



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 in adult men for the treatment of non-distant metastatic castration resistant prostate cancer (nm-CRPC) who are at high risk of developing metastatic disease.

ERLEADA is indicated for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC) in combination with androgen deprivation therapy (ADT).

Dosage and Administration

For nm-CRPC, ERLEADA should only be administered to patients who:

- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, with high risk for development of metastases, defined as PSADT $\leq$ 10 months. PSADT is calculated using at least 3 PSA values obtained during continuous ADT;
- Castration-resistant prostate cancer demonstrated during continuous ADT, defined as 3 PSA rises at least 1 week apart, with the last PSA > 2 ng/mL;
- Surgically or medically castrated, with testosterone levels of < 50 ng/dL. If the patient is medically castrated, dosing with a GnRH analogue;
- Are absence of **distant metastases**, including central nervous system (CNS) and vertebral or meningeal involvement, or history of distant metastases (with exception: pelvic lymph nodes < 2 cm in short axis (N1) located below the iliac bifurcation are included).

Dosage

The recommended dose of ERLEADA is 240 mg (four 60 mg tablets) administered orally once daily. Swallow the tablets whole. ERLEADA can be taken with or without food.

Patients should also receive a gonadotropin-releasing hormone (GnHR) analog concurrently or should have had bilateral orchidectomy.

Dose modification

If a patient experiences a $\geq$ Grade 3 toxicity or an intolerable side effect, hold dosing until symptoms improve to $\leq$ 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)

Of the 1327 subjects who received ERLEADA in clinical studies, 19% of subjects were less than 65 years, 41% of subjects were 65 years to 74 years, and 40% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Renal impairment

A dedicated renal impairment study for ERLEADA 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/1.73m²) compared to subjects with baseline normal renal function (eGFR $\geq$ 90 mL/min/1.73m²). 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/1.73m²).

Hepatic impairment

A dedicated hepatic impairment study compared the systemic exposure of apalutamide and N-desmethyl apalutamide in subjects with baseline mild or moderate hepatic impairment (Child-Pugh Class A or B, respectively) versus healthy controls with normal hepatic function. The systemic exposure of apalutamide and N-desmethyl apalutamide was similar in subjects with mild or moderate baseline hepatic impairment compared to subjects with normal hepatic function. 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).

Administration

ERLEADA should be administered orally once daily, with or without food. Swallow the tablets whole. ERLEADA should be prescribed by physicians experienced in the use of anti-cancer therapies.

Contraindications

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

Patients who are hypersensitive to this drug or to any excipients.

Warnings and Precautions

Falls and fractures

Falls and fractures occurred in patients receiving ERLEADA. Patients should be evaluated for fractures and fall risk before starting ERLEADA and should continue to be monitored and managed for fractures according to established treatment guidelines and use of bone-targeted agents should be considered.

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

ERLEADA is not recommended in patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, recent stroke (within one year), primary brain tumours or brain metastases. If a seizure develops during treatment with ERLEADA, treatment should be discontinued permanently. The risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold.

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.

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. 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 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 or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

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.

Androgen deprivation therapy may prolong the QT interval

QT Prolongation: 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, physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating Erleada.

Interactions

Medications that inhibit CYP2C8

CYP2C8 plays a role in the elimination of apalutamide and in the formation of its active metabolite. In a drug-drug interaction study, the C_{max} of apalutamide decreased by 21% while AUC increased by 68% following co-administration of apalutamide 240 mg single dose with gemfibrozil (strong CYP2C8 inhibitor). For the active moieties (sum of apalutamide plus the potency adjusted active metabolite), C_{max} decreased by 21% while AUC increased by 45%. No initial dose adjustment is necessary when ERLEADA is co-administered with a strong inhibitor of CYP2C8 (e.g., gemfibrozil, clopidogrel) however, a reduction of the Erleada dose based on tolerability should be considered. Mild or moderate inhibitors of CYP2C8 are not expected to affect the exposure of apalutamide.

Medications that inhibit CYP3A4

CYP3A4 plays a role in the elimination of apalutamide and in the formation of its active metabolite. 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). For the active moieties (sum of apalutamide plus the potency adjusted active metabolite), C_{max} decreased by 22% while AUC was again similar. No initial dose adjustment is necessary when Erleada is co-administered with a strong inhibitor of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) however, a reduction of the Erleada dose based on tolerability should be considered. 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. Based on the drug-drug interaction study results with strong CYP3A4 inhibitor or strong CYP2C8 inhibitor, CYP3A4 or CYP2C8 inducers are not expected to have clinically relevant effects on the pharmacokinetics of

apalutamide and the active moieties therefore no dose adjustment is necessary when Erleada is co-administered with inducers of CYP3A4 or CYP2C8.

