# PRODUCT NAME
ERLEADA® (apalutamide) tablets

# DOSAGE FORMS AND STRENGTHS
ERLEADA® 60 mg tablets contain 60 mg of apalutamide.
Slightly yellowish to greyish green, oblong-shaped, film-coated (FC) tablets, debossed with "AR 60" on one side.

For excipients, see *Pharmaceutical Information - List of Excipients*.

# CLINICAL INFORMATION
## Indications
ERLEADA® is indicated for the treatment of patients with
- metastatic castration-sensitive prostate cancer (mCSPC)
- non-metastatic, castration-resistant prostate cancer (nm-CRPC) who are at high risk of developing metastatic disease (see *Clinical studies*).

## Dosage and Administration
### Dosage
The recommended dose of ERLEADA® is 240 mg (four 60 mg tablets) administered orally once daily.

Medical castration with gonadotropin releasing hormone analogue (GnRHa) should be continued during treatment in patients not surgically castrated.

### Alternative Method of Administration
For patients who have difficulty swallowing tablets whole, the recommended dose of ERLEADA® tablets may be mixed with 4 ounces (120 mL) of applesauce. Do not crush the tablets. Stir applesauce upon introduction of whole tablets as well as at 15 minutes and 30 minutes afterwards until tablets are dispersed (well mixed with no chunks remaining). Using a spoon, swallow the mixture right away. Rinse the mixture container with 2 ounces of water and immediately drink the contents. Repeat the rinse with 2 ounces of water one more time to ensure the whole dose is taken. The mixture should be consumed within one hour of preparation (see *Pharmacological Properties - Pharmacokinetic Properties*).

### Dose modification
If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, hold dosing until symptoms improve to ≤ Grade 1 or original grade, then resume at the same dose or a reduced dose (180 mg or 120 mg), if warranted.

### Missed dose(s)
If the patient misses a dose, it should be taken as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose.

### Special populations
#### *Pediatrics (17 years of age and younger)*
The safety and effectiveness of ERLEADA® in children have not been evaluated.
There is no relevant use of ERLEADA® in pediatric patients aged 17 years and younger.

#### *Elderly (65 years of age and older)*
No dose adjustment is necessary for elderly patients (see *Clinical studies and Pharmacokinetic Properties*).

#### *Renal impairment*
No dosage adjustment is necessary for patients with mild to moderate renal impairment. No data are available in patients with severe renal impairment or end-stage renal disease (eGFR $\leq$ 29 mL/min/1.73m$^2$) (see *Pharmacokinetic Properties*).

#### *Hepatic impairment*
No dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh Class C) (see *Pharmacokinetic Properties*).

### Administration
ERLEADA® should be administered orally once daily, with or without food. Swallow the tablets whole.

## Contraindications
ERLEADA® is contraindicated in women who are or may become pregnant (see *Pregnancy, Breast-feeding and Fertility*).

## Warnings and Precautions

### Falls and fractures

Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In SPARTAN, a randomized study of patients with nmCRPC, fracture was reported for 11.7% of subjects treated with ERLEADA® and 6.5% of subjects treated with placebo. Half of the subjects experienced a fall within 7 days before the fracture event in both treatment groups. Falls were reported for 15.6% of subjects treated with ERLEADA® versus 9.0% of subjects treated with placebo. Evaluate patients for fracture and fall risk. In TITAN, a randomized study of patients with mCSPC, nonpathological fractures occurred in 6% of patients treated with ERLEADA® and in 5% of patients treated with placebo.

### Ischemic heart disease and ischemic cerebrovascular disorders

Ischemic heart disease and ischemic cerebrovascular disorders, including events leading to death, occurred in patients treated with ERLEADA®. Monitor for signs and symptoms of ischemic heart disease and ischemic cerebrovascular disorders. Optimize management of risk factors, such as hypertension, diabetes, or dyslipidemia.

In a randomized study SPARTAN, ischemic heart disease occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study TITAN, ischemic heart disease occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from ischemic heart disease.

In the SPARTAN study, with a median exposure of 32.9 months for ERLEADA® and 11.5 months for placebo, ischemic cerebrovascular disorders occurred in 4% of patients treated with ERLEADA® and 1% of patients treated with placebo (see *Adverse Reactions*). In the TITAN study, ischemic cerebrovascular disorders occurred in a similar proportion of patients in the ERLEADA® (1.5%) and placebo (1.5%) groups. Across the SPARTAN and TITAN studies, 2 patients (0.2%) treated with ERLEADA® and no patients treated with placebo died from an ischemic cerebrovascular disorder.

Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within six months of randomization were excluded from the SPARTAN and TITAN studies.

### Seizure

Permanently discontinue ERLEADA® in patients who develop a seizure during treatment.

In two randomized studies, SPARTAN and TITAN, five subjects (0.4%) treated with ERLEADA® and two subjects (0.2%) treated with placebo experienced a seizure. In these studies, subjects with a history of seizure or predisposing factors for seizure were excluded. No seizures occurred in two other studies that enrolled 145 subjects. There is no clinical experience in re-administering ERLEADA® to patients who experienced a seizure.

### Severe Cutaneous Adverse Reactions (SCAR)

Rare postmarketing cases of SCAR (including drug reaction with eosinophilia and systemic symptoms [DRESS] and Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN]), which can be life-threatening or may lead to death, have been reported with androgen receptor inhibitors including ERLEADA®. SCAR was not reported in clinical trials TITAN and SPARTAN. Discontinue ERLEADA® immediately if signs or symptoms of SCAR develop (see *Adverse Reactions – Postmarketing data*).

### Concomitant use with other medicinal products

Apalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products (see *Interactions*). A review of concomitant medicinal products should therefore be conducted when apalutamide treatment is initiated. Concomitant use of apalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters (see *Interactions*) should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If ERLEADA® is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin), additional International Normalised Ratio (INR) monitoring should be conducted (see *Interactions*).

### Recent cardiovascular disease

Patients with clinically significant cardiovascular disease in the past 6 months including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias were excluded from the clinical studies. Therefore, the safety of apalutamide in these patients has not been established. If ERLEADA® is prescribed, patients with clinically significant cardiovascular disease should be monitored for risk factors such as hypercholesterolaemia, hypertriglyceridaemia, or other cardio-metabolic disorders (see *Adverse Reactions*). Patients should be treated, if appropriate, after initiating ERLEADA® for these conditions according to established treatment guidelines.

### Androgen deprivation therapy may prolong the QT interval

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see *Interactions*), physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating ERLEADA®.

## Interactions

### Medications that inhibit CYP2C8

In a drug-drug interaction study, the $C_{max}$ of apalutamide decreased by 21% while AUC increased by 68% following co-administration of ERLEADA® as a 240 mg single dose with gemfibrozil (strong CYP2C8 inhibitor). Simulations suggest that gemfibrozil may increase the steady-state $C_{max}$ and AUC of apalutamide by 32% and 44%, respectively. For the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound active metabolite), the steady-state $C_{max}$

and AUC may increase by 19% and 23%, respectively (see Figure 1). No initial dose adjustment is necessary however, consider reducing the ERLEADA® dose based on tolerability (see *Dosage and Administration – Dose modification*). Mild or moderate inhibitors of CYP2C8 are not expected to affect the exposure of apalutamide.

### Medications that inhibit CYP3A4

In a drug-drug interaction study, the $C_{max}$ of apalutamide decreased by 22% while AUC was similar following co-administration of ERLEADA® as a 240 mg single dose with itraconazole (strong CYP3A4 inhibitor). Simulations suggest that ketoconazole (strong CYP3A4 inhibitor) may increase the steady-state $C_{max}$ and AUC of apalutamide by 38% and 51%, respectively. For the active moieties, the steady-state $C_{max}$ and AUC may increase by 23% and 28%, respectively (see Figure 1). No initial dose adjustment is necessary however, consider reducing the ERLEADA® dose based on tolerability (see *Dosage and Administration – Dose modification*). Mild or moderate inhibitors of CYP3A4 are not expected to affect the exposure of apalutamide.

### Medications that induce CYP3A4 or CYP2C8

The effects of CYP3A4 or CYP2C8 inducers on the pharmacokinetics of apalutamide have not been evaluated *in vivo*. Simulations suggest that rifampin (strong CYP3A4 and moderate CYP2C8 inducer) may decrease the steady-state $C_{max}$ and AUC of apalutamide by 25% and 34%, respectively. For the active moieties, the steady-state $C_{max}$ and AUC may decrease by 15% and 19%, respectively (see *Figure 1*).

### Acid lowering agents

Apalutamide is not ionizable under relevant physiological pH condition, therefore acid lowering agents (e.g. proton pump inhibitor, $H_2$-receptor antagonist, antacid) are not expected to affect the solubility and bioavailability of apalutamide.

### Medications that affect transporters

In vitro, apalutamide and its N-desmethyl metabolite are substrates for P-gp but not BCRP, OATP1B1, and OATP1B3. Because apalutamide is completely absorbed after oral administration, P-gp does not limit the absorption of apalutamide and therefore, inhibition or induction of P-gp is not expected to affect the bioavailability of apalutamide.

### Effect of ERLEADA® on drug metabolizing enzymes

*In vitro* studies showed that apalutamide and N-desmethyl apalutamide are moderate to strong CYP3A4 and CYP2B6 inducers, are moderate inhibitors of CYP2B6 and CYP2C8, and weak inhibitors of CYP2C9, CYP2C19, and CYP3A4. Apalutamide and N-desmethyl apalutamide do not affect CYP1A2 and CYP2D6 at therapeutically relevant concentrations.

In humans, ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9. In a drug-drug interaction study using a cocktail approach, co-administration of ERLEADA® with single oral doses of sensitive CYP substrates resulted in a 92% decrease in the AUC of midazolam (CYP3A4 substrate), 85% decrease in the AUC of omeprazole (CYP2C19 substrate), and 46% decrease in the AUC of S-warfarin (CYP2C9 substrate). ERLEADA® did not cause clinically meaningful changes in exposure to the CYP2C8 substrate (see *Figure 1*). Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4,

CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of efficacy if medication is continued. If given with warfarin, monitor International Normalized Ratio (INR) during ERLEADA® treatment.

