up before data cut-off	Date last known to be alive	Yes
Patient lost to follow-up without contact after randomization	Date of randomization	Yes
Time to Pain Progression		
Recorded pain progression during the study	Date of the first assessment that qualified as pain progression	No
No baseline BPI-SF assessments	Date of randomization	Yes
Discontinued the study before the post-baseline BPI-SF assessments	Date of randomization	Yes
Death during the study before pain progression	Date of last visit the patient was known not to have progressed or randomization date whatever comes later	Yes
Patient has no recorded pain progression at data cut-off	Date of last visit the patient was known not to have progressed or randomization date whatever comes later	Yes
Patient lost to follow-up before data cut-off	Date of last visit the patient was known not to have progressed or randomization date whichever comes later	Yes
Patient taking opioids for any reason within 4 weeks prior to randomization	Date of randomization	Yes

Situation	End Date on or prior to cut-off date	Censored
Time to Initiation of First Cytotoxic Chemotherapy		
Recorded cytotoxic chemotherapy during the study	Date of the first assessment that qualified as cytotoxic chemotherapy	No
Death during the study before cytotoxic chemotherapy	Date of last visit at which cytotoxic chemotherapy question was collected or randomization date whatever comes later	Yes
Patient has no recorded cytotoxic chemotherapy at data cut-off	Date of last visit at which cytotoxic chemotherapy question was collected or randomization date whatever comes later	Yes
Patient lost to follow-up before data cut-off	Date of last visit at which cytotoxic chemotherapy question was collected or randomization date whatever comes later	Yes
Time to First Symptomatic Skeletal Event		
Recorded SSE event during the study	Date of the first assessment that qualified as SSE	No
Patient has no recorded SSE event at data cut-off	Date of last SSE assessment before data cut-off	Yes
Patient lost to follow-up before data cut-off	Date of last SSE assessment or randomization date, whichever comes later	Yes

Source: SAP v4.2.2 Tables 2, 9, 10, 11, and 12

Patient reported outcomes (PROs) were assessed using four instruments: European Quality of Life 5-Domain Scale 3 Level (EQ-5D-3L), Functional Assessment of Cancer Therapy – Prostate (FACT-P), Brief pain inventory – short form (BPI-SF), and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate cancer module (EORTC-QLQ-PR25). See Section 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability and Section 18.5 Additional Clinical Outcome Assessment Analyses for a detailed review of these PROs.

Reviewer’s comment:

- 1. The protocol defined disease progression in non-osseous tissue according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, excluding progression in pelvic lymph nodes (i.e., below the aortic bifurcation). The decision to not consider progression of asymptomatic disease in pelvic lymph nodes as events in the primary efficacy endpoint of MFS was consistent with the Agency’s EOP2 and SPA recommendation that this is more consistent with loco-regional progression and is better captured in a secondary or exploratory endpoint of progression-free survival.*
- 2. This statistical analysis plan led to several potential scenarios where patients with disease progression could stay on treatment. These include if localized-only progression of disease was found by BICR, if metastatic disease was determined to be present by investigator but not confirmed by BICR, and if new bone metastases were suspected by BICR review of a bone scan but confirmatory anatomic imaging was negative.*
- 3. Patients were to be unblinded in the active follow up phase once the MFS analysis was completed. Study sites were informed of the Bayer/Steering committee decision to move to the open-label phase on 26 October 2018. On 30 October 2018, each site received an email*

including the treatment assignment of patients enrolled at that site followed by a telephone call. Patients on the placebo arm were allowed to receive darolutamide during the open-label phase. This cross-over could confound the final analyses of overall survival and other secondary endpoints but not the analyses included in this review based on a data cutoff date of 03 September 2018.

Statistical Analysis Plan

Sample Size Calculation

The study was designed to target 385 MFS events which would provide approximately 91% power to detect a statistically significant difference in MFS at a two-sided significance level of 0.05. The assumed hazard ratio was 0.65, but accounting for 5% of patients with baseline metastases, it could be diluted to 0.71. Accounting for 40 months accrual time and a 40% dropout rate, it was planned that the study would require approximately 1500 patients (1000 darolutamide, 500 placebo) randomized in a 2:1 ratio to achieve the required number of MFS events. The sample size calculation was determined using a simulation-based algorithm.

Reviewer's Comments: The applicant initially targeted a treatment effect size of MFS HR=0.75. Later, based on data from the PROSPER and SPARTAN trials, they decided that this was too conservative and adjusted the sample size accordingly (see description of protocol Amendment #3 below).

Under efficacy review by reader pool 2, some patients were classified retrospectively as having metastases at baseline. This occurred even though all patients had to have an independent evaluation of radiological images for no baseline metastases to be eligible for randomization. At the November 2017 Type A meeting, FDA advised the applicant that these patients should be counted as having MFS events on the date of randomization. The applicant adjusted the number of events to account for the non-informative baseline metastases events.

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 grouped by 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

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 (PSA doubling time and use of bone sparing agents). The hazard ratio with a two-sided 95% confidence interval was derived from a stratified Cox proportional hazards model with the same two stratification factors used in the stratified log-rank test. Censoring rules for the primary analysis of MFS are summarized in Table 15 above.

The secondary and tertiary time-to-event endpoints, including but not limited to, overall survival (OS), time to pain progression, time to initiation of first cytotoxic chemotherapy, time to first symptomatic skeletal event, time to PSA progression, and progression-free survival (PFS) were all analyzed using methods similar to the primary MFS analysis.

Secondary endpoints were to be tested in the following hierarchical order only if the primary endpoint MFS was significant:

1. Overall survival (OS)
2. Time to pain progression (TTPP)
3. Time to initiation of first cytotoxic chemotherapy for prostate cancer (CYTOC)
4. Time to first symptomatic skeletal event (SSE)

There was no interim analysis for the primary endpoint MFS. The analyses of secondary endpoints at the time of the primary MFS analysis are considered interim analyses with final analyses conducted at the end of the study. A rho-family spending function with parameter $\rho=10$ was used to determine stopping boundaries for efficacy at the interim and final analyses. Based on an assumed 140 OS events at interim and 240 OS events at final analysis, the alpha boundary was set at 0.0005 at interim and 0.0495 at final, but boundaries will be recalculated using EAST based on the number of events actually observed.

The secondary endpoints will be tested in the pre-specified sequence shown above. If at any point a secondary endpoint is not significant at the interim analysis, it will then be tested at final analysis followed by the remaining endpoints in the testing sequence. This testing strategy is described in Table 16 through Table 18 below.

Table 16: Interim Analysis for Significance

	140 OS events
	Interim analysis
OS interim dataset	test at z1
	if positive ↓
TTPP interim dataset	test at z1
	if positive ↓
CYTOC interim dataset	test at z1
	if positive ↓
SSE interim dataset	test at z1

Source: SAP v4.2.2 Table 6

Table 17: Final Analysis for Significance

Assuming OS interim analysis was not positive:

		240 OS events
		Final analysis
OS final dataset	OS interim not positive →	test at z2
		if positive ↓
TTPP interim dataset*		test at z2
		if positive ↓
CYTOC final dataset		test at z2
		if positive ↓
SSE final dataset		test at z2

*TTPP is a more subjective endpoint, therefore an analysis of TTPP which includes a large portion of data collected under open-label conditions is not considered meaningful. In case TTPP would be tested in the final analysis, the interim dataset would be used also for this test procedure.

Source: SAP v4.2.2 Table 7

Table 18: Final Analysis for Significance, Scenario 2

Assuming OS interim analysis was positive and TTPP interim analysis was not positive:

		240 OS events
		final analysis
OS final dataset	OS interim was positive	no test
TTPP interim dataset*	TTPP interim not positive 	test at z2
		if positive 
CYTOC final dataset		test at z2
		if positive 
SSE final dataset		test at z2

*TTPP is a more subjective endpoint, therefore an analysis of TTPP which includes a large portion of data collected under open-label conditions is not considered meaningful. In case TTPP would be tested in the final analysis, the interim dataset would be used also for this test procedure.

Source: SAP v4.2.2 Table 8

Reviewer's comments:

- 1. The hierarchical testing procedure controlled the overall 2-sided type I error rate of the secondary endpoints at 5%.*
- 2. The rho spending function is more conservative at interim and less conservative at final analysis compared to the O'Brien-Fleming spending function. This approach was considered acceptable.*
- 3. With the exception of overall survival, the other secondary endpoints are subject to patient and investigator bias. Many events captured for the secondary endpoints of time to pain progression, time to cytotoxic chemotherapy, and time to SSE were likely to occur after the MFS event in the follow-up stage, which may limit interpretability of the results.*
- 4. The actual database cut-off date for the primary analysis (Sept. 3, 2018) was when 437 MFS events were reached, not when 385 MFS events were reached as planned. According to the applicant, this was due to a delay in obtaining approvals for protocol amendment 3. The increased number of events may have caused the MFS analysis to be overpowered. A sensitivity analysis was conducted based on a data cutoff when approximately 385 events had occurred, and results were consistent with the primary analysis. See the Sensitivity Analyses of MFS section for more details.*

Protocol Amendments

The original protocol, Version 1.0, was dated 10 MAR 2014.

Protocol amendment 1, protocol Version 2.0, dated 24 November 2014, made the following key changes:

- Clarified the definition of progression in soft tissue to exclude progression in lymph nodes in the pelvis below the aortic bifurcation.
- Amended the eligibility criterion related to PSA values to allow patients with 3 rising PSA values at least 1 week apart during ADT to enroll. The observation period of PSA values that could be used in the calculation of PSADT was extended from 6 to 12 months.
- Extended the collection period of pain data from the end of the follow-up period to the time of documented pain progression.
- Added “suspected disease progression” as a reason for an unscheduled visit, and chest, abdomen and pelvic CT/MRI or x-ray and bone scan were added as options for assessments that could be performed at the unscheduled visit.
- Stipulated that another systemic antineoplastic therapy could be initiated no sooner than 7 days after the last dose of study treatment, and the end-of-study treatment visit was to take place 28 days after the last dose (instead of 7 days) for patients who discontinued study treatment and started subsequent antineoplastic therapy.
- Limited the exclusion criterion for osteoclast-targeted therapy to patients using this therapy for prevention of SREs (not for osteoporosis at a dose and schedule indicated for osteoporosis).

Protocol amendment 2 (protocol Version 3.0), dated 19 July 2016, reflected the sponsorship change from Orion to Bayer. In addition, certain inclusion and exclusion criteria were clarified, and requirements for monitoring drug-drug interactions were revised.

Protocol amendment 3 (protocol Version 4.0), dated 26 February 2018, made the following key changes:

- Increased the assumed treatment effect size from a hazard ratio of 0.75 (requiring 572 MFS events) to 0.65 (requiring approximately 385 MFS events).
- Added an option for patients to receive open-label darolutamide at the time of study treatment code unblinding should the study results support a positive benefit/risk assessment for darolutamide.

Reviewer comment: The key changes made by the three protocol amendments above were consistent with the Agency’s recommendations and did not bias or confound interpretation of the results of the trial.

SAP Amendments

The original SAP version 1.0 dated 14 May 2015 was based on clinical study protocol amendment 1.

SAP version 2.0, dated 15 March 2017, made the following modifications to SAP version 1.0:

- Changes were made to the sample size and justification to reflect the higher estimation

of the treatment effect (HR of 0.75 was changed to 0.70) and statistical considerations were condensed

- A safety analysis set (SAF) was described
- Censoring rules were updated for secondary efficacy variables and the sensitivity analysis of MFS
- A description was added for placebo patients being allowed to receive open-label darolutamide treatment
- “Time to ECOG PS deterioration” was added as an exploratory endpoint
- Clarified that there was no planned formal interim analysis for the primary endpoint

SAP version 2.1, dated 22 June 2017 updated the planned number of randomized patients from approximately 1200 to approximately 1300.

SAP version 3.0, dated 12 March 2018, made the following key changes:

- Changes were made to the sample size and justification due to identification of patients with metastases at baseline, a secondary analysis of MFS was added with censoring rules adjusted accordingly, and several sensitivity analyses of MFS were added
- The hierarchical order of the analysis of secondary endpoints was updated to be: OS, time to pain progression, time to first symptomatic skeletal event, time to cytotoxic chemotherapy. The second sequential test of secondary endpoints was modified to occur when approximately 240 OS events have been observed.
- The per protocol analysis set (PPS) was removed and the intent-to-treat analysis set (ITT) was named the full analysis set (FAS)

SAP version 4.0, dated 10 August 2018, made the following key changes:

- MFS and PFS analyses were updated for handling of patients with baseline metastasis
- The hierarchy of secondary analyses was updated to: OS, time to pain progression, time to cytotoxic chemotherapy, time to first symptomatic skeletal event
- Time to first opioid use for cancer pain was added as an additional endpoint
- In the section for patient disposition, the number of patients who discontinued study treatment due to increased PSA without documented metastasis was added
- Additional laboratory parameters to be analyzed in baseline characteristics were included
- Flags were added related to the independent central image reading process with a table showing all available flags
- Subgroups of interest were modified for MFS and OS, safety subgroups were updated
- Analysis of special topics TEAEs was added

SAP version 4.1, dated 13 September 2018, mainly corrected the definition of TEAE.

SAP version 4.2, dated 20 September 2018, mainly added details related to submissions in and out of the US for the analysis of MFS.

Additionally, post-hoc analyses were specified in 3 SAP supplements:

- SAP supplement 1, version 1.0, dated 25 October 2018 described analyses of TEAEs based on grouped terms and the risk difference and risk ratio for special topics defined in the main SAP
- SAP supplement 2, version 1.0, dated 5 November 2018 described sensitivity analyses to time to pain progression, details of subsequent antineoplastic therapy and/or cytotoxic chemotherapy for patients who discontinued study treatment, and descriptive statistics for follow-up time
- SAP supplement 2, version 1.1, dated 26 November 2018, described analyses related to the location of baseline metastasis and prevalence of the most common treatment-emergent AEs for special topics
- SAP supplement 3, version 1.0, dated 10 January 2019, described the following analyses: summary of patients reported with selected concomitant medications that are certain substrates, summary of patients from European countries, reasons for discontinuation of study drug treatment due to “judgment of investigator” or “personal reason”, MFS sensitivity analysis excluding patients with the primary reason for permanent discontinuation of study treatment of “judgment of investigator” or “personal reason” and without MFS events, waterfall plots for individual percent change in PSA from baseline at week 16, a summary of patients reported with concomitant statins which are BCRP substrates, and a summary of TEAEs for the subgroup of patients with or without present medical history in the SOC “Cardiac history”

8.1.2. Study Results

Compliance with Good Clinical Practices

The clinical protocol states that the trial was conducted in compliance with International Conference on Harmonization Good Clinical Practices.

Financial Disclosure

Please refer to Appendix 12.2 for details.

Data Quality and Integrity

The electronic submission for this supplemental NDA, including Protocols, Statistical Analysis Plan (SAP), Clinical Study Reports (CSRs) and SAS transport datasets, is located in the network path: \\cdsesub1\evsprod\nda212099\002.

The overall data quality and integrity were acceptable to the reviewers. The submitted datasets were generally consistent and variables were 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.

Patient Disposition

ARAMIS was conducted at 409 centers in 36 countries with 139 patients (9%) accrued from the U.S. The trial was initiated on September 12, 2014, and the clinical cutoff date was September 3, 2018.

A total of 1509 patients were randomized in a 2:1 ratio to study treatment with darolutamide (n = 955) or placebo (n = 554). Of the randomized patients, 99.9% of the patients in the darolutamide arm and all patients in the placebo arm received at least one dose of study drug. At the data cutoff, 64.4% of the patients in the darolutamide arm and 36.1% of the patients in the placebo arm continued study treatment.

The most common reason for treatment discontinuation both arms was centrally confirmed metastasis (33.0% of those who discontinued in the darolutamide arm, and 36.4% of those who discontinued in the placebo arm). Similar proportions of patients in each treatment arm discontinued because of adverse events.

Table 19. ARAMIS Patient Disposition

	Darolutamide	Placebo
Randomized	955 (100%)	554 (100%)
Study drug never administered	1/955 (0.1%)	0/554
Started treatment	954/955 (99.9%)	554/554 (100%)
Treatment ongoing	615/955 (64.4%)	200/554 (36.1%)
Discontinued treatment	339/955 (35.5%)	354/554 (63.9%)
Adverse event ¹	86 (9.0%)	47 (8.5%)
Confirmed metastasis	112 (11.7%)	129 (23.3%)
Judgment of the investigator	54 (5.7%)	91 (16.4%)
Other	6 (0.6%)	2 (0.4%)
Personal reason	68 (7.1%)	78 (14.1%)
Protocol deviation	13 (1.4%)	7 (1.3%)
Entered follow-up	291/955 (30.5%)	332/554 (59.9%)
Follow-up ongoing	117/291 (40.2%)	169/332 (50.9%)
Discontinued follow-up	174/291 (59.8%)	163/332 (49.1%)

¹ four patients died on study, and their reasons for discontinuation were listed as an adverse event.

Source: dataset ADDS; variables, EXNYOVL, DSCAT, DSDECOD, TRTP

We note the discrepancy between the number of metastasis events in the primary MFS analysis (darolutamide 18.8% and placebo 32.5%) and patients who withdrew for centrally confirmed metastasis darolutamide 11.7% and placebo 23.3%). Table 20 summarizes potential reasons for this discrepancy.

Table 20. Reasons for Discrepancy between MFS Events and Discontinuations due to Metastasis

	Darolutamide (N = 955)	Placebo (N = 554)
Discontinued for reasons other than confirmed metastasis and then later (at least one week) developed metastasis	24 (2.5%)	10 (1.8%)
Developed a metastasis but stayed on treatment (for at least one week) and later discontinued for other reasons	35 (3.7%)	50 (9.0%)
Censored for other reasons in the MFS analysis before treatment discontinuation due to metastasis	13 (1.4%)	16 (2.9%)

Source: ADTTE where PARAMCD = "MFS", ADDS where DSSCAT = "STUDY TREATMENT DISCONTINUATION", ADSL

Because more patients in the placebo arm than the darolutamide arm discontinued the study treatment because of "judgement of the investigator" or "personal reason", the review team examined these two categories more closely, especially because patients and investigators were not blinded to PSA results.

Table 21. ARAMIS Patient Withdrawal for Investigator Judgement or Personal Reason

		Darolutamide N = 955	Placebo N = 554
Judgement of the Investigator	All	54 (5.7%)	91 (16.4%)
	Disease progression- investigator assessed	37 (3.9%)	60 (10.8%)
	Investigator decision	6 (0.6%)	6 (1.1%)
	Other	2 (0.2%)	0
	Cannot attend study procedures	1 (0.1%)	0
	Patient safety	1 (0.1%)	0
	PSA increase	6 (0.6%)	16 (2.9%)
	Patient decision	0	1 (0.2%)
	Protocol non-compliance	1 (0.1%)	2 (0.4%)
Start of new therapy	2 (0.2%)	6 (1.1%)	
Personal Reason	All	68 (7.1%)	78 (14.1%)
	Adverse event	3 (0.3%)	1 (0.2%)
	Consent withdrawn	52 (5.4%)	49 (8.8%)
	Rising PSA	2 (0.2%)	6 (1.1%)
	Start of new therapy	1 (0.1%)	8 (1.4%)
	Treatment of second cancer	1 (0.1%)	0
	Disease progression	2 (0.2%)	0
	Lost to follow up	1 (0.1%)	0
	Other	0	4 (0.7%)
	Cannot attend study procedures	0	2 (0.4%)
	Patient relocated	0	1 (0.2%)
	Patient decision	11 (1.2%)	24 (4.3%)
	Rising PSA	0	4 (0.7%)
	Start of new therapy	5 (0.5%)	4 (0.7%)
	Disease progression	2 (0.2%)	4 (0.7%)
Start of new therapy	1 (0.1%)	0	

Source: CSR Table 14.1

Reviewer's comments:

1. *PSA results were not blinded, and more patients in the placebo arm than the darolutamide arm discontinued the trial because of rising PSA.*
2. *Patients listed as discontinuing the trial because of adverse events include 21 patients who died on-treatment (14 on the darolutamide arm and 7 on the placebo arm), and the treatment discontinuation reason was AE.*

The CRF did not provide “rising PSA” as a selection for the primary reason for treatment discontinuation, so the data collected cannot be queried directly for this. As a surrogate, the sponsor compared between treatment arms the percent rise in PSA from nadir in patients who discontinued study drug without metastasis.

Table 22. Increase in PSA from Nadir in Patients Discontinuing Study Drug without Metastasis

	Darolutamide N = 955	Placebo N = 554
Discontinued study drug without metastasis	188/955 (19.7%)	175/554 (31.6%)
Percent Increase in PSA from nadir	88/188 (46.8%)	136/175 (77.7%)
>0 to <25%	13/88 (14.8%)	5/136 (3.7%)
≥25 to <50%	7/88 (8.0%)	13/136 (9.6%)
≥50 to 100%	8/88 (9.1%)	30/136 (22.1%)
≥100 to 150%	11/88 (12.5%)	16/136 (11.8%)
≥150%	49/88 (55.7%)	72/136 (52.9%)
Actual increase in PSA from nadir (ng/mL)	88/188 (46.8%)	136/175 (77.7%)
>0 to <3	35/88 (39.8%)	17/136 (12.5%)
≥3 to <12	19/88 (21.6%)	43/136 (31.6%)
≥12 to <37	17/88 (19.3%)	36/136 (26.5%)
≥37	17/88 (19.3%)	40/136 (29.4%)

Source: CSR Table 8-3

Reviewer Comment:

1. *A higher percentage of patients in the placebo arm compared to the darolutamide arm discontinued study drug without metastasis (31.6% vs. 19.7%), and this difference appears to be driven by patients who had an increase in PSA from nadir (77.7% vs. 46.8%).*
2. *In patients who discontinued study drug without metastases who had a rise in PSA, patients on the darolutamide arm had smaller increases in PSA from nadir compared to the placebo arm (e.g. less than 12 unit increase in PSA in approximately 60% on the darolutamide arm vs 44% on the placebo arm, respectively).*
3. *Overall, more patients discontinued study drug without BIRC-confirmed metastasis and with concurrent rise in PSA from nadir on the placebo arm than on the darolutamide arm (24.5% vs. 9.2% overall). Sensitivity analyses were conducted to address this concern, and results were consistent with the primary analysis. See the Sensitivity Analyses for MFS section for more details.*

Protocol Violations/Deviations

Protocol deviations were classified as major or important. Major protocol deviations affected analysis set eligibility or treatment arm assignment. Important deviations did not exclude a patient from an analysis population.

There was one major protocol deviation: one patient randomized to darolutamide never received treatment and was therefore excluded from the safety analysis population. Protocol deviations were distributed similarly between treatment arms.

Table 23. AMARIS Protocol Violations

	Darolutamide N=955 n (%)	Placebo N=554 n (%)
Total	651/955 (68.2%)	403/955 (72.7%)
Major	1 (0.1%)	0
Treatment deviations	1 (0.1%)	0
Important	650/955 (68.1%)	403/955 (72.7%)
Inclusion/exclusion criteria not met	24/650 (3.7%)	10/403 (2.5%)
Randomization errors	47/650 (7.2%)	36/403 (8.9%)
Treatment deviations	20/650 (3.1%)	21/403 (5.2%)
Time schedule deviations	1/650 (0.2%)	1/403 (0.2%)
Procedure deviations	567/650 (87.2%)	356/403 (88.3%)
Prohibited concomitant treatment	17/650 (2.6%)	25/403 (6.2%)
Failure to continue GnRH	18/650 (2.8%)	9/403 (2.2%)
Incorrect/delayed ICF	169/650 (26.0%)	91/403 (22.6%)
Blind broken (potential or actual)	2/650 (0.3%)	3/403 (0.7%)
GCP breach	25/650 (3.8%)	15/403 (3.7%)
Drug storage, handling, return process	3/650 (0.5%)	4/403 (1.0%)
IRB/IEC requirement non-compliance	1/650 (0.2%)	0/403 (0%)
Incorrect/delayed ancillary ICF	32/650 (4.9%)	21/403 (5.2%)

GCP = Good Clinical Practice; GnRH = Gonadotropin releasing hormone; ICF = Informed consent form; IRB/IEC = independent review board / independent ethics committee

Source: dataset ADDV; variables USUBJID, DVCAT, DVDECOD, TRT01A

Reviewer's comment: Although a high percentage of patients on both arms had protocol deviations related to procedure deviations, most of these deviations likely did not affect overall trial integrity. Prohibited concomitant medications appeared to have been used slightly more frequently on the placebo arm, however overall frequency of these events was low and likely did not affect overall trial results.

Table of Demographic Characteristics

The median age of patients in ARAMIS was 74.0 years in both treatment arms, and 87% of patients were age 65 or older. By race, most patients were White (79%) followed by Asian (13%) and Black (4%). Twelve percent of randomized patients were from North America, 12% from Asia Pacific and 76% of patients from the rest of the world.

Table 24. ARAMIS Population Demographics

	Darolutamide N = 955	Placebo N = 554
Age (years)		
Mean ± SD	73.9 ± 7.8	73.2 ± 8.2
Median	74.0	74.0
Range	48-95	50-92
Race		
White	760 (79.6%)	434 (78.3%)
Asian	122 (12.8%)	71 (12.8%)
Black	28 (2.9%)	24 (4.3%)
Missing	36 (3.8%)	19 (3.4%)
Other	9 (0.9%)	6 (1.1%)
Geographic region		
North America	108 (11.3%)	76 (13.7%)
Asia Pacific	119 (12.5%)	67 (12.1%)
Rest of World	728 (76.2%)	411 (74.2%)

Source: dataset ADSL; variables USUBJID TRT01P, AGE, RACE, CNTYGR1

Reviewer's comments:

1. Only 3% of patients in this international trial were black, making the study population not fully representative of US patients with nmCRPC.
2. Overall, there were no important imbalances in the demographics of the study population.
3. We note that the median age of 74 years was identical to that of SPARTAN and PROSPER. There were differences in geographical regions of enrolment that may have slightly impacted factors such as treatment history. See Table 28. ARAMIS Population Prior Prostate Cancer Treatment for further discussion.

Table 25. ARAMIS Population Baseline Performance Status and Organ Function

	Darolutamide N = 955	Placebo N = 554
Renal function		
GFR ≥ 90 mL/min	412 (43.1%)	230 (41.5%)
60 ≥ GFR < 90 mL/min	423 (44.3%)	248 (44.8%)
30 ≥ GFR < 60 mL/min	119 (12.5%)	76 (13.7%)
15 ≥ GFR < 30mL/min	1 (0.1%)	0
Hepatic function		
Bili and AST ULN	864 (90.5%)	509 (91.9%)
Bili > ULN to 1.5 x ULN or bili ULN and AST > ULN	89 (9.3%)	43 (7.8%)
Bili > 1.5 to 3 x ULN, any AST	2 (0.2%)	1 (0.2%)
Missing	0	1 (0.2%)
ECOG performance status		
0	650 (68.1%)	391 (70.6%)
1	305 (31.9%)	163 (29.4%)

Source: dataset ADSL; variables EGFR, HEPIM, BASEECOG

Randomization was stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no). The median PSADT was 4.4 months in the darolutamide arm and 4.7 months in the placebo arm, and the use of osteoclast targeted therapy was reported for 3.8% and 5.1% of patients at randomization in darolutamide and placebo arms, respectively. ECOG performance status at baseline was 0 in most patients in both treatment arms. Most patients in both treatment arms had a Gleason score of ≥ 7 . The most frequent tumor stages in both arms were in the T3 group (43.5% in the darolutamide arm vs. 39.0% in the placebo arm). Ninety percent of patients had negative regional lymph nodes by central imaging review.

Table 26. ARAMIS Population Baseline Disease Characteristics

	Darolutamide N = 955	Placebo N = 554
PSA (ng/mL)		
Mean $\pm$ SD	18.7 $\pm$ 37.2	19.8 $\pm$ 45.2
Median	9.0	9.7
Range	0.3 – 858.3	1.5 – 885.2
PSA doubling time (months)^a		
Mean $\pm$ SD	4.8 $\pm$ 2.4	4.9 $\pm$ 2.8
Median	4.4	4.7
Range	0.7 – 11.0	0.7 – 13.2
Gleason score		
< 7	217 (22.7%)	142 (25.6%)
≥ 7	711 (74.5%)	395 (71.3%)
Missing	27 (2.8%)	17 (3.1%)
Tumor stage		
T1 Neither palpable nor visible by imaging	19 (2.0%)	13 (2.3%)
T2 Confined within prostate	110 (11.5%)	58 (10.5%)
T3 Extends through the prostate capsule	172 (18.0%)	87 (15.7%)
T4 Fixed or invades adjacent structures other than seminal vesicles	42 (4.4%)	26 (4.7%)
TX Cannot be assessed	46 (4.8%)	35 (6.3%)
Missing	26 (2.7%)	15 (2.7%)
Positive regional lymph nodes by central imaging review		
No	855 (89.5%)	488 (88.1%)
Yes	100 (10.5%)	66 (11.9%)
Time since becoming castration-resistant (months)		
N	954	553
Mean $\pm$ SD	11.7 $\pm$ 19.0	12.8 $\pm$ 22.8
Median	5.5	5.9
Range	0.0 – 170.4	0.1 – 233.0
Time since initial diagnosis		
N	950	548
Mean $\pm$ SD	94.8 $\pm$ 55.3	94.9 $\pm$ 59.4
Median	86.2	84.2
Range	2.6 – 337.5	0.5 – 344.7

^a from case reports form, not IVRS

Source: 1. datasets AD5L; variables UPSADMN; GLEASON, PTCLAS, TICARN, TIDFDN
2. dataset ADTR; variables TRTESTCD, TRACPTFL, VISNUM, USUBJID

Reviewer's comment: The trial arms appeared well balanced with respect to baseline disease characteristics. We note the 11% of patients with positive regional lymph nodes at baseline, which although not biopsy-proven, would appear to indicate patients with higher risk disease. This is similar to, for example, SPARTAN in which 15% of patients had enlarged pelvic lymph nodes at baseline. A sensitivity analysis was conducted to control for the presence of enlarged pelvic lymph nodes at baseline; see Table 50. ARAMIS MFS in Disease Characteristic Subgroups.

Concordance and discordance between the stratification values collected in the IVRS compared to the CRF are shown below. Concordance was high between the IVRS and CRF values across both arms. The primary analysis was conducted using stratification with values collected by IVRS to follow the intent-to-treat principle. Sensitivity analyses were conducted using stratification with values collected by CRF.

Table 27. Concordance between IVRS and CRF Stratification Factor Values

	Darolutamide N=955		Placebo N=554	
	IVRS			
Baseline value of PSADT (CRF)	≤6 months	>6 months	≤6 months	>6 months
≤6 months	653 (68.4)	16 (1.7)	360 (65.0)	11 (2.0)
>6 months	14 (1.5)	272 (28.5)	11 (2.0)	172 (31.0)
Baseline bone-targeted therapy (CRF)	No	Yes	No	Yes
No	912 (95.5)	7 (0.7)	516 (93.1)	10 (1.8)
Yes	12 (1.3)	24 (2.5)	6 (1.1)	22 (4.0)

Table 28. ARAMIS Population Prior Prostate Cancer Treatment

	Darolutamide N = 955	Placebo N = 554
Prior procedures as primary therapy	954 (99.9%)	554 (100.0%)
Active surveillance	12 (1.3%)	7 (1.3%)
Chemical castration	403 (42.2%)	252 (45.5%)
Orchiectomy	91 (9.5%)	50 (9.0%)
Other, specify	32 (3.4%)	22 (4.0%)
Prostatectomy	239 (25.0%)	134 (24.2%)
Radiotherapy	177 (18.5%)	89 (16.1%)
Number of prior hormonal therapies		
1	177 (18.5%)	103 (18.6%)
2	727 (76.1%)	420 (75.8%)
Not applicable (because of surgical castration)	51 (5.3%)	31 (5.6%)
Baseline osteoclast-targeted therapy		
Yes	919 (96.2%)	526 (94.9%)
No	36 (3.8%)	28 (5.1%)

Source: datasets ADSL, ADCM; variables TRTP, PHTS, OSTTATPY, CMSCAT, CMTRT

Reviewer's comment: A total of 639 (42%) patients received prior definitive local therapy (prostatectomy or radiation). Two other trials in patients with nmCRPC, the SPARTAN trial comparing apalutamide to placebo and PROSPER trail comparing enzalutamide to placebo, reported prior prostatectomy or radiotherapy in 77% and 54% of patients respectively; the 42%

reported with ARAMIS is slightly lower and may reflect differing practice pattern per geographic makeup of trial participants, specifically the fact that ARAMIS had the lowest percentage overall of patients enrolled in North America and the highest overall percentage of patients enrolled in the rest of the world (Table 29).

Table 29. Cross-Trial Prior Definitive Therapy by Geographic Region

	SPARTAN (Apalutamide) (N = 1207)	PROSPER (Enzalutamide) N = 1401	ARAMIS (Darolutamide) N = 1509
Age (median)	74 years	74 years	74 years
Prior definitive surgery or radiotherapy	77%	54%	42.3%
Geographic region			
N America	34%	15%	12%
Europe	50%	49%	38%
Rest of World	16%	37%	50%

A sensitivity analysis was conducted to control for prior history of definitive local therapy at baseline; see Table 50. ARAMIS MFS in Disease Characteristic Subgroups.