Acid lowering agents

Apalutamide is not ionizable under relevant physiological pH condition, therefore acid lowering agents (e.g. proton pump inhibitor, H₂-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.

The effect of apalutamide on CYP2B6 substrates has not been evaluated in vivo and the net effect is presently unknown. When substrates of CYP2B6 (e.g., efavirenz) are administered with ERLEADA, monitoring for an adverse reaction and evaluation for loss of efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma 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. 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}. 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.

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 - Pregnancy*).

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.

It is unknown whether apalutamide/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Erleada should not be used during breast-feeding.

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. However, seizures have been reported in patients taking Erleada. Patients should be advised of this risk in regards to driving or operating 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 ($\geq 15\%$) reported in the randomized clinical study that occurred more commonly ($\geq 2\%$) 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 $\geq 2\%$ 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), and rare ($\geq 1/10000$ 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 ($\geq 15\%$) reported in the randomized clinical study that occurred more commonly ($\geq 2\%$) 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 $\geq 2\%$ 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), and rare ($\geq 1/10000$ 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. Skin rash included rash, rash maculo-papular, rash generalised, 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, and rash vesicular. 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 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 and by frequency category based on incidence in clinical trials or epidemiology studies, when known.

Table 3: Adverse Reactions Identified During Postmarketing Experience with Apalutamide		
System Organ Class Adverse Reaction	Frequency Category Estimated from Spontaneous Reporting Rates ^b	Frequency Category Estimated from Clinical Trials with ERLEADA
Metabolism and nutrition disorders		
Decreased appetite	Uncommon	Very common
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease ^a	Not known	Not known
Skin and subcutaneous tissue disorders		
Stevens-Johnson syndrome/Toxic epidermal necrolysis ^a	Rare	Not known
^a The adverse reaction was not identified from clinical trials		
^b Postmarketing spontaneous reporting rates were based on estimated exposure of person-years of treatment		

Overdose

There is no known specific antidote for apalutamide overdose. In the event of an overdose, ERLEADA should be stopped and general supportive measures should be undertaken until clinical toxicity has been diminished or resolved. Adverse reactions in the event of an overdose has not yet been observed, it is expected that such reactions would resemble the adverse reactions listed above.

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 1 and 2.

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	
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

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. 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), previous treatment for localized disease (yes or no), 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), previous treatment for localized disease (yes or no), and Gleason score at diagnosis (≤7 vs. >7).

Figure 1: Kaplan-Meier Plot of Updated Overall Survival (OS); Intent-to-treat mCSPC Population (TITAN)

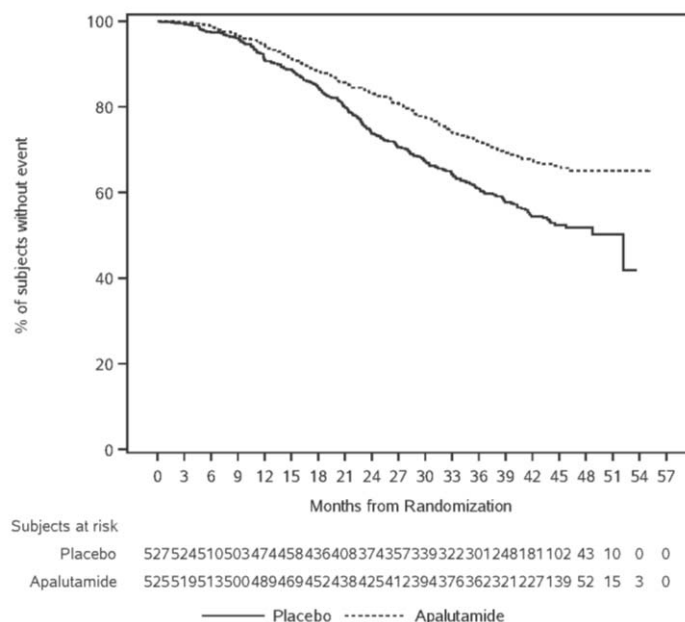