Induction of CYP3A4 by apalutamide suggests that UDP-glucuronosyl transferase (UGT) may also be induced via activation of the nuclear pregnane X receptor (PXR). Concomitant administration of ERLEADA® with medications that are substrates of UGT can result in lower exposure to these medications. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of efficacy.

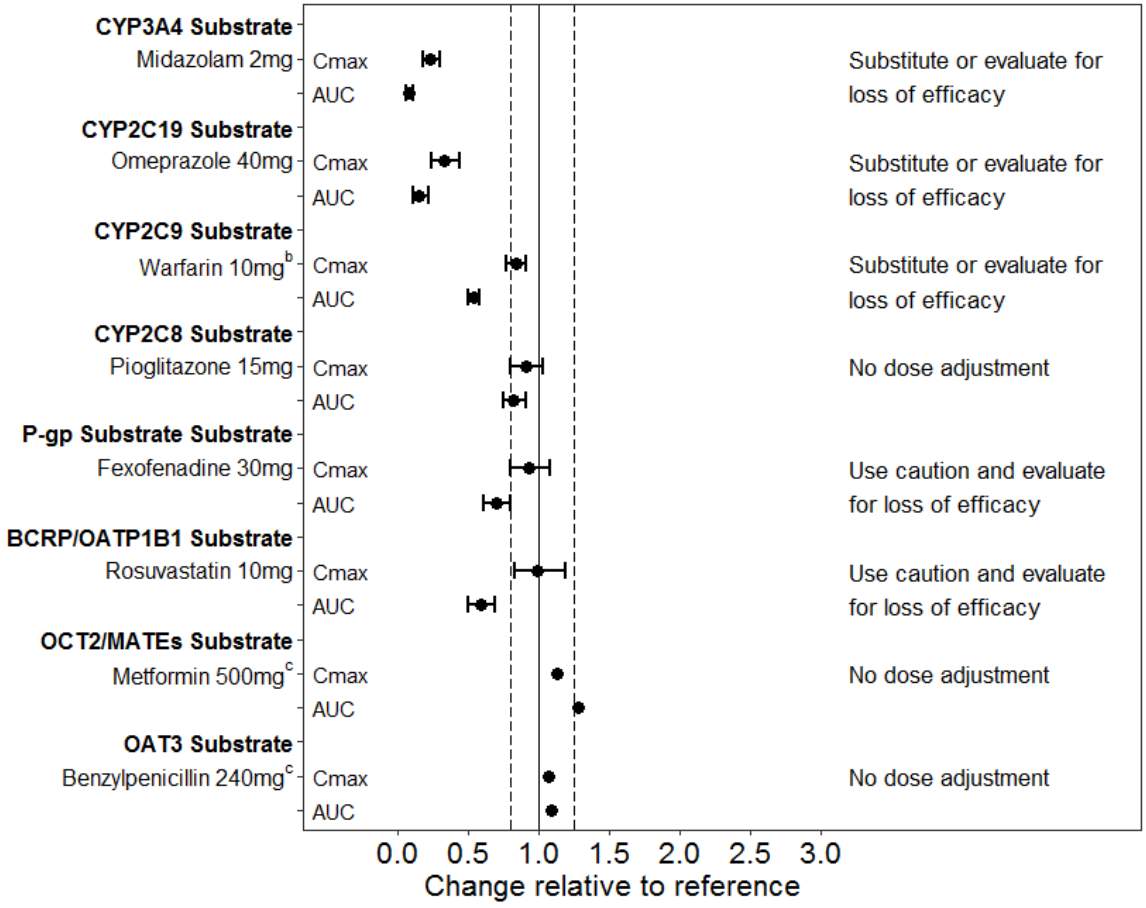
### Effect of apalutamide on drug transporters

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. A drug-drug interaction study using a cocktail approach showed that co-administration of ERLEADA® with single oral doses of sensitive transporter substrates resulted in a 30% decrease in the AUC of fexofenadine (P-gp substrate) and 41% decrease in the AUC of rosuvastatin (BCRP/OATP1B1 substrate) but had no impact on $C_{max}$ (see *Figure 1*). Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of efficacy if medication is continued.

Based on *in vitro* data, inhibition of organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3) and multidrug and toxin extrusions (MATEs) by apalutamide and its N-desmethyl metabolite cannot be excluded. No *in vitro* inhibition of organic anion transporter 1 (OAT1) was observed. Simulations suggest that apalutamide does not cause clinically meaningful changes in exposure to metformin (OCT2/MATEs substrate) and benzylpenicillin (OAT3 substrate) (see *Figure 1*).

**Figure 1: Effects of ERLEADA® on Other Medications**

| Population Characteristics | PK | Ratio and 90% Confidence Interval [a] | Recommendation |
|---|---|---|---|
| **CYP3A4 Substrate** | | | |
| Midazolam 2mg | Cmax | | Substitute or evaluate for loss of efficacy |
| | AUC | | |
| **CYP2C19 Substrate** | | | |
| Omeprazole 40mg | Cmax | | Substitute or evaluate for loss of efficacy |
| | AUC | | |
| **CYP2C9 Substrate** | | | |
| Warfarin 10mg[b] | Cmax | | Substitute or evaluate for loss of efficacy |
| | AUC | | |
| **CYP2C8 Substrate** | | | |
| Pioglitazone 15mg | Cmax | | No dose adjustment |
| | AUC | | |
| **P-gp Substrate Substrate** | | | |
| Fexofenadine 30mg | Cmax | | Use caution and evaluate for loss of efficacy |
| | AUC | | |
| **BCRP/OATP1B1 Substrate** | | | |
| Rosuvastatin 10mg | Cmax | | Use caution and evaluate for loss of efficacy |
| | AUC | | |
| **OCT2/MATEs Substrate** | | | |
| Metformin 500mg[c] | Cmax | | No dose adjustment |
| | AUC | | |
| **OAT3 Substrate** | | | |
| Benzylpenicillin 240mg[c] | Cmax | | No dose adjustment |
| | AUC | | |




[a] combination/no combination
[b] S-warfarin was measured in the study
[c] based on simulations

### GnRH analog

In mCSPC subjects receiving leuprolide acetate (a GnRH analog) co-administered with apalutamide, PK data indicated that apalutamide had no apparent effect on the steady-state exposure of leuprolide.

## Pregnancy, Breast-feeding and Fertility

### Pregnancy

ERLEADA® is contraindicated in women who are or may become pregnant. Based on its mechanism of action, ERLEADA® may cause fetal harm when administered during pregnancy. There are no data available with the use of ERLEADA® during pregnancy.

### Contraception
ERLEADA® may be harmful to a developing fetus. Patients having sex with female partners of reproductive potential should use a condom along with another highly effective contraceptive method during treatment and for 3 months after the last dose of ERLEADA® (see *Pregnancy, Breast-feeding and Fertility*).

### Breast-feeding
There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed infant, or the effect on milk production.

### Fertility
Based on animal studies, ERLEADA® may impair fertility in males of reproductive potential (see *Non-Clinical Information*).

## Effects on Ability to Drive and Use Machines
No studies on the effects of ERLEADA® on the ability to drive or use machines have been performed. It is not anticipated that ERLEADA® will affect the ability to drive and use machines.

## Adverse Reactions
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of apalutamide based on the comprehensive assessment of the available adverse event information. A causal relationship with apalutamide cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

### Metastatic Castration-sensitive Prostate Cancer (mCSPC)
TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA® at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA® and 18 months (range: 0.1 to 34 months) in patients who received placebo.

The most common adverse reactions (≥15%) reported in the randomized clinical study that occurred more commonly (≥2%) in the ERLEADA® arm were arthralgia, fatigue, rash, hypertension, and hot flush.

Ten patients (2%) who were treated with ERLEADA® and 16 patients (3%) treated with placebo died from adverse events (within 30 days of last dose). ERLEADA® was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%).

Table 1 shows adverse reactions on the ERLEADA® arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. ARs are

also listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), and rare (≥ 1/10000 to < 1/1000). Within each frequency grouping, ARs are presented in order of decreasing frequency.

**Table 1: Adverse Reactions in TITAN (mCSPC)**

| System/Organ Class | | ERLEADA® N=524 | | Placebo N=527 | |
|---|---|---|---|---|---|
| **Adverse Reaction** | **Frequency Category[a]** | **All Grades %** | **Grade 3-4 %** | **All Grades %** | **Grade 3-4 %** |
| **General disorders and administration site conditions** | | | | | |
| Fatigue[c] | very common | 19.7 | 1.5 | 16.7 | 1.1 |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Arthralgia[c] | very common | 17.4 | 0.4 | 14.8 | 0.9 |
| Muscle spasm | common | 3.1 | 0 | 1.9 | 0 |
| **Skin and subcutaneous tissue disorders** | | | | | |
| Rash[b] | very common | 27.9 | 6.3 | 8.9 | 0.8 |
| Pruritus | very common | 10.7 | 0.2 | 4.6 | 0.2 |
| **Nervous system disorders** | | | | | |
| Dysgeusia | common | 3.2 | 0 | 0.6 | 0 |
| Ischemic cerebrovascular disorders[g] | common | 1.5 | 0.6 | 1.5 | 0.2 |
| Seizure | uncommon | 0.6 | 0.2 | 0.4 | 0 |
| **Metabolism and nutrition disorders** | | | | | |
| Hypercholesterolemia | common | 4.6 | 0.4 | 0.8 | 0 |
| Hypertriglyceridemia | common | 3.4 | 0.6 | 1.3 | 0.4 |
| **Cardiac disorders** | | | | | |
| Ischemic Heart Disease[d] | common | 4.4 | 2.3[e] | 1.5 | 0.6[e] |
| **Vascular disorders** | | | | | |
| Hot flush | very common | 22.7 | 0 | 16.3 | 0 |
| Hypertension | very common | 17.7 | 8.4 | 15.6 | 9.1 |
| **Gastrointestinal disorders** | | | | | |
| Diarrhea | common | 9.4 | 0.2 | 6.1 | 0.2 |
| **Endocrine disorders** | | | | | |
| Hypothyroidism[f] | common | 6.5 | 0 | 1.1 | 0 |

[a] Adverse reaction frequencies presented are based on the placebo-controlled period of the clinical study
[b] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
[c] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
[d] Includes angina pectoris, angina unstable, myocardial infarction, acute myocardial infarction, coronary artery occlusion, coronary artery stenosis, acute coronary syndrome, arteriosclerosis coronary artery, cardiac stress test abnormal, troponin increased, myocardial ischemia
[e] Includes Grades 3-5
[f] Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine decreased, autoimmune thyroiditis, thyroxine free decreased, tri-iodothyronine decreased
[g] Includes transient ischemic attack, cerebrovascular accident, cerebrovascular disorder, ischemic stroke, carotid arteriosclerosis, carotid artery stenosis, hemiparesis, lacunar infarction, lacunar stroke, thrombotic cerebral infarction, vascular encephalopathy, cerebellar infarction, cerebral infarction, and cerebral ischemia

At the time of final study analysis with a median treatment duration of 39 months, no new safety concerns were identified.

### Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized double-blind, placebo-controlled, multi-center clinical study, enrolled subjects who had nm-CRPC. In this study, subjects received ERLEADA® at a dose of 240 mg daily in combination with androgen deprivation therapy (ADT) in the treatment arm and placebo with ADT in the control arm.

The most common adverse reactions (≥15%) reported in the randomized clinical study that occurred more commonly (≥2%) in the ERLEADA® arm were fatigue, skin rash, weight decreased, arthralgia, and fall.

Discontinuations due to adverse events were reported for 11% of subjects treated with ERLEADA® and 7% of subjects treated with placebo. At the time of the analysis, 23.6% of subjects were still on ERLEADA®.

Table 2 shows adverse reactions on the ERLEADA® arm in SPARTAN that occurred with a ≥ 2% absolute increase in frequency compared to placebo or were events of special interest. ARs are also listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), and rare (≥ 1/10000 to < 1/1000). Within each frequency grouping, ARs are presented in order of decreasing frequency.

**Table 2: Adverse Reactions due to ERLEADA® in SPARTAN**

| System/Organ Class | | ERLEADA® N=803 | | Placebo N=398 | |
|---|---|---|---|---|---|
| **Adverse Reaction** | **Frequency Category[a]** | **All Grades %** | **Grade 3-4 %** | **All Grades %** | **Grade 3-4 %** |
| **General disorders and administration site conditions** | | | | | |
| Fatigue[e] | very common | 30.4 | 0.9 | 21.1 | 0.3 |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Arthralgia[e] | very common | 15.9 | 0 | 7.5 | 0 |
| **Skin and subcutaneous tissue disorders** | | | | | |
| Skin rash[b] | very common | 24.7 | 5.2 | 6 | 0.3 |
| Pruritus[e] | common | 6.2 | 0.2 | 1.5 | 0 |
| **Nervous system disorders** | | | | | |
| Ischemic cerebrovascular disorders[f] | common | 4.0 | 1.6 | 1.0 | 0.8 |
| Seizure | uncommon | 0.2 | 0 | 0 | 0 |
| **Metabolism and nutrition disorders** | | | | | |
| Hypercholesterolemia | common | 6.1 | 0 | 1.5 | 0 |
| Hypertriglyceridemia | common | 3.5 | 0.6 | 0.8 | 0.3 |
| **Injury, poisoning and procedural complications** | | | | | |
| Fall[e] | very common | 15.6 | 1.7 | 9.0 | 0.8 |
| Fracture[c] | very common | 11.7 | 2.7 | 6.5 | 0.8 |
| **Investigations** | | | | | |
| Weight decreased[e] | very common | 16.1 | 1.1 | 6.3 | 0.3 |
| **Endocrine disorders** | | | | | |
| Hypothyroidism[d] | common | 8.1 | 0 | 2.0 | 0 |

[a] Adverse reaction frequencies presented are based on the placebo-controlled period of the clinical study
[b] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
[c] Includes rib fracture, lumbar vertebral fracture, spinal compression fracture, spinal fracture, foot fracture, hip fracture, humerus fracture, thoracic vertebral fracture, upper limb fracture, fractured sacrum, hand fracture, pubis fracture, acetabulum fracture, ankle fracture, compression fracture, costal cartilage fracture, facial bones fracture, lower limb fracture, osteoporotic fracture, wrist fracture, avulsion fracture, fibula fracture, fractured coccyx, pelvic fracture, radius fracture, sternal fracture, stress fracture, traumatic fracture, cervical vertebral fracture, femoral neck fracture, tibia fracture
[d] Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine decreased, autoimmune thyroiditis, thyroxine free decreased, tri-iodothyronine decreased
[e] Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
[f] Includes transient ischemic attack, cerebrovascular accident, cerebrovascular disorder, ischemic stroke, carotid arteriosclerosis, carotid artery stenosis, hemiparesis, lacunar infarction, lacunar stroke, thrombotic cerebral infarction, vascular encephalopathy, cerebellar infarction, cerebral infarction, and cerebral ischemia. Addition of adverse reaction was based on data of the final analysis with a median exposure of 32.9 months for ERLEADA® and 11.5 months for placebo

### *Skin rash*

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, skin rash associated with ERLEADA® was most commonly described as macular or maculo-papular. Adverse reactions of skin rash were reported for 26% of subjects treated with ERLEADA® versus 8% of subjects treated with placebo. Grade 3 skin rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) versus placebo (0.5%). There were no reported events of drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome (SJS) in clinical trials.

The onset of skin rash occurred at a median of 83 days of ERLEADA® treatment and resolved within a median of 78 days from onset of rash for 78% of subjects. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of subjects received systemic corticosteroids. Among subjects with skin rash, dose interruption occurred in 28% and dose reduction occurred in 14% (see *Dosage and Administration – Dose modification*). Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®. Skin rash led to ERLEADA® treatment discontinuation in 7% of subjects who experienced skin rash.

### *Hypothyroidism*

In the combined data of two randomized, placebo-controlled studies, SPARTAN and TITAN, hypothyroidism was reported for 8% of subjects treated with ERLEADA® and 2% of subjects treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. There were no grade 3 or 4 adverse reactions. Hypothyroidism occurred in 30% of subjects already receiving thyroid replacement therapy in the ERLEADA® arm and in 3% of subjects in the placebo arm. In subjects not receiving thyroid replacement therapy, hypothyroidism occurred in 7% of subjects treated with ERLEADA® and in 2% of subjects treated with placebo. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted (see *Interactions - Effect of ERLEADA® on drug metabolizing enzymes*).

### *Postmarketing data*

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 3). Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the table, the frequencies are provided according to the following convention:

| | |
|---|---|
| Very common | ≥ 1/10 (≥10%) |
| Common | ≥ 1/100 and < 1/10 (≥1% and < 10%) |
| Uncommon | ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%) |
| Rare | ≥ 1/10000 and < 1/1000 (≥0.01 and < 0.1%) |
| Very rare | < 1/10000, including isolated reports (< 0.01%) |
| Not known | Cannot be estimated from the available data |

In Table 3, adverse reactions are presented by frequency category based on spontaneous reporting rates, when known.

**Table 3: Adverse Reactions Identified During Postmarketing Experience with Apalutamide**

| **System Organ Class**<br>Adverse Reaction | **Frequency Category Estimated from Spontaneous Reporting Rates[c]** |
|---|---|
| **Metabolism and nutrition disorders** | |
| Decreased appetite | Uncommon |
| **Respiratory, thoracic and mediastinal disorders** | |
| Interstitial lung disease[a] | Uncommon |
| **Skin and subcutaneous tissue disorders** | |
| Drug reaction with eosinophilia and systemic symptoms[a,b] | Rare |
| Stevens-Johnson syndrome/Toxic epidermal necrolysis[a,b] | Rare |

[a] The adverse reaction was not identified from clinical trials and the frequency was not known. Frequency is calculated by "Rule of 3"
[b] See Warnings and Precautions section
[c] Postmarketing spontaneous reporting rates were based on estimated exposure of person-years of treatment

## Overdose

There is no known specific antidote for apalutamide overdose. No dose-limiting toxicities were observed at 480 mg daily (double the recommended daily dose).

It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose.

### Treatment

In the event of an overdose, stop ERLEADA®, undertake general supportive measures until clinical toxicity has been diminished or resolved.

# PHARMACOLOGICAL PROPERTIES

## Pharmacodynamic Properties

Pharmacotherapeutic group: anti-androgens, ATC code: L02BB05 apalutamide

## Mechanism of action

Apalutamide is an orally administered, selective Androgen Receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide prevents AR nuclear translocation, inhibits DNA binding, impedes AR-mediated transcription, and lacks androgen receptor agonist activity in preclinical studies. In mouse models of prostate cancer, apalutamide administration causes decreased tumor cell proliferation and increased apoptosis leading to potent antitumor activity. A major metabolite, N-desmethyl apalutamide, exhibited one-third the *in vitro* activity of apalutamide.

## Pharmacodynamic effects

### *Effect on QT/QTc interval and cardiac electrophysiology*

The effect of apalutamide 240 mg once daily on the QTc interval was assessed in an open-label, uncontrolled, multi-center, single-arm dedicated QT study in 45 subjects with CRPC. The maximum mean QTcF change from baseline was 12.4 ms (2-sided 90% upper CI: 16.0 ms). An exposure-QT analysis suggested a concentration-dependent increase in QTcF for apalutamide and its active metabolite.

## Clinical studies

The efficacy of ERLEADA® was established in two randomized placebo-controlled multicenter Phase 3 clinical studies of subjects with mCSPC (TITAN) or nmCRPC (SPARTAN). All subjects in these studies received concomitant GnRH analog or had prior bilateral orchiectomy.