The most common prior medications for prostate cancer were the gonadotropin releasing-hormone agonists bicalutamide, leuprorelin, goserelin, and triptorelin, and the antiandrogens flutamide, and cyproterone.

Table 30. Prior Prostate Cancer Drug Therapy (>2 patients in either arm)

	Darolutamide N = 955	Placebo N = 554
Any	916 (95.9%)	530 (95.7%)
Bicalutamide	642 (67.2%)	358 (64.6%)
Leuprorelin, Leuprorelin acetate	483 (50.6%)	295 (53.2%)
Goserelin, Goserelin acetate	309 (32.4%)	174 (31.4%)
Triptorelin, Triptorelin acetate, Triptorelin embonate	286 (29.9%)	155 (28.0%)
Flutamide	121 (12.7%)	79 (14.3%)
Cyproterone, Cyproterone acetate	110 (11.5%)	60 (10.8%)
Degarelix, Degarelix acetate	61 (6.4%)	34 (6.1%)
Buserelin, Buserelin acetate	40 (4.2%)	29 (5.2%)
Diethylstilbestrol	11 (1.2%)	5 (0.9%)
Finasteride	10 (1.0%)	5 (0.9%)
Chlormadinone acetate	6 (0.6%)	5 (0.9%)
Histrelin, Histrelin acetate	6 (0.6%)	6 (1.1%)
Dexamethasone	5 (0.5%)	3 (0.5%)
Dutasteride	4 (0.4%)	2 (0.4%)
Gonadorelin, Gonadorelin diacetate tetra hydrate	4 (0.4%)	3 (0.5%)
Hexestrol	4 (0.4%)	0
Nilutamide	4 (0.4%)	5 (0.9%)
Octreotide	3 (0.3%)	0
Prednisone	3 (0.3%)	3 (0.5%)
Tamsulosin, Tamsulosin hydrochloride	3 (0.3%)	0

Source: dataset ADCM; variables CMCAT, TRTP, CMDECOD

Demographic and disease characteristics by region

The North American population was only 12% of the total population enrolled in ARAMIS. The North America population consisted mostly of patients from the US (76% of randomized patients from North America). The Asia Pacific population (12% of randomized patients) consisted of patients from Japan (51%), South Korea (41%) and Taiwan (Province of China, 8%). The ROW population consisted mostly of patients from Europe (85% of randomized patients from ROW). Tables 31 and 32 summarize select baseline demographic and disease characteristics by geographic region.

Table 31. Select Baseline Demographic and Physical Characteristics by Region

	ROW (N = 1139)	North America (N = 184)	Asia Pacific (N = 186)
Age (years)			
Median (range)	74 (50, 94)	74 (48, 95)	77 (56, 90)
Race, n (%)			
Missing	50 (4.4%)	5 (2.7%)	0
Asian	3 (0.3%)	4 (2.2%)	186 (100%)
Black	26 (2.3%)	26 (14.1%)	0
Other	15 (1.3%)	0	0
White	1045 (91.7%)	149 (81.0%)	0
Body mass index (kg/m²)			
Median (range)	28.3 (17.9, 44.6)	29.4 (19.2, 44.2)	24.2 (16.9, 33.1)
ECOG performance status			
0	762 (66.9%)	139 (75.5%)	140 (75.3%)
1	377 (33.1%)	45 (24.5%)	46 (24.7%)

Source: dataset ADSL; variables TRT01P, CNTYGR1, AGE, RACE, BASEBMI, and BASEECOG

Table 32. Select Baseline Disease Characteristics by Region

	ROW (N = 1139)	North America (N = 184)	Asia Pacific (N = 186)
Prior hormonal therapies (n)			
1	232 (20.4%)	42 (22.8%)	6 (3.2%)
≥ 2	827 (72.6%)	141 (76.6%)	179 (96.2%)
Not applicable (prior orchiectomy)	80 (7.0%)	1 (0.5%)	1 (0.5%)
PDADT (months)			
Median (range)	4.49 (0.74, 11.97)	4.87 (0.93, 13.19)	4.85 (0.66, 13.2)
Primary tumor stage			
T1	2 (1.7%)	1 (1.5%)	3 (1.6%)
T2	11 (9.2%)	4 (6.0%)	15 (8.1%)
T3	7 (5.9%)	6 (9.0%)	13 (7.0%)
T4	13 (10.9%)	10 (14.9%)	23 (12.4%)
TX	1 (0.8%)	1 (1.5%)	2 (1.1%)
Missing	1 (0.8%)	1 (1.5%)	2 (1.1%)
Gleason score			
Missing	34 (3.0%)	7 (3.8%)	3 (1.6%)
<7	311 (27.3%)	35 (19.0%)	13 (7.0%)
≥ 7	794 (69.7%)	142 (77.2%)	170 (91.4%)
Time since initial diagnosis (months)			
Median (range)	85.6 (1.3-263.2)	106.4 (0.5-344.7)	67.8 (11.9-230.9)
Time since becoming castrate-resistant (months)			
Median (range)	5.52 (0.10, 233.02)	7.92 (0.23, 143.67)	4.11 (0.03, 93.56)
Definitive local therapy			
Prostatectomy	23.0%	41.8%	18.3%
Radiation	18.2%	25.5%	6.5%

Source: datasets ADSL, ADCM; variables TRT01P, CNTYGR1, PHTS, UPSADMN, PTCLS, GLEASON, TIDFDN, TICARN, CMSCAT, CMTRT

Reviewer's comments: Baseline demographic and disease characteristics appeared comparable by geographic region with the following exceptions:

- 1. Patients from North America were more likely to have received definitive local therapy. As mentioned previously, since only 12% of patients overall in ARAMIS were from North America, representing a much lower overall percentage of enrolled patients than SPARTAN and PROSPER, this likely explains why only 42% had prior definitive local therapy compared to these trials.*
- 2. The median times from initial diagnosis to study entry and from becoming castration resistant to study entry were longer for patients from North America compared to patients from the Asia Pacific region and the rest of the world.*
- 3. North American patients most frequently had a tumor stage at diagnosis in the T2 group, as compared to the T3 group for patients from Asia Pacific and the rest of the world.*
- 4. The Asia Pacific population was more likely than patients from North America or the rest of the world to have received two or more lines of prior hormonal treatment.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Investigators were to record the amount of study drug dispensed to each patient. Any remaining study drug was to be returned to the study center at the start-of-open-label-treatment visit and at the end-of-study visit. Treatment compliance, expressed as the percentage of planned dose taken, averaged 98.9% in the darolutamide arm and 99.4% in the placebo arm.

Table 33. ARAMIS Treatment Compliance (safety population)

Treatment Compliance	Darolutamide (N = 954)	Placebo (N = 554)
Mean $\pm$ SD	98.9% $\pm$ 5.4%	99.4% $\pm$ 4.1%
Median	100%	100%
Range	45.8 – 100%	49.7 – 100%

Source: dataset ADEX; variables TRTA, AVAL

Reviewer's comment: Treatment compliance overall was high in both study arms.

Efficacy Results – Primary Endpoint

MFS was defined as the time from randomization to confirmed metastasis or death from any cause, whichever occurred first. Deaths before documented metastasis and not later than 32 (+1) weeks after the last evaluable scan were included in this analysis. The analysis included all randomized patients. At the September 3, 2018 clinical cutoff date, 437 MFS events had occurred (221 patients [23.1%] in the darolutamide arm and 216 patients [39.0%] in the placebo arm). There was a statistically significant improvement in MFS for patients on darolutamide compared to placebo with a stratified hazard ratio of 0.413 (95% CI: 0.341, 0.500; two-sided stratified log-rank p-value <0.0001). The estimated median MFS was 40.4 months

(95% CI: 34.3, NE) for darolutamide vs. 18.4 months (95% CI: 15.5, 22.3) for placebo. The Kaplan-Meier plot is shown in Figure 17.

Table 34. ARAMIS Primary MFS Analysis

	Darolutamide N = 955	Placebo N = 554
Patients with event, n (%)	221 (23.1%)	216 (39.0%)
Death	41 (4.3%)	19 (3.4%)
Metastasis post-baseline	130 (13.6%)	158 (28.5%)
Metastasis at baseline	50 (5.2%)	39 (7.0%)
Patients censored, n (%)	734 (76.9%)	338 (61.0%)
Censored at last MFS-free tumor assessment	673 (70.5%)	226 (40.8%)
Censored at last tumor assessment before death	0	2 (0.4%)
Censored at last tumor assessment before new anticancer therapy	39 (4.1%)	86 (15.5%)
Censored on randomization date	22 (2.3%)	24 (4.3%)
Median ¹ MFS (95% CI), months	40.4 (34.3, NE)	18.4 (15.5, 22.3)
Stratified ² HR (95% CI)	0.413 (0.341, 0.500)	
Two-sided stratified ² log-rank p-value	<0.0001	

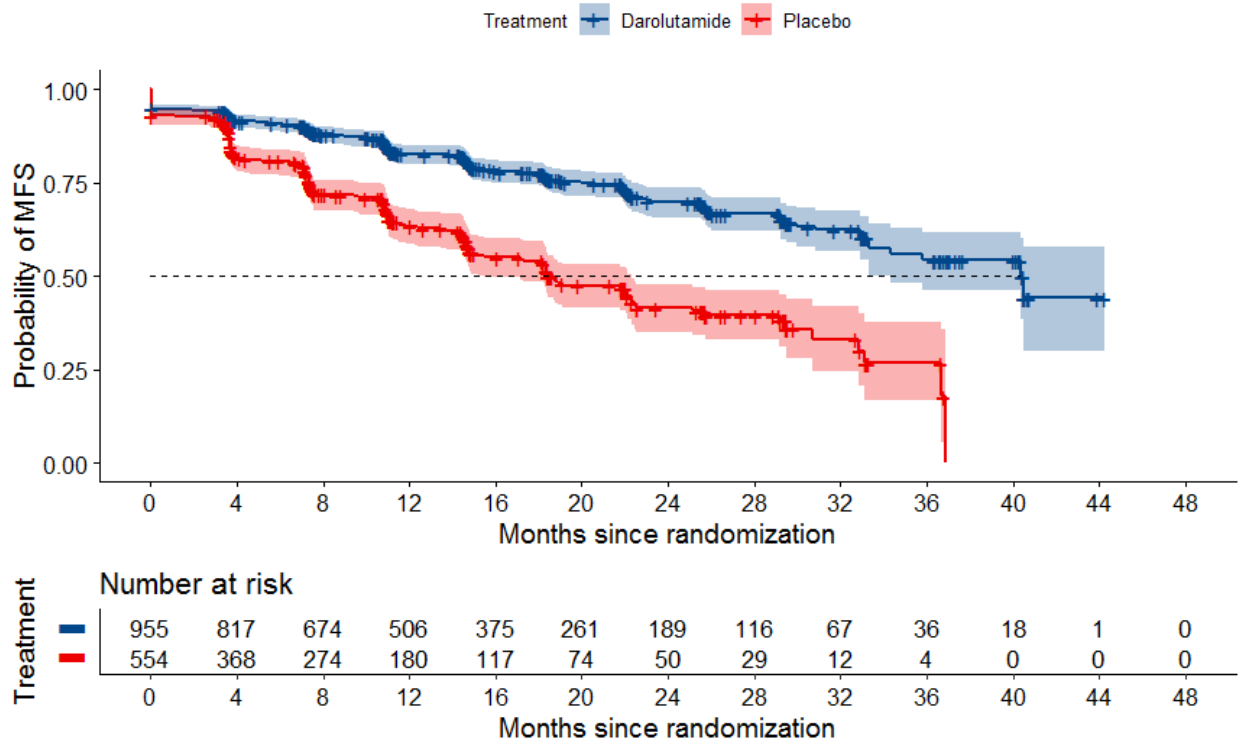
NE=Not Estimable

¹ Based on Kaplan-Meier estimates

² Stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no)

Source: dataset ADTTE; variables PARAM, AVLC, CNSR, EVNTDESC, CNSDTDSC, and TRT01P

Figure 16. Kaplan-Meier Plot for Primary MFS Analysis



Source: ADTTE where PARAMCD = "MFS"

Reviewer's comments:

1. *This difference in median MFS (~22 months) is clinically meaningful. Please note that the median estimate of the darolutamide arm is not robust as it is driven by one or two events only at the tail of the curve.*
2. *The placebo arm underperformed relative to the assumption that median MFS would be 25 months in this arm. The shorter median may be due to the 7% of patients on the placebo arm with metastasis at baseline who were treated as having events at baseline. However, we note that median MFS of the placebo arm in ARAMIS was 18.4 months compared to 16.2 months on SPARTAN and 14.7 months on PROSPER. Thus, the baseline assumption of 25 months for median MFS for the placebo arm was likely overly optimistic.*
3. *As described previously, the imaging charter had 2 separate reader pools (one for eligibility and one for efficacy). Since efficacy reader assessments started at baseline (rather than only post-baseline), there were cases where the efficacy read identified metastases at baseline even though the eligibility read had determined no metastases. This was a design flaw that resulted in 89 patients (50 in the darolutamide arm and 39 in the placebo arm) with baseline metastasis. This likely led to documentation of approximately one-fifth of the patients as having metastases at baseline [darolutamide- 50/221 (22.6%) and placebo- 39/216 (18.1%)]. Sensitivity analyses were conducted to address this issue and results are discussed in the section below.*
4. *The proportional hazards (PH) assumption used in the MFS analysis appears acceptable. Using a scaled residual test, there was no evidence that the PH assumption did not hold (p -value=0.178 for the stratified Cox PH model and p -value=0.184 for the unstratified Cox PH model).*
5. *Analyzing the MFS data using a Bayesian approach showed consistent results even when using an informative prior centered around no effect. With a non-informative prior, the Bayesian posterior mean of the stratified hazard ratio was 0.413 with a 95% highest posterior density (HPD) interval of 0.344 to 0.504. With an informative prior centered around no effect, the Bayesian posterior mean of the stratified hazard ratio was 0.510 (95% HPD interval: 0.431, 0.600). Table 35 shows Bayesian posterior estimates that the hazard ratio falls below certain limits. Even under an informative prior suggesting no effect, the probability that the hazard ratio falls below 0.6 is 97.6%.*

Table 35: Posterior Estimates of Hazard Ratio

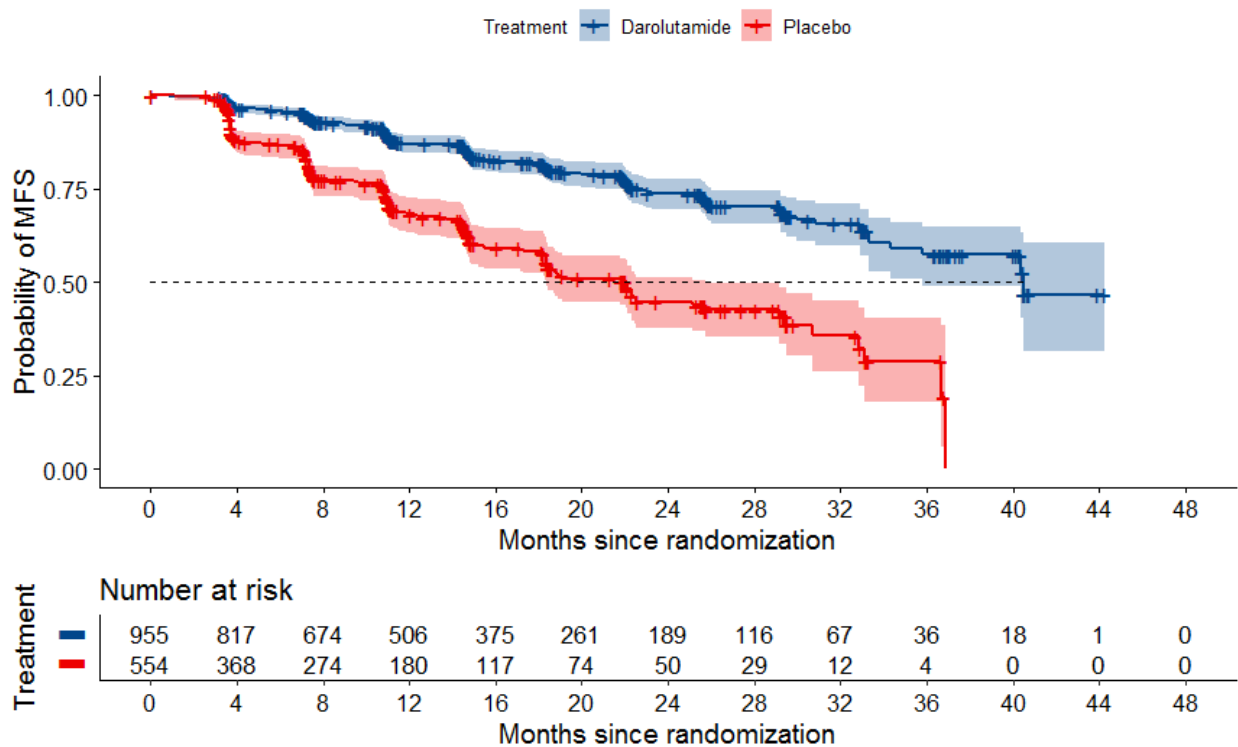
	Non-informative Prior	Informative Prior
Posterior Prob(HR < 0.6)	~99.9%	97.6%
Posterior Prob(HR < 0.5)	97.6%	40.7%
Posterior Prob(HR < 0.4)	36.7%	0.2%

Source: Reviewer's Analysis. The informative prior assumes $\log(\text{HR}) \sim N(-0.01, 0.03)$.

Sensitivity Analyses of MFS

Of the 437 MFS events in the primary analysis, 89 events (50 on the darolutamide arm and 39 on the placebo arm) were metastases at baseline. As a secondary/sensitivity analysis, the applicant analyzed MFS with baseline metastases censored at the date of randomization. With a total of 348 events (171 on the darolutamide arm and 177 on the placebo arm) in this analysis, the stratified hazard ratio was 0.356 (95% CI: 0.287, 0.441). The estimated median MFS was 40.5 months (95% CI: 35.8, NE) on the darolutamide arm compared to 22.1 months (95% CI: 18.3, 25.8) on the placebo arm. The Kaplan-Meier plot is shown in Figure 18.

Figure 17. Kaplan-Meier Plot for MFS with Metastases at Baseline Censored



Source: ADTTE where PARAMCD = "SAMFSBAS"

Reviewer's Comments: The results from both MFS analyses showed a consistent treatment effect, whether treating the baseline metastases as events (primary analysis) or censored (secondary analysis) at randomization. The KM plots shown in Figure 17. and Figure 18. show that when baseline metastases are treated as events at randomization, there is a slight drop at time zero that shifts the KM curves for both treatment arms down. Since there are relatively more metastases at baseline on the placebo arm (7.0%) compared to the darolutamide arm (5.2%), the placebo curve drops a bit more. This may account for why the estimated median MFS on the placebo arm is slightly lower in the primary analysis (baseline metastases as events) compared to the secondary analysis.

FDA conducted an additional sensitivity analysis considering a worst-case scenario where baseline metastases are considered events on the darolutamide arm and censored on the placebo arm. This resulted in a stratified HR of 0.49 (95% CI: 0.40, 0.60) with an estimated difference in median PFS of 18.3 months (40.4 months on the darolutamide arm and 22.1 months on the placebo arm), which still represents a consistent treatment benefit in favor of darolutamide.

The primary analysis of MFS was planned to occur when approximately 385 MFS events occurred in the ITT population, but the actual analysis was based on 437 MFS events. FDA conducted a sensitivity analysis with a data cutoff of April 26, 2018 which was when the 385th MFS event occurred. The results of this sensitivity analysis were consistent with the primary analysis showing a stratified HR of 0.43 (95% CI: 0.35, 0.53). The estimated median MFS on the placebo arm was 18.8 months (95% CI: 17.3, 22.5) and not reached on the darolutamide arm.

FDA also conducted sensitivity analyses to address the issue described the Patient Disposition section regarding the imbalance in patients who discontinued study drug without metastasis but with a concurrent rise in PSA from nadir. Patients who discontinued study drug without metastasis and with PSA rising whose MFS times were later than the time of treatment discontinuation were censored at the time of treatment discontinuation.

Out of the 224 patients who discontinued study drug without metastasis (per central review) and with concurrent rise in PSA from nadir, 37 (18 in the darolutamide arm and 19 in the placebo arm) had an MFS time (event or censored) later than the time of treatment discontinuation. Additionally, 22 of the 37 were deaths in the primary analysis with 10 of the 22 dying within 7 days of treatment discontinuation. Thus, an additional sensitivity analysis was conducted keeping deaths within 7 days of treatment discontinuation as events.

Results are shown in Table 36 and were consistent with what was seen in the primary analysis of MFS.

Table 36. FDA Sensitivity Analyses of MFS addressing patients who discontinued study drug without metastasis and with PSA rising

Sensitivity Analysis	Darolutamide		Placebo		Stratified ¹ HR (95% CI)
	Events/N (%)	Median (months)	Events/N (%)	Median (months)	
Censoring patients who discontinued without metastasis but with PSA rising at the time of treatment discontinuation	208/955 (21.8)	40.5	207/554 (37.4)	21.8	0.41 (0.33, 0.50)
Censoring patients who discontinued without metastasis but with PSA rising at the time of treatment discontinuation (deaths within 7 days of treatment discontinuation counted as events)	213/955 (22.3)	40.5	212/554 (38.3)	18.7	0.40 (0.33, 0.49)

¹ Stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no)

The applicant conducted several other sensitivity analyses using different censoring rules/event dates and stratification values to assess the robustness of the MFS results as follows:

1. Censoring patients who died before documented metastasis
2. Considering all prohibited new anti-cancer treatment that started prior to documented metastasis as event
3. Using stratification data from the CRF
4. Without including stratification factors in the model
5. Using MFS data based on investigator assessment
6. Considering all deaths independent of the time of occurrence of MFS as events
7. Using the event at the date of the first post-baseline scan with metastasis instead of the event at randomization, for patients with baseline metastasis. If no metastasis was documented in post-baseline scans, the patient was censored at the last available scan date. In case the patient did not have any post-baseline scans, the event would remain at baseline and the patient was censored at randomization.
8. Excluding patients whose primary reason for permanent discontinuation of study treatment was “judgement of investigator” or “personal reason” who did not have an MFS event

Table 37. Applicant Sensitivity Analyses of MFS

Sensitivity Analysis	Darolutamide		Placebo		HR ¹ (95% CI)
	Events/N (%)	Median (months)	Events/N (%)	Median (months)	
SA1	180/955 (18.8)	40.5	197/554 (35.6)	22.1	0.37 (0.30, 0.46)
SA2	263/955 (27.5)	34.3	306/554 (55.2)	13.7	0.35 (0.29, 0.41)
SA3	221/955 (23.1)	40.4	216/554 (39.0)	18.4	0.41 (0.34, 0.49)
SA4	221/955 (23.1)	40.4	216/554 (39.0)	18.4	0.42 (0.34, 0.50)
SA5	282/955 (29.5)	33.3	274/554 (49.5)	14.6	0.40 (0.34, 0.47)
SA6	229/955 (24.0)	40.4	227/554 (41.0)	18.4	0.41 (0.34, 0.50)
SA7	215/955 (22.5)	40.5	215/554 (38.8)	18.4	0.39 (0.32, 0.47)
SA8	221/879 (25.1)	40.4	216/443 (48.8)	15.2	0.37 (0.30, 0.44)

¹ Stratified hazard ratios are reported except for SA4

Reviewer’s Comment: All sensitivity analyses showed a consistent treatment effect in favor of darolutamide with estimated hazard ratios ranging from 0.35 to 0.42.

Concordance between BICR and Investigator

Based on independent blinded central reading, 23.1% of patients in the darolutamide arm and 39.0% in the placebo arm had an MFS event; based on the investigator assessment, 29.5% of patients in the darolutamide arm and 49.5% in the placebo arm had an MFS event. Overall concordance was 86.3% concordance in the darolutamide arm, 78.3% concordance in the placebo arm.

Table 38. ARAMIS BICR-Investigator Concordance for MFS

Investigator reading	Treatment		Independent blinded central reading		
			Event	No event	All, n (%)
Darolutamide		Event	186 (19.5%)	96 (10.1%)	282 (29.5%)
		No event	35 (3.7%)	638 (66.8%)	673 (70.5%)
		All, n (%)	221 (23.1%)	734 (76.9%)	955 (100%)
Placebo		Event	185 (33.4%)	89 (16.1%)	274 (49.5%)
		No event	31 (5.6%)	249 (44.9%)	280 (50.5%)
		All, n (%)	216 (39.0%)	338 (61.0%)	554 (100%)

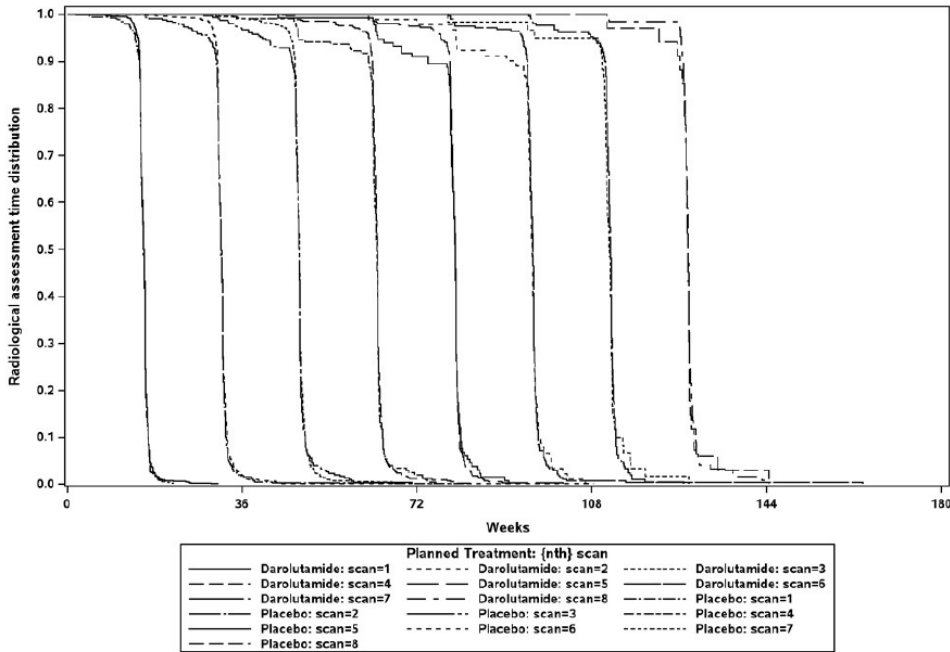
Source: dataset ADTTE; variables PARAMCD, TRTP, and CNSR

Reviewer's comment: Concordance between investigators and BICR was similar between the darolutamide and placebo arms. Discordance was slightly higher on the placebo arm compared to the darolutamide arm (21.7% vs. 13.7%). There were more patients with MFS events by investigator assessment compared to central review (36.8% vs. 29.0%), particularly in the placebo arm. To evaluate whether there is an investigator bias favoring darolutamide in the MFS analysis, we calculated the early discordance rate (EDR) and late discordance rate (LDR) for each arm. A negative differential discordance for the EDR and/or a positive differential discordance for the LDR would suggest a bias in the investigator assessment favoring the darolutamide arm. Analysis results showed a positive discordance in EDR (0.04) and a negative discordance in LDR (-0.03), thus there is no evidence of investigator assessment bias in favor of darolutamide.

Timing of Tumor Assessments

The chest, abdomen, and pelvis CT/MRI and bone scans were to be performed at screening (baseline) and every 16 weeks until confirmed metastasis. Figure 19 shows the Kaplan-Meier curves of time to tumor assessments which are mostly overlapping across arms. The relative timing of tumor evaluations is summarized in Table 39. Both show that there are no notable differences between treatment arms with respect to the timing of assessments.

Figure 18. Kaplan-Meier curves of time to tumor assessments



Source: CSR Figure 9-5

Table 39. Relative timing of tumor evaluation

Actual Scan	Scheduled Interval	Actual Interval, Median in weeks (min, max)	
		Darolutamide (N=955)	Placebo (N=554)
1	16 weeks	15.86 (1.7, 31.0)	15.71 (1.7, 21.9)
2	32 weeks	31.86 (6.1, 108.4)	31.71 (16.0, 68.7)
3	48 weeks	47.86 (31.0, 82.9)	47.86 (28.0, 71.0)
4	64 weeks	63.86 (40.4, 82.9)	63.71 (30.6, 75.9)
5	80 weeks	79.86 (62.9, 102.1)	79.86 (43.4, 90.9)
6	96 weeks	95.86 (78.6, 163.9)	95.71 (62.0, 106.7)
7	112 weeks	111.86 (95.0, 126.9)	111.64 (78.3, 128.0)
8	128 weeks	127.86 (111.0, 144.4)	127.86 (111.1, 144.4)
9	144 weeks	143.86 (127.0, 149.1)	143.86 (129.0, 146.0)
10	160 weeks	160.00 (158.0, 163.0)	159.71 (158.4, 160.3)
11	176 weeks	175.43 (173.7, 177.0)	175.57 (175.6, 175.6)
12	192 weeks	191.71 (191.0, 192.4)	N/A

Source: CSR Table 14.2.1/155

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints were tested with a hierarchical gatekeeping procedure in the following order (see Statistical Analysis Plan above):

- Overall survival (OS)

- Time to pain progression (TTPP)
- Time to cytotoxic chemotherapy (CYTOC)
- Time to first symptomatic skeletal event (SSE)

Reviewer's comments:

1. *The use of a hierarchical testing scheme for secondary endpoints to control overall type I error rate is statistically sound.*
2. *As communicated in 2013 (see Section 3.2 above), the Agency supports the collection of data on pain and initiation of concomitant medications such as opiates and cytotoxic chemotherapy for supportive analyses in this study population. At that time, the Agency also advised that both pain intensity and analgesic use at baseline and throughout the trial should be captured for the time to pain progression endpoint, and analgesic use should be collected using patient-reported analgesic log which is administered over the same time period as pain assessment. However, ARAMIS did not use a patient-reported analgesic log and opiate use information was collected in the concomitant medication case report form.*
3. *Many of the events comprising the secondary endpoints of time to pain progression, time to initiation of cytotoxic chemotherapy, and time to first SSE occurred after patients had experienced their MFS events. These results would likely be immature at the time of the primary MFS analysis. Per the SAP, an updated analysis of time to initiation of cytotoxic chemotherapy and time to first SSE will be performed at the time of final OS analysis (240 OS events).*

Overall survival

At the time of the data cut-off, 136 (56.7%) of the 240 OS events planned for the final OS analysis had occurred. The stratified HR for the OS analysis was 0.706 (95% CI: [0.501, 0.994]; $p = 0.045$). The median was not reached in either treatment arm. As the pre-specified alpha significance level for this interim analysis of OS was 0.0005, the result is not considered statistically significant.

Table 40. ARAMIS Interim Overall Survival Results

	Darolutamide N = 955	Placebo N = 554
Patients with event, n (%)	78 (8.2%)	58 (10.5%)
Patients censored, n (%)	877 (91.8%)	496 (89.5%)
Median ¹ OS (95% CI), in months	NE (44.4, NE)	NE (NE, NE)
Stratified ² HR (95% CI)	0.706 (0.501, 0.994)	
Two-sided stratified ² log-rank p-value	0.045	

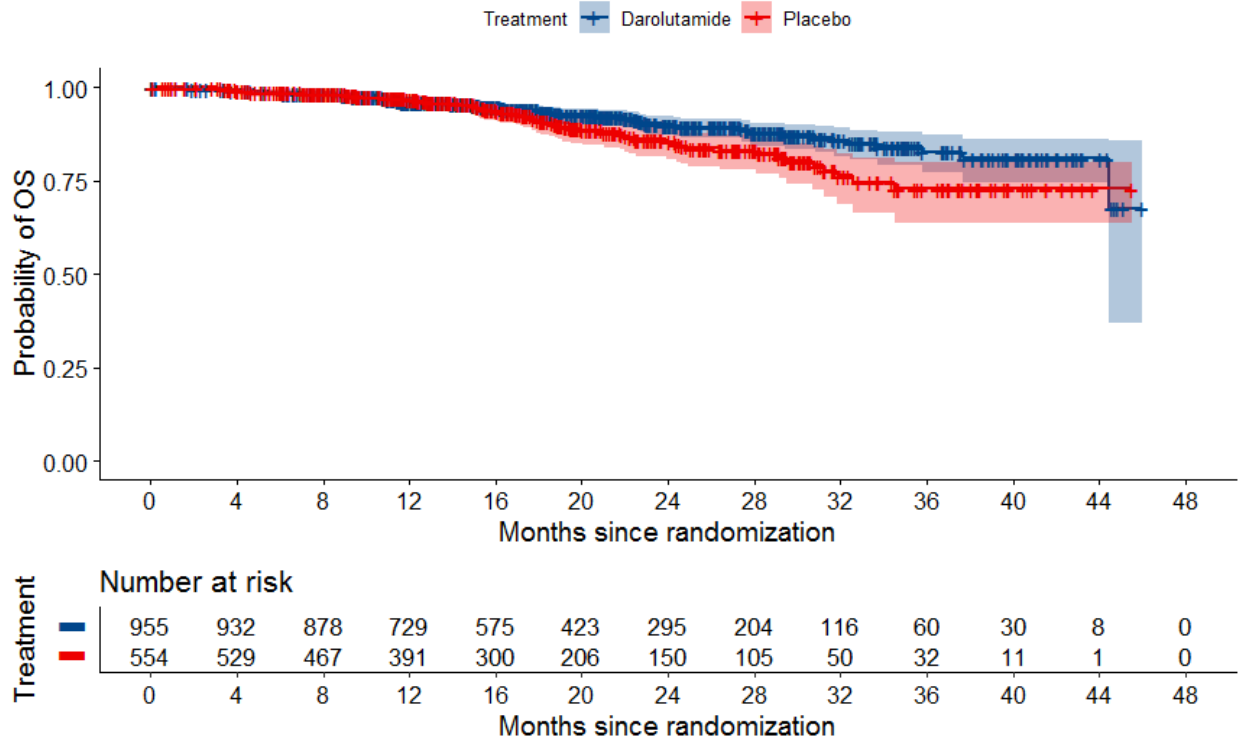
NE=Not Estimable

¹ Based on Kaplan-Meier estimates

² Stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no)

Source: dataset ADTTE; variables PARAM, AVLC, CNSR, and TRT01P

Figure 19. Kaplan-Meier Plot of Overall Survival Interim Analysis



Source: ADTTE where PARAMCD = "DEATH"

Reviewer's Comment: Since OS was not statistically significant at this interim analysis, the remaining key secondary endpoints in the testing hierarchy, i.e., time to pain progression, time to initiation of cytotoxic chemotherapy, and time to first symptomatic skeletal event, could only be summarized descriptively and no statistical inference could be made.

Time to pain progression

The protocol defined time to pain progression as the time from randomization to an increase of 2 or more points (on an 11-point scale) from baseline in the "worst pain in the last 24 hours" item (Question 3) of the BPI-SF (taken as a 7-day diary average for post-baseline scores), or the initiation of short- or long-acting opioids for cancer pain, whichever came first (see Statistical Analysis Plan above). To more clearly identify an asymptomatic population, patients who were taking opioids for any reason within 4 weeks prior to randomization were censored from the time to pain progression analysis on the date of randomization.

As of the cut-off date, 26.3% of the patients in the darolutamide arm and 32.1% of the patients in the placebo arm had pain progression. The estimated median time to pain progression was 40.3 months (95% CI: 33.2, 41.2) in the darolutamide arm compared with 25.4 months (95% CI: 19.1, 29.6) in the placebo arm, and the stratified HR was 0.647 (95% CI: 0.533, 0.785).

Table 41. ARAMIS Time to Pain Progression

	Darolutamide N = 955	Placebo N = 554
Patients with event, n (%)	251 (26.3%)	178 (32.1%)
Patients censored, n (%)	704 (73.7%)	376 (67.9%)
Patients censored at randomization, n (%)	92 (13.1%)	70 (18.6%)
Median ¹ time(95%CI), in months	40.3 (33.2, 41.2)	25.4 (19.1, 29.6)
Stratified ² HR (95% CI)	0.647 (0.533, 0.785)	

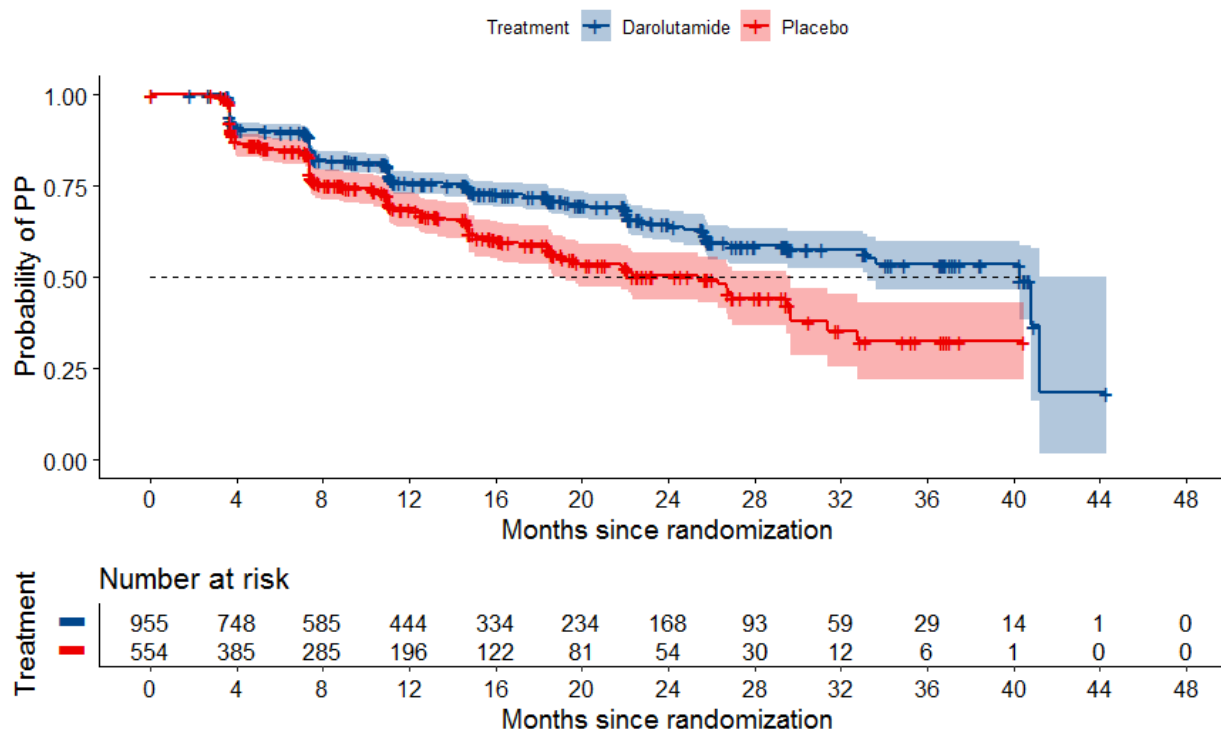
NE=Not Estimable

¹ Based on Kaplan-Meier estimates

² Stratified by PSADT (≤6 months vs. >6 months) and use of osteoclast-targeted therapy (yes vs. no)

Source: dataset ADTTE; variables PARAM, AVLC, CNSR, and TRT01P

Figure 20. Kaplan-Meier Plot for Time to Pain Progression



Source: ADTTE where PARAMCD = "PP"

Reviewer's comments:

1. The 100% completion rates (all questions completed) for BPI-SF were high (>90%) on treatment across both treatment arms. See Section 18.5 Additional Clinical Outcome Assessment Analyses for more details.

For Q3 of the BPI-SF, there was data available for 1501 patients (8 patients had no data). In addition to the 8 patients with no data, there were a total of 155 patients with either no baseline pain score (87/155) or no post-baseline pain score (68/155). In the TTPP analysis, all patients with no data were censored at the date of randomization. The majority (152/155; 98%) of patients with no baseline or post-baseline pain score were

also censored at the date of randomization. The remaining 3 patients had a pain progression event due to initiation of opioids for cancer pain.

- The baseline pain scores based on Q3 (worst pain) of the BPI-SF for all patients with a baseline score are shown in Table 42. Forty-seven percent of patients had no baseline pain; this was included in labeling as a baseline characteristic of the trial population. We also note this in the context of the inclusion criteria for ARAMIS that stipulated that patients should be asymptomatic at study entry. The fact that only 47% of patients reported no baseline pain on the BPI-SF may indicate a discrepancy in the investigator's assessment of the absence of pain compared to the patient's own description of baseline pain. We also note that baseline pain scores could potentially reflect both cancer-specific and non-cancer related pain.*

Table 42. Baseline Pain Scores based on BPI-SF Q3

	Darolutamide (N=955)	Placebo (N=554)	Total (1509)
All patients with baseline score	896 (94%)	518 (94%)	1414 (94%)
Baseline score			
0	455 (51%)	253 (46%)	708 (47%)
(0, 1]	105 (12%)	66 (12%)	171 (11%)
(1, 2]	90 (10%)	52 (9%)	142 (9%)
(2, 3]	67 (7%)	53 (10%)	120 (8%)
(3, 4]	44 (5%)	27 (5%)	71 (5%)
>4	135 (15%)	67 (12%)	202 (13%)

Source: Reviewer's Analysis

- The protocol definition of time to pain progression was consistent with the Agency's presubmission recommendations.*
- Pain progression was characterized by either an increase of 2 or more points from baseline in Q3 of the BPI-SF or the initiation of short- or long-acting opioids for cancer pain, whichever came first. Table 43 shows a breakdown of the types of pain progression events by arm. The majority (93.7%) of patients with pain progression had a 2+ increase in BPI-SF Q3.*

Table 43. Pain Progression Event Types

	Darolutamide (N = 955)	Placebo (N = 554)
Patients with Pain Progression	251/955 (26%)	178/554 (32%)
Patients with a 2+ increase in BPI-SF Q3	237/251 (94%)	165/178 (93%)
Patients who initiated opioids for cancer pain	14/251 (6%)	13/178 (7%)

Note: Patient (b) (6) experienced a 2+ increase and initiated opioids for cancer pain on (b) (6) but is counted in the 2+ increase category.

Source: Reviewer's Analysis

- In this analysis, pain progression could have occurred before or after patients experienced an MFS event. Prior to developing metastasis, the patients in this population*

are largely asymptomatic, so the timing of the TTPP endpoint may be impacted by the timing of the MFS endpoint. There was a total of 103 patients (51 in the darolutamide arm and 52 in the placebo arm) who experienced pain progression after their MFS event and a total of 168 patients (84 in the darolutamide arm and 84 in the placebo arm) whose TTPP time was censored after their MFS event. FDA conducted a sensitivity analysis where patients with a TTPP time later than their MFS event time were censored at their MFS event time. Results are shown in Table 44 and the Kaplan-Meier plot is shown in Figure 22. The treatment effect shown was consistent with what was seen in the pre-specified analysis of TTPP, so the impact of TTPP events occurring after metastasis appears minimal.

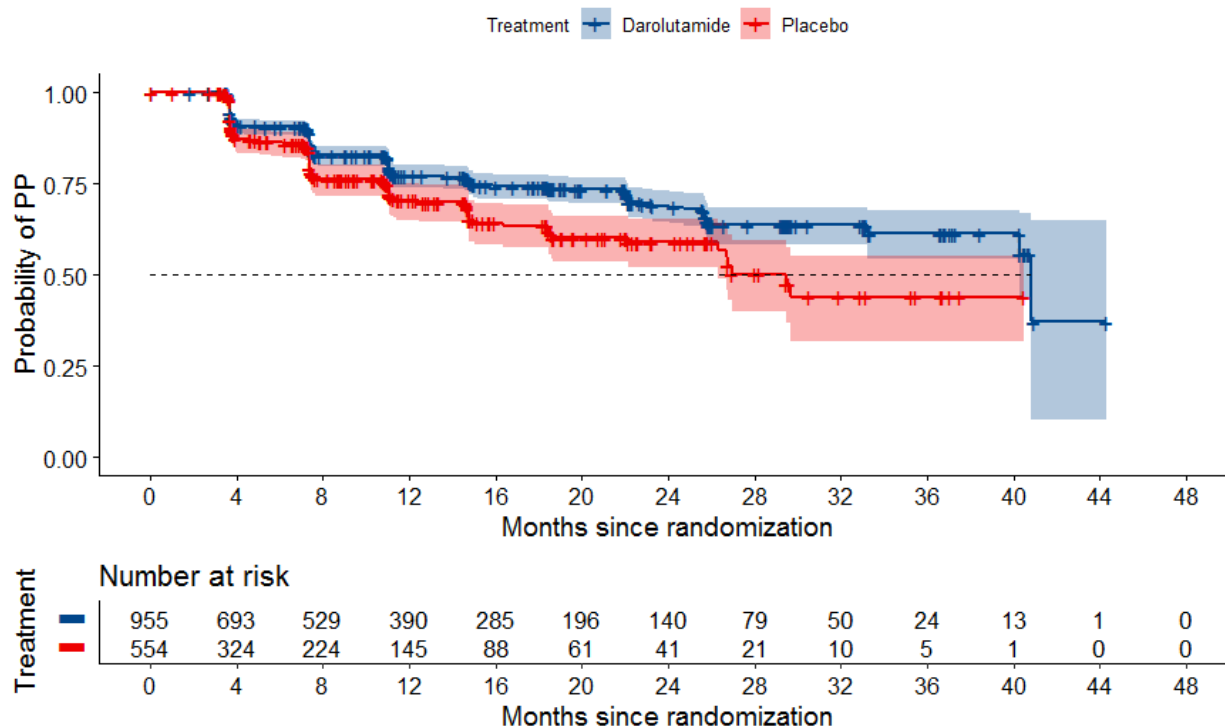
Table 44. FDA Sensitivity Analysis of Time to Pain Progression

	Darolutamide (n=955)	Placebo (n=554)
Number of events	200 (21%)	126 (23%)
Median (95% CI), in months	40.8 (40.3, NE)	29.5 (26.3, NE)
Unstratified HR	0.67 (0.54, 0.84)	

NE=Not Estimable

Source: Reviewer's Analysis

Figure 21. Kaplan-Meier Plot for FDA Sensitivity Analysis of Time to Pain Progression



Source: Reviewer's Analysis

- The majority of patients (86.6%) with a 2+ increase from baseline only experienced a 2+ increase once. For the most part, patients were not followed beyond their first 2+ increase, so there was not enough data available to conduct a sensitivity analysis based

on confirmed pain progression (2+ increase followed by a 2+ increase on the subsequent visit).

- 7. As noted, 53% of patients reported pain at baseline, which is relatively high in this patient population. A fifth of the patients with metastases on study (N= 89/347) had metastases at baseline. If these 89 patients were excluded from the time to pain progression analysis, the results are generally similar: stratified HR of 0.65 (95% CI: 0.53, 0.80), estimated median is 40.3 months on the darolutamide arm and 26.3 months on the placebo arm. Considering that it is difficult to differentiate whether pain is related cancer or not, the size of effect, sensitivity analysis results, and the fact that a prolonged TTPP is consistent and plausible with a prolonged in MFS and efficacy of darolutamide in this placebo-controlled trial, improvement in TTPP will be included descriptively in the label.*

Time to initiation of cytotoxic chemotherapy

Altogether 7.6% of patients in the darolutamide arm and 14.3% of patients in the placebo arm started treatment with cytotoxic chemotherapy for prostate cancer during the study (per protocol, cytotoxic chemotherapy could be initiated at the earliest 7 days after the end of study treatment). The median time to initiation of cytotoxic chemotherapy was 38.2 months (95% CI: 35.5, 41.9) in the placebo arm and was not reached in the darolutamide arm.

Table 45. ARAMIS Time to Initiation of Cytotoxic Chemotherapy

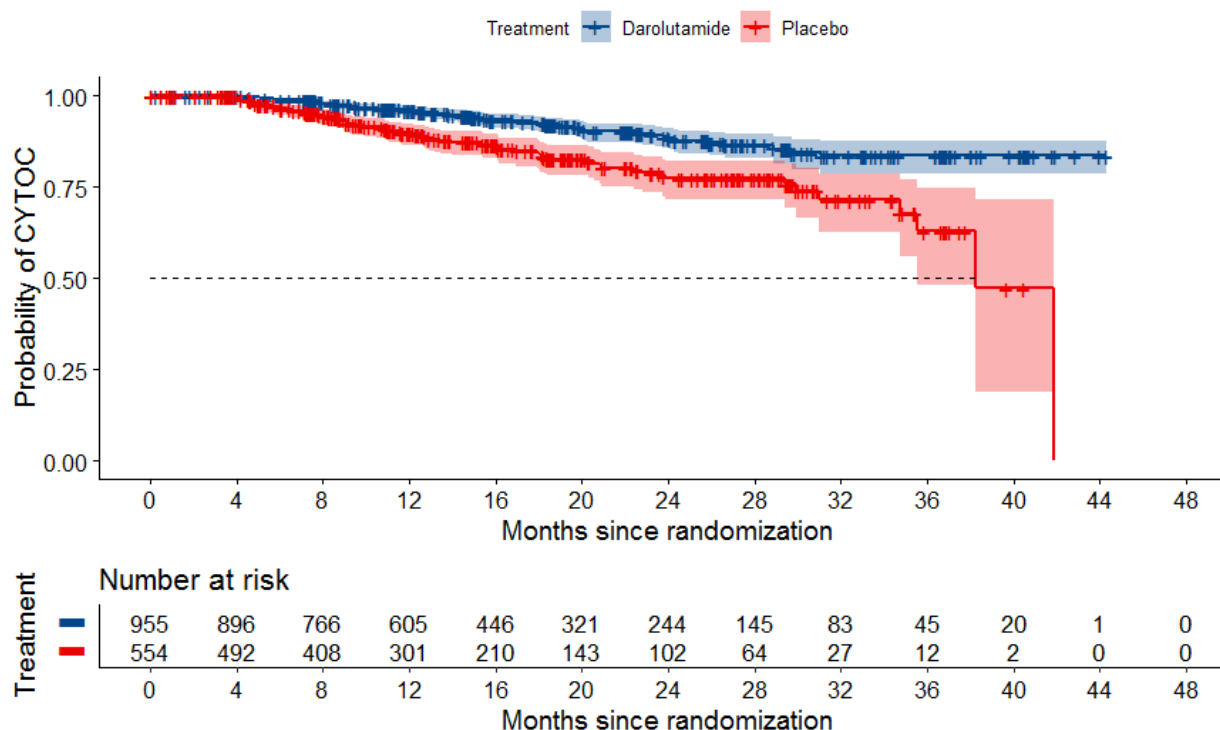
	Darolutamide N = 955	Placebo N = 554
Patients with event, n (%)	73 (7.6%)	79 (14.3%)
Patients censored, n (%)	882 (92.4%)	475 (85.7%)
Median ¹ time (95% CI), in months	NE (NE, NE)	38.2 (35.5, 41.9)
Stratified ² HR (95% CI)	0.433 (0.314, 0.595)	

NE=Not Estimable

1 Based on Kaplan-Meier estimates

2 Stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no) Source: dataset ADTTE; variables PARAM, AVLCL, CNSR, and TRT01P

Figure 22. Kaplan-Meier Plot for Time to Initiation of Cytotoxic Chemotherapy



Source: ADTTE where PARAMCD = "CYTOC"

Reviewer's comments:

1. The protocol definition of time to initiation of cytotoxic therapy was consistent with the Agency's presubmission recommendations.
2. The analysis of this secondary endpoint is supportive of the primary endpoint. However, we note that the event rate is low across both arms (7.6% vs. 14.3%), so the data is immature, and these results are hard to interpret. Per the SAP, an updated analysis of time to initiation of cytotoxic chemotherapy will be performed at the time of final OS analysis.

Time to first symptomatic skeletal event

Overall, few SSEs were reported during the trial. Most SSEs reported were EBRT to relieve skeletal symptoms (12 of 16 patients with an event in the darolutamide arm and 11 of 18 patients with an event in the placebo arm). The median time to first SSE was not reached in either treatment arm.

Table 46. ARAMIS Time to First Symptomatic Skeletal Event

	Darolutamide N = 955	Placebo N = 554
Patients with event, n (%)	16 (1.7%)	18 (3.2%)
Patients censored, n (%)	939 (98.3%)	536 (96.8%)
Median ¹ time (95% CI), in months	NE (NE, NE)	NE (NE, NE)
Stratified ² HR (95% CI)	0.428 (0.218, 0.842)	

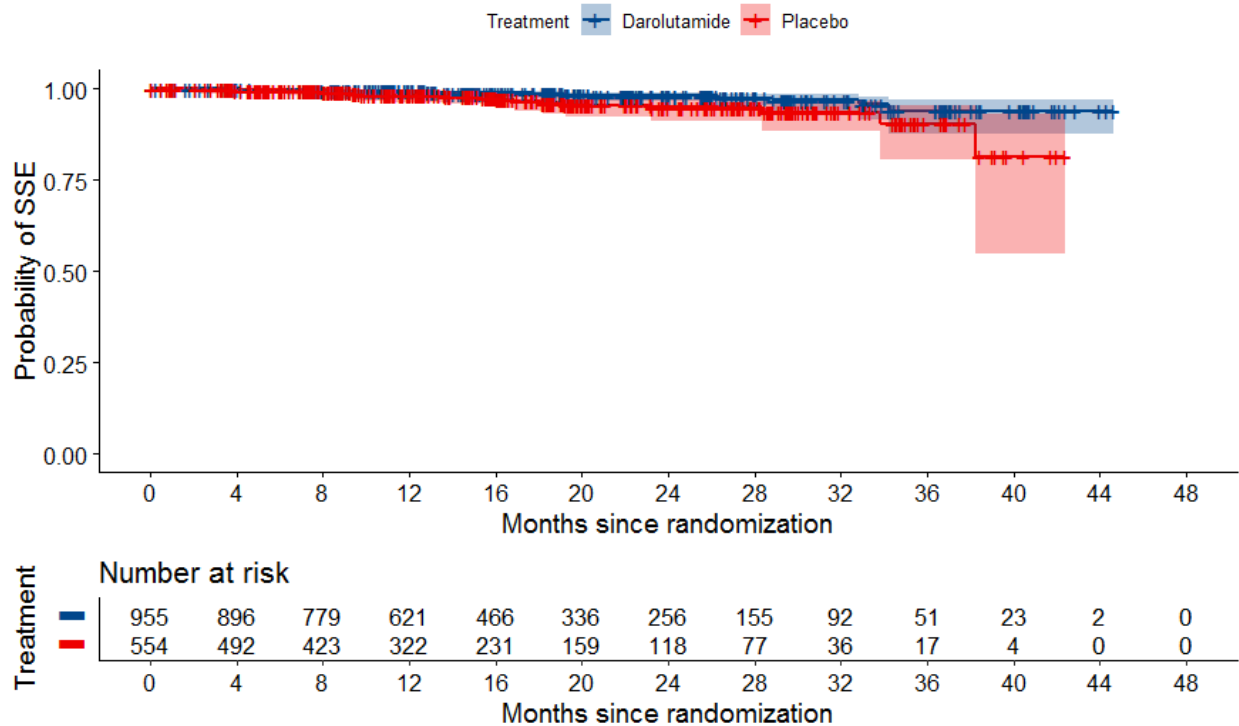
NE=Not Estimable

¹ Based on Kaplan-Meier estimates

² Stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no)

Source: dataset ADTTE; variables PARAM, AVLC, CNSR, and TRT01P

Figure 23. Kaplan-Meier Plot for Time to First Symptomatic Skeletal Event



Source: ADTTE where PARAMCD = "SSEFS"

Reviewer's comments:

1. The protocol definition of time to first symptomatic skeletal event was consistent with the Agency's presubmission recommendations.
2. The results of this secondary endpoint are supportive of the primary endpoint. However, we note that the event rate is very low across both arms (1.7% vs. 3.2%), so the data is

immature, and these results are hard to interpret. Per the SAP, an updated analysis of time to first SSE will be performed at the time of final OS analysis.

Dose/Dose Response

See Section 6.3.2 of this review.

Durability of Response

Not applicable, as a conventional analysis of response rates is not possible in nmCRPC.

Persistence of Effect

Duration of response is included in Efficacy Results described below.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Time to PSA progression

PSA was to be tested at screening, every 16 weeks during the study treatment and at the end of treatment visit. PSA progression was defined as an increase of PSA of $\geq 25\%$ and an absolute increase of ≥ 2 ng/ml above the nadir, confirmed by a consecutive value obtained 3 or more weeks later. PSA progression was only declared if observed at Week 16 or later after randomization.

Overall, 23.7% of patients in the darolutamide arm and 66.4% of patients in the placebo arm experienced PSA progression. The median time to PSA progression was longer in the darolutamide arm than in the placebo arm (33.1 months [95% CI: 25.9, NE] vs. 7.3 months [95% CI: 3.9, 7.4]) in the placebo arm.

Table 47. ARAMIS Time to PSA Progression

	Darolutamide N = 955	Placebo N = 554
Patients with event, n (%)	226 (23.7%)	368 (66.4%)
Patients censored, n (%)	729 (76.3%)	186 (33.6%)
Median ¹ time (95% CI), in months	33.1 (25.9, NE)	7.3 (3.9, 7.4)
Stratified ² HR (95% CI)	0.130 (0.109, 0.156)	

¹ Based on Kaplan-Meier estimates

² Stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no)

Source: dataset ADTTE; variables PARAM, AVL, CNSR, and TRT01P

Progression-free Survival

PFS was an additional/tertiary endpoint. At the time of the primary MFS analysis, there were a total of 513 PFS events (255 on the darolutamide arm and 258 on the placebo arm). The stratified hazard ratio was 0.380 (95% CI: 0.319, 0.454) in favor of the darolutamide arm. The

estimated median PFS was 36.8 months (95% CI: 32.9, NE) on the darolutamide arm and 14.8 months (95% CI: 11.8, 18.4) on the placebo arm.

Table 48. ARAMIS Progression-free Survival

	Darolutamide (N=955)	Placebo (N=554)
Patients with event, n (%)	255 (26.7%)	258 (46.6%)
Patients censored, n (%)	700 (73.3%)	296 (53.4%)
Median ¹ time (95% CI), in months	36.8 (32.9, NE)	14.8 (11.8, 18.4)
Stratified ² HR (95% CI)	0.380 (0.319, 0.454)	

¹ Based on Kaplan-Meier estimates

² Stratified by PSADT (≤6 months vs. >6 months) and use of osteoclast-targeted therapy (yes vs. no)

Source: dataset ADTTE; variables PARAM, AVLC, CNSR, and TRT01P

Reviewer's Comments: *In the applicant's definition of PFS, the radiological progression component of PFS was derived by taking all distant metastasis events as determined for the MFS endpoint, adding all local radiological progression events per RECIST evaluation, and choosing whatever came first in cases where both types of radiological progression were observed. There were only 38 (4.0%) patients on the darolutamide arm and 47 (8.5%) patients on the placebo arm with locoregional-only progression. The treatment effect of darolutamide in terms of PFS was consistent with what was observed in terms of MFS. The overall percentage of patients with locoregional-only progression (6%) was considered informative and was included in labeling.*

HRQoL variables

ARAMIS assessed HRQoL during treatment and follow-up period using the FACT-P, EORTC-QLQ-PR25, EQ-5D-3L and BPI-SF questionnaires. Except that data collected from BPI-SF was reviewed for a secondary efficacy endpoint, i.e., time to pain progression, the other 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. Time to pain progression review is located in Section of secondary efficacy endpoint and review of other patient reported data is located in Section 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability and in Section 18.5 Additional Clinical Outcome Assessment Analyses.

Additional Analyses Conducted on the Individual Trial

The following three tables present exploratory analyses of MFS in various subpopulations according to demographic subgroup, disease characteristics, and prior treatment. In all of these analyses, subjects with metastases at baseline were not censored.

Table 49. ARAMIS MFS in Demographic Subgroups

Variable and Subgroup	N			HR [95% CI]	Median (mo.)	
	Total	Events	Censored		Darol (N=955)	Placebo (N=554)
Age (years)						
<65	197	72	125	0.591 (0.368, 0.948)	26.02	17.15
65 – 74	589	170	419	0.349 (0.257, 0.473)	NE	18.3
75 – 84	593	155	438	0.432 (0.313, 0.595)	40.37	25.16
≥85	130	40	90	0.509 (0.271, 0.958)	40.51	18.33
Geographical region						
Asia Pacific	186	42	144	0.350 (0.187, 0.654)	NE	21.81
North America	184	49	135	0.185 (0.098, 0.351)	NE	14.75
ROW	1139	346	793	0.471 (0.380, 0.584)	40.37	18.69
Race/ethnicity						
Asian	193	45	148	0.324 (0.177, 0.593)	NE	21.81
Black/African Amer.	52	11	41	0.000 (0.000, NE)*	NE	12.42
Other	15	5	10	0.484 (0.077, 3.047)	NE	14.82
White	1194	361	833	0.432 (0.351, 0.533)	40.37	18.36
Hispanic/Latino	47	14	33	0.865 (0.288; 2.600)	29.2	A

Source: datasets ADSL and ADTTE; variables AGE, RACE, CNTYGR1, PARAM, AVLC, CNSR, and TRT01P

*HR rounded to zero

Table 50. ARAMIS MFS in Disease Characteristic Subgroups

Variable and Subgroup	N			HR [95% CI]	Median (mo.)	
	Total	Events	Censored		Darol (N=955)	Placebo (N=554)
Baseline PSADT						
≤6 months	1040	323	717	0.413 (0.330, 0.516)	34.33	17.15
>6 months	469	114	355	0.376 (0.258, 0.547)	NE	30.68
PSADT Quartiles, in months						
[0.662, 2.97]	378	146	232	0.476 (0.341, 0.665)	29.2	11.5
(2.97, 4.45]	377	97	280	0.452 (0.300, 0.679)	NE	22.1
(4.45, 6.57]	377	105	272	0.325 (0.220, 0.482)	NE	18.4
(6.57, 13.2]	377	89	288	0.375 (0.246, 0.572)	NE	32.8
Baseline PSA						
≤10	793	176	617	0.392 (0.290, 0.528)	NE	22.34
>10 to ≤20	337	102	235	0.482 (0.322, 0.722)	35.78	22.11
>20	379	159	220	0.392 (0.285, 0.538)	29.24	10.91
Gleason score						
<7	359	101	258	0.423 (0.284, 0.630)	40.37	22.34
≥7	1106	321	785	0.402 (0.322, 0.502)	NE	18.33
Baseline presence of regional pathological lymph nodes						
No	1343	368	975	0.417 (0.520, 0.313)	40.76	22.25
Yes	166	69	97	0.297 (0.178, 0.491)	35.52	9.488

Table 51. ARAMIS MFS in Prior Treatment Subgroups

Variable and Subgroup	N			HR [95% CI]	Median (mo.)	
	Total	Events	Censored		Daro (N=955)	Placebo (N=554)
Prior Definitive Local Therapy						
No	621	186	435	0.439 (0.328, 0.588)	40.51	18.89
Yes	888	251	637	0.400 (0.310, 0.515)	34.33	18.36
Baseline osteoclast-targeted therapy						
No	1445	416	1029	0.433 (0.356, 0.526)	40.37	18.76
Yes	64	21	43	0.220 (0.084, 0.573)	NE	11.83

Source: datasets ADSL and ADTTE; variables RNDOSTNY, PARAM, AVL, CNSR, and TRT01P

Reviewer's comments:

1. MFS results were generally comparable across the subgroups examined.
2. The effect on MFS was preserved across all quartiles of PSA doubling time. For this reason, the labeled indication will not restrict use to those with a specific PSA doubling time despite this being an inclusion criterion.
3. There were few patients in certain race/ethnicity subgroups including Black/African American (n=52) and Hispanic/Latino (n=47). No outlier subgroups were identified.

8.1.3 Assessment of Efficacy Across Trials

The efficacy claims for darolutamide in the proposed indication are based on a randomized, placebo-controlled, multicenter Phase 3 trial 17712 (ARAMIS) of darolutamide in patients with nmCRPC. In addition, supporting efficacy data from Phase 1/2 studies (17829, 18035, 17830, 17719) in mCRPC patients were reviewed. In view of the differences in patient populations (e.g. nmCRPC vs. mCRPC) and in study designs, analysis sets and definitions of variables between these studies, no pooled analysis of efficacy was performed, and efficacy results are presented separately for each study.

8.1.4 Integrated Assessment of Effectiveness

The efficacy of darolutamide in patients with nmCRPC is supported by data from a single, multinational, randomized, placebo-controlled clinical trial (ARAMIS). The primary endpoint of BIRC-assessed MFS was longer in patients treated with darolutamide (estimated median 40.4 months) compared to placebo (estimated median 18.4 months). This difference is both statistically significant (HR 0.413, P<0.0001) and clinically meaningful.

The results of the secondary endpoints of OS, time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, time to first SSE also support the primary efficacy endpoint. OS results were not mature at the time of the clinical cutoff, with 136 (56.7%) of deaths reported, and the final OS result will be submitted when available as part of a post-marketing requirement.

Exploratory analyses of BIRC-assessed MFS in patient subpopulations according to demographic

and disease characteristics, and prior treatment were generally consistent with the primary analysis.

Patient-reported outcomes were collected in ARAMIS using the BPI-SF, FACT-P, the EQ-5D-3L, and EORTC-QLQ-PR25 questionnaires. The MFS result was supported by a delay in time to pain progression, defined as a at least 2-point worsening from baseline of the pain score on Brief Pain Inventory-Short Form or initiation of opioids, in patients treated with NUBEQA as compared to placebo. Pain progression was reported in 28% of all patients on study.