### *TITAN: Metastatic Castration-sensitive Prostate Cancer (mCSPC)*

TITAN was a randomized, double-blind, placebo-controlled, multinational, multicenter clinical trial in which 1052 subjects with mCSPC were randomized (1:1) to receive either ERLEADA® orally at a dose of 240 mg once daily (N = 525) or placebo once daily (N = 527). All subjects in the TITAN trial received concomitant GnRH analog or had prior bilateral orchiectomy. Subjects were stratified by Gleason score at diagnosis, prior docetaxel use, and region of the world. Subjects with both high- and low-volume mCSPC were eligible for the study.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 68 years (range 43-94) and 23% of subjects were 75 years of age or older. The racial distribution was 68% Caucasian, 22% Asian, and 2% Black. Sixty-three percent (63%) of subjects had high-volume disease and 37% had low-volume disease. Sixteen percent (16%) of subjects had prior surgery, radiotherapy of the prostate or both. A majority of subjects had a Gleason score of 7 or higher (92%). Sixty-eight percent (68%) of subjects received prior treatment with a first-generation anti-androgen in the non-metastatic setting. All subjects except one in the placebo group, had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry. Among the subjects who discontinued study treatment (N = 271 for placebo and N = 170 for ERLEADA®), the most common reason for discontinuation in both arms was disease progression. A greater proportion (73%) of subjects treated with placebo received subsequent anti-cancer therapy compared to subjects treated with ERLEADA® (54%).

The major efficacy outcome measures of the study were overall survival (OS) and radiographic progression-free survival (rPFS). An updated OS analysis was conducted at the time of final study analysis when 405 deaths were observed with a median follow-up of 44 months. Results from this

updated analysis were consistent with those from the pre-specified interim analysis. Efficacy results of TITAN are summarized in Table 4 and Figures 2 and 3.

| **Table 4: Summary of Efficacy Results – Intent-to-treat mCSPC Population (TITAN)** | | |
|---|---|---|
| **Endpoint** | **ERLEADA® N=525** | **Placebo N=527** |
| **Primary Overall Survival[a]** | | |
| Deaths (%) | 83 (16%) | 117 (22%) |
| Median, months (95% CI) | NE (NE, NE) | NE (NE, NE) |
| Hazard ratio (95% CI)[b] | 0.671 (0.507, 0.890) | |
| p-value[c] | 0.0053 | |
| **Updated Overall Survival[d]** | | |
| Deaths (%) | 170 (32%) | 235 (45%) |
| Median, months (95% CI) | NE (NE, NE) | 52 (42, NE) |
| Hazard ratio (95% CI)[b] | 0.651 (0.534, 0.793) | |
| p-value[c] | <0.0001 | |
| **Overall Survival by IPCW** | | |
| Median, months (95% CI) | NE | 40 |
| Hazard ratio (95% CI) | 0.520 (0.423, 0.639) | |
| **Radiographic Progression-free Survival** | | |
| Disease progression or death (%) | 134 (26%) | 231 (44%) |
| Median, months (95% CI) | NE (NE, NE) | 22.08 (18.46, 32.92) |
| Hazard ratio (95% CI)[b] | 0.484 (0.391, 0.600) | |
| p-value[c] | <0.0001 | |

[a] This is based on the pre-specified interim analysis with a median follow-up time of 22 months.

[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors active treatment.

[c] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).

[d] Median follow-up time of 44 months.

NE=Not Estimable

IPCW=Inverse Probability of Censoring Weighting analysis

A statistically significant improvement in OS and rPFS was demonstrated in subjects randomized to receive ERLEADA® compared with subjects randomized to receive placebo in the primary analysis. At the time of updated OS analysis, a pre-specified sensitivity analysis using the inverse probability censoring weighted (IPCW) log-rank test was conducted to adjust for subject crossover from placebo to apalutamide. The improvement in OS was demonstrated even though 39% of subjects in the placebo arm crossed over to receive ERLEADA®, with a median treatment of 15 months on ERLEADA® crossover.

Consistent improvement in rPFS was observed across the following subject subgroups: disease volume (high vs low), prior docetaxel use (yes or no), and Gleason score at diagnosis (≤7 vs. >7).

Consistent improvement in OS was observed across the following subject subgroups: disease volume (high vs low), and Gleason score at diagnosis (≤7 vs. >7).

**Figure 2:** **Kaplan-Meier Plot of Updated Overall Survival (OS); Intent-to-treat mCSPC Population (TITAN)**

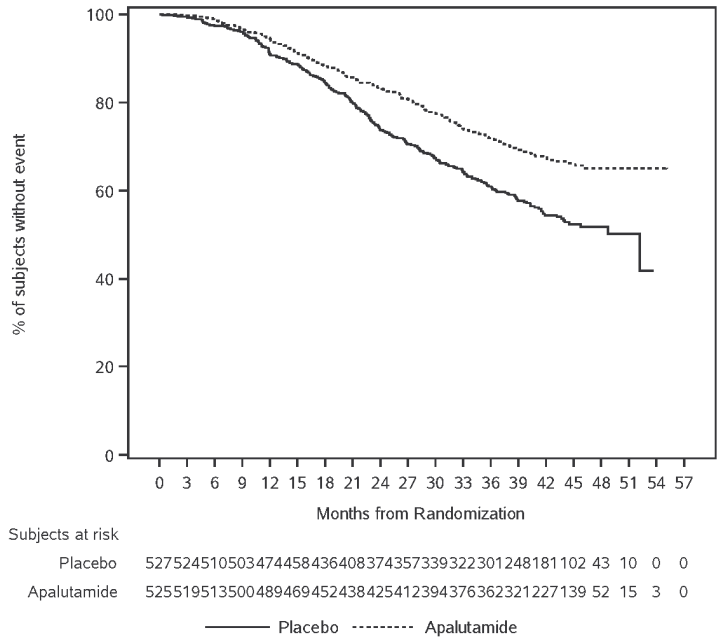
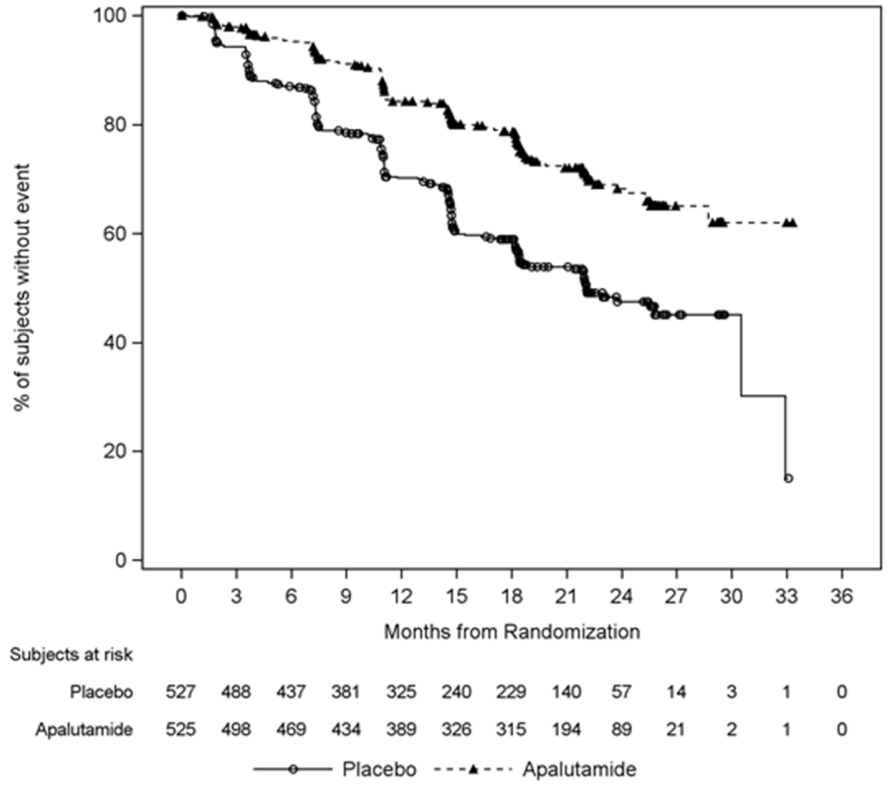



**Figure 3:** **Kaplan-Meier Plot of Radiographic Progression-Free Survival (rPFS); Intent-to-treat mCSPC Population (TITAN)**



Treatment with ERLEADA® statistically significantly delayed the initiation of cytotoxic chemotherapy (HR = 0.391, 95% CI = 0.274, 0.558; p < 0.0001), resulting in a 61% reduction of risk for subjects in the treatment arm compared to the placebo arm.

There were no differences between treatment groups in health-related quality of life, as measured by mean change from baseline FACT-P total scores in cycles 2 through 31. Mean change scores ranged from -1.00 to 2.93 for subjects treated with ERLEADA® and -4.12 to 3.69 for subjects treated with placebo (nominal p values > 0.05 for all cycles).

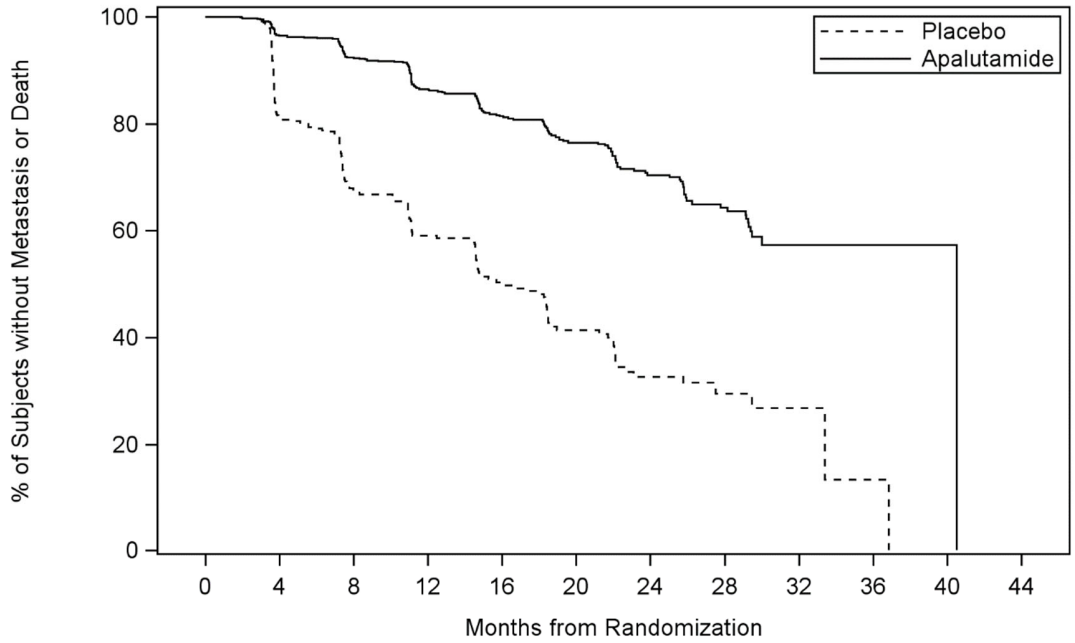
### *SPARTAN: Non-metastatic, Castration-resistant Prostate Cancer (nmCRPC)*