In conclusion, the efficacy of darolutamide administered with continued ADT 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

8.2.1 Safety Review Approach

The primary safety analysis of darolutamide was conducted on data submitted from the pivotal double-blind Phase 3 trial ARAMIS. The safety population consisted of a total of 1508 men who received either darolutamide at 600 mg BID (N=954) or placebo (N=554) concurrently with ADT who have undetectable metastases by conventional imaging techniques (i.e. computed tomography [CT], magnetic resonance imaging [MRI], bone scan [BS]). Supportive safety data was submitted from 173 patients as a pooled analysis from completed uncontrolled Phase 1 and 2 studies of darolutamide in patients with metastatic castrate resistant prostate cancer.

1. Study 17829 ARADES, including Extension Study 18035: Phase 1 open-label, non-randomized, uncontrolled, multicenter, first in man, dose-escalation and Phase 2 open-label, randomized, uncontrolled, multicenter (n=134)
2. Study 17830 ARAFOR: Open-label, randomized, multicenter, 2-component trial (n=30)
3. Study 17719 Japanese Phase 1 open-label, non-randomized, uncontrolled, single center, dose escalation (n=9)

The safety analysis dataset consisted of 954 patients treated with darolutamide and 554 patients treated with placebo who had received at least one dose of darolutamide prior to the data cut-off of September 3, 2018. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

Reviewer Comments.

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 was reasonable.
3. To review the AE datasets, the following terms were pooled:

Table 52. Preferred Terms Pooled

Term	Preferred Terms
Bone fracture	Ankle fracture Cervical vertebral fracture Clavicle fracture Femoral neck fracture Femur fracture Fibula fracture Foot fracture Fracture Hand fracture Hip fracture Humerus fracture Lumbar vertebral fracture Patella fracture Pathological fracture Radius fracture Rib fracture Scapula fracture Skull fracture Spinal compression fracture Spinal fracture Traumatic fracture Ulna fracture Upper limb fracture Wrist fracture
Breast disorder/gynecomastia	Breast discomfort Breast induration Breast pain Breast tenderness Gynaecomastia Nipple pain
Cardiac disorder	Acute coronary syndrome Acute myocardial infarction Angina pectoris Angina unstable Aortic arteriosclerosis Aortic stenosis Arrhythmia Arrhythmia supraventricular

Term	Preferred Terms
	Arteriosclerosis Arteriosclerosis coronary artery Atrial fibrillation Atrial flutter Atrioventricular block Atrioventricular block complete Atrioventricular block first degree Atrioventricular block second degree Bradycardia Bundle branch block left Bundle branch block right Cardiac arrest Cardiac disorder Cardiac failure Cardiac failure acute Cardiac failure chronic Cardiac failure congestive Cardiac flutter Cardiogenic shock Cardiovascular insufficiency Conduction disorder Coronary artery disease Coronary artery occlusion Coronary artery stenosis Defect conduction intraventricular Extrasystoles Myocardial infarction Myocardial ischaemia Sinus arrhythmia Sinus bradycardia Sinus node dysfunction Supraventricular extrasystoles Tachycardia Tachycardia paroxysmal Ventricular extrasystoles Ventricular fibrillation Ventricular tachycardia
Heart Failure	Cardiac failure Cardiac failure acute Cardiac failure chronic Cardiac failure congestive

Term	Preferred Terms
	Cardiogenic shock Cardiovascular insufficiency
Ischemic Heart Disease	Acute coronary syndrome Acute myocardial infarction Myocardial infarction Myocardial ischaemia Angina pectoris Angina unstable Arteriosclerosis Arteriosclerosis coronary artery Coronary artery disease Coronary artery occlusion Coronary artery stenosis Hypertensive heart disease
CNS vascular disorders	Cerebral infarction Cerebral ischaemia Cerebrovascular accident Haemorrhage intracranial Ischaemic stroke Subarachnoid haemorrhage Subdural haematoma Transient ischaemic attack
Depressed mood disorders	Depressed mood Depression
Diabetes mellitus and hyperglycemia	Diabetes mellitus Diabetes mellitus inadequate control Diabetic ketoacidosis Diabetic metabolic decompensation Glucose urine present Glycosuria Hyperglycaemia Type 2 diabetes mellitus Blood glucose increased
Fall	Fall
Fatigue	Asthenia Fatigue

Term	Preferred Terms
Hypertension	Blood pressure increased Blood pressure systolic increased Essential hypertension Hypertension
Mental impairment disorders	Amnesia Cognitive disorder Dementia Dementia Alzheimer's type Memory impairment Senile dementia Vascular dementia
Rash	Dermatitis Erythema Rash Rash macular Rash maculo-papular Rash papular Rash pustular
Seizures	Partial seizures Seizure
Vasodilation and flushing	Flushing Hot flush
Weight decreased	Weight decreased
<i>Source: ADAE dataset</i>	

8.2.2 Review of the Safety Database

Overall Exposure

Table 53: Overall Exposure

	Darolutamide, N=954 N (%)	Placebo, N=554 N (%)
Treatment Duration (months)		
Mean (SD)	16.79 (9.46)	12.30 (8.32)

Median (Min, Max)	14.8 mo. (0, 44.3)	11.0 mo. (0.1, 40.5)
Treated for ≤ 12 mo.	374 (39%)	332 (60%)
Treated for >12 to ≤ 24 mo.	360 (38%)	160 (30%)
Treated for >24 mo.	220 (23%)	62 (11%)
Discontinuation due to AE	85 (9%)	48 (9%)
Dose Reductions due to AE	52 (6%)	7 (1.3%)
Dose Interruptions due to AE	119 (13%)	48 (9%)
<i>Source ADAE and ADEX datasets</i>		

At the time of the data cut-off date, 64% of patient on the darolutamide arm and 36% of patients on the placebo arm were continuing to receive study treatment.

Characteristics of the safety population:

The safety (N=1508) and efficacy (N=1509) populations were similar in characteristics. Detailed information regarding the characteristics of the efficacy population can be found in section 8.1.2. The majority of the trial population consisted of geriatric patients (88% percent of patients were ≥65 years and 48% of patients were ≥ 75 years). The trial population primarily consisted of Caucasian (79%) and Asian (13%) patients.

Patients who have received treatment with an osteoclast-targeted therapy to prevent skeletal-related events within 12 weeks of randomization were excluded from trial participation, although those receiving osteoclast-targeted therapy for the treatment of osteoporosis were allowed on study. Patients with clinically significant cardiac disease, including uncontrolled hypertension, stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association (NYHA) Class III or IV congestive heart failure were also excluded from trial.

Reviewer comment. The size, degree of investigational drug exposure and patient composition of the safety population was adequate to provide sufficient characterization of the adverse event profile associated with darolutamide in the target population. The exclusion of patients with clinically significant cardiovascular disease and those receiving osteoclast-targeted bone therapy at dosages indicated for the prevention of skeletal-related events related to solid tumor malignancies limits the generalizability of the safety results to these populations. In addition, due to the predominance of Caucasian and Asian patients on trial, the safety results may not reflect potential treatment toxicity in non-Caucasian or non-Asian populations.

Of note, patients with a medical history of seizures and patients who were at risk for seizure or taking medications that may lower the seizure threshold were not excluded from participation in this trial as the molecular structure of darolutamide results in less penetration of the blood-brain barrier at clinically efficacious doses. However, the number of these patients included was low.

Adequacy of the safety database:

The size of the safety database and the extent of darolutamide exposure were sufficient to characterize the safety profile of darolutamide for the treatment of a serious and life-threatening condition. Supportive safety data was provided from a large randomized trial of darolutamide in combination with ADT and docetaxel in metastatic hormone sensitive prostate cancer which has not reached primary completion and is expected to provide additional data to characterize the safety of darolutamide.

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. No major issues were identified at any of the sites. There were no issues regarding submission quality.

Categorization of Adverse Events

The safety and tolerability assessment of darolutamide was based on the frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to treatment interruptions, AEs leading to dose reductions, select AEs of interest, clinical laboratory assessments (including hematology, serum chemistry, and liver and thyroid function tests) and vital sign measurements. Adverse events were coded using MedDRA Version 21.0. 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 grade for severity using the National Cancer Institute (NCI) Common Technology Criteria for Adverse Events (CTCAE) Version 4.03.

The applicant identified what they termed as special topics in the pivotal trial for further analysis. Special topics were defined as events/disorders representing potential or known risks associated with ADT or with novel anti-androgens. Special topics associated with ADT included bone fracture, fall, fatigue/asthenic conditions, weight decreased, cardiovascular disorders, hypertension, vasodilatation and flushing, diabetes mellitus and hyperglycemia, mental impairment disorders, depressed mood disorders, and breast disorders; while special topics seizure and rash were associated with novel anti-androgen therapy.

Adverse event data was collected throughout the trial and up to only 28+7 days in the post-

treatment period.

Reviewer comment. The Applicant's definition of AE that constituted special topics were predefined. Further analysis of cardiovascular events is discussed below. See section 8.1 for terms that were pooled for that analysis. These special topics are equivalent to what are usually termed adverse events of special interest, or AESI.

Routine Clinical Tests

The sponsor planned to conduct the following routine assessments on clinic visits scheduled on Day 1, 15, and 29 of Cycle 1, Week 16 and every subsequent 16 weeks, unless otherwise specified:

- Physical examination including weight
- Adverse events collected throughout study and follow up period
- ECOG Performance status (stating at 16 weeks)
- 12-lead ECG, BP and HR
- CBC with differential
- Clinical laboratory chemistry including BUN, serum creatinine, sodium, potassium, calcium, LDH (chromogranin A collected at visit 1 only) and urinalysis
- Liver function tests including albumin, ALT, AST, alkaline phosphatase, total bilirubin, total protein
- Total PSA (not collected Day 15 or 29 of Cycle 1)
- Testosterone (not collected Day 15 or 29 of Cycle 1)
- Chest, abdomen and pelvis CT/MRI (starting at 16 weeks)
- Bone scan (stating at 16 weeks)
- BPI-SF, EORTC-QLQ-PR25, FACT-P or PCS or FACT-P, EQ-5D-3L questionnaires (C1D1 and every 16 weeks. FACT-P was assessed at week 16 only and PCS subscale of FACT-P assessed at subsequent 16-week visits. EQ-5D-3L assessed at week 16 visit only and end-of-treatment visit.

Visits during Cycle 1 had to occur between 3-5 days of the schedule date. All subsequent visits had to occur within 7 days of schedule date. Adverse event data was collected until 28 + 7 days following the last administration of study drug or study discontinuation/termination. For patients that discontinued study drug during the double-blind period before confirmed metastasis and not initiating subsequent anti-cancer therapy, AEs and SAEs considered to be related to study treatment or procedures were collected every 16 weeks from End-of-Treatment Visit. The protocol also followed patients with confirmed metastases or who received subsequent treatment after unblinding for AEs or SAEs considered related to study treatment or procedures every 16 weeks.

Reviewer comment. The schedule of routine laboratory testing, clinical testing and clinical evaluations for patients enrolled in the trial, including assessment of adverse events and vital signs, was sufficient although noted to be less frequent than routine assessments

performed in other trials of drugs in the same drug class. Refer to Section 8.2.4 for further discussion regarding impact of assessment interval on AE evaluation. Evaluation for AEs continued for 28 days post-treatment which is likely reasonable for identification of late-onset AEs.

8.2.4 Safety Results

Table 54 presents an overview of safety in the ARAMIS trial.

Table 54. Overview of Safety, ARAMIS

Total number of patients with at least one:	Darolutamide (N = 954) N (%)	Placebo (N = 554) N (%)
Grade 5 AE	37 (3.9%)	18 (3.2%)
Grade 3-4 AE	258 (27%)	125 (23%)
SAE	237 (25%)	111 (20%)
AE leading to treatment discontinuation	85 (9%)	48 (9%)
<i>Source: ADAE dataset</i>		

Deaths

Deaths in the safety population of ARAMIS are summarized in Table 50. Listed deaths include deaths during treatment and occurring up to 30 days after the last dose of study drug as of the database lock date (September 3, 2018). Overall 3.9% of patients receiving darolutamide and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for the darolutamide arm. Patient narratives were reviewed for attribution of death due to treatment-emergent adverse events.

Table 55. Deaths on study, ARAMIS

	Darolutamide (N = 954) N (%)	Placebo (N = 554) N (%)
Total Deaths	37 (3.9%)	18 (3.2%)
Deaths within 30 days of last dose	23 (2.4%)	11 (2%)
Deaths attributed to disease progression	3 (0.3%)	1 (0.2%)
Deaths attributed to other/unknown causes	14 (1.5%)	3 (0.5%)

Source: ADAE dataset

Of the reported TEAEs with an outcome of death, the applicant identified one that was determined to be a result of darolutamide-related toxicity. This patient died from intestinal perforation. On FDA review, an additional 10 patients were considered to have died due to toxicity that was at least possibly darolutamide-related. These patients died from fall (1), cardiac arrest (1), myocardial infarction (1), cardiac failure (4), cardiac disorder (1), coronary artery disease (1), and aortic dissection (1).

Table 56. Brief Summaries of darolutamide-related deaths, ARAMIS

Adverse Event	Brief case description	Days from last dose to death
Intestinal perforation Patient (b) (6) <i>Reviewer note: Intestinal perforation is not a known toxicity related to ADT, however occurred while on darolutamide therapy.</i>	A 78-year-old man with a remote history of colon resection and cholecystectomy experienced a Grade 4 small intestinal perforation on Day 434.	0
Fall Patient (b) (6) <i>Reviewer note: Fall and fracture are known toxicities related to ADT.</i>	An 82-year-old man with prior history of myocardial infarction experienced Grade 3 fall from stairs resulting in Grade 5 injuries on Day 75.	0
Cardiac Arrest Patient (b) (6) <i>Reviewer note: Coronary artery disease and myocardial infarction are known toxicities related to ADT.</i>	An 87-year-old man with a history of MI, CABG, hypercholesterolemia and hypertension experienced Grade 5 cardiac arrest on Day 695.	1
Myocardial Infarction Patient (b) (6) <i>Reviewer note: Coronary artery disease and myocardial infarction are known toxicities related to ADT, however appears to occur in the setting of increased body temperature and other clinical</i>	A 74-year-old man with history of hypertension, hypercholesterolemia, abdominal aortic atherosclerosis, peripheral arterial disease and chronic obstructive pulmonary disease presented with Grade 1 increased body temperature on Day 20. His condition	4

Adverse Event	Brief case description	Days from last dose to death
<i>decline. The etiology of the myocardial infarction is unclear, however occurred while on darolutamide therapy.</i>	deteriorated, and he required hospitalization on Day 32 with Grade 3 increased body temperature. He experienced worsening cardiac function during admission and had fatal MI on Day 37.	
Cardiac Failure Patient (b) (6) <i>Reviewer note: Cardiovascular disease is a known toxicity related to ADT. Although this patient also experienced severe respiratory distress and anemia, his exposure to darolutamide makes a causal relationship plausible.</i>	An 87-year-old-man with history of hypertension, chronic venous insufficiency, and chronic obstructive pulmonary disease was hospitalized on Day 690 with severe respiratory distress and severe anemia. He experienced cardiac failure on the same day and died.	Date unknown (approximately 13)
Cardiac Disorder Patient (b) (6) <i>Reviewer note: Cardiovascular disease is a known toxicity related to ADT.</i>	A 74-year-old man with obesity experienced Grade 5 cardiac disorder on Day 112 thought to be related to chronic cardiac ischemia.	15
Aortic Dissection Patient (b) (6) <i>Reviewer note: Cardiovascular disease is a known toxicity related to ADT.</i>	A 68-year-old man with history of hypertension and obesity developed Grade 5 aortic dissection on Day 490	1
Cardiac Failure Patient (b) (6) <i>Reviewer note: Cardiovascular disease is a known toxicity related to ADT.</i>	An 84-year-old man with a history of coronary heart disease with CABG and PCI, hypertension, diabetes mellitus, and arrhythmia experienced Grade 5 cardiac failure on Day 938.	0
Cardiac Failure Patient (b) (6) <i>Reviewer note: Cardiovascular disease is a known toxicity</i>	A 76-year-old man with history of hypertensive cardiomyopathy and heart failure experienced Grade 5 cardiac failure on Day 455.	0

Adverse Event	Brief case description	Days from last dose to death
<i>related to ADT.</i>		
Cardiac Failure Patient (b) (6) <i>Reviewer note: Cardiovascular disease is a known toxicity related to ADT.</i>	A 78-year-old man with history of hypertensive cardiomyopathy, ischemic stroke, and aortocoronary bypass experienced Grade 5 cardiac failure on Day 167	0
Coronary Artery Disease Patient (b) (6)	An 84-year-old-man with a history of coronary artery disease and coronary bypass, hypertension and obesity experienced Grade 5 coronary artery disease on Day 422.	20
<i>Source: Patient narratives</i>		

Reviewer comment: There was one death on study secondary to fall. Although fall is a known toxicity related to ADT, the incidence of fall events was infrequent and did not warrant additional warning or precaution.

Serious Adverse Events

Non-fatal serious adverse events (SAEs) occurred in 25% of patients on the darolutamide arm and in 20% of patients on the placebo arm. The overall incidence of any one particular SAE was low. The most frequent SAEs (>1%) were urinary retention and pneumonia. Urinary tract infection (0.7% vs 0) is the only SAE that occurred at an incidence >0.5% greater on the darolutamide arm than placebo arm.

Table 57. Serious Adverse Events in >0.5% of patients, ARAMIS

	Darolutamide, N=954 N (%)	Placebo, n=554 N (%)
Urinary retention	15 (1.6%)	18 (3.2%)
Pneumonia	13 (1.4%)	6 (1.1%)
Hematuria	10 (1.0%)	6 (1.1%)
Atrial fibrillation	8 (0.8%)	3 (0.5%)
Cardiac failure	8 (0.8%)	4 (0.7%)
Urinary Tract Infection	7 (0.7%)	0
Urinary tract obstruction	6 (0.6%)	2 (0.4%)
<i>Source: ADAE dataset</i>		

Reviewer comment. SAEs were uncommon on this trial and when present did not occur at a clinically significantly higher incidence on the darolutamide arm compared to placebo.

Dropouts and/or Discontinuations Due to Adverse Effects

There were 85 (9%) patients on the darolutamide arm and 48 (9%) patients on the placebo arm who permanently discontinued due to adverse events. In the full safety analysis population there were 142 patients on the darolutamide arm and 178 patients on the placebo arm that discontinued treatment due to investigator judgement or personal/other reasons.

Table 58. Adverse Events Resulting in Permanent Discontinuation in >1 patient

	Darolutamide, N=954		Placebo, N=554	
	N	%	N	%
Cardiac failure	4	0.4%	4	0.7%
Death	4	0.4%	1	0.2%
Cardiac Arrest	2	0.2%	2	0.4%
Abdominal Pain	2	0.2%	0	0
Diarrhea	2	0.2%	0	0
General physical health deterioration	2	0.2%	0	0
Pneumonia	2	0.2%	0	0
Blood creatinine increased	2	0.2%	0	0
Pancreatic carcinoma	2	0.2%	0	0
Cerebral Infarction	2	0.2%	0	0
Ischemic stroke	2	0.2%	2	0.4%
Pulmonary embolism	2	0.2%	1	0.2%

Source: ADAE dataset

Dose Interruptions Due to Adverse Effects

Dose Interruptions due to adverse events occurred in 119 (13%) patients on the darolutamide arm and 48 (9%) patients on the placebo arm. The most common ($\geq 0.5\%$) adverse events leading to treatment interruptions were hypertension, diarrhea, and pneumonia.

Dose Reductions Due to Adverse Effects

Dose reductions due to adverse events occurred in 52 (6%) patients on the darolutamide arm and 7 (1.3%) patients on the placebo arm. Dose reductions were rare on this trial but were most frequently due to fatigue (0.7%).

Reviewer comment. Overall the incidence of dose interruptions or reductions due to adverse events was rare suggesting darolutamide is reasonably tolerated in this population.

Significant Adverse Events

The sponsor identified Special Topics AEs in ARAMIS which were defined as events/disorders representing potential or known risks associated with ADT or with novel anti-androgens. These included events associated with ADT such as bone fracture, fall, fatigue/asthenic conditions, weight decreased, cardiovascular disorders, hypertension, vasodilatation and flushing, diabetes mellitus and hyperglycemia, mental impairment disorders, depressed mood disorders, and breast disorders/gynecomastia. Special topics associated with novel anti-androgen therapy included seizure and rash. Refer to Table 47 for pooled terms.

There were 407 (43%) of patients on the darolutamide arm and 184 (33%) of patients on the placebo arm that experienced an adverse event special topic. Ninety-three (10%) patients on the darolutamide arm and 33 (6%) patients on the placebo arm experienced a Grade 3 or 4 Special Topics AE. The most common Special Topics AEs were cardiac disorders, reported in 154 (16%) patients on the darolutamide arm and 49 (9%) patients on the placebo arm, and fatigue, reported in 151 (16%) patients on the darolutamide arm and 63 (11%) patients on the placebo arm.

Other Special Topics AEs such as falls (3.8% in darolutamide arm vs 4.2% in placebo arm), fractures (4.2% in darolutamide arm vs 3.6% in placebo arm), and rash (3% in darolutamide arm vs 0.9% in placebo arm) were relatively uncommon in this trial.

Reviewers comment. Special Topics AEs were predefined, and these special topics are equivalent to what are usually termed adverse events of special interest, or AESI.

Treatment Emergent Adverse Events and Adverse Reactions

Overall the incidence of treatment emergent adverse events was low in the ARAMIS trial. The most common adverse event reported was fatigue (16%) on the darolutamide arm. Grade 3-4 adverse events were also infrequent with the most common reported event being hypertension (3.1%) on the darolutamide arm. For pooled terms, refer to Table 52.

Table 59. Grade 1-4 Adverse Events in ≥ 5% of Patients in ARAMIS

	Darolutamide, N=954		Placebo, N=554	
	All Grades N (%)	Grade 3-4 N (%)	All Grades N (%)	Grade 3-4 N (%)
General Disorders and Administration				

	Darolutamide, N=954		Placebo, N=554	
	All Grades N (%)	Grade 3-4 N (%)	All Grades N (%)	Grade 3-4 N (%)
Fatigue	151 (16%)	6 (0.6%)	63 (11%)	6 (1.1%)
Musculoskeletal and Connective Tissue Disorders				
Back pain	84 (8.8%)	4 (0.4%)	50 (9.0%)	1 (0.2%)
Arthralgia	77 (8.1%)	3 (0.3%)	51 (9.2%)	2 (0.4%)
Pain in extremity	57 (6.0%)	0	17 (3%)	1 (0.2%)
Gastrointestinal Disorders				
Diarrhea	66 (6.9%)	0	31 (5.6%)	1 (0.2%)
Constipation	60 (6.3%)	0	34 (6.1%)	0
Nausea	48 (5.0%)	2 (0.2)	32 (5.8%)	0
Vascular Disorders				
Hypertension	63 (6.6%)	30 (3.1%)	29 (5.2%)	12 (2.2%)
Hot flush	50 (5.2%)	0	23 (4.2%)	0
Blood and Lymphatic System Disorders				
Anemia	53 (5.6%)	8 (0.8%)	25 (4.5%)	2 (0.4%)
Infections and Infestations				
Urinary tract infection	47 (4.9%)	6 (0.6%)	28 (5.1%)	3 (0.5%)
<i>Source: ADAE dataset</i>				

Reviewer comment. During the review, we noted that the incidence of some of the more commonly reported treatment emergent adverse events (fatigue, diarrhea, hypertension and nausea) on the placebo arm of ARAMIS were reported at a lower frequency in this trial than on the control arms of monotherapy trials of other drugs in the same drug class and disease setting (enzalutamide and apalutamide). Although there are limitations to cross-trial comparisons, this led to a concern that there might have been general underreporting of adverse events overall in ARAMIS, as placebo arms in these very similar trials with very similar characteristics of enrolled patients would presumably be expected to have a very similar toxicity profile. The applicant responded to our inquiry regarding this discrepancy in reported toxicity profile of the ARAMIS placebo arm by hypothesizing that a difference in the frequency of AE assessment in ARAMIS compared to the SPARTAN trial might account for the difference in reported incidence of these events on the placebo arm. Of note, the frequency of adverse event assessment and PRO collection were almost identical in ARAMIS and PROSPER trials.

The applicant conducted AE focused monitoring prior to unblinding and reported that they did not observe any evidence of underreporting of TEAEs in ARAMIS.

The FDA conducted an internal analysis of investigator-reported and patient-reported outcomes (PRO) assessments of fatigue in the ARAMIS trial and compared this to fatigue reporting in SPARTAN. In general, investigator-reported fatigue in both trials was less frequent than reports of fatigue elicited through PRO measures, although this difference in reporting was identified at a higher degree in the ARAMIS data.

Consideration was also given to the potential effect of patient geographic distribution on event reporting. In ARAMIS, 46% of the patient population was treated in the U.S., Western Europe, or Australia (9.2% of patients treated in the U.S.) while 80% of patients enrolled on SPARTAN were treated in the same geographic region (28% of patients treated in the U.S.).

Although there are many limitations to cross-trial assessments, the difference in AE reporting in the placebo arm of ARAMIS compared to the placebo arms of other drugs in this drug class and this disease setting is notable. There are multiple potential contributing factors as discussed, including underlying differences in the patient populations that may limit generalizability of the AE profile of ARAMIS to the target population. However, any apparent reduction in AEs on the darolutamide arm compared to other drugs in this disease setting is limited by a cross-trial comparison. In addition, such a comparison is also subject to the same issues that appear to have affected the reported incidence of these AEs in the placebo arm of ARAMIS compared to the placebo arms of trials of other drugs in this disease setting.

Laboratory Findings

Laboratory values were graded according to CTCAE v4.03 and evaluation of laboratory abnormalities was based on the worst grade of each laboratory event after the start of treatment. All laboratory abnormalities were primarily CTCAE Grade 1-2 and Grade 3-4 events were rare. The most common hematology events include all grade anemia, leukopenia, neutropenia, lymphopenia and thrombocytopenia. The most common chemistry abnormalities were hyperkalemia, increased creatinine, increased AST, and increased blood bilirubin. Other hepatic laboratory abnormalities were uncommon. There were no cases of Hy's law. The most common Grade 3-4 abnormality was neutropenia, which occurred in 3.5% of patients on the darolutamide arm and 0.2% of patients on the placebo arm.

Table 60. Laboratory Abnormalities on ARAMIS

	Darolutamide (N)	Darolutamide Grade 1-4%	Darolutamide Grade 3-4%	Placebo (N)	Placebo Grade 1-4%	Placebo Grade 3-4%
Hematology						

	Darolutamide (N)	Darolutamide Grade 1-4%	Darolutamide Grade 3-4%	Placebo (N)	Placebo Grade 1-4%	Placebo Grade 3-4%
Anemia	950	85%	0.7%	551	77%	0.9%
White blood cell decreased	951	20%	1.2%	552	12%	1.1%
Neutrophil count decreased	951	20%	4%	552	9%	0.5%
Lymphocyte count decreased	951	53%	4%	552	47%	3%
Platelet count decreased	951	19%	0.2%	551	17%	0.2%
Chemistry						
Hyperkalemia	951	20%	1.1%	551	17%	1.3%
Creatinine increased	951	29%	0.6%	551	29%	0.9%
Aspartate aminotransferase increased	951	23%	0.5%	551	14%	0.2%
Blood bilirubin increased	950	16%	0.1%	551	7%	0
Hyponatremia	951	12%	1.6%	551	13%	1.1%
Hypercalcemia	942	9%	0	548	11%	0
Hypocalcemia	951	19%	0	551	17%	0
<i>Source: ADXT dataset</i>						

Vital Signs

No differences were observed in changes of mean or median values between the treatment arms over the course of the study.

Electrocardiograms (ECGs)

In ARAMIS, ECGs were collected at baseline, Days 1, 15 and 29 of Cycle 1, at week 16 and every 16 weeks thereafter. Baseline ECG abnormalities were more frequently noted in the patients on the darolutamide study arm than the placebo arm but were consistent with the patients' medical history of cardiac disorders. Analysis of ECG data by study visit did not identify any significant changes in ECG related to treatment arm or any significant changes from baseline.

QT

The QT-IRT team reviewed the data from a subset of approximately 500 patients in the ARAMIS

trial. No large QTc prolongation effect (i.e. >20 ms) of darolutamide was detected in the QT assessment.

Immunogenicity

Not applicable

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Cardiac disorder

The risk of cardiovascular disease is increased for patients on prolonged androgen deprivation therapy. There was a limited incidence of risk factors for cardiovascular disease in patients on the darolutamide arm. These included hypertension (7% all grade), hypercholesterolemia (0.3% all grade), hypertriglyceridemia (0.3% all grade), and hyperglycemia (0.9% all grade). There was a high prevalence of ongoing comorbid medical conditions at time of enrollment in this patient population. These past medical conditions included hypertension (65% v 64%), obesity (60% v 60%), cardiac disorders (46% v 40%), hypercholesterolemia (13% v 13%), and diabetes mellitus (11% v 12%). Cardiac disorders in the darolutamide arm were reviewed as a pooled term and included conduction, ischemic, and heart failure events (See Table 47 for pooled terms). There were 154 (16%) patients on the darolutamide arm with a cardiac disorder adverse event compared to 49 (9%) on the placebo arm. Grade 3-5 cardiac disorder adverse events were also more frequent on the darolutamide arm (6% v 3%). There were 20 (2.1%) patients on the darolutamide arm and 6 (0.9%) patients on the placebo arm who had heart failure events. Exposure adjusted incidence rates (EAIR) of heart failure events on the darolutamide arm were 2.8% compared to 3.3% on the placebo arm. Incidence of Grade 3-5 heart failure adverse events were comparable on the darolutamide and placebo arms (1% v 0.7%). There were 41 (4%) patients on the darolutamide arm and 19 (3.4%) patients on the placebo arm who had ischemic cardiac events. EAIR of ischemic cardiac events on the darolutamide arm were 1.5% compared to 0.9% on the placebo arm. Incidence of Grade 3-5 ischemic cardiac events were slightly more frequent on the darolutamide arm compared to placebo (2.4% v 1.3%).

Reviewer comment. All grade and Grade 3-4 cardiac disorder adverse events were more common in the darolutamide arm compared to placebo. This may be explained by the known increased risk of cardiovascular disease associated with androgen deprivation, the slight numeric increase of ongoing cardiac disorders at enrollment in the darolutamide arm, and increased exposure to darolutamide on the treatment arm. Differences in adverse event incidence between the two arms did not persist when EAIR were calculated for heart failure and ischemic cardiac events. No clear difference was observed in Grade 5 cardiac disorder TEAEs where the incidence was comparable in the darolutamide arm (1.0% vs. 1.4% observed in the placebo arm). However, when used in larger population after marketing, a numerical difference observed on the study may become more obvious due to increased incidence of cardiac disorders such as ischemic heart disease and heart failure. These adverse reactions will

be followed post marketing. The sponsor provided further data from analysis of cardiac TEAEs and observed that a medical history of a cardiac disorder appeared to be more common in patients experiencing cardiac TEAEs. The numbers of patients with ischemic cardiac events and heart failure events were added to section 6 of product labeling. However, based on the above evaluation, additional warning and precaution regarding cardiac events was not added to the label.

8.2.5.2 Seizure

Increased risk of seizure has been observed in patients treated with novel anti-androgens. In pre-clinical and clinical trials of darolutamide, there was no indication of increased seizure potential which may be attributed to its structure and low penetration of the blood brain barrier. Twelve patients with history of seizure were enrolled onto the darolutamide arm. There were no seizure events in any of the patients on the darolutamide arm with medical history of seizure. Two patients (0.2%) on the darolutamide arm and 1 (0.2%) on the placebo arm experienced an adverse event of seizure. One patient (██████████^{(b) (6)}) with a remote history of syncope (1988) experienced a Grade 3 ischemic stroke on Day 108. Darolutamide was temporarily discontinued. He subsequently presented on Day 457 with Grade 2 seizure. He was treated with anticonvulsant and sedative. The patient remained on study drug and no further events of seizure were noted. The patient's death occurred on Day 482 and was attributed to diarrhea. The second patient (██████████^{(b) (6)}) had no related past medical history but reported recurrent episodes of several minutes of loss of consciousness without falls since April 2016. He experienced Grade 1 partial seizures on Day 262. An EEG performed during hospitalization revealed potential signs of epileptiform activity. No pathologic findings were noted on CT scan of the head. He was treated with anticonvulsant and continued study drug until metastases were confirmed on Day 870. No additional potential cases of seizure were identified.

Reviewer comment. Despite allowing patients with a known history of seizure to enroll on ARAMIS, there were no seizure events in any of the 12 patients on the darolutamide arm with a known medical history of seizure. The fact that these patients were enrolled in ARAMIS may be of clinical relevance to practitioners and was thus included in the baseline demographics in section 14 of the label, especially since patients with a known history of seizure were not enrolled in the trials that led to approval of apalutamide or enzalutamide in this setting. We do note that there was one case in which a patient receiving darolutamide who experienced a grade 1 seizure as described above (Patient ██████████^{(b) (6)}) may have had a questionable history of prior seizure activity.