A total of 1207 subjects with nm-CRPC were randomized 2:1 to receive either ERLEADA® orally at a dose of 240 mg once daily in combination with ADT (medical castration or surgical castration) or placebo with ADT in a multicenter, double-blind, clinical trial (SPARTAN). Subjects enrolled had a Prostate Specific Antigen (PSA) Doubling Time (PSADT) ≤ 10 months. All subjects who were not surgically castrated received ADT continuously throughout the study. Seventy-three percent (73%) of subjects received prior treatment with a first-generation anti-androgen; 69% of subjects received bicalutamide and 10% of subjects received flutamide. Systemic corticosteroids were not allowed at study entry. PSA results were blinded and were not used for treatment discontinuation. Subjects randomized to either arm were to continue treatment until disease progression defined by blinded central imaging review (BICR), initiation of new treatment, unacceptable toxicity or withdrawal. Upon development of distant metastatic disease, subjects were offered ZYTIGA as an option for the first subsequent treatment after study treatment discontinuation.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 74 years (range 48-97) and 26% of subjects were 80 years of age or older. The racial distribution was 66% Caucasian, 5.6% Black, 12% Asian, and 0.2% Other. Seventy-seven percent (77%) of subjects in both treatment arms had prior surgery or radiotherapy of the prostate. A majority of subjects had a Gleason score of 7 or higher (81%). Fifteen percent (15%) of subjects had <2 cm pelvic lymph nodes at study entry. All subjects enrolled were confirmed to be non-metastatic by blinded central imaging review and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) performance status score of 0 or 1 at study entry.

Metastasis-free survival (MFS) is defined as the time from randomization to the time of first evidence of BICR-confirmed bone or soft tissue distant metastasis or death due to any cause, whichever occurred first. Treatment with ERLEADA® significantly improved MFS. ERLEADA® decreased the risk of distant metastasis or death by 72%. The median MFS for ERLEADA® was 41 months and was 16 months for placebo (see *Figures 4* and *5*).

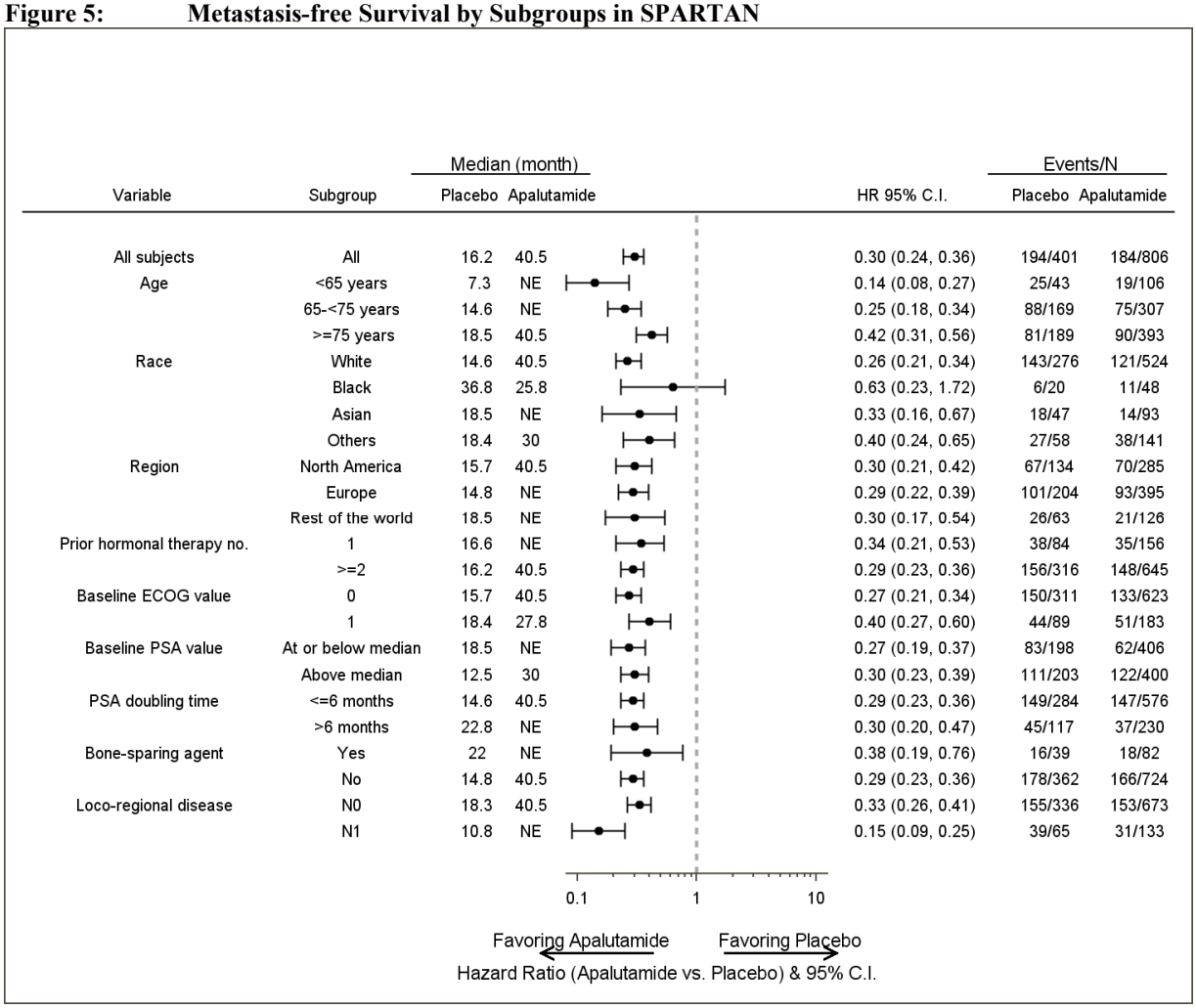
**Figure 4: Kaplan-Meier Metastasis-Free Survival (MFS) Curve in SPARTAN**




Subjects at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 401 | 291 | 220 | 153 | 91 | 58 | 34 | 13 | 5 | 1 | 0 | 0 |
| Apalutamide | 806 | 713 | 652 | 514 | 398 | 282 | 180 | 96 | 36 | 16 | 3 | 0 |

**Figure 5: Metastasis-free Survival by Subgroups in SPARTAN**




– All subjects = Intent-to Treat population
– The non-stratified analysis is presented in Figure 5

Subjects treated with ERLEADA® and ADT showed significant improvement over those treated with ADT alone for the following secondary endpoints of time to metastasis (TTM), progression-free survival (PFS), and time to symptomatic progression. In addition, overall survival (OS) and time to initiation of cytotoxic chemotherapy were also significantly improved (see *Table 5* for Interim Analysis and *Table 6* for Final Analysis).

**Table 5: Summary of Efficacy Analysis (SPARTAN) at Interim Analysis[a]**

| Endpoint | ERLEADA® (N=806) Median (months) | Placebo (N=401) Median (months) | HR (95% CI) p value[b] |
|---|---|---|---|
| Metastasis Free Survival (MFS)[c] | 40.5 | 16.2 | 0.28 (0.23-0.35) < 0.0001 |
| Time to Metastasis (TTM)[c] | 40.5 | 16.6 | 0.27 (0.22-0.34) < 0.0001 |
| Progression-free Survival (PFS)[c] | 40.5 | 14.7 | 0.29 (0.24-0.36) < 0.0001 |

| | | | |
|---|---|---|---|
| Time to Symptomatic Progression | NR | NR | 0.45 (0.32-0.63)<br>< 0.0001[d] |
| Overall Survival (OS) | NR | 39.0 | 0.70 (0.47-1.04)<br>0.0742 |
| Time to Initiation of Cytotoxic Chemotherapy | NR | NR | 0.44 (0.29-0.66)<br>< 0.0001 |

NR = Not reached

[a] Median follow-up time of 20.3 months

[b] p value from stratified log-rank test

[c] Assessed by BICR and unchanged for final analysis

[d] Actual p value – 0.00000356; hence, OBF-type efficacy boundary of 0.00008 is crossed in the interim analysis for Symptomatic Progression

**Table 6: Summary of Efficacy Analysis (SPARTAN) at Final Analysis[a]**

| **Endpoint** | **ERLEADA® (N=806) Median (months)** | **Placebo (N=401) Median (months)** | **HR (95% CI) p value[b]** |
|---|---|---|---|
| Overall Survival (OS) | 73.9 | 59.9 | 0.78 (0.64-0.96)<br>0.0161 |
| Time to Symptomatic Progression | NR | NR | 0.57 (0.44-0.73)<br>< 0.0001[c] |
| Time to Initiation of Cytotoxic Chemotherapy | NR | NR | 0.63 (0.49-0.81)<br>0.0002 |