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

Patient-Reported Outcomes (PRO) were assessed in the ARAMIS trial using the BPI-SF, FACT-P, EORTC-QLQ-PR25, and EQ-5D-3L questionnaires. The main method of PRO assessment was the FACT-P. The FACT-G is a general HRQoL PRO instrument intended for use in a variety of chronic

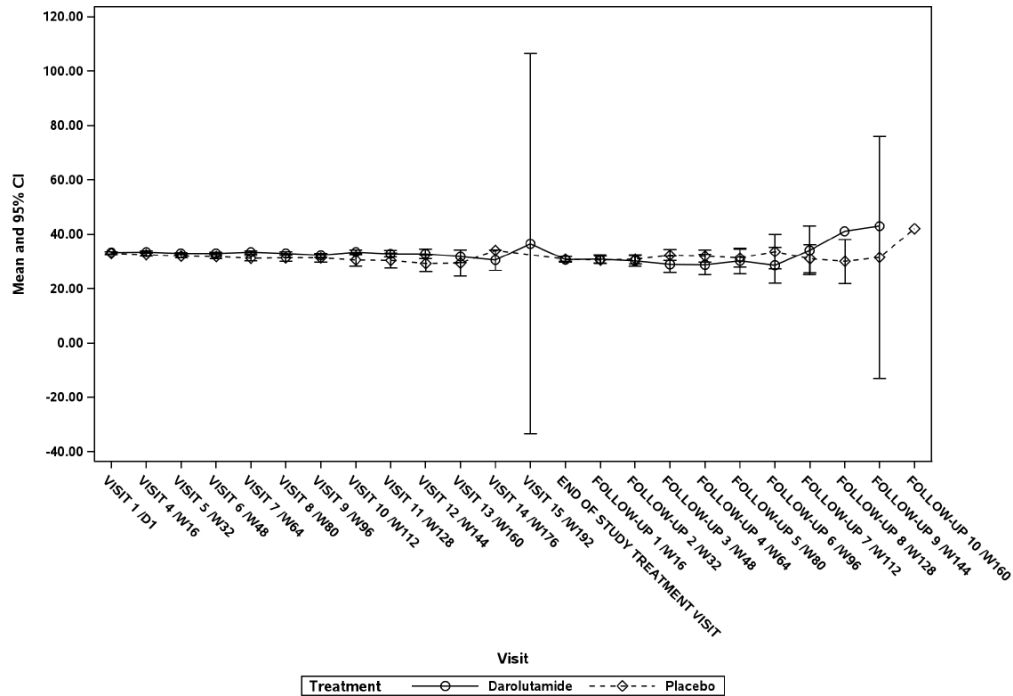
diseases. It consists of a total of 27 questions assessing the patient across four domains: physical, social/family, emotional and functional. Each question is answered on a 5-point scale ranging from 0 (Not at all) to 4 (Very much). FACT-P is an additional 12-item subscale assessing the prostate cancer domain. The BPI-SF is a 9-item questionnaire used to assess the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The EORTC-QLQ-PR25 is a HRQoL questionnaire consisting of 25 prostate cancer-specific items assessing physical symptoms, emotional states and sexual function. The EQ-5D-3L is a two-part general HRQoL instrument that consists of a descriptive system evaluating five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) on three levels (no problem, some problems, and extreme problems) and a visual analogue scale with endpoints labeled "Best imaginable health state" and "Worst imaginable health state" to determine patients' self-assessment of their health.

Responses to the PRO questionnaires were collected every 16 weeks. The FACT-P was assessed at week 16 only and prostate cancer subscale (PCS) of FACT-P assessed at subsequent 16-week visits. EQ-5D-3L was assessed at week 16 visit only and end-of-treatment visit. Patients that discontinued study drug prior to unblinding and confirmed metastasis, had confirmed metastasis or who elected to receive a subsequent treatment after unblinding continued to be followed with PRO assessment every 16 weeks until confirmed metastases, death or end of study. The applicant reports 100% PRO completion rates for FACT-P PCS up to Week 64 were greater than 90% in both treatment arms.

Overall no conclusive difference was observed in FACT-P Prostate Cancer Subscale score over time during the first 64 weeks (Figure 24).

Figure 24: Mean FACT-P Prostate Cancer Subscale Score Over Time

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Source: Figure 1/41 in Applicant response to PRO IR dated 5/22/19

Reviewer comment. *Interpreting the impact of the various composite scores analyzed on the safety and tolerability of darolutamide is difficult due to methods of assessment that include reports of emotional state and functionality that can be influenced by non-drug factors. Therefore, these measures may not be truly reflective of the effects of the drug being evaluated. Although the prostate cancer subscale of the FACT-P was used in this trial the items are more relevant in assessing symptoms associated with disease and treatment in the early prostate cancer setting as opposed to patients with castration-resistant disease.*

There was a high rate of completion of the PRO assessments in ARAMIS increasing the reliability and decreasing potential bias of the results.

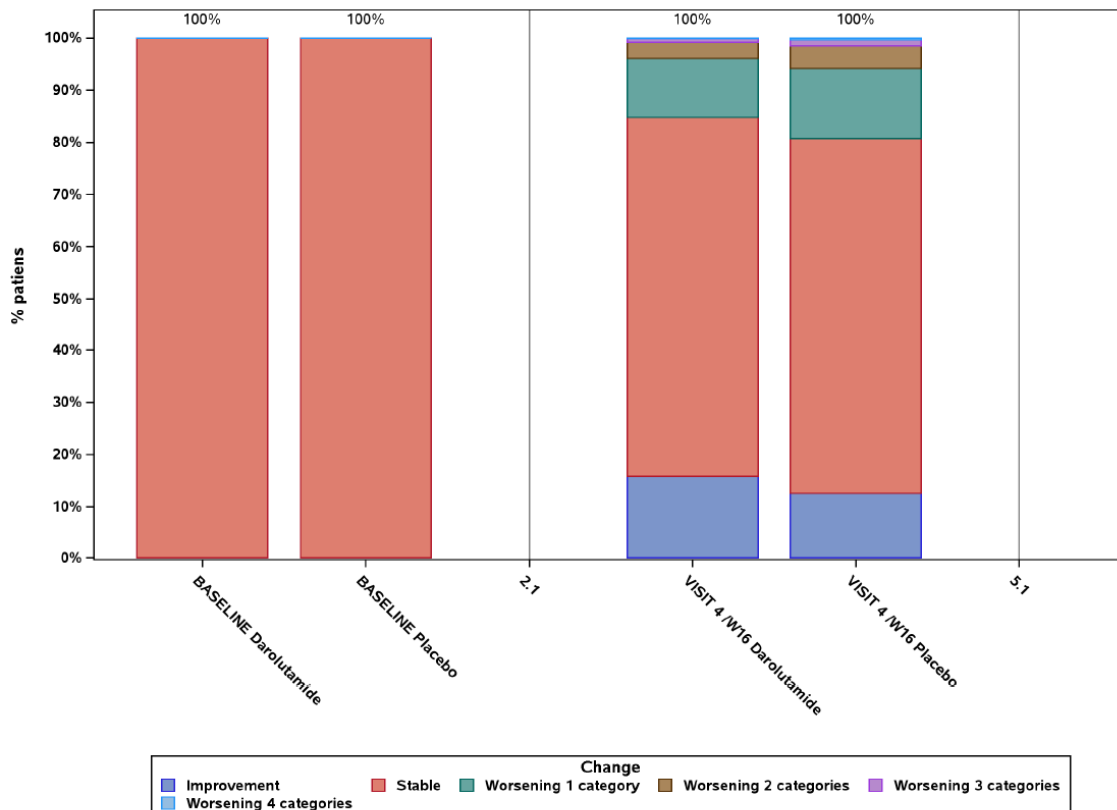
Several items from the FACT-G and EORTC-QLQ-PR25 were identified for further exploratory analysis to provide a more descriptive and informative assessment of drug and disease effects in this patient population. The items chosen included:

- **FACT GP1- “I have a lack of energy”**
- **FACT GP2- “I have nausea”**
- **FACT GP5- “I am bothered by the side effects of treatment”**
- **FACT GF1- “I am able to work (including work at home)”**
- **FACT C2- “I am losing weight”**
- **FACT P1- “I have aches and pains that bother me”**

- **FACT P7- “I have difficulty urinating”**
- **EORTC QLQ-PR25 #39- “Have your daily activities been limited by your urinary problems?”**
- **EORTC QLQ-PR25 #40- “Have your daily activities been limited by your bowel problems?”**

For items FACT-GP1, FACT-GP2, FACT-GP5 and FACT-GF1 data was available for baseline and Week 16. Most patients were stable in their responses from baseline. For items FACT-C2, FACT-P1 and FACT-P7 data was available up to Week 96 (6 post-baseline assessments). The majority of patients were stable in their responses from baseline. For items #39 and 40 of the EORTC QLQ-PR25 data was available for up to Week 96 (6 post-baseline assessments). Data also demonstrates that responses were stable from baseline for the majority of patients.

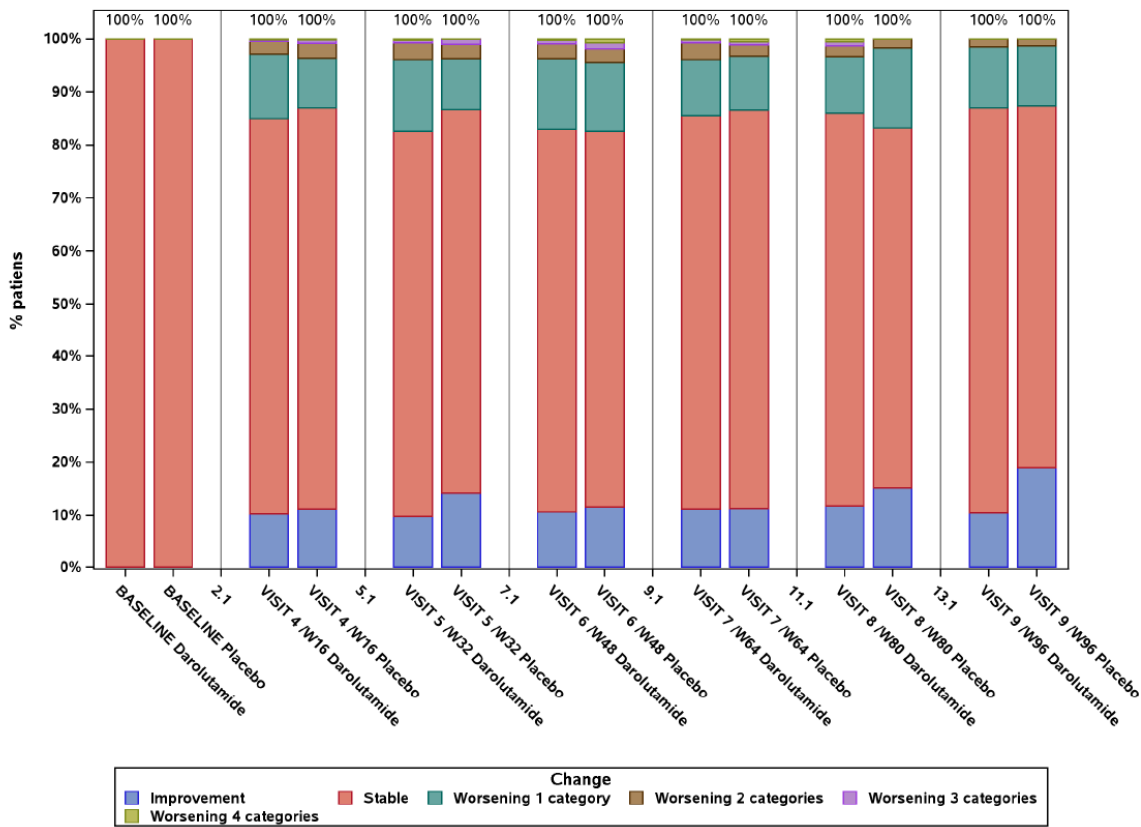
Figure 25: Change from Baseline of Responses by Arm: FACT-GP5 – “I am bothered by the side effects of treatment”



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Source: Figure 1/54 in Applicant response to PRO IR dated 5/22/19

Figure 26: Change from Baseline by Arm: FACT-C2 – “I am losing weight”



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Source: Figure 1/58 in Applicant response to PRO IR dated 5/22/19

Reviewer comment. The exploratory analysis of the PROs suggest darolutamide is well tolerated and that function is not adversely affected by darolutamide over a long duration. Further review of specific items did not identify an area with discordant change compared to baseline over time.

See Section 18.5 Additional Clinical Outcome Assessment Analyses for detailed PRO results.

8.2.7 Safety Analyses by Demographic Subgroups

Subgroup analyses based on age and race were not performed as the patient population in ARAMIS was entirely male and predominantly Caucasian. Subgroup analyses were performed based on age. Of the 954 patients who received darolutamide in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. Grade 3-4 adverse events occurred in 30% of patient 65 years or older and 34% of patients 75 years or older on the darolutamide arm compared to 28% (104/375) of patients 65 years or older and 32% (68/210) of patients 75 years or older on placebo. No overall differences in safety or efficacy were observed between these patients and younger patients.

Table 61. Grade 1-4 Adverse Reactions in >5% of Patients Treated with Darolutamide by Age

	< 65 years N = 113 (%)		65-74 years N = 373 (%)		≥ 75 years N = 468 (%)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
All	94 (83%)	22 (19%)	322 (86%)	85 (23%)	402 (86%)	125 (27%)
Fatigue	17 (15%)	1 (0.9%)	45 (12%)	0	72 (15%)	3 (0.6%)
Arthralgia	12 (11%)	0	38 (10%)	3 (0.8%)	38 (8%)	0
HTN	9 (8%)	3 (3%)	34 (9%)	9 (2%)	35 (7%)	18 ((4%)
Hot flush	9 (8%)	0	24 (6%)	3 (0.8%)	19 (4%)	0

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

Carcinogenicity studies were not conducted.

Human Reproduction and Pregnancy

Darolutamide is not indicated for use in females and its safety and efficacy have not been established in females. Based on its mechanism of action, darolutamide can cause fetal harm and pregnancy loss. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide.

Pediatrics and Assessment of Effects on Growth

Darolutamide has not been studied in a pediatric population. The Initial Pediatric Study Population waiver was granted based on the low incidence of prostate cancer in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The maximum tolerated dose was not identified during the Phase 1/2 development of darolutamide. There were also no dose-limiting toxicities noted for doses up to 900 mg BID. This was also the maximum dose evaluated at a BID schedule. Doses over 700 mg BID exceed

the limit of absorption. There is no evidence to suggest a risk for dependence on darolutamide. 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

Darolutamide has not yet been approved in any market.

Expectations on Safety in the Postmarket Setting

Darolutamide was well tolerated in the safety analysis population with low incidence of adverse events. There is low expectation for safety events in the postmarketing setting.

8.2.11 Integrated Assessment of Safety

The safety profile of darolutamide in patients with non-metastatic castration-resistant prostate cancer is acceptable. The size of the safety database and the duration of darolutamide exposure were sufficient to characterize the safety of darolutamide for the treatment of a serious and life-threatening condition. There were relatively few discontinuations due to adverse events on this trial and the proportion was comparable on the darolutamide and placebo arms (9% each). Overall survival data are immature at this time, and there is a numerical trend toward overall survival, which further supports the safety of darolutamide. Notable toxicities include fatigue, pain in extremity, and rash. There were rare events of seizure and no seizure events in the 12 patients receiving darolutamide with a known prior history of seizure. This reviewer does not recommend a risk evaluation and mitigation strategy (REMS) given the current safety profile of darolutamide. Recommendations for safe and effective use of darolutamide will be made in labeling, including a patient information inset.

8.3 Statistical Issues

There were no major statistical issues with this application. The applicant submitted an NDA for the NME darolutamide based on results from the ARAMIS study. The study enrolled 1509 patients with a primary endpoint of MFS as determined by BICR. Secondary endpoints included OS, time to pain progression, time to first symptomatic skeletal event, and time to initiation of cytotoxic chemotherapy. The primary analysis of MFS was statistically significant, but OS results were still immature.

The primary analysis of MFS was conducted with a cutoff date of 3 September 2018 at which point 437 MFS events had occurred (221 in the darolutamide arm and 126 in the placebo arm). Results showed a statistically significant improvement in MFS for patients on darolutamide compared to placebo with a stratified hazard ratio of 0.413 (95% CI: 0.341, 0.500; two-sided stratified log-rank p-value <0.0001). The estimated median MFS was 40.4 months (95% CI: 34.3, NE) for darolutamide compared to 18.4 months (95% CI: 15.5, 22.3) for placebo. Results were

consistent across sensitivity analyses and no apparent outliers were observed in subgroup analyses.

There was an interim analysis for OS conducted at the time of the primary analysis of MFS. Results from the interim analysis showed that 136 (56.7%) of the 240 OS events planned for the final OS analysis had occurred. The stratified HR for the interim OS analysis was 0.706 (95% CI: [0.501, 0.994]; $p = 0.045$), and medians were not reached in either treatment arm. These results were not considered statistically significant as the p -value was greater than the pre-specified interim alpha boundary of 0.0005. Since OS was not statistically significant at its interim analysis, the remaining key secondary endpoints of time to pain progression, time to first symptomatic skeletal event, and time to initiation of cytotoxic chemotherapy could only be summarized descriptively. Results from the analyses of the remaining secondary endpoints were all supportive of the primary endpoint. A qualitative description of the time to pain progression results was included in labeling. However, data for the endpoints of time to initiation of cytotoxic chemotherapy and time to first SSE were immature (low event rates) limiting the interpretation of their results. Per the applicant's SAP, updated analyses of time to initiation of cytotoxic chemotherapy and time to first SSE will be performed at the time of final OS analysis.

8.4 Conclusions and Recommendations

The safety profile of darolutamide in patients with NM-CRPC is acceptable. The size of the safety database and duration of exposure of darolutamide were sufficient to characterize the safety of darolutamide for the treatment of a serious and life-threatening condition. The proportion of patients that discontinued treatment due to an adverse event was relatively small and equivalent in the darolutamide and placebo arms. The applicant identified what they termed as adverse event special topics which included events associated with ADT such as bone fracture, fall, fatigue/asthenic conditions, weight decreased, cardiovascular disorders, hypertension, vasodilatation and flushing, diabetes mellitus and hyperglycemia, mental impairment disorders, depressed mood disorders, and breast disorders/gynecomastia and events associated with novel anti-androgen therapy such as seizure and rash. Incidence of seizure was rare on both trial arms. None of the patients on the darolutamide arm with a known history of seizure had a seizure event while on trial. All disciplines agree that darolutamide has a favorable risk-benefit profile, and do not identify any issues that would preclude approval.

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X

Primary Statistical Reviewer

X

Statistical Team Leader

X

Primary Clinical Reviewer

X

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The Division did not refer this efficacy supplement to an advisory committee because darolutamide is not the first drug in this class, the safety profile is acceptable in this indication, and the clinical trial design is similar to that used previously in this class.

10 Pediatrics

Darolutamide 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.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

Summary of Significant Labeling Changes		
Section	Proposed Labeling	Approved Labeling (as of July 24, 2019)
Highlights of Labeling		
Warnings and Precautions	Embryo-Fetal Toxicity	FDA removed (b) (4) in Highlights and multiple labeling sections (i.e., Sections 5, 8, 17) consistent with OHOP best labeling practices.
Drug Interactions	(b) (4) (b) (4)	FDA revised to the following: • Combined P-gp and Strong or Moderate CYP3A Inducers: Avoid concomitant use. (7.1) • Combined P-gp and Strong CYP3A Inhibitors: Monitor patients more frequently for NUBEQA adverse reactions. (7.1) FDA revised to: • BCRP Substrates: Avoid concomitant use of drugs that are BCRP substrates. If the concomitant use cannot be avoided, monitor patients more frequently for adverse reactions and consider dose reduction of the BCRP substrate drugs.
Use in Specific Populations	None.	FDA added darolutamide dose modifications for patients with severe renal impairment and moderate hepatic impairment.
Full Prescribing Information		
2. Dosage and Administration	2.1 Recommended Dosage ...	FDA revised this subsection to improve prominence and to align and ensure that patients receiving NUBEQA also receive a GnRH analog concurrently or

		have had a bilateral orchiectomy.
	2.3 Recommended Dosage in Patients with Severe Renal Impairment <i>(Subsection added by FDA)</i>	FDA added this subsection.
	2.4 Recommended Dosage in Patients with Moderate Hepatic Impairment <i>(Subsection added by FDA)</i>	FDA added this subsection.
5. Warnings and Precautions	4.1 Embryo-Fetal Toxicity ...	FDA revised this subsection (and subsection 8.3) to advise males with female partners of reproductive potential to use contraception during and for 1 week (Applicant proposed (b) (4) (b) (4)) after the last dose. This was based on darolutamide half-lives following the last dose expected to be teratogenic based on mechanism of action. <i>See the Section 5 of this review for more information.</i>
5. Adverse Reactions	...	FDA made the following revisions: - Removed the statement (b) (4) - Added statements to provide the overall incidence of, and most common, serious adverse reactions (including deaths) observed in the ARAMIS trial. - Added statements to provide the most common NUBEQA ARs leading to permanent discontinuation (cardiac failure and death), dosage interruption (hypertension,

		diarrhea, and death), and dosage reductions (fatigue, hypertension, nausea). - Added information on the rates of ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).
6. Drug Interactions	7.1 Effect of Other Drugs on NUBEQA (b) (4) ...	FDA revised this subsection as follows: - Revised the heading to Combined P-gp and Strong or Moderate CYP3A4 Inhibitors for better accuracy. - Added statements to “Avoid concomitant use” - Removed (b) (4) proposed by the Applicant to be consistent with OHOP best labeling practices. - Added the “Combined P-gp and Strong CYP3A4 Inhibitors” subsection, advice to monitor patients more closely for adverse reactions, and modify NUBEQA dosage as needed.
	7.2 Effects of NUBEQA ...	FDA revised this subsection as follows: - Added that increases in the exposure of BCRP substrates may increase the risk of BCRP substrate-related toxicities. - Added statements to avoid concomitant use, monitor patients for adverse reactions, and consider dose reduction of the BCRP substrate drugs. - Removed (b) (4)

		(b) (4) proposed by the Applicant to be consistent with OHOP best labeling practices.
7. Use in Specific Populations	7.1 Pregnancy Risk Summary ...	FDA revised this subsection as follows: - Removed (b) (4) since this statement may imply a contraindication. - Added (may cause fetal harm) “and loss of pregnancy” to the risk summary statements. - Added “Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide.” - Added “There are no human data on the use of NUBEQA in pregnant females.” - Removed statements regarding (b) (4) since this is information required and covered in subsection 8.3.
	8.3 Females and Males of Reproductive Potential ...	<i>See Labeling Recommendations, subsection 5.1 for corresponding FDA revisions.</i>
	8.5 Geriatric Use ...	FDA revised this subsection to describe the 954 patients who received NUBEQA in ARAMIS and the percentages of patients who were 65 years and 75 years and older. FDA removed the statement that (b) (4)
	8.6 Renal Impairment <i>(Subsection added by FDA)</i>	FDA added this subsection to describe higher NUBEQA exposures in severe renal impairment and recommended dose reductions; and to identify the lack of information for

		patients with end stage renal disease.
	8.7 Hepatic Impairment <i>(Subsection added by FDA)</i>	FDA added this subsection to describe higher NUBEQA exposures in moderate hepatic impairment and recommended dose reductions; and to identify the lack of information for patients with severe hepatic impairment.
10. Overdosage	...	FDA revised this section to remove “no dose limiting toxicities” being observed at the highest dose studied to avoid implying that safety has been established at a higher unapproved dosage. FDA revised this section to clarify that saturable absorption at higher than recommended doses is not expected “in patients with intact hepatic and renal function”.
11. Description	...	FDA added the following: “Darolutamide is an optically active with a specific rotation value $[\alpha]_{20D} = 72.2$ $^{\circ}\text{mL}/(\text{dm}^{\circ}\text{g})$, white to greyish- or yellowish white crystalline powder, that is soluble in tetrahydrofuran, but practically insoluble in aqueous medium. Darolutamide has a pKa of 11.75.”
12. Clinical Pharmacology	12.1 Mechanism of Action ...	FDA added “In addition, darolutamide functioned as a progesterone receptor (PR) antagonist <i>in vitro</i> (approximately 1% activity compared to AR)” based on the pharmacology data reviewed in sub section 5.3.

		FDA revised to remove (b) (4) [Redacted] in accordance with the <i>FDA Guidance for Clinical Pharmacology (IV.A.)</i>. FDA removed (b) (4) [Redacted]
	12.2 Pharmacodynamics (b) (4) [Redacted] <i>Cardiac Electrophysiology</i> ...	FDA revised to “The exposure-response analysis between darolutamide and the change in PSA indicates that darolutamide exposure at 600 mg twice daily results in an average of 90% reduction in PSA from baseline.” FDA removed (b) (4) [Redacted] and revised to “no large mean increase in QTc (i.e., > 20 ms) was detected” based on OND/OHOP best labeling practices.
	12.3 Pharmacokinetics ...	FDA revised to clarify that steady state is reached 2 -5 days (Applicant proposed (b) (4) days) after repeated dosing and

		reordered the information throughout this section to be more consistent with FDA labeling guidance. FDA revised the <i>Specific Populations</i> information to  severe renal impairment and moderate hepatic impairment. FDA added statements to describe increased exposures in these patients based on FDA Clinical Pharmacology review findings. FDA revised and reorganized the <i>Drug Interaction Studies</i> information as follows: - To “Combined P-gp and Strong CYP3A4 Inducers”, added the expected decreased darolutamide exposure range for moderate CYP3A4 inducers (36 – 58%). - Removed “” - Added: <i>In Vitro Studies</i> In vitro, darolutamide inhibits OATP1B1 and OATP1B3. Darolutamide did not inhibit the major CYP enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) or transporters (MRP2, BSEP, OATs, OCTs, MATEs, OATP2B1, and NTCP) at clinically relevant

13. Nonclinical Toxicology	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	concentrations.” FDA revised this section and merged the applicable information from 13.2 to be more concise. FDA added fertility study findings from rats and dogs (i.e., tubular dilation of testes; atrophy of seminal vesicles, testes, prostate gland, and epididymides) and provided the doses and human equivalent exposure levels studied. FDA removed potentially misleading statements regarding (b) (4) 
14. Clinical Studies	...	FDA revised the study characteristics and demographic information as follows: - Clarified that the “prior anti-androgen therapy” received by patients consisted of “(bicalutamide or flutamide)”. - Revised demographic results to identify the percentage of patients with ECOG 0 or 1 performance status at baseline. - Added that there were 12 patients enrolled in ARAMIS with a prior history of seizure. - Added “At baseline, 47% patients reported no pain on the Brief Pain Inventory-Short Form (a 7-day diary average of the daily worst pain item).”

		FDA revised the study results as follows: - Added the definition for MFS, the major efficacy outcome measure. - Removed endpoint descriptions and results from the text and efficacy results table (Table 3) for (b) (4) - Added "Locoregional-only progression occurred in 6% of patients overall." - (b) (4) added "OS data were not mature at the time of final MFS analysis (57% of the required number of events)." - Removed the statements (b) (4) - (b) (4) revised the results statement to the following: "The MFS result was

		supported by a delay in time to pain progression, defined as at least a 2-point worsening from baseline of the pain score on Brief Pain Inventory-Short Form or initiation of opioids, in patients treated with NUBEQA as compared to placebo. Pain progression was reported in 28% of all patients on study.”
16. How Supplied/Storage and Handling	...	FDA removed [REDACTED] (b) (4) [REDACTED] based on FDA CMC Review findings.
17. Patient Counseling Information	<u>Embryo-Fetal Toxicity</u> ...	See <i>Labeling Recommendations, subsection 5.1 for corresponding FDA revisions.</i>

11.2 Patient Labeling

The following revisions (high level summary) were made to the Applicant’s proposed Patient Information for NUBEQA:

- To the “Before taking NUBEQA, tell your healthcare provider about all your medical conditions, including if you:” section, FDA added statements to inform the healthcare provider of kidney or liver problems, and if pregnant or planning to become pregnant.
- To the “What are the possible side effects of NUBEQA?” section, FDA added decreased white blood cells (neutropenia) and changes in liver function tests.
- To the “How should I store NUBEQA?” section, FDA deleted [REDACTED] (b) (4)
[REDACTED]

For complete details, see the FDA DMPP/OPDP review filed under this NDA.

12 Risk Evaluation and Mitigation Strategies (REMS)

The applicant did not submit a REMS with this application or risk management plan with this application. The Division of Risk Management and DOP1 agree that a REMS is not necessary to ensure the benefits of darolutamide outweigh its risks. The serious risk associated with

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darolutamide of embryo-fetal toxicity will be addressed in the warnings and precautions section of the label. The approved androgen receptor inhibitors enzalutamide and apalutamide also do not have a boxed warning in their respective labels or have required a REMS for approval.

13 Postmarketing Requirements and Commitment

The FDA recommends a Postmarketing Commitment for NDA 212099 to require the applicant to submit a final clinical study report for ARAMIS with final OS analysis. This OS analysis is important to confirm the benefit-risk profile of apalutamide, assess based on MFS in this application.

14 Division Director (DHOT)

X

15 Division Director (OCP)

X

16 Division Director (OB) Comments

X

17 Division Director (Clinical) Comments

In a randomized, double-blind, placebo-controlled trial (ARAMIS), over 1500 patients with high risk (PSADT of 10 months or less), nmCRPC were administered either darolutamide or placebo. MFS based on the BICR assessment was the primary endpoint and secondary endpoints included overall survival (OS), time to pain progression (TTPP), time to first symptomatic skeletal event (SSE), and time to initiation of first cytotoxic chemotherapy.

At the final analysis of MFS, a statistically significant improvement was demonstrated for the darolutamide arm compared to placebo [HR of 0.41; 95%CI 0.34, 0.50]. OS data were immature. Because OS did not reach statistical significance, other secondary endpoints could not be tested for statistical significance, as prespecified. The median TTPP, however, was 40 months on the darolutamide arm compared to 25 months on the placebo arm [HR 0.65; 95% CI 0.54, 0.79] and was included in the label descriptively. Per the SAP, an updated analysis of time to initiation of cytotoxic chemotherapy and time to first SSE will be performed at the time of final OS analysis, expected in 2020. The applicant has agreed to a PMC to submit the results for FDA review after the final OS analysis.

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The toxicity profile of darolutamide is acceptable. Notably, ARAMIS was the first trial in the same class of drugs that enrolled patients with a history of seizures, based on non-clinical finding that the drug did not cross the blood-brain barrier. None of these patients (N=12 treated with darolutamide) had a seizure on study in this limited sample size. The incidence of ischemic heart disease and cardiac failure was slightly higher the investigational arm and was included in section 6 (Adverse Reactions) of the label.

The risk-benefit ratio is favorable for darolutamide in patients with nmCRPC. All disciplines recommend approval of darolutamide for the proposed indication. I concur with their recommendation.

X

Amna Ibrahim MD,
Deputy Director, DOP1

17 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit assessment was also reviewed by Drs. Weinstock, Brave and Brewer and I agree with their assessment. My signature below represents an approval recommendation for the clinical portion of this application under the OCE and an approval recommendation of the application under CDER.

X

18 Appendices

18.1 References

Moilanen, A-M, R Riikonen, R Oksala, L Ravanti, L, E Aho, G Wohlfahrt, PS Nykänen, OP Törmäkangas, JJ Palvimo and P Kallio, 2015, Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. Science Reports, 5(12007):1-11.

18.2 Financial Disclosure

[Insert text here]

Covered Clinical Study (Name and/or Number): ARAMIS

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2122		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
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: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
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): 1		

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

18.3 Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

18.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.5.1 Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of two darolutamide diastereomers; S,R-darolutamide (BAY 1896951 or ORM-16497) and S,S-darolutamide (BAY 1896952 or ORM-16555); and the major darolutamide metabolite keto-darolutamide (BAY 1896953 or ORM-15341) was measured in the clinical pharmacology and biopharmaceutics studies. The concentration of darolutamide diastereomers and its metabolite were quantified in human plasma using liquid chromatography with LC-MS/MS detection methods. Summary method performance of a bioanalytical method to measure S,S-darolutamide, S,R-darolutamide and keto-darolutamide in human plasma in clinical studies are listed in **Table 49**. Cross validation of the methods used to measure human plasma concentrations of darolutamide diastereomers and its metabolite between two methods that used different chromatographic conditions was performed and demonstrated that both methods provided comparable results. A summary of these results is provided in **Table 50**. Across all methods used in the clinical studies, the quantification range was 5.00 to 5000 ng/mL for each of the 3 analytes. Overall, the precision, accuracy, selectivity and performance of the methods used to analyze darolutamide diastereomers and its metabolite in plasma were acceptable and within the FDA guidance recommended criteria. Gilteritinib was stable up to 506 days at -20 and after up to 5 freeze and thaw cycles in the plasma samples. Incurred sample reanalysis met the acceptance criteria for all studies which requires that at least 2/3 of the reanalyzed samples to fall within 20% of the original concentration.

Table 62. Summary method performance of a bioanalytical method to measure S,S-darolutamide, S,R-darolutamide and keto-darolutamide in human plasma

Bioanalytical method validation report name, amendments, and hyperlinks	1. Validation of a Method for the Determination of ORM-16497, ORM-16555 and ORM-15341 in Human Plasma Samples 2. Amendment No. 01 to the Method Validation Report 3. Addendum No. 01 to the Method Validation Report [All 3 documents are within 1 report, Bayer Report ID R-9969]		
Method description	Human plasma concentrations of S,S-darolutamide, S,R-darolutamide and Keto-darolutamide were determined using solid phase extraction followed by chiral liquid chromatography – tandem mass spectrometry (LC-MS/MS) at (b) (4) utilizing stable labeled internal standards. The method was validated with respect to accuracy, precision, linearity, sensitivity and specificity according to pertinent international guidelines.		
Materials used for calibration curve & concentration	Reference Materials: 1. ODM-201 (1:1 mixture of diastereoisomers), 2000 µg/mL 2. ORM-15341 (keto-darolutamide), 1000 µg/mL 3. ORM- (b) (4) (13C3 labeled internal standard for ODM-201), 2000 µg/mL 4. ORM- (b) (4) (13C3 labeled internal standard for ORM-15341), 1000 µg/mL 5. Blank K2EDTA human plasma		
Validated assay range	5.00 to 5000 ng/mL for each of the 3 analytes		
Material used for QCs & concentration	Reference Materials: 1. ODM-201 (1:1 mixture of diastereoisomers), 2000 µg/mL 2. ORM-15341 (keto-darolutamide), 1000 µg/mL 3. ORM- (b) (4) (13C3 labeled internal standard for ODM-201), 2000 µg/mL 4. ORM- (b) (4) (13C3 labeled internal standard for ORM-15341), 1000 µg/mL 5. Blank K2EDTA human plasma		
Minimum required dilutions (MRDs)	Not Applicable		
Source & lot of reagents (LBA)	Not Applicable		
Regression model & weighting	Linear regression using the 1/x ² weighting factor		
Validation parameters	Method validation summary		Acceptability
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	9	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ		Acceptable
	S,S-darolutamide S,R-darolutamide Keto-darolutamide	-12.2 to 3.8% -12.6 to 3.3% -12.9 to 3.7%	
QCs performance during accuracy & precision	Cumulative precision (%CV) from LLOQ to ULOQ		Acceptable
	S,S-darolutamide S,R-darolutamide Keto-darolutamide	≤ 2.7% ≤ 3.2% ≤ 2.6%	
	Cumulative accuracy (%bias) in 5 QCs		
	QCs: S,S-darolutamide S,R-darolutamide Keto-darolutamide	2.0 to 15.3% 1.0 to 15.0% 0.8 to 16.7%	Acceptable

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	Inter-batch %CV QCs: S,S-darolutamide ≤ 3.1% S,R-darolutamide ≤ 2.9% Keto-darolutamide ≤ 2.8% Total error QCs S,S-darolutamide Not S,R-darolutamide Applicable Keto-darolutamide	Acceptable
Selectivity & matrix effect	6 independent sources of blank plasma were analyzed. For the selectivity test, in all blank and zero samples the response at the retention time of each analyte was ≤ 20.0% of the mean response for each analyte in the 6 samples spiked at 5.00 ng/mL, and in all blank samples the response at the retention time of the internal standards was ≤ 5.0% of the mean response for the internal standards in the 6 samples spiked at 5.00 ng/mL. Actual ranges of bias interference for blank and zero samples for each analyte were: S,S-darolutamide: 0.0 to 9.1% S,R-darolutamide: 0.0 to 9.6% Keto-darolutamide: 0.0 to 10.8% In blank samples the IS interference was always 0.0%. The degree of matrix variability is acceptable as the highest CV of the found concentrations was 3.3% and the highest bias was 19% of the nominal concentration. For the matrix effect test, tested at 15.0 and 4000 ng/mL, the highest CV observed over the 6 relative matrix factors (considering the 3 analytes) was 1.4%. No issues were observed, and the results were within the pre-defined acceptance criteria.	Acceptable
Interference & specificity	The method is selective with respect to acetylsalicylic acid, ibuprofen, ketoprofen and methadone. The response in two blank samples spiked with these xenobiotics at the retention time of each of the 3 analytes and internal standards was 0.0% of the response for each of the 3 analytes and internal standards in the LLOQ sample. For quality control samples spiked with these xenobiotics, the range of the observed bias was from 0.5 to 6.8% across the 3 analytes. No issues were observed, and the results were within the pre-defined acceptance criteria	Acceptable
Hemolysis effect	One source of hemolytic plasma was tested, prepared by spiking 2% v/v human whole blood into human K2EDTA plasma at a concentration of 5 ng/mL for each of the 3 analytes. The range of the observed bias was from -7.6% to 7.1% across the 3 analytes, so the results demonstrate that plasma hemolysis has no impact on the determination of the 3 analytes. No issues were observed, and the results were within the pre-defined acceptance criteria	Acceptable
Lipemic effect	The effect of hyperlipidemic samples was not tested in the original	Acceptable

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	assay validation (b) (4) – document issue date 12-Oct-2011. However, the effect was investigated in a second assay validation (b) (4) document issue date 12-Oct-2016) which was cross validated with the original assay validation (see later text). 3 individual lots of hyperlipidemic plasma were tested at blank, low and high QC levels for each of the 3 analytes. The range of the observed bias was from -6.1% to 12.8% across the 3 analytes, so the results demonstrate that plasma hyperlipidemia has no impact on the determination of the 3 analytes. No issues were observed, and the results were within the pre-defined acceptance criteria	
Dilution linearity & hook effect	Not applicable	
Bench-top/process stability	Spiked plasma samples containing each of the 3 analytes listed were prepared at 15, 4000 and 40000 ng/mL. The samples were stored unprotected from light for 24 hours at room temperature. The range of the observed bias was from -2.3% to 9.2% across the 3 analytes, demonstrating that each analyte is stable for up to 24 hours in human plasma at room temperature. Bias: S,S-darolutamide -1.9 to 9.2% S,R-darolutamide -1.2 to 8.9% Keto-darolutamide -2.3 to 6.7%	Acceptable
Freeze-Thaw stability	Spiked plasma samples containing each of the 3 analytes listed were prepared at 15, 4000 and 40000 ng/mL. The fresh samples were frozen and thawed five times between nominal freezer temperatures of -20°C and -70°C and room temperature. The range of the observed bias was from 1.3% to 10.0% across the 3 analytes, demonstrating that each analyte is stable through five freeze/thaw cycles in human plasma. Bias: S,S-darolutamide - 1.3 to 9.9% S,R-darolutamide - 1.7 to 9.8% Keto-darolutamide - 2.5 to 10.0%	Acceptable
Long-term storage	Spiked plasma samples containing each of the 3 analytes listed were prepared at 15, 4000 and 40000 ng/mL. The fresh samples were frozen at -20°C and -70°C and room temperature and stored for up to 187 days. The range of the observed bias was from -14.8% to 11.4% across the 3 analytes. Bias: S,S-darolutamide -14.2 to 11.4% S,R-darolutamide -14.0 to 9.8% Keto-darolutamide -14.8 to 9.2% Subsequently, an additional long-term frozen plasma stability experiment was performed at -20°C for 506 days at 15 and 4000 ng/mL, the range of the observed bias being from -11.5% to -8.9% across the 3 analytes. Bias: S,S-darolutamide -10.9 to -10.6% S,R-darolutamide -11.5 to -8.9%	Acceptable

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	Keto-darolutamide -10.3 to -10.0%	
Parallelism	Not applicable	
Carry over	The assay method shows no unacceptable carryover for any of the analytes: in each batch used for the determination of accuracy and precision, responses (peak area) of co-eluting peaks in the blank samples analyzed directly following the sample at the highest calibration standard and the last validation sample at the highest concentration were $\leq 17.8\%$ of the mean analyte response (peak area) found for the validation samples at the lowest concentration analyzed in the same batch. As a precautionary measure at least one blank sample has to be placed directly following samples with a (suspected) high concentration. Carry over (% of LLOQ) S,S-darolutamide - 0.0 to 9.9% S,R-darolutamide - 0.0 to 12.2% Keto-darolutamide - 0.0 to 17.8%	Acceptable
Method performance in study number 17829 Source: Module 5.3.3.2, Clinical Report 17829, Appendix 16.1.10.1		
Assay passing rate	34 out of 35 analytical runs were accepted in this study, including those for the ISR assessment, for a pass rate of 97.1%	Acceptable
Standard curve performance	- Cumulative bias range: -4.2% to 3.5% - Cumulative precision: $\leq 6.2\%$ CV	Acceptable
QC performance	- Cumulative bias range: -4.8 to 2.5% - Cumulative precision: $\leq 10.7\%$ CV	Acceptable
Method reproducibility	Incurring sample reanalysis was performed in 10% of study samples. ISR results for each of the 3 analytes were within the acceptance criteria: 98.4% for S,S-darolutamide, 90.5% for S,R-darolutamide, and 100.0% for keto-darolutamide.	Acceptable
Study sample analysis/stability	Study samples were received between 20 April 2011 and 08 July 2013, stored at a nominal -70°C and all samples were analyzed within the validated stability period. At the time of analysis, the maximum storage period at a nominal -70°C was 187 days.	
Method performance in study number 17830 Source: Module 5.3.1.1, Clinical Report 17830, Appendix 16.1.10.1		
Assay passing rate	ISR was not assessed in this study as it had been performed previously in study 17829 (ARADES). However, all analytical runs that were started (21) were accepted for a pass rate of 100%	Acceptable
Standard curve performance	- Cumulative bias range: -4.6% to 7.2% - Cumulative precision: $\leq 3.8\%$ CV	Acceptable
QC performance	- Cumulative bias range: -4.0 to 2.0% - Cumulative precision: $\leq 4.2\%$ CV	Acceptable
Method reproducibility	ISR was not performed in this study (see above, 'Assay Passing Rate'). However as above, all analytical runs that were started (21) were accepted, with cumulative statistics for standard curves and QC performance being well within the accepted bioanalytical guidelines.	Acceptable
Study sample analysis/stability	Study samples were received between 26 April 2013 and 12 September 2013, stored at a nominal -20°C and all samples were analyzed within the validated stability period. At the time of analysis, the maximum storage period at a nominal -20°C was 187 days. This was extended subsequently to 506 days.	
Method performance in study number 17719		

Source: Module 5.3.3.2, Clinical Report 17719, Appendix 16.1.10.1		
Assay passing rate	All analytical runs (8), including those for the ISR assessment, were accepted in this study for a 100% pass rate	Acceptable
Standard curve performance	- Cumulative bias range: -6.8% to 5.6% - Cumulative precision: $\leq 4.3\%$ CV	Acceptable
QC performance	- Cumulative bias range: 2.8% to 9.3% - Cumulative precision: $\leq 7.2\%$ CV	Acceptable
Method reproducibility	Incurring sample reanalysis was performed in 10% of study samples. The pre-defined acceptance criteria were met for all 3 analytes: 92.6% for BAY1896951 and 100% for each of BAY1896952 and BAY1896953.	Acceptable
Study sample analysis/stability	Study samples were received between 29 April 2015 and 16 September 2015, stored at -20°C and all samples were analysed within the validated stability period. At the time of analysis, the maximum storage period at a nominal -20°C was 506 days.	
Method performance in study number 17712		
Source: Module 5.3.5.1, Clinical Report 17712, Appendix 16.1.10.1		
Assay passing rate	38 out of 43 analytical runs were accepted in this study for a pass rate of 88.4%	Acceptable
Standard curve performance	- Cumulative bias range: -3.4% to 2.4% - Cumulative precision: $\leq 5.1\%$ CV	Acceptable
QC performance	- Cumulative bias range: -4.3 to 0.0% - Cumulative precision: $\leq 5.7\%$ CV	Acceptable
Method reproducibility	Incurring sample reanalysis was not performed as this had been performed previously in study 17829 (ARADES). All cumulative statistics for standard curves and QC performance were well within the accepted bioanalytical guidelines. However, because the 506-day long term frozen plasma stability window was insufficient for all the samples received late in the study (maximum stability window required was 952 days) a long term frozen plasma stability experiment was performed with the first 36 study samples reanalyzed after storage to demonstrate a longer stability period. 100% of the reanalyzed study samples met the ISR acceptance criteria for all 3 analytes.	Acceptable
Study sample analysis/stability	Study samples were received between 15 January 2015 and 05 September 2018 and stored at -20°C. The 506-day long term frozen plasma stability window was insufficient for all the samples received late in the study (maximum stability window required was 952 days), so a long-term frozen plasma stability experiment was performed with the first 36 study samples reanalyzed after storage to demonstrate a longer stability period. 100% of the reanalyzed study samples met the ISR acceptance criteria. This provides stability coverage for 931 days (covering all except 2 samples received in the study). In addition, a long-term frozen stability experiment with spiked samples is in progress which will cover the required 952 days. The outcome will be reported in an Appendix to this study report in November 2019. In addition, 5 samples were analyzed after 6 freeze/thaw cycles (maximum validated number of freeze/thaw cycles is 5). The additional experiment to demonstrate the validation of 6 freeze/thaw cycles will be performed with the additional long-term frozen stability experiment.	

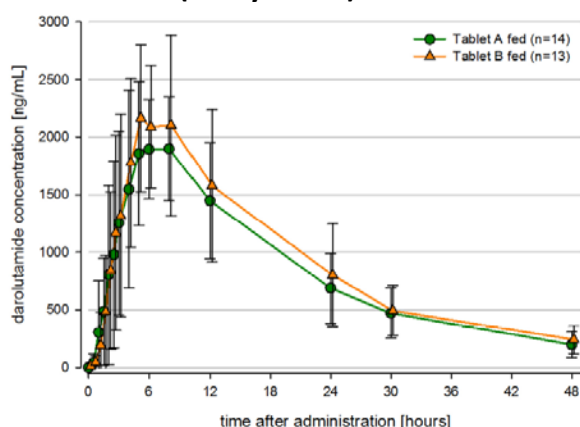
Table 63. Summary of human plasma method R-9969 modifications and cross-validation results

Bioanalytical method validation report name and hyperlink	Validation of an LC-MS/MS method for the determination of two diastereoisomers (BAY1896951, BAY1896952) and the metabolite BAY1896953 in human plasma (K2EDTA). [Bayer Report ID R-11257]		
Changes in method	Original Method LC Column: Chiral AGP, 150x 4.0 mm, 5 µm, 40°C New Method LC Column: Chiralpak AGP, 150 x 2.0 mm, 5 µm		
New validated assay range if any	BAY1896953 Calibration Range: 10.0 to 10,000 ng/mL (Range for other 2 analytes remains 5.0 to 5,000 ng/mL)		
Validation parameters	Cross-validation performance		Acceptability
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-4.8% to 3.8%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 7.0%	Acceptable
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in QCs	-6.0% to 7.3%	Acceptable
	Inter-batch %CV	≤7.4%	Acceptable
	Percent total error (TE)	≤ x%	N/A
Cross-validation	Numbers of spiked or incurred samples analyzed and result	60 samples, 96.6% passed	Acceptable
List other parameters	Clarification: This method was established at a different CRO than the original method with the minor modifications listed.		

19.5.2 Relative Bioavailability Study

Although the to-be-marketed formulation used in the phase 3 clinical study, different capsule and tablet formulations have been used in the early clinical development studies that assessed the clinical pharmacokinetics characteristics of darolutamide. Two different dosage forms were developed, a 100 mg powder-in-capsule for early Phase 1/2 studies, and a 300 mg tablet for subsequent clinical studies and commercial use. The applicant performed relative bioavailability study to determine the relative bioavailability of two ODM-201 tablet products (tablet A and tablet B) compared to the capsule (reference) product in subjects with mCRPC. Tablet B was the same formulation as tablet A with an alternative, coarser grade of the drug substance. The mean concentration-time profile of darolutamide from Tablet A containing finer material (d50 = (b) (4) μm) was similar to that from Tablet B containing coarse drug substance material (d50 = (b) (4) μm) under fed conditions (**Figure 25**). The relative bioavailability ratio of darolutamide (AUC_{48}) for tablet A was 1.06 and for tablet B was 0.968 when the capsule was used as a reference formulation in the fed state (**Table 51**).

Figure 27. Mean concentration-time profile of darolutamide in two groups of 15 subjects each, one group receiving Tablet A (d50: (b) (4) μm) and the other Tablet B (d50: (b) (4) μm) under fed conditions (Study 17830)



Source: Summary of clinical pharmacology

Table 64. Relative bioavailability of ODM-201 for Tablet A and Tablet B.

Formulation	Ratio estimate	AUC_{48} $\text{h} \times \text{ng/ml}$		Ratio estimate	C_{max} ng/ml	
		Lower 90 %	Upper 90%		Lower 90 %	Upper 90%
Tablet A fed/ capsule fed	1.060	0.906	1.241	1.157	0.986	1.357
Tablet B fed/ capsule fed	0.968	0.824	1.137	0.996	0.860	1.153

Source: Summary of clinical pharmacology

19.5.3 Pharmacometrics Review

19.5.3.1 Population PK analysis

Introduction

The main objectives of this analysis were the following:

- (b) To assess the variability in the PK of darolutamide, each of the two diastereomers (S,R)-darolutamide and (S,S)-darolutamide, and in the PK of the active metabolite (keto-darolutamide) based on the PK data from study 17712.
- (c) To enhance the covariate search by also including the phase 1-2 studies 17829 and 17830.

Model development

Data

The study design, study population, and timing of blood samples varied among the 3 clinical studies. Brief descriptions of the studies included are presented in **Table 65**.

The final data file for analysis contained 1877 PK observations of (S,R)-darolutamide or (S,S)-darolutamide or keto-darolutamide from 393 nmCRPC patients. Table 66 provides summary statistics of the baseline demographic covariates in the initial analysis dataset and the clean dataset.

Table 65. Summary of Studies with PK Sampling Included in Population PK Analysis

Clinical study no.	Description	Treatment	Number of subjects planned
#17712 [2]	Phase 3, randomized in nmCRPC	600 mg BID (tablet A), placebo (2:1)	Active (n=1000) Placebo (n=500)
#17829 [3]	Phase 1-2 safety, tolerability and efficacy study in patients with metastatic prostate cancer	Phase 1 dose escalation part: 100, 200, 300, 500, 700, 900 mg BID. Phase 2 expansion part: 100, 200, 700 mg BID.	Dose escalation (n=24) Expansion (n=110)
#17830 [4]	Phase 1, bioavailability study in patients with metastatic prostate cancer	3 doses per subject: • 600 mg tablet (A or B) fed state • 600 mg tablet (A or B) fasted state • 600 mg capsule fed state 7 day washout period between doses.	30 (PK component)

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Clinical study no.	Planned PK sampling scheme
#17712 [2] (PK subgroup)	trough: 10 to 14 hours after the previous dose early: 1 to 4 hours after the previous dose late: 4 to 8 hours after the previous dose 600 subjects were originally planned to have one or two PK samples* drawn on each of three occasions: Day 15, Day 29, Week 16
# 17829 [3]	Dose escalation part: Day 1: 0 (pre-dose), 0.5, 1, 1.5, 3, 5, 8, 12, 23.5 hours after dose. Day 7 ± 2 days: 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 8 hours after dose. Days 14, 21, 28: Single PK sample 1-3 hours after dosing at home. Expansion part: Single sample drawn at visit 5 (day 28) and visit 7 (week 12) 1-3 hours after dosing.
# 17830 [4]	0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 (day 2), 30 (day 2), 48 (day 3) hours post dose.

* a series of two PK samples could either consist of a *trough* and an *early* sample or of two *late* samples.

(Source: Applicant's Population PK report 18651, Table 9-1,2)

Table 66. Summary of Baseline Demographic Covariates for Analysis

Covariate / unit	Statistic	Study			
		17829	17830	17712	All
	n	122	30	388 ^a	540
Age at baseline (years)	Min	53	54	48	48
	Max	83	86	95	95
	Median	68	68	75	73
	Arith. mean	69.0	68.5	74.9	73.2
	Arith. s.d.	7.25	7.30	8.09	8.30
	Arith. CV (%)	11	11	11	11
	Geo. mean	68.58	68.16	74.4	72.7
	Geo. s.d.	1.11	1.11	1.12	1.12
	Geo. CV (%)	11	11	11	12
Serum albumin at baseline (g/L)	Min	27	27	34	27
	Max	48	48.3	52	52
	Median	38	42.3	42	42
	Arith. mean	38.2	41.4	42.9	41.2
	Arith. s.d.	4.54	4.70	2.66	3.66
	Arith. CV (%)	12	11	6	9
	Geo. mean	38.0	41.1	42.0	41.0
	Geo. s.d.	1.13	1.13	1.07	1.10
	Geo. CV (%)	12	12	6	9
Alanine aminotransferase level at baseline (U/L)	Min	5.0	10.0	4.0	4.0
	Max	193	58	105	193
	Median	16.5	16.5	17.0	17.0
	Arith. mean	21.73	21.07	20.37	20.72
	Arith. s.d.	23.0	10.9	12.0	15.1
	Arith. CV (%)	106	52	59	73
	Geo. mean	17.4	19.1	18.1	18.0
	Geo. s.d.	1.78	1.54	1.58	1.62
	Geo. CV (%)	62	45	48	51
Aspartate aminotransferase level at baseline (U/L)	Min	13.0	13.0	8.0	8.0
	Max	123.0	64.0	68.0	123.0
	Median	23.0	25.5	21.0	21.0
	Arith. mean	26.9	27.7	22.2	23.6
	Arith. s.d.	15.8	10.7	7.6	10.4
	Arith. CV (%)	59	38	34	44
	Geo. mean	24.4	26.0	21.1	22.1
	Geo. s.d.	1.49	1.44	1.36	1.41
	Geo. CV (%)	42	37	32	35
Estimated glomerular filtration rate at baseline (eGFR) (mL/min/1.73m ²)	Min	37.9	38.3	27.2	27.2
	Max	143.3	151.3	177.0	177.0
	Median	86.9	93.0	80.3	82.0
	Arith. mean	86.1	95.2	81.3	83.2
	Arith. s.d.	21.1	30.0	20.6	21.6
	Arith. CV (%)	25	31	25	26
	Geo. mean	83.4	90.4	78.7	80.3
	Geo. s.d.	1.29	1.41	1.30	1.31
	Geo. CV (%)	26	35	27	28
Patient height at baseline (cm)	Min	160.0	159.0	147.5	147.5
	Max	190.5	186.0	196.0	196.0
	Median	175.0	176.0	172.0	172.7
	Arith. mean	175.5	175.4	172.0	173.0

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	Arith. s.d.	5.89	6.35	7.89	7.55				
	Arith. CV (%)	3	4	5	4				
	Geo. mean	175.4	175.3	171.8	172.8				
	Geo. s.d.	1.03	1.04	1.05	1.04				
	Geo. CV (%)	3	4	5	4				
Serum creatinine at baseline (SCRE) (µmol/L)	Min	50.0	48.0	42.6	42.6				
	Max	154.0	157.0	206.4	206.4				
	Median	78.0	72.5	81.4	80.6				
	Arith. mean	82.4	77.8	85.5	84.4				
	Arith. s.d.	19.3	24.3	20.9	20.8				
	Arith. CV (%)	23	31	24	25				
	Geo. mean	80.4	74.6	83.6	82.1				
	Geo. s.d.	1.25	1.33	1.25	1.26				
	Geo. CV (%)	22	29	23	23				
Total bilirubin at baseline (BILI) (µmol/L)	Min	3.0	5.0	2.8	2.8				
	Max	21.0	28.0	26.9	28.0				
	Median	7.0	11.5	8.5	8.0				
	Arith. mean	7.4	12.5	9.4	9.1				
	Arith. s.d.	3.0	5.8	4.1	4.1				
	Arith. CV (%)	41	46	44	46				
	Geo. mean	6.87	11.25	8.60	8.30				
	Geo. s.d.	1.45	1.59	1.50	1.52				
	Geo. CV (%)	38	49	43	44				
Patient bodyweight at baseline (kg)	Min	56.7	67.9	41.2	41.2				
	Max	132.0	118.7	135.0	135.0				
	Median	84.3	88.3	83.2	84.0				
	Arith. mean	86.5	89.6	83.8	84.7				
	Arith. s.d.	14.3	12.5	16.7	16.0				
	Arith. CV (%)	17	14	20	19				
	Geo. mean	85.3	88.8	82.1	83.2				
	Geo. s.d.	1.18	1.15	1.23	1.21				
	Geo. CV (%)	16	14	21	20				
Covariate	Category	17829		17830		17712^a		All	
		N	%	N	%	N	%	N	%
Ethnicity	White	116	95.1	30	100	292	75.3	438	81.1
	Black or African American	5	4.1	0	0.0	12	3.1	17	3.1
	Asian	1	0.8	0	0.0	76	19.6	77	14.3
	NA	0	0.0	0	0.0	8	2.1	8	1.5
Geographical region - Japan	Rest of world	122	100	30	100	330	85.1	482	89.3
	Japan	0	0	0	0.0	58	14.9	58	10.7
Hepatic function at baseline based on NCI-ODWG criteria	Normal	122	100	30	100	330	85.1	482	89.3
	Mild	0	0.0	0	0.0	58	14.9	58	10.7
Renal function at baseline	Normal	48	39.3	19	63.3	122	31.4	189	35.0
	Mild	59	48.4	7	23.3	209	53.9	275	50.9
	Moderate	15	12.3	4	13.3	56	14.4	75	13.9
	Severe	0	0.0	0	0.0	1	0.3	1	0.2

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Covariate	Class	17712 ^a	
		N	%
BCPR inhibitor	Certain	58	14.9
	Possible	64	16.5
CYP34A inducer	Certain	2	0.5
	Possible	3	0.8
CYP34A inhibitor	Certain	84	21.6
	Possible	89	22.9
P-GP inducer	Certain	0	0
	Possible	1	0.3
P-GP inhibitor	Certain	78	20.1
	Possible	86	22.2
Protein pump inhibitor	Certain	59	15.2
	Possible	65	16.8
UGT1A9 inducer	Certain	0	0
	Possible	0	0
UGT1A9 inhibitor	Certain	11	2.8
	Possible	11	2.8

Variable	N	Mean	Std Dev	Median	Minimum	Maximum
AGE	393	74.9414758	8.0739020	76.0000000	48.0000000	95.0000000
WGHT	393	83.2030534	16.7792203	83.0000000	41.2000000	135.0000000
HGHT	393	171.7480916	7.9437598	172.0000000	147.5000000	198.5000000
EGFR	393	81.5266109	20.6243166	81.0008000	27.2987000	177.7916000
ALBU	393	42.0712468	2.6745232	42.0000000	34.0000000	52.0000000
BILI	393	9.4694140	4.0789890	8.5520000	2.7366000	26.8532000
AST	393	22.2417303	7.5986766	21.0000000	8.0000000	68.0000000
ALT	393	20.4122137	11.9410992	17.0000000	4.0000000	105.0000000
PROT	393	68.1170483	4.7954634	68.0000000	55.0000000	84.0000000
Variable			Frequency	Percent	Cumulative Frequency	Cumulative Percent
JPN	Rest		332	84.48	332	84.48
	Japan		61	15.52	393	100.00
Race	White		292	74.30	292	74.30
	Black		11	2.80	303	77.10
	Asian		83	21.12	386	98.22
	Other		7	1.78	393	100.00
Renal Impairment	Normal		123	31.30	123	31.30
	Mild		214	54.45	337	85.75
	Moderate		55	13.99	392	99.75
	Severe		1	0.25	393	100.00
NCI	Normal		361	91.86	361	91.86
	Mild		32	8.14	393	100.00

(Source: Applicant's Population PK report 18651, Table B3-4; note that Hepatic function (NCI) Mild: Normal should be 56: 330 in the initial data)

Final model

The final model simultaneously described all three analytes: keto-darolutamide, back to (S,S)-darolutamide and to a lesser extent also to (S,R)-darolutamide used a simplified combined 1-

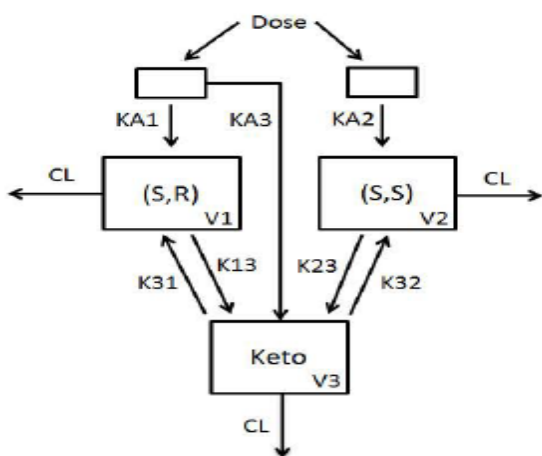
compartment model with all three analytes sharing the same volume of distribution and clearance.

Inter-individual variability (IIV) for log-transformed PK parameters was modelled assuming a standard normal distribution for patient level random effects. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Covariate analysis

Selected covariates, including demographics (age, bodyweight, height, ethnicity, geographical region – Japan, serum creatinine, estimated glomerular filtration rate, renal function, serum albumin, serum total protein, serum bilirubin, aspartate aminotransferase level, alanine aminotransferase level, hepatic function, were assessed on the two model parameters that had IIV (CL, RR) using a stepwise forward selection/backward elimination procedure. The model structure is shown in **Figure 26**.

Figure 28. Final model structure



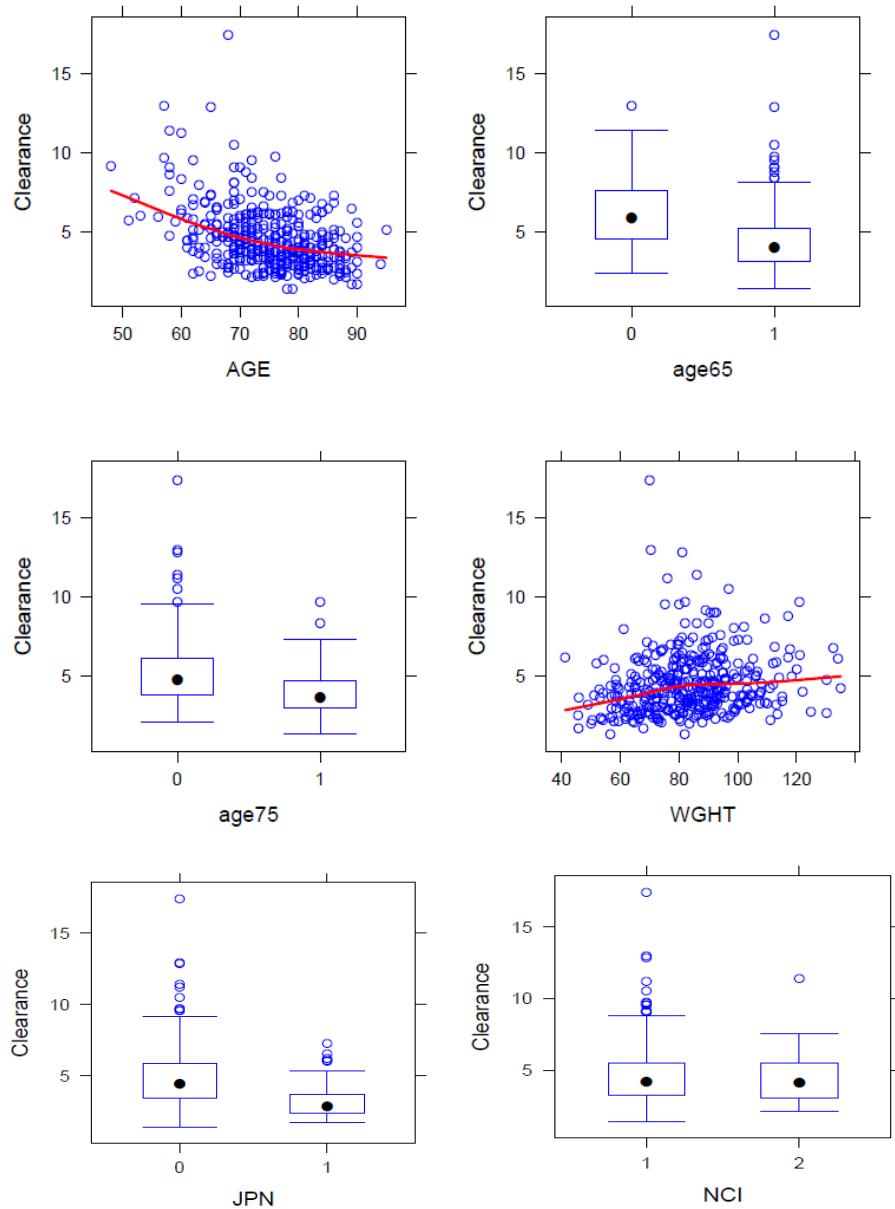
CL, clearance; KA1, absorption rate constant for (S,R)-darolutamide; KA2, absorption rate constant for (S,S)-darolutamide; KA3, absorption rate constant for keto-darolutamide; K_{nm} , rate constants between keto-darolutamide and (S,R)- and (S,S)-darolutamide; CL_{pop} , estimated CL for a typical patient; V1, volume of distribution for (S,R)-darolutamide; V2, volume of distribution for (S,S)-darolutamide; V3, volume of distribution for keto-darolutamide; RR, parameter describing the conversion ratio of keto-darolutamide to either (S,R)-darolutamide or (S,S)-darolutamide; θ_{RR} , estimated value of parameter describing the conversion ratio of keto-darolutamide to either (S,R)-darolutamide or (S,S)-darolutamide for a typical patient.

(Source: Applicant's Population PK report 18651, Figure 13-8)

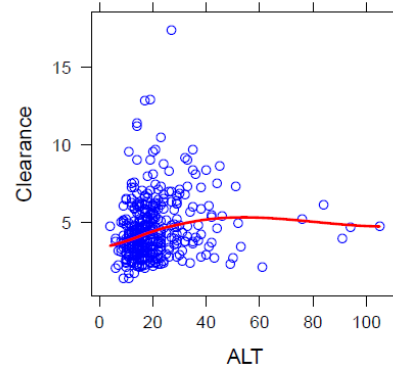
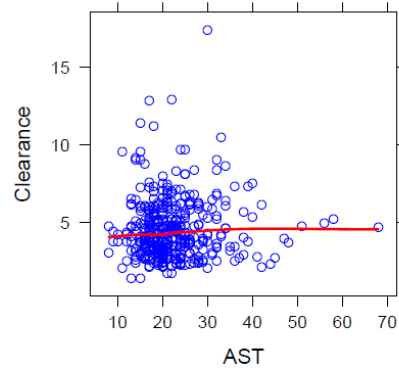
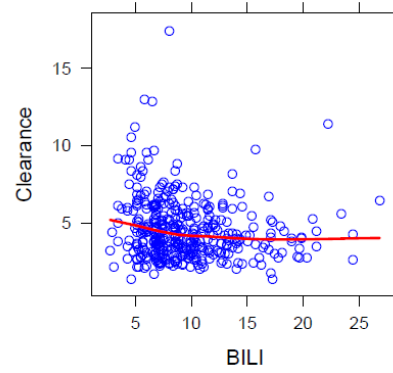
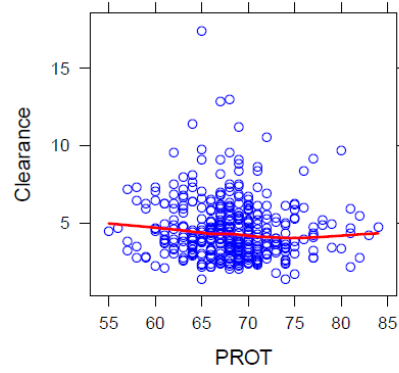
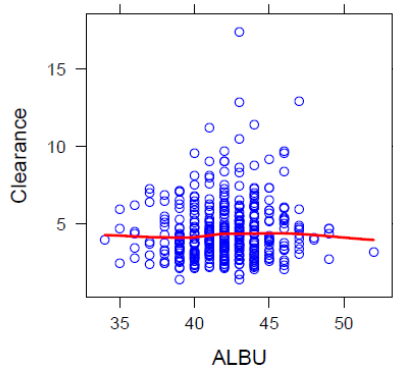
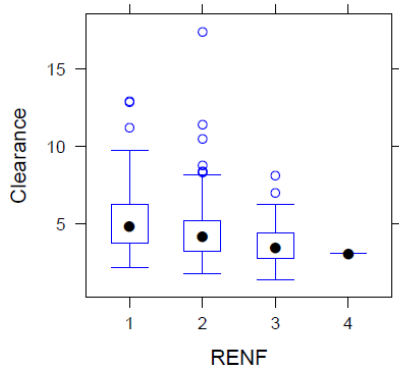
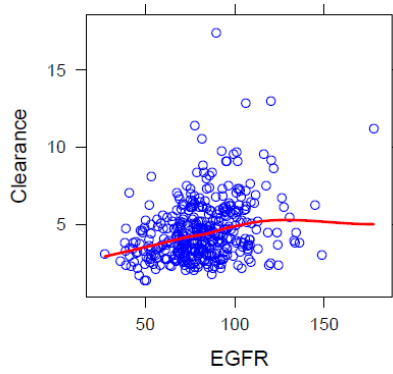
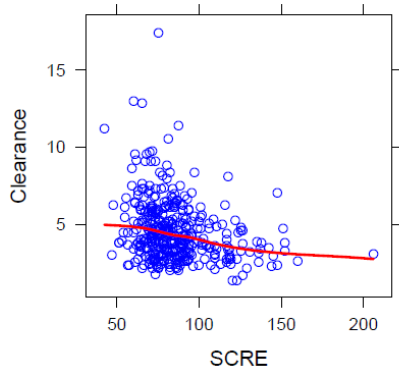
The reviewer's analysis of covariates effect on PK was similar to that of the applicant. The effects of covariates including demographics (age (including 2 age groups: age $\geq$ 65 or not (age65=1 or 0) and age $\geq$ 75 or not (age75=1 or 0), weight, ethnicity, and geographical region – Japan), and baseline lab parameters (serum creatinine, estimated glomerular filtration rate,

renal function, serum albumin, serum total protein, serum bilirubin, aspartate aminotransferase level, alanine aminotransferase level, and hepatic function) are illustrated in **Figure 27**.

Figure 29. Covariate Effects on PK parameters



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Results

The parameter estimates for the final covariate model in the Phase III population PK analysis are listed in **Table 67**. The goodness-of-fit plots for the final covariate model for all data are shown in **Figure 28**. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in **Figure 29**.

The multivariate analysis demonstrated that CL decreased with increasing age and increasing serum creatinine, and that the conversion ratio (RR) was affected by aspartate aminotransferase (AST) levels; those patients with a higher aspartate aminotransferase level converted more keto-darolutamide to (S,R)-darolutamide and less to (S,S)-darolutamide than those with a lower level. There was also a geographical effect on CL, with patients in Japan having a clearance that is 70.9% of that from patients in the rest of the world. The significant covariate relationships seemed clinically plausible: the clearance of darolutamide has a renal component and its decrease with increasing age and with increasing serum creatinine is not surprising; patients in the geographic region of Japan are generally smaller and that fact could be related to their lower clearance compared to patients in the rest of the world; and patients with a higher aspartate aminotransferase level may have poorer hepatic function and convert more keto-darolutamide to (S,R)-darolutamide and less to (S,S)-darolutamide. The decrease in clearance is translated into increased exposure (AUC(0-12)ss) of all analytes. Within the PK subgroup, the 90% CI of the geometric mean of the following ratios lay outside 1.25: being older than 65 years compared to being younger, living in Japan compared to rest of the world. However, for renal function being moderately impaired compared to normal renal function and for Asian compared to non-Asian, the 90% CI of the geometric mean was still including 1.25. The locations of the subgroup ratios were expected from the covariates in the selected phase 3 popPK model.

Table 67. Parameter Estimates for the Final Model

Theta	Description	Estimate	FIX	SE	RSE	95%CI	[lower,	init,	upper]
1	TH1 [CLpop]	4.57	-	0.0919	2%	4.39- 4.75	0	4.26	20
2	TH2 [V shared]	74.3	-	2.83	3.8%	68.753- 79.847	0	74.3	200
3	TH3 [KA S-R]	0.172	-	0.0148	8.6%	0.143- 0.201	0	0.172	5
4	TH4 [KMET]	0.12	-	0.012	10%	0.096- 0.144	0	0.131	5
5	TH5 [KRET]	0.449	-	0.0118	2.6%	0.426- 0.472	0	0.457	5
6	TH6 [RRpop]	-2.56	-	0.0793	3.1%	-2.715- -2.405	-20	-2.52	10
7	TH7 [KA S-S]	0.0953	-	0.0077	8.1%	0.08- 0.11	0	0.093	3
8	TH8 [KA Keto]	0.973	-	0.0797	8.2%	0.817- 1.129	0	0.944	10
9	TH9 [MAGE]	-0.0149	-	0.0023	15.3%	-0.019- -0.01	-1	-0.02	1
10	TH10 [MJPN]	0.7	-	0.0363	5.2%	0.629- 0.771	0	0.727	5
11	TH11 [MAST]	0.0234	-	0.0046	19.7%	0.014- 0.032	-5	0.022	5
12	TH12 [SCE]	-0.0044	-	0.0009	20.4%	-0.006-	-1	0.001	1

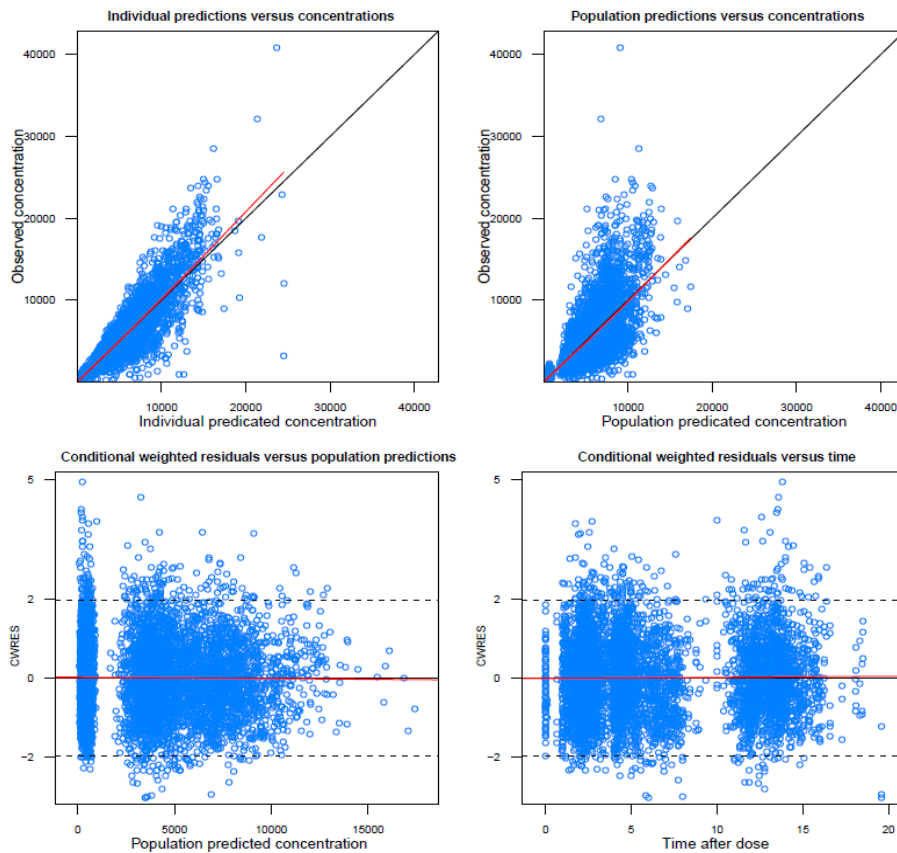
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-0.003

Omega	Description	Estimate	SE	RSE	Etabar	p val	Shrinkage
1,1	[IIV-CL]	0.108	0.0081	7.5%	-0 (0.016)	0.9972	2.8%
2,2	[IIV-RR]	0.263	0.0463	17.6%	0.023 (0.02)	0.2438	24.4%

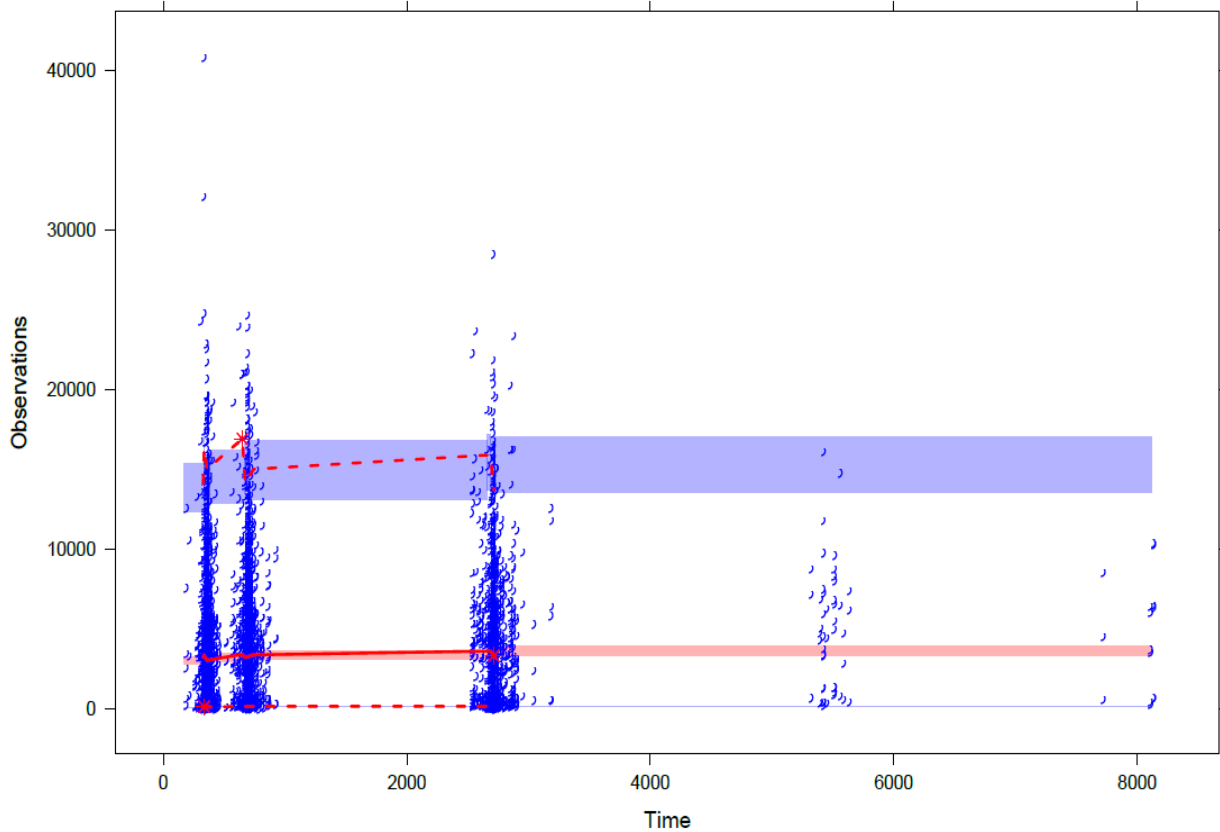
Sigma	Description	Estimate	SE	RSE	Shrinkage
1,1	.	0.148	0.0065	(4.4%)	6%
2,2	.	0.0616	0.0023	(3.7%)	4.5%
3,3	.	0.103	0.0047	(4.5%)	3.5%

Figure 30. Goodness-of-fit plots for final covariate model



The black line in the observed vs IPRED plots represents the line of unity ($y=x$). The black line in the IWRES vs PRED/TIME/Dose plots represents the horizontal line ($y=0$). The red line represents a smooth regression line.

Figure 31. VPC plots for final covariate model



Note: Legend: blue dots: observations; red solid and dashed lines: the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; pink and light blue areas: confidence intervals of median and percentiles of predicted concentrations at each time bin.

Reviewer's comments: *The applicant's population PK analysis is acceptable. The goodness-of-fit plots and the visual predictive check indicate that the updated population PK model is adequate in characterizing the PK profile of darolutamide in subjects with nm-CRPC. The applicant's analyses were verified by the reviewer, with no significant discordance identified.*

More specifically, the developed model was used to support the current submission as outlined in Table 55.

Table 68. Specific Comments on Applicant’s Final Population PK model

Utility of the final model			Reviewer’s Comments
Support labeling statements about intrinsic and extrinsic factors	Intrinsic factor	No clinically significant differences in the pharmacokinetics of darolutamide were observed based on age (48-95 years), race (White, Japanese, non-Japanese Asian, Black or African American) (b) (4) (b) (4) The pharmacokinetics of darolutamide has not been studied in patients with end-stage renal disease receiving dialysis (eGFR <15 mL/min/1.73m²) or severe hepatic (Child-Pugh C) impairment.	(b) (4)
	Extrinsic factor	CYP3A4 and P-gp Inducers; CYP3A4, P-gp and BCRP Inhibitors; and CYP, BCRP, or P-gp substrates.	The assessment does not rely on popPK analyses.
Derive exposure metrics for	C _{min} , C _{max} , and AUC(0-12) _{ss}	The applicant’s final model is generally acceptable for generating exposure metrics for	

Exposure-response analyses		exposure-response analyses.
Predict exposures at alternative dosing regimen	N.A.	

19.5.3.2 Exposure Response Analysis

The sponsor performed exposure-response (ER) analyses using three separate datasets derived from the clean data of study 17712:

- a dataset consisting of all patients who received either placebo or darolutamide (n=1419) for selection of baseline covariates for subsequent ER analyses
- a dataset consisting of all patients treated with darolutamide that also provided PK samples (PK subgroup, n=383) for evaluating the influence of exposure metrics on efficacy
- a dataset consisting of all patients treated with darolutamide regardless of whether they provided PK samples or not (actively treated, n=904) to evaluate the influence of PSA-related covariates on efficacy

The multivariate Cox proportional hazard analyses were conducted to evaluate the influence of pre-selected baseline covariates on MFS. The covariate selection process led to two covariates remained to be significant on MFS: PSA doubling time (months) at baseline (PSADT) and PSA value at baseline below or above median (PSA_CAT). ER analyses based on the PK subgroup did not identify significant relationship between pre-defined exposure covariates and MFS.

Reviewer' comments: *Only 42% (383/904) of patients treated with darolutamide provided PK sample. Results from ER analysis based on a subset of patients in phase 3 trial should be interpreted with caution. The same analyses were repeated using the dataset for all patients actively treated, in which the exposure in the patients without PK sampling was imputed from their individual covariate values using the selected phase 3 population PK model. The results from imputation method were not validated. Therefore, the validity of the ER analyses based on all patients actively treated (e.g. including those without PK samples) is not warranted.*

18.5 Additional Clinical Outcome Assessment Analyses

Patient reported outcomes (PRO) data were assessed for the ARAMIS study using the following questionnaires: European Quality of Life 5-Domain Scale 3 Level (EQ-5D-3L), Functional Assessment of Cancer Therapy – Prostate (FACT-P), Brief pain inventory – short form (BPI-SF), and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate cancer module (EORTC-QLQ-PR25).

Instruments

The **EQ-5D-3L** is a generic quality of life preference-based instrument that measures utility and health status. It contains a descriptive system that measures 5 health dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) based on 3 levels of response (1: no problem, 2: some problems, and 3: extreme problems). These five health dimensions are summarized into a single score known as the EQ-5D-3L index score, which ranges from -0.59 to 1 with higher scores representing better health states. It also contains a visual analog scale (EQ-VAS) where respondents self-rate their health status on a vertical graduated visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Reviewer's 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 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.

FACT-P assesses prostate cancer-related quality of life. It contains 5 domains: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and additional concerns (prostate cancer subscale [PCS]). Each item is scored on a 5-point (0-4) scale. All subscale items are summed to a total that makes up the subscale (or domain) score. The FACT-G is made up of the first four domains (PWB, SWB, EWB, and FWB). The trial outcome index (TOI) is the sum of PWB, FWB, and PCS. The FACT-P total score is the sum of the scores of 39 items of the questionnaire and ranges from 1 to 156 with higher scores indicating better quality of life for prostate cancer patients.

Reviewer's 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.

The **BPI-SF** assesses clinical pain related to cancer and derives two scores: pain severity and pain interference. The questionnaire is completed daily over a 7-day period and averages during the period of reporting are calculated (fewer than 4 reports out of the 7 days constitutes

missing data). The pain severity score is the mean score of 4 questions assessing pain at its “worst”, “least”, “average”, and “right now” (current pain). The pain interference score is the mean of seven interference items (general activity, walking ability, normal work, mood, enjoyment of life, relations with others, and sleep). Pain progression in the time to pain progression secondary endpoint was defined as an increase of ≥ 2 points from baseline in question 3 of the BPI-SF (related to the worst pain in the last 24 hours) taken as a 7-day average, or initiation of short or long-acting opioids for pain, whichever comes first.

Reviewer’s Comments: BPI-SF question 3 appears to be fit-for-purpose to assess pain intensity in this study. See Section 8.1.2 for our assessment of the time to pain progression secondary endpoint.

The **EORTC-QLQ-PR25** assesses prostate cancer-related quality of life. The prostate cancer module is a 25-item questionnaire including subscales assessing urinary symptoms (8 items), bowel symptoms (4 items), hormonal treatment-related symptoms (6 items), incontinence aid (1 item), sexual activity (2 items), and sexual functioning (4 items). The sexual activity and sexual functioning scales constitute the functional scales and the rest constitute the symptom scales.

Reviewer’s Comments: The PR25 disease module contains many questions related to urinary and sexual dysfunction and localized symptoms likely more related to post-surgical and radiation changes. These symptoms may be less likely to be responsive to the positive or negative effects of systemic treatment in a castration-resistant prostate cancer population.

PRO Statistical Analysis Plan

The PRO analyses were performed in the FAS. The applicant presented descriptive statistics on observed data for the FACT-P (each domain score including the PCS and the FACT-P total score), EQ-5D-3L (index score and VAS), EORTC-QLQ-PR25 (each subscale score), and BPI-SF (pain severity and pain interference scores) at each assessment time and the change from baseline for these measures by treatment arm. These analyses included patients with baseline assessments, questionnaires under unscheduled or not planned visits per protocol were not included, and the frequency of missing assessments by treatment arm were summarized. Additionally, the mean difference in the time-adjusted AUC between the two treatment arms was estimated using an analysis of covariance (ANCOVA) model with covariates for baseline PRO scores and stratification factors as recorded in IVRS. The least-square mean estimate, standard errors, and 95% CIs were estimated for each treatment arm and the difference in treatment arms.

Reviewer’s Comments: These PRO analyses are considered exploratory as they were not included in the testing hierarchy and Type I error was not controlled for multiple comparisons.

Schedule of Assessments

According to the study event schedule in the protocol, all PROs were collected on Day 1, Week 16, and every subsequent 16 weeks (with a few exceptions) during the double-blind study treatment period. EQ-5D-3L and FACT-P were not assessed at any subsequent visits after Week 16, but the PCS subscale of FACT-P was. All PROs were assessed at the end of study treatment visit 28 days (+7 days) after last dose.

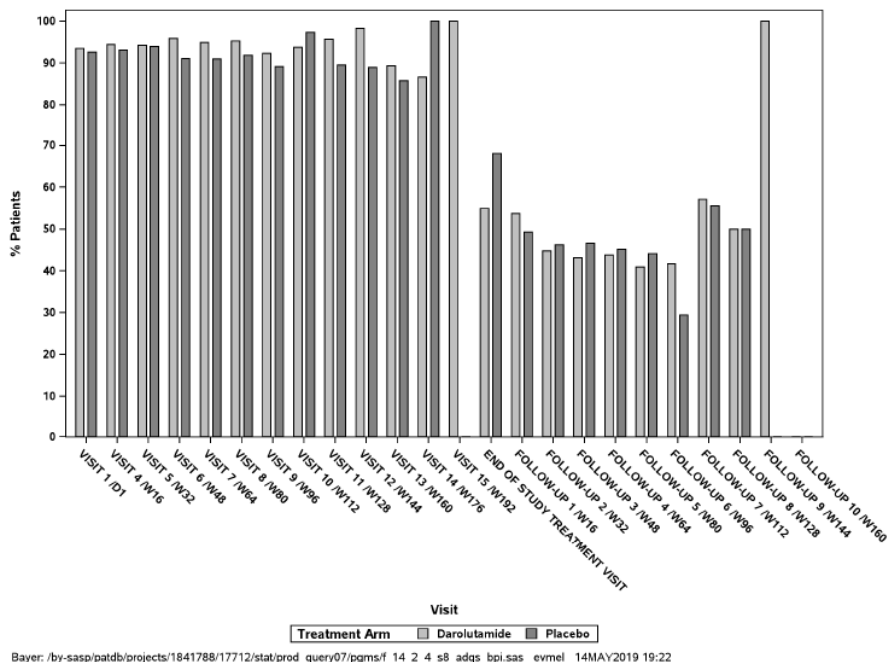
Completion Rates

In response to a PRO IR, the applicant calculated completion rates for each instrument among patients who are expected to have PRO assessments. Figure 30. through Figure 34. summarize the 100% completion rates (all questions completed for instrument or scale) for each PRO instrument.

The 100% completion rates for BPI-SF were high (>90%) across both treatment arms until the end of study treatment visit. For FACT-P, the 100% completion rates were low overall (<50%) but were high (>80%) across both treatment arms for the FACT-P PCS subscale until the end of study treatment visit. For EORTC-QLQ-PR25, the 100% completion rate was high (>85%) across both treatment arms until the end of study treatment visit. For EQ-5D-3L, the 100% completion rate was high (>90%) across both treatment arms until the end of study treatment visit.

Reviewer's Comments: Note that the end of study treatment visit does not occur at the same time point for each subject. If data collected after the end of study treatment were included in the visit assessments (rather than categorized as follow-up), completion rates may be lower.

Figure 32. 100% completion rate for BPI-SF

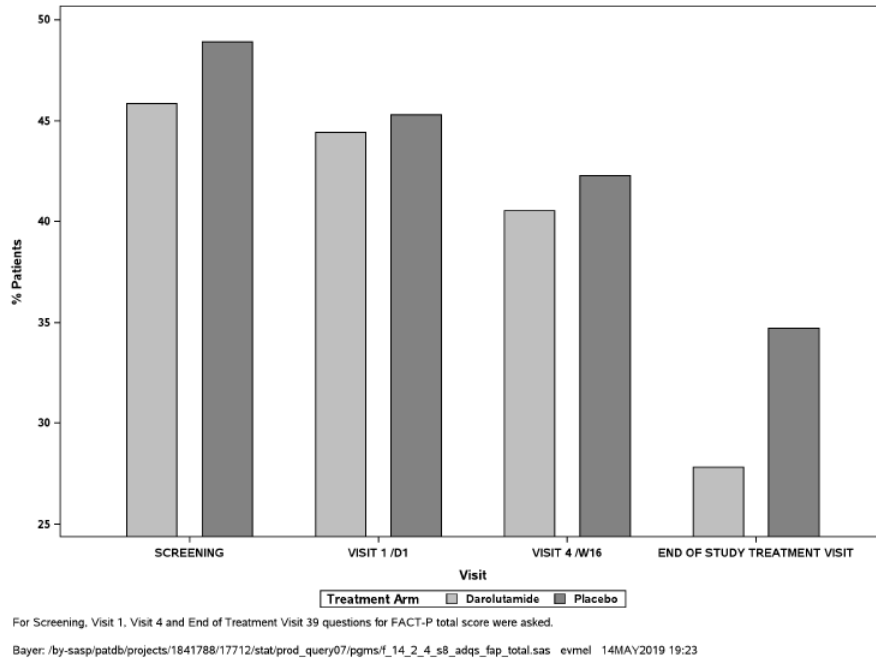


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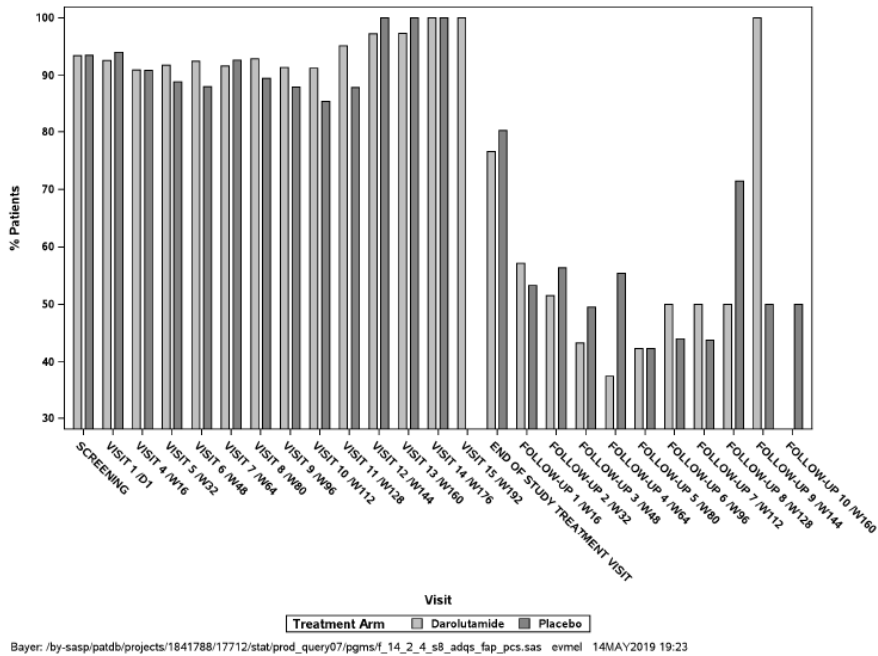
Source: Figure 1/11 in Applicant response to PRO IR dated 5/22/19

Figure 33. 100% completion rate for FACT-P



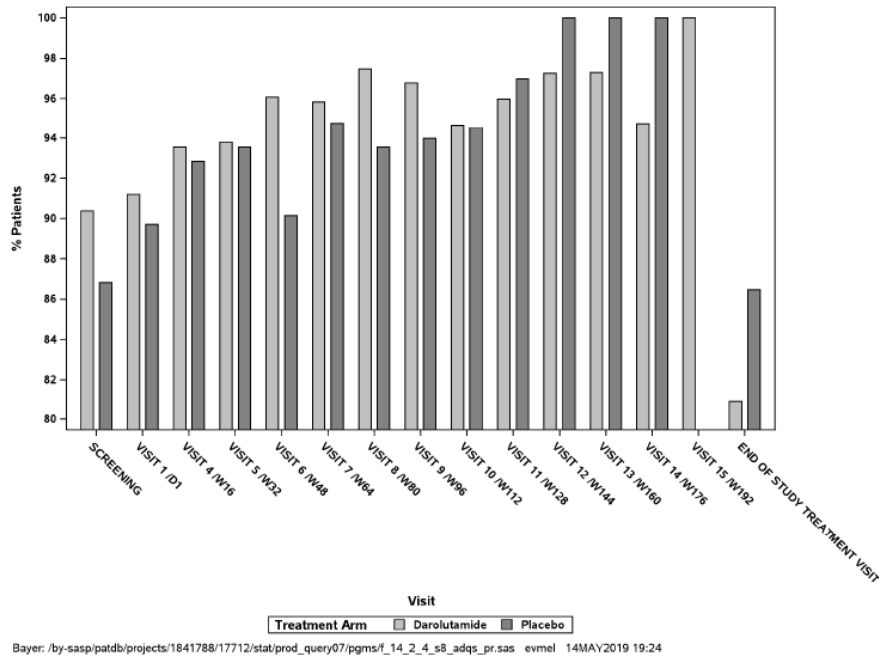
Source: Figure 1/12 in Applicant response to PRO IR dated 5/22/19

Figure 34. 100% completion rate for FACT-PPCS



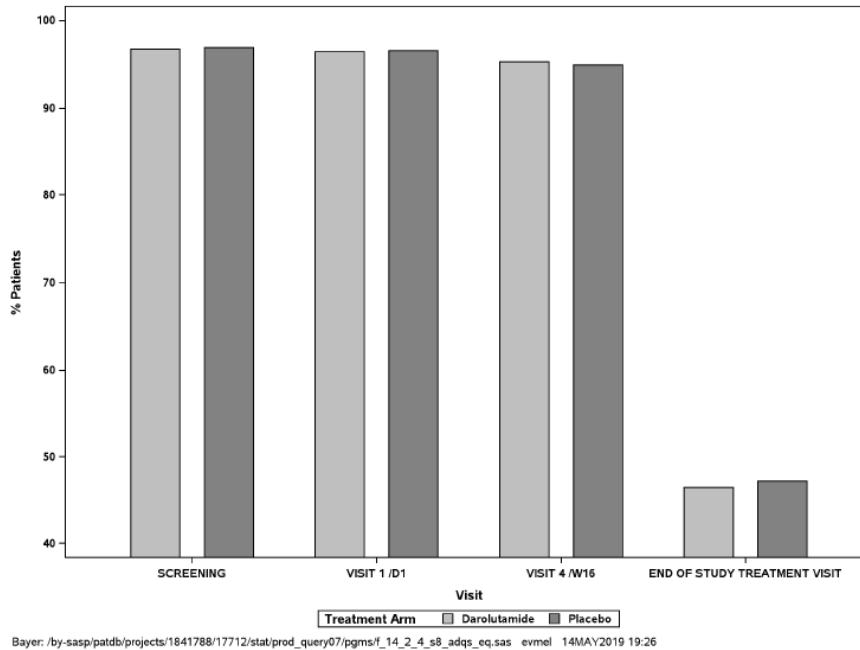
Source: Figure 1/13 in Applicant response to PRO IR dated 5/22/19

Figure 35. 100% completion rate for EORTC-QLQ-PR25



Source: Figure 1/14 in Applicant response to PRO IR dated 5/22/19

Figure 36. 100% completion rate for EQ-5D-3L



Source: Figure 1/20 in Applicant response to PRO IR dated 5/22/19

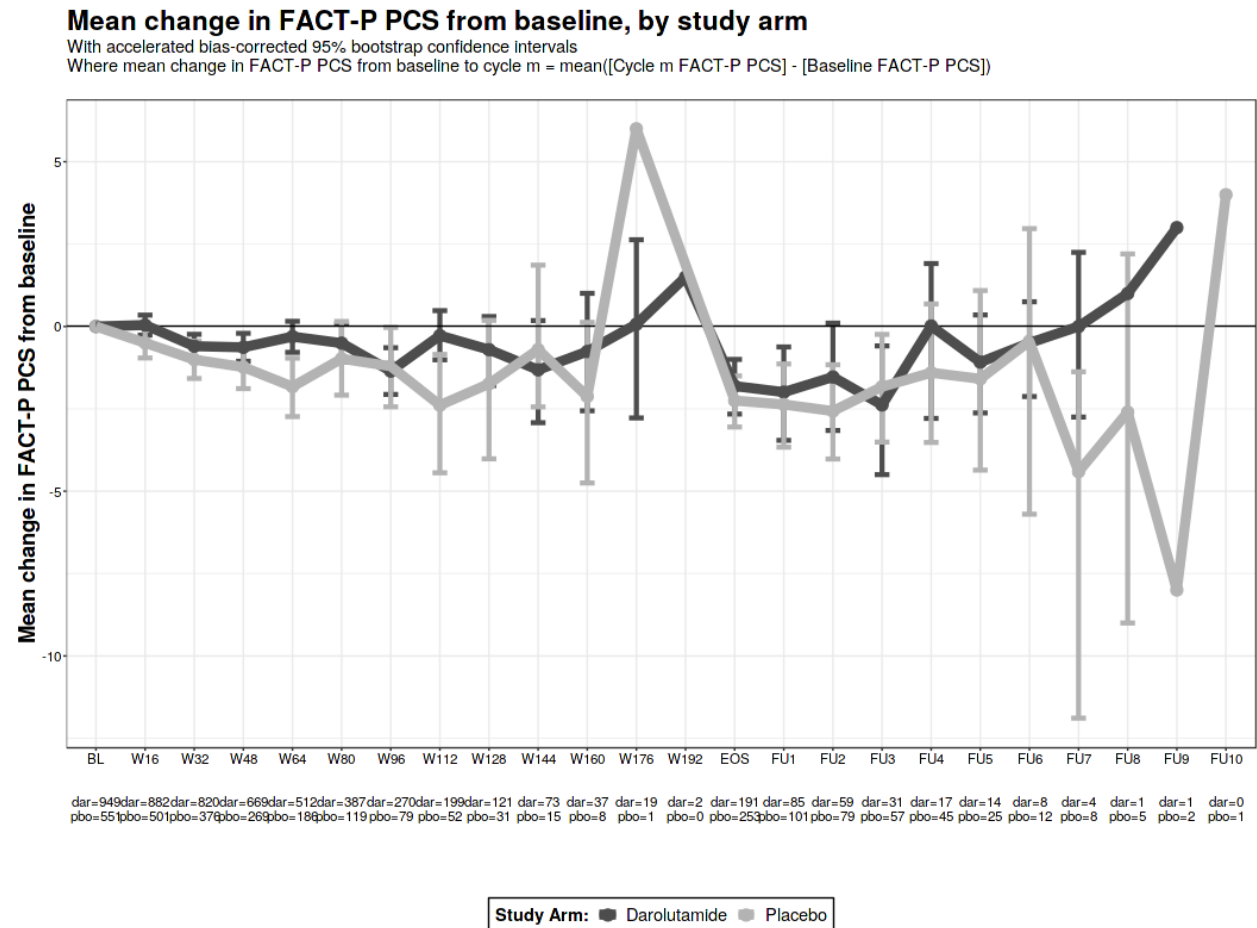
PRO Results

The FDA PRO IR focused on analyses of subscales from the FACT-P and EORTC-QLQ-PR25.