NR = Not reached

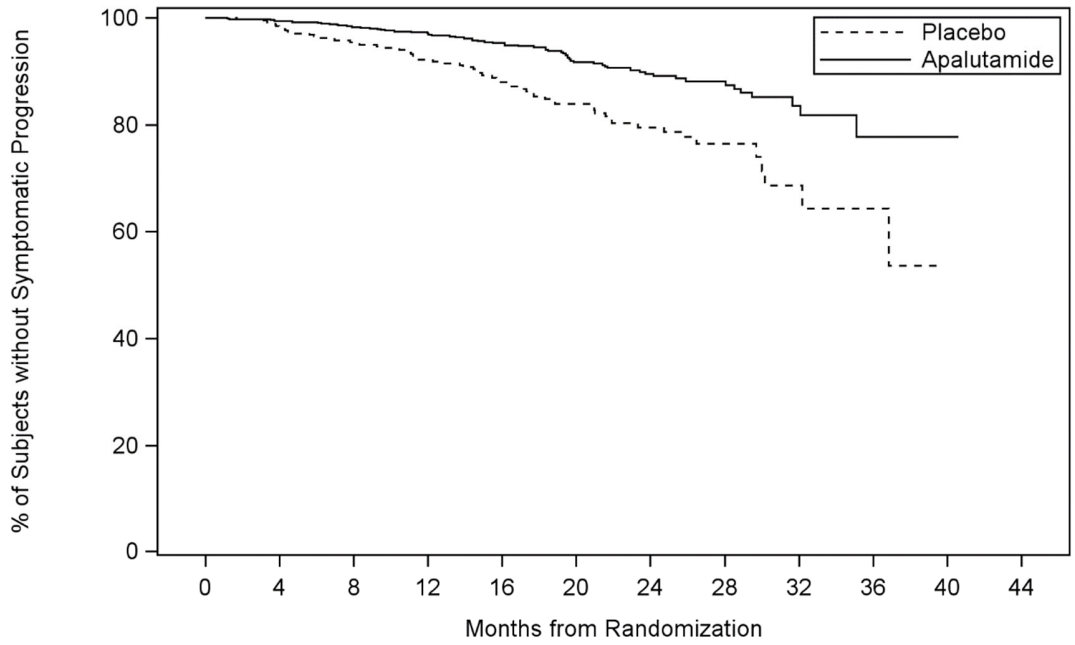
[a] Median follow-up time of 52.0 months

[b] p value from stratified log-rank test

[c] Actual p value – 0.00000356 at the first interim analysis; hence, OBF-type efficacy boundary of 0.00008 is crossed for Symptomatic Progression

At the interim analysis, treatment with ERLEADA® significantly decreased the risk of symptomatic progression by 55% compared with placebo (see *Table 5* and *Figure 6*). The final analysis corroborated that treatment with ERLEADA® decreased the risk of symptomatic progression by 43% compared with placebo (see *Table 6* and *Figure 7*).

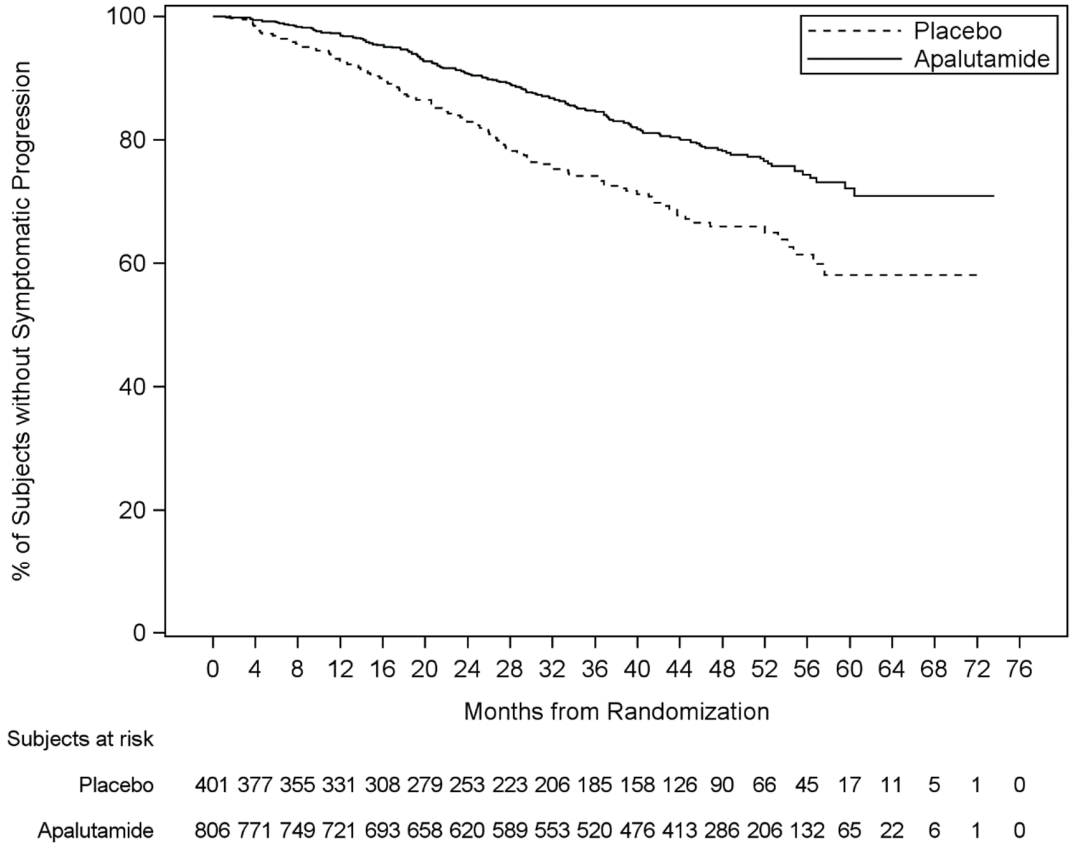
**Figure 6:** **Kaplan-Meier Plot of Time to Symptomatic Progression; Intent-to-treat Population in SPARTAN at Interim Analysis**




Subjects at risk

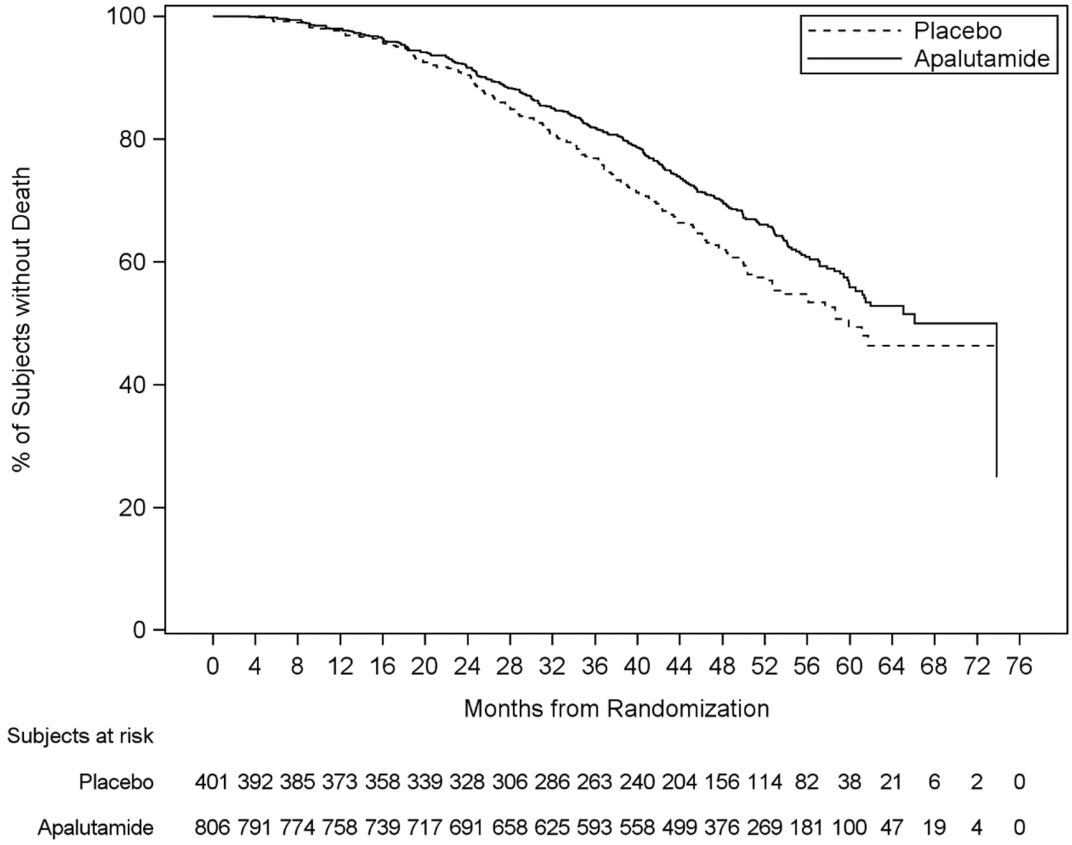
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 401 | 373 | 344 | 270 | 206 | 152 | 96 | 45 | 17 | 7 | 0 | 0 |
| Apalutamide | 806 | 769 | 732 | 601 | 478 | 344 | 226 | 127 | 49 | 19 | 4 | 0 |

**Figure 7: Kaplan-Meier Plot of Time to Symptomatic Progression; Intent-to-treat Population in SPARTAN at Final Analysis**



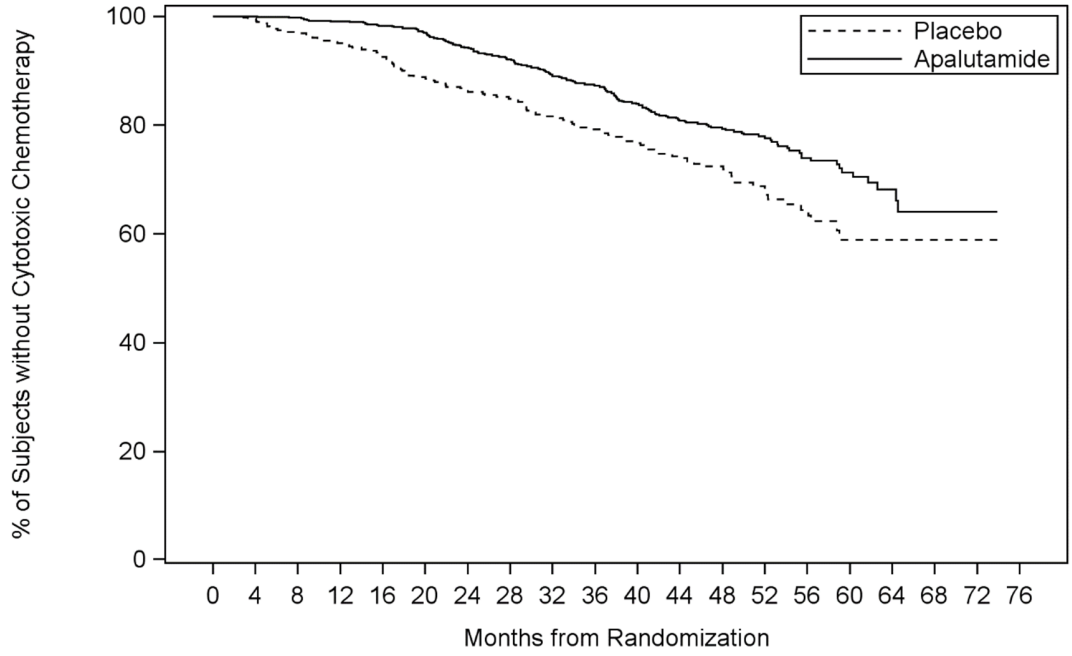

At the interim analysis, with median follow-up time of 20.3 months, 62 (7.7%) subjects in the ERLEADA® arm died compared to 42 (10.5%) subjects in the placebo arm. The median survival for the ERLEADA® arm was not reached compared to 39.03 months with a 95% CI of (39.03, NE) for the placebo arm. Statistical significance was not reached in overall survival at the pre-specified interim analysis. At the final analysis, with median follow-up time of 52.0 months, results showed that treatment with ERLEADA® significantly decreased the risk of death by 22% compared with placebo (HR=0.784; 95% CI: 0.643, 0.956; 2-sided p=0.0161). The median OS was 73.9 months for the ERLEADA® arm and 59.9 months for the placebo arm. The pre-specified alpha boundary ($p \leq 0.046$) for this final analysis was crossed and statistical significance was achieved.