Analyses of FACT-P

For all FACT-P subscales other than the PCS subscale, data was limited as it was only collected until Week 16 and at end of treatment. Figure 35. shows the average change from baseline by arm for the FACT-P PCS subscale along with 95% confidence intervals. Positive values in mean change from baseline imply improved outcomes while negative values imply worsened outcomes. There appears to be no conclusive difference in FACT-P PCS score over time between the two arms.

Figure 37. Mean change from baseline for FACT-P PCS score



Source: Reviewer's Analysis

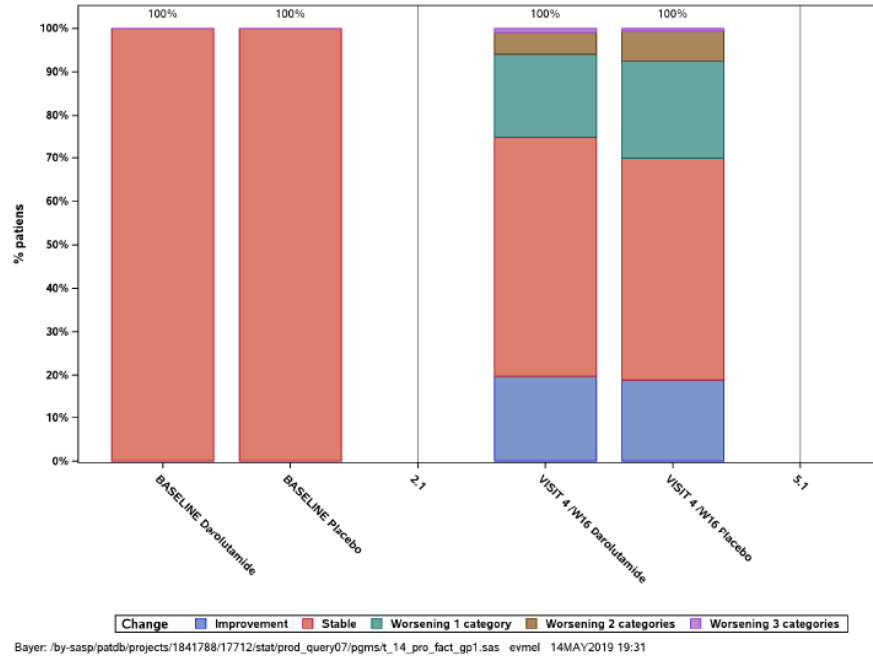
The following item-level responses from FACT-P were also assessed:

- FACT GP1- "I have a lack of energy"
- FACT GP2- "I have nausea"
- FACT GP5- "I am bothered by the side effects of treatment"
- FACT GF1- "I am able to work (including work at home)"
- FACT C2- "I am losing weight"
- FACT P1- "I have aches and pains that bother me"
- FACT P7- "I have difficulty urinating"

Descriptive bar charts for the distribution of change in response categories from baseline by arm for each of these items are shown in Figure 36. through Figure 42. For FACT GP1, GP2, GP5, and GF1, there was only information on one assessment after baseline, so it's hard to characterize what happens post-baseline. For FACT C2, there is slightly more worsening from baseline on the darolutamide arm compared to placebo in the first few assessments (Week 16

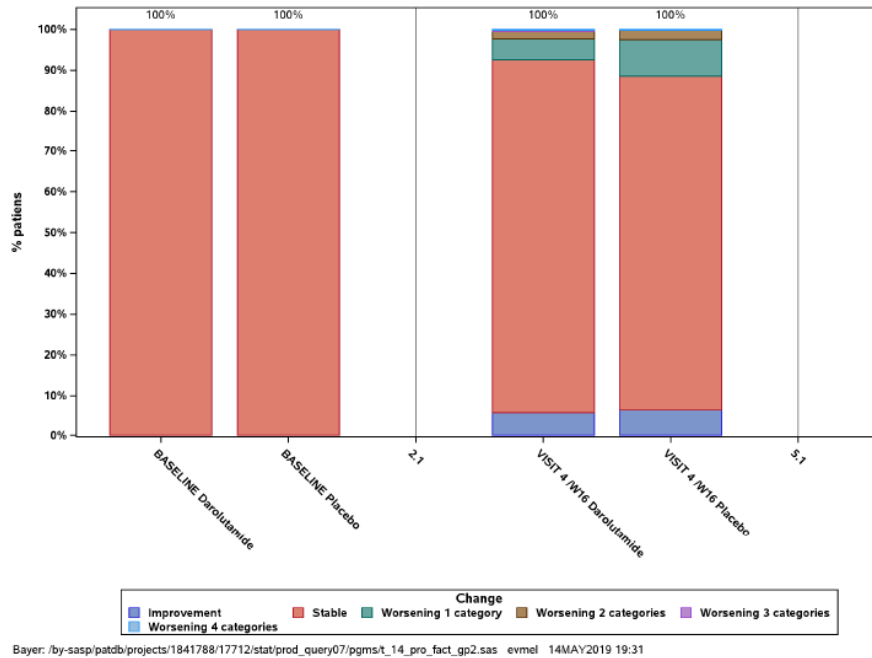
and Week 32) but the pattern does not seem to hold. For FACT P1 and P7, there appears to be slightly more worsening on the placebo arm compared to darolutamide across all assessments.

Figure 38. Change from Baseline of Responses by Arm: FACT GP1 – “I have a lack of energy”



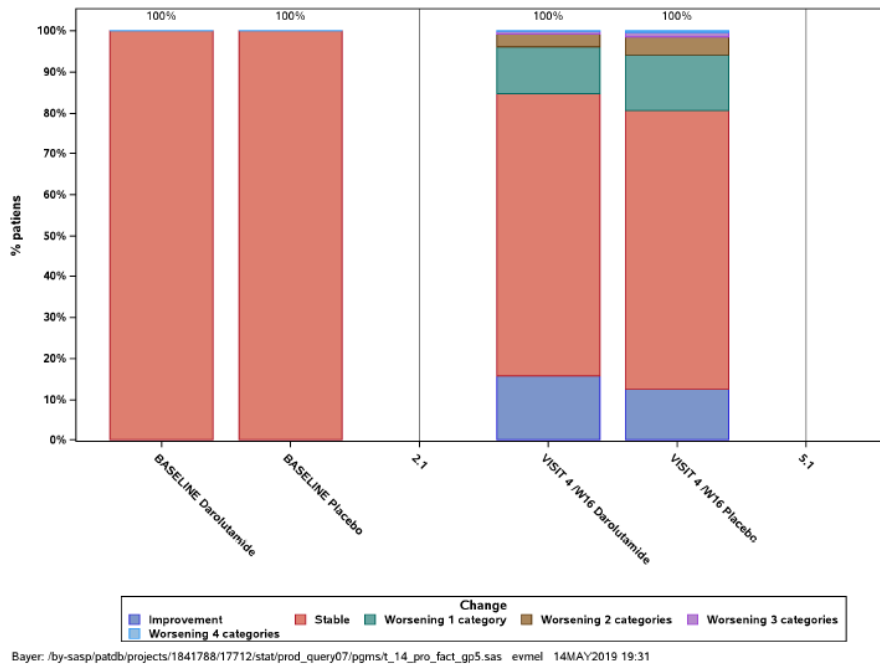
Source: Figure 1/50 in Applicant response to PRO IR dated 5/22/19

Figure 39. Change from Baseline of Response by Arm: FACT GP2 – “I have nausea”



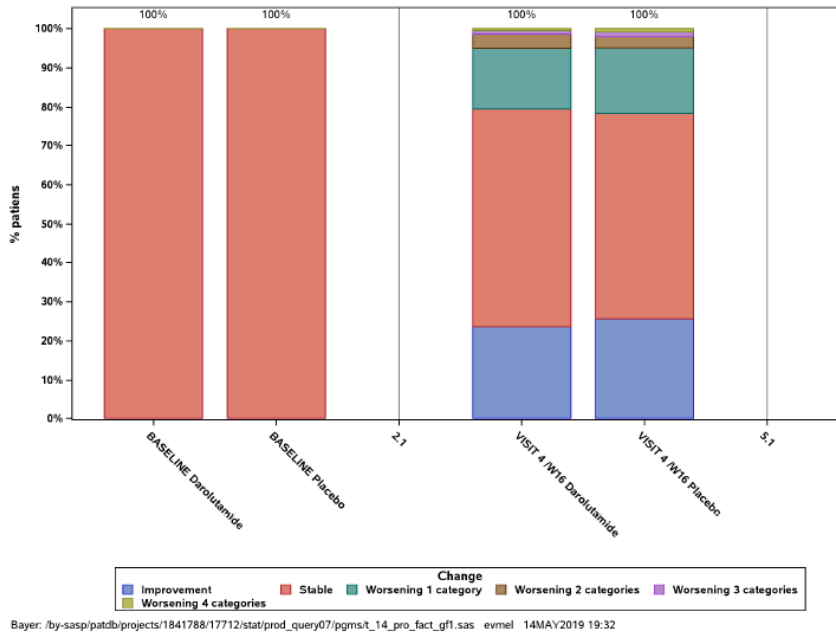
Source: Figure 1/52 in Applicant response to PRO IR dated 5/22/19

Figure 40. Change from Baseline of Responses by Arm: FACT GP5 – “I am bothered by the side effects of treatment”



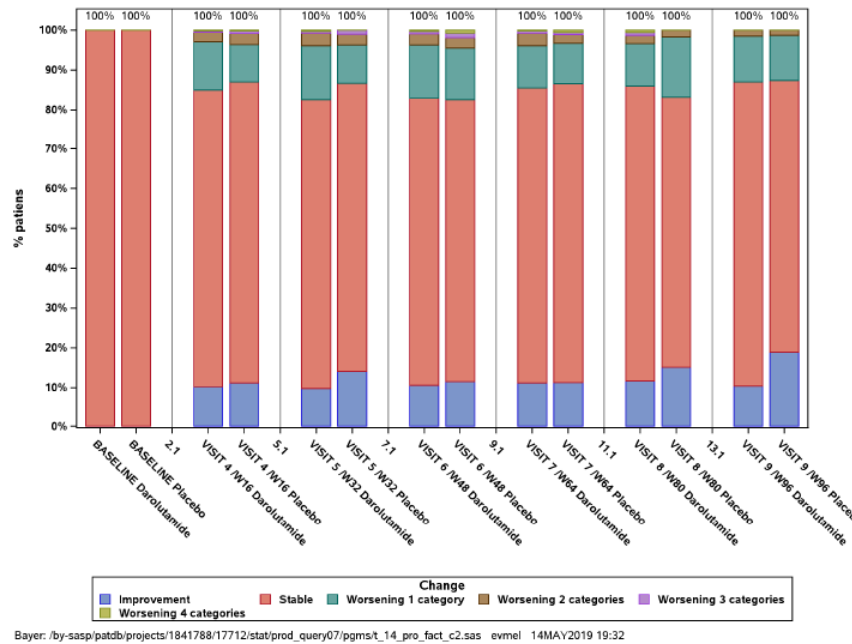
Source: Figure 1/54 in Applicant response to PRO IR dated 5/22/19

Figure 41. Change from baseline of Responses by Arm: FACT GF1 – “I am able to work (including at home)”



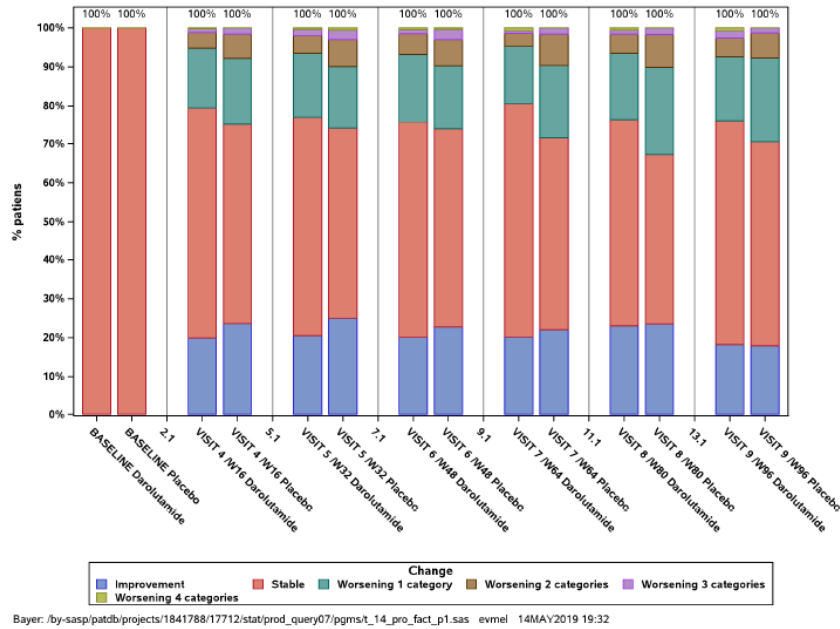
Source: Figure 1/56 in Applicant response to PRO IR dated 5/22/19

Figure 42. Change from Baseline of Responses by Arm: FACT C2 – “I am losing weight”



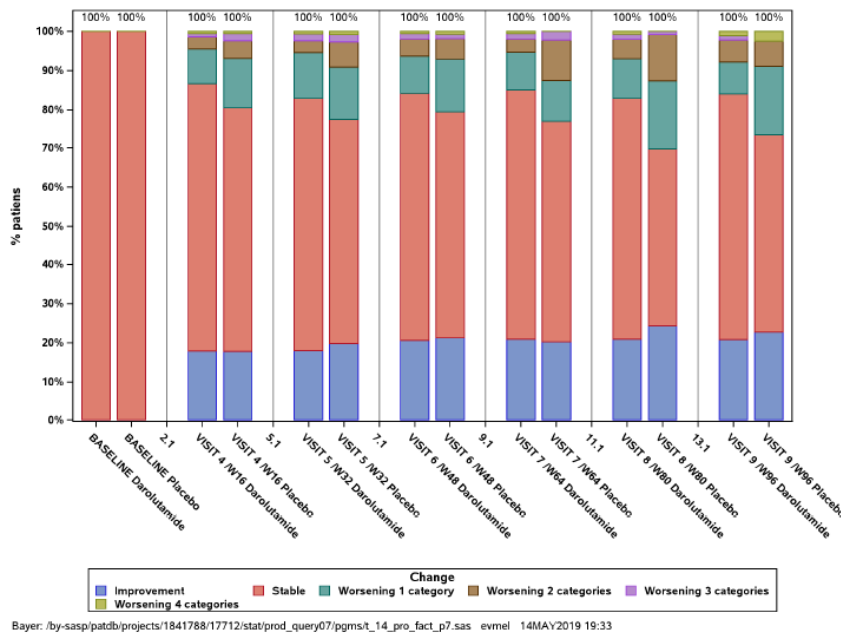
Source: Figure 1/58 in Applicant response to PRO IR dated 5/22/19

Figure 43. Change from Baseline of Responses by Arm: FACT P1 – “I have aches and pains that bother me”



Source: Figure 1/60 in Applicant response to PRO IR dated 5/22/19

Figure 44. Change from Baseline of Responses by Arm: FACT P7 – “I have difficulty urinating”

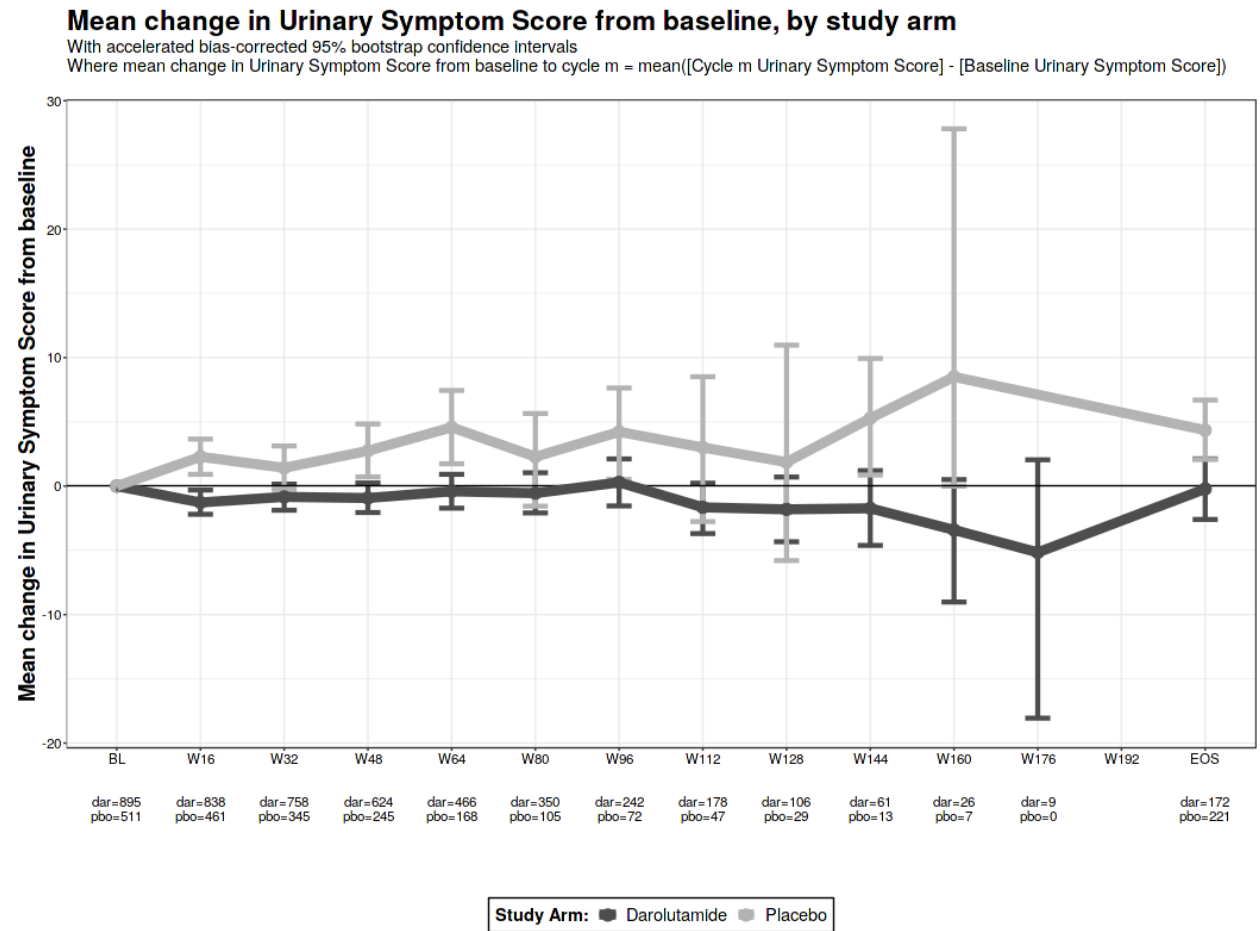


Source: Figure 1/62 in Applicant response to PRO IR dated 5/22/19

Analyses of EORTC-QLQ-PR25

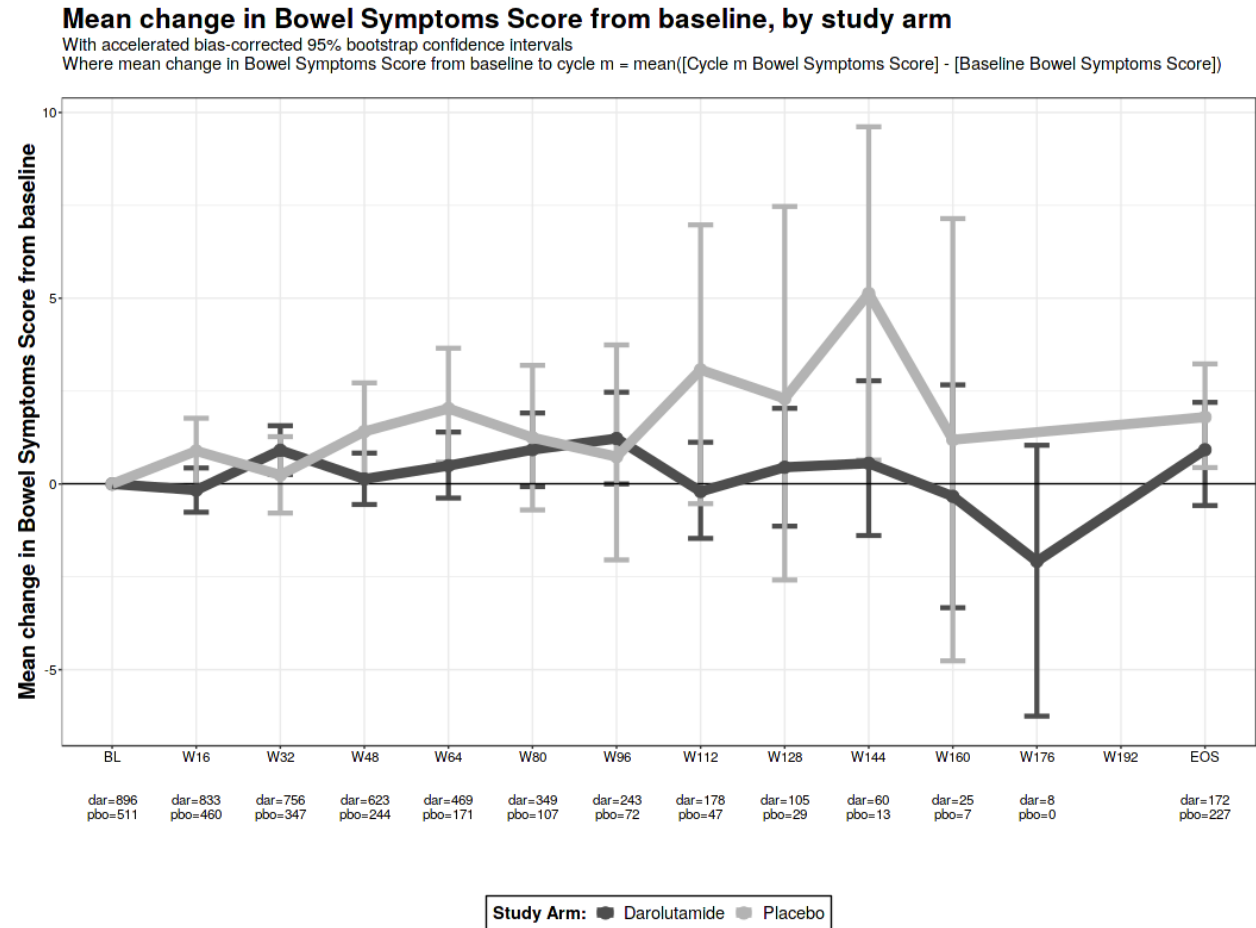
Figure 43. and Figure 44. show the average change from baseline by arm for select subscales of the EORTC-QLQ-PR25 along with 95% confidence intervals. For these subscales, lower scores represent better outcomes. The darolutamide arm appears to be better than the placebo arm across all assessments for the urinary symptom score and after Week 96 for the bowel symptoms score though sample sizes are small.

Figure 45. Mean Change from Baseline for Urinary Symptom Score



Source: Reviewer's Analysis

Figure 46. Mean Change from Baseline for Bowel Symptoms Score



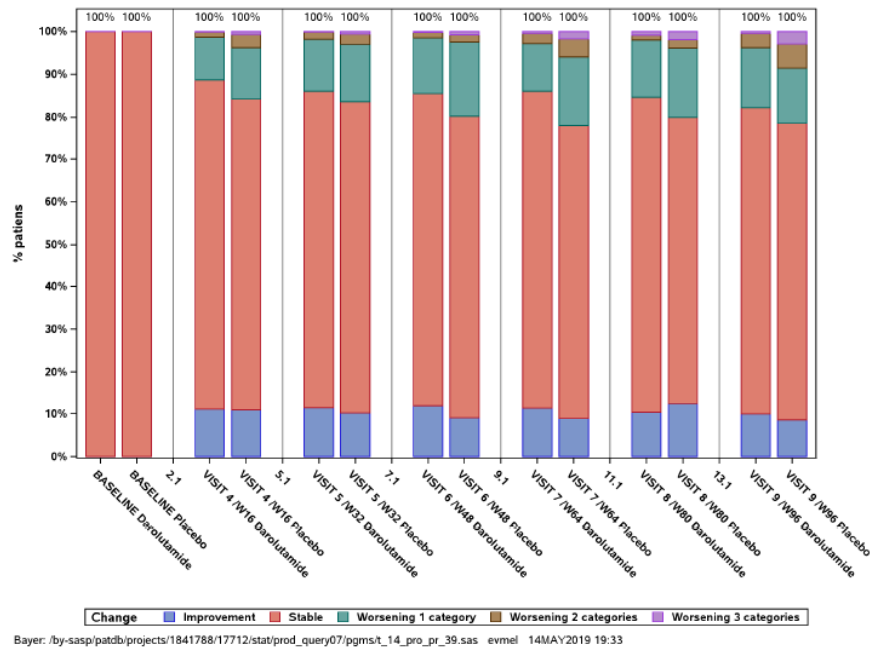
Source: Reviewer's Analysis

The following item-level responses from EORTC-QLQ-PR25 were also assessed:

- EORTC QLQ-PR25 #39- "Have your daily activities been limited by your urinary problems?"
- EORTC QLQ-PR25 #40- "Have your daily activities been limited by your bowel problems?"

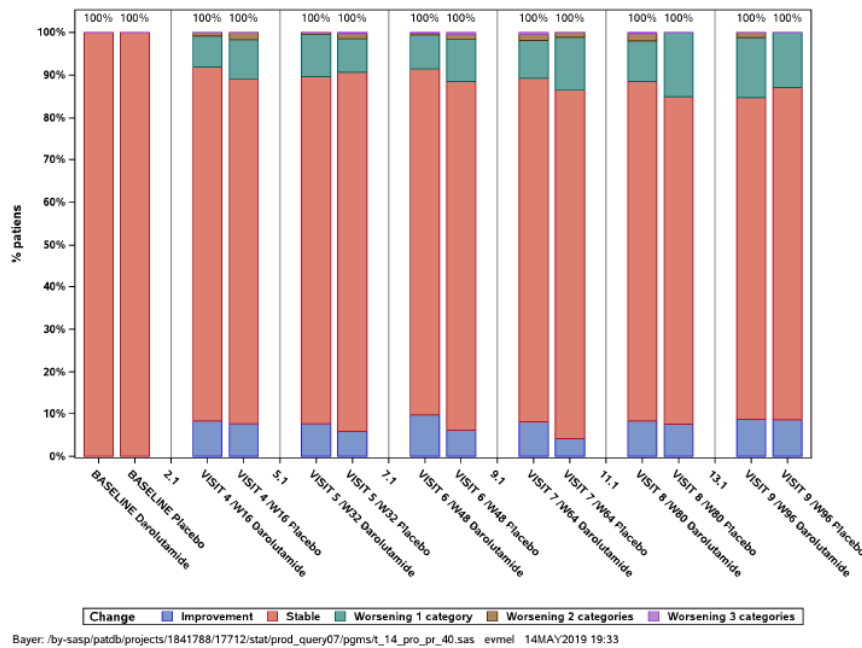
Descriptive bar charts for the distribution of change in response categories from baseline by arm for each of these items are shown in Figure 45. and Figure 46.. For both items #39 and #40, there appears to be slightly more worsening on the placebo arm compared to darolutamide across all assessments.

Figure 47. Change from Baseline of Responses by Arm: EORTC-QLQ-PR25 #39 – “Have your daily activities been limited by your urinary problems?”



Source: Figure 1/64 in Applicant response to PRO IR dated 5/22/19

Figure 48. Change from Baseline of Responses by Arm: EORTC-QLQ-PR25 #40 – “Have your daily activities been limited by your bowel problems?”



Source: Figure 1/66 in Applicant response to PRO IR dated 5/22/19

¹ Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7–30.

² Smith MR, Cook R, Lee K-A, et al. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. *Cancer* 2011; 117: 2077–2085.

³ Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate specific antigen doubling time. *J Clin Oncol* 2013; 31: 3800–3806.

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/s/

MITCHELL T CHAN
07/30/2019 11:49:03 AM

ANN M TRENTACOSTI on behalf of WILLIAM F PIERCE
07/30/2019 11:59:29 AM
Signing on behalf of William Pierce

WIMOLNUT N MANHENG
07/30/2019 12:34:49 PM

TIFFANY RICKS
07/30/2019 12:35:27 PM

HISHAM H QOSA
07/30/2019 12:39:44 PM

JUNSHAN QIU
07/30/2019 12:57:24 PM

JUNSHAN QIU on behalf of JINGYU YU
07/30/2019 12:58:11 PM

HONG ZHAO on behalf of PENGFEI SONG
07/30/2019 01:06:57 PM

JOYCE H CHENG
07/30/2019 01:11:25 PM

SHENGHUI TANG on behalf of LIJUN ZHANG
07/30/2019 01:17:59 PM

DANIEL L SUZMAN on behalf of MICHAEL H BRAVE
07/30/2019 01:39:52 PM

JAMIE R BREWER
07/30/2019 01:42:22 PM

CHANA WEINSTOCK
07/30/2019 01:45:10 PM

CHANA WEINSTOCK
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JOHN K LEIGHTON
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BRIAN P BOOTH on behalf of NAM ATIQUR RAHMAN
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RAJESHWARI SRIDHARA
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AMNA IBRAHIM
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MARC R THEORET
07/30/2019 04:06:56 PM