**Figure 8: Kaplan-Meier Plot of Time to Overall Survival (OS); Intent-to-treat Population in SPARTAN at Final Analysis**




At the final analysis, treatment with ERLEADA® significantly decreased the risk of initiating cytotoxic chemotherapy by 37% compared with placebo (HR = 0.629; 95% CI: 0.489, 0.808; p = 0.0002) demonstrating statistically significant improvement for ERLEADA® versus placebo. The median time to the initiation of cytotoxic chemotherapy was not reached for either treatment arm.

**Figure 9: Kaplan-Meier Plot of Time to Initiation of Cytotoxic Chemotherapy: Intent-to-treat Population in SPARTAN at Final Analysis**



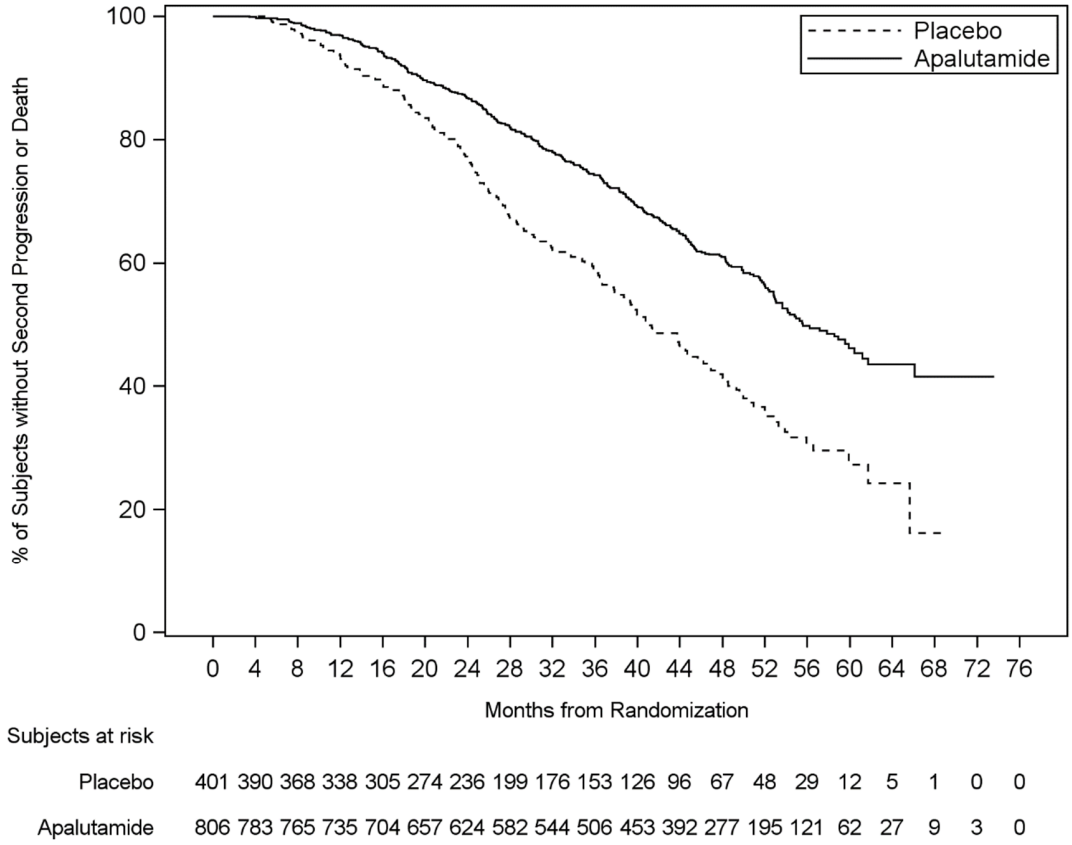

Subjects at risk

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 401 | 388 | 371 | 352 | 327 | 302 | 283 | 266 | 247 | 224 | 200 | 173 | 128 | 89 | 63 | 26 | 16 | 4 | 2 | 0 |
| Apalutamide | 806 | 787 | 763 | 739 | 711 | 687 | 646 | 610 | 565 | 535 | 492 | 436 | 314 | 225 | 152 | 84 | 35 | 14 | 4 | 0 |

If eligible and without evidence of disease progression, subjects treated with placebo were given the opportunity to cross-over to treatment with ERLEADA® at time of unblinding. After unblinding, 19% of the randomized placebo population crossed over to ERLEADA®. Of all the randomized subjects, a greater proportion of subjects in the placebo arm received subsequent therapy (285/401, 71%) compared with the ERLEADA® arm (386/806, 48%).

At the interim analysis, post-progression survival (PFS-2, defined as the time to death or disease progression by PSA, radiographic, or symptomatic progression on or after first subsequent therapy) was longer for subjects treated with ERLEADA® compared to those treated with placebo (HR = 0.489; 95% CI: 0.361, 0.662; $p < 0.0001$). Final analysis of PFS-2 confirmed a 44% reduction in risk of PFS-2 with ERLEADA® versus placebo (HR = 0.565; 95% CI: 0.471, 0.677; $p < 0.0001$).

**Figure 10: Kaplan-Meier Plot of Second Progression-Free Survival (PFS-2); Intent-to-treat Population in SPARTAN at Final Analysis**




There were no detrimental effects to overall health-related quality of life with the addition of ERLEADA® to ADT and a small but not clinically meaningful difference in change from baseline in favor of ERLEADA® observed in the analysis of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score and subscales.

## Pharmacokinetic Properties

Following repeat once-daily dosing, apalutamide exposure ($C_{max}$ and area under the concentration curve [AUC]) increased in a dose-proportional manner across the dose range of 30 to 480 mg. Following administration of 240 mg once daily, apalutamide steady state was achieved after 4 weeks and the mean accumulation ratio was approximately 5-fold relative to a single dose. At steady-state, mean (CV%) $C_{max}$ and AUC values for apalutamide were 6 µg/mL (28%) and 100 µg.h/mL (32%), respectively. Daily fluctuations in apalutamide plasma concentrations were low, with mean peak-to-trough ratio of 1.63. An increase in apparent clearance (CL/F) was observed with repeat dosing, likely due to induction of apalutamide's own metabolism.

At steady-state, the mean (CV%) $C_{max}$ and AUC values for the major active metabolite, N-desmethyl apalutamide, were 5.9 µg/mL (18%) and 124 µg.h/mL (19%), respectively. N-desmethyl apalutamide is characterized by a flat concentration-time profile at steady-state with a mean peak-to-trough ratio of 1.27. Mean (CV%) AUC metabolite/parent drug ratio for N-desmethyl apalutamide following repeat-dose administration was about 1.3 (21%). Based on

systemic exposure, relative potency, and pharmacokinetic properties, N-desmethyl apalutamide likely contributed to the clinical activity of apalutamide.

### Absorption
After oral administration, median time to achieve peak plasma concentration ($t_{max}$) was 2 hours (range: 1 to 5 hours). Mean absolute oral bioavailability is approximately 100%, indicating that apalutamide is completely absorbed after oral administration.

Administration of apalutamide to healthy subjects under fasting conditions and with a high-fat meal resulted in no clinically relevant changes in $C_{max}$ and AUC. Median time to reach $t_{max}$ was delayed about 2 hours with food (see *Figure 11*) (see *Dosage and Administration*).

Following oral administration of 4x60 mg apalutamide tablets dispersed in applesauce, $C_{max}$ and AUC were 28% and 5% higher, respectively, when compared to administration of 4 intact 60 mg tablets under fasting condition (see *Dosage and Administration*).

### Distribution
The mean apparent volume of distribution at steady-state of apalutamide is about 276 L. The volume of distribution of apalutamide is greater than the volume of total body water, indicative of extensive extravascular distribution.

Apalutamide and N-desmethyl apalutamide are 96% and 95% bound to plasma proteins, respectively, and mainly bind to serum albumin with no concentration dependency.

### Metabolism
Following single oral administration of $^{14}$C-labeled apalutamide 240 mg, apalutamide, the active metabolite, N-desmethyl apalutamide, and an inactive carboxylic acid metabolite accounted for the majority of the $^{14}$C-radioactivity in plasma, representing 45%, 44%, and 3%, respectively, of the total $^{14}$C-AUC.

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

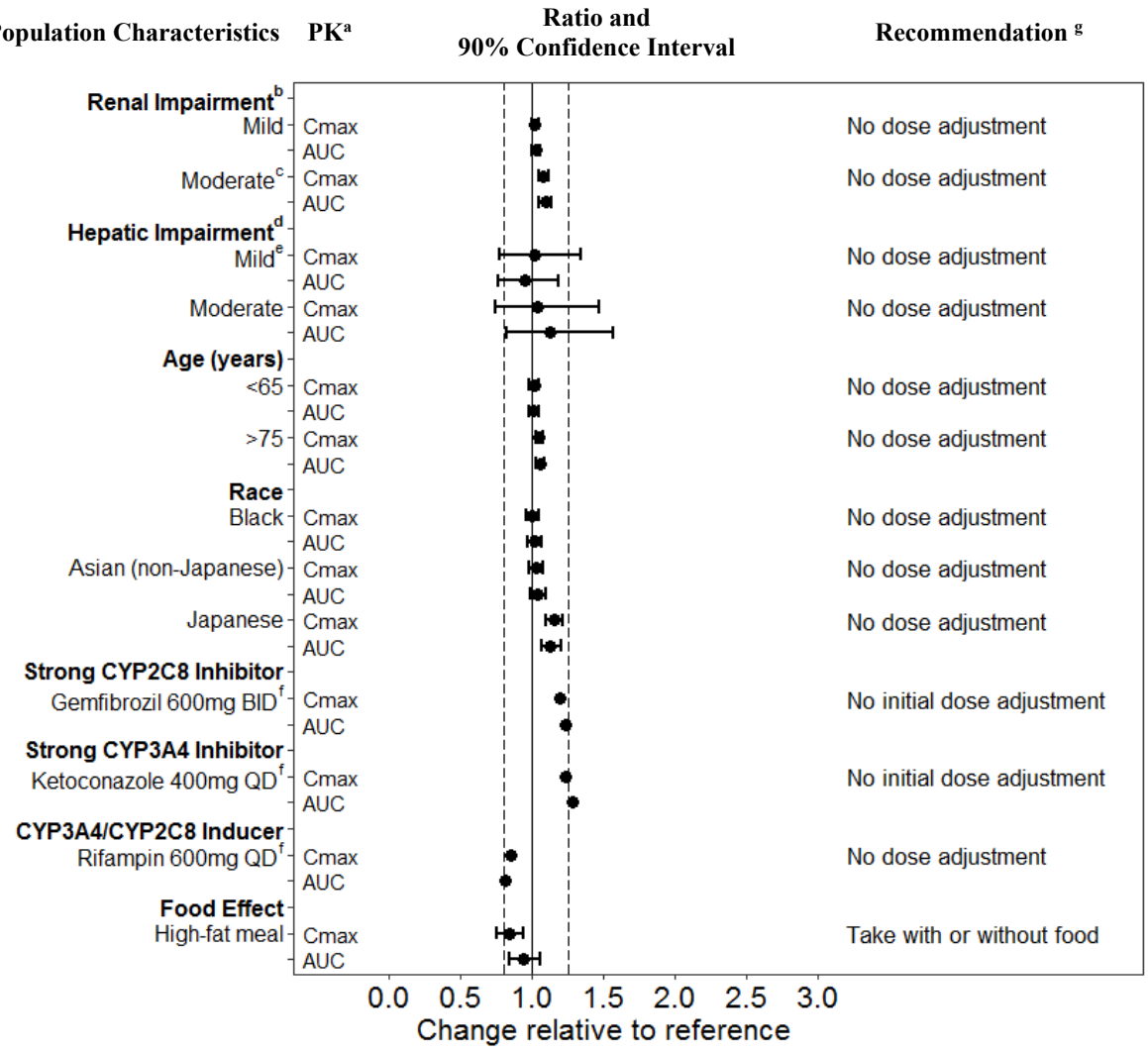
### Elimination
Apalutamide, mainly in the form of metabolites, is eliminated primarily via urine. Following a single oral administration of radiolabeled apalutamide, 89% of the radioactivity was recovered up to 70 days post-dose: 65% was recovered in urine (1.2% of dose as unchanged apalutamide and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

The CL/F of apalutamide is 1.3 L/h after single dosing and increases to 2.0 L/h at steady-state after once-daily dosing. The mean effective half-life for apalutamide in subjects is about 3 days at steady-state.

## Special populations

The effects of renal impairment, hepatic impairment, age, race, and other extrinsic factors on the pharmacokinetics of apalutamide are summarized in Figure 11.

**Figure 11: Effects of Intrinsic/Extrinsic Factors and Other Medications on ERLEADA®**



– [a] Pharmacokinetic (PK) parameters ($C_{max}$ and AUC) are for apalutamide, except in the drug interaction studies, where they are for active moieties (i.e., unbound apalutamide + potency adjusted unbound N-desmethyl apalutamide)
– [b] Degree of renal impairment was determined based on eGFR using the modification of diet in renal disease (MDRD) study equation; normal (≥90 mL/min/1.73m$^2$), mild (60-89 mL/min/1.73m$^2$), moderate (30-59 mL/min/1.73m$^2$)
– [c] Data included 2 subjects with severe renal impairment (≤29 mL/min/1.73m$^2$)
– [d] Degree of hepatic impairment was determined based on Child-Pugh classification; mild (Child-Pugh A), moderate (Child-Pugh B)
– [e] A population PK analysis demonstrated that mild hepatic impairment (based on the National Cancer Institute criteria) does not influence the exposure of apalutamide
– [f] Effects on steady-state PK of active moieties based on simulations
– [g] See Dosage and Administration, Special Populations and Interactions

No clinically significant differences in the pharmacokinetics of apalutamide and N-desmethyl apalutamide were observed in subjects with mild (eGFR 60-89 mL/min/1.73m$^2$) or moderate renal impairment (eGFR 30-59 mL/min/1.73m$^2$), mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, age ranging from 18 to 94 years, or between different races.

### *Renal Impairment*
A dedicated renal impairment study for apalutamide has not been conducted. Based on the population pharmacokinetic analysis using data from clinical studies in subjects with castration-resistant prostate cancer (CRPC) and healthy subjects, no significant difference in systemic exposure was observed in subjects with pre-existing mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] between 30 to 89 mL/min/1.73 m$^2$; N=585) compared to subjects with baseline normal renal function (eGFR ≥ 90 mL/min/1.73 m$^2$; N=372). The potential effect of severe renal impairment or end stage renal disease (eGFR ≤29 mL/min/1.73m$^2$) have not been established due to insufficient data.

### *Hepatic Impairment*
A dedicated hepatic impairment study compared the systemic exposure of apalutamide and N- desmethyl apalutamide in subjects with baseline mild hepatic impairment (N=8, Child-Pugh Class A, mean score = 5.3) or moderate hepatic impairment (N=8, Child-Pugh Class B, mean score = 7.6) versus healthy controls with normal hepatic function (N=8). Following a single oral 240 mg dose of apalutamide, the geometric mean ratio (GMR) for AUC and $C_{max}$ for apalutamide in subjects with mild impairment was 95% and 102%, respectively, and the GMR for AUC and $C_{max}$ of apalutamide in subjects with moderate impairment was 113% and 104%, respectively, compared to healthy control subjects. Clinical and pharmacokinetic data are not available for patients with severe hepatic impairment (Child-Pugh Class C).

## NON-CLINICAL INFORMATION
## Carcinogenicity and Mutagenicity
Apalutamide was not carcinogenic in a 6-month study in the male transgenic (Tg.rasH2) mouse at doses up to 30 mg/kg per day, which is 1.2 and 0.5 times for apalutamide and N-desmethyl apalutamide respectively, the clinical exposure (AUC) at the recommended clinical dose of 240 mg/day.

In the 24-month oral carcinogenicity study in male Sprague-Dawley rats, apalutamide was administered by oral gavage at doses of 5, 15 and 50 mg/kg/day (0.2, 0.7, and 2.5 times the AUC in patients (human exposure at recommended dose of 240 mg), respectively) for 100 weeks. Apalutamide-related neoplastic findings included an increased incidence of testicular Leydig cell adenoma and carcinoma at doses greater than or equal to 5 mg/kg/day, mammary adenocarcinoma and fibroadenoma at 15 mg/kg/day or 50 mg/kg/day, and thyroid follicular cell adenoma at 50 mg/kg/day. These findings were considered rat-specific and therefore of limited relevance to humans.

Apalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either *in vitro* chromosome aberration test, the *in vivo* rat micronucleus assay or the *in vivo* rat Comet assay.

## Reproductive Toxicology

Male fertility is likely to be impaired by treatment with apalutamide based on findings in repeat-dose toxicology studies which were consistent with the pharmacological activity of apalutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), atrophy, aspermia/hypospermia, degeneration and/or hyperplasia or hypertrophy in the reproductive system were observed at ≥ 25 mg/kg/day in rats (1.4 times the human exposure based on AUC) and ≥ 2.5 mg/kg/day in dogs (0.9 times the human exposure based on AUC).

In a fertility study in male rats, a decrease in sperm concentration and motility, copulation and fertility rates (upon pairing with untreated females) along with reduced weights of the secondary sex glands and epididymis were observed following 4 weeks of dosing at ≥ 25 mg/kg/day (approximately equal to the human exposure based on AUC). Effects on male rats were reversible after 8 weeks from the last apalutamide administration.

In a developmental toxicity study in the rat, apalutamide affected pregnancy including survival. Mean anogenital distance was moderately to markedly shorter for fetuses (females and males) at 25 and 50 mg/kg/day. In rats, shortening of the anogenital distance in male offspring after fetal exposure to anti-androgenic compounds is a well-known adverse effect on morphological development which can often be correlated with reproductive disorders later in life.

# PHARMACEUTICAL INFORMATION

## List of Excipients

Tablet core
Colloidal anhydrous silica
Croscarmellose sodium
Hydroxypropyl methylcellulose-acetate succinate (HPMC-AS)
Magnesium stearate
Microcrystalline cellulose
Microcrystalline cellulose (silicified)

Film-coat
Iron oxide black (E172)
Iron oxide yellow (E172)

Polyethylene glycol
Polyvinyl alcohol (partially hydrolyzed)
Talc
Titanium dioxide

## Incompatibilities
Not applicable.

## Shelf Life
See expiry date on the outer pack.

## Storage Conditions
Keep out of the sight and reach of children.
Store at or below 30ºC. Store in original package to protect from light and moisture. Do not discard desiccant.

## Nature and Contents of Container
ERLEADA® is available in opaque, high-density polyethylene bottles with child-resistant polypropylene closure and induction seal liner. Each bottle contains 120 tablets and a desiccant.

## Instructions for Use and Handling and Disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

## BATCH RELEASER
Janssen Ortho LLC
State Road 933, Km 0.1, Mamey Ward,
Gurabo, Puerto Rico (PR) 00778
USA

## PRODUCT REGISTRANT
Johnson & Johnson International (Singapore) Pte. Ltd.
2 Science Park Drive
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Singapore Science Park 1
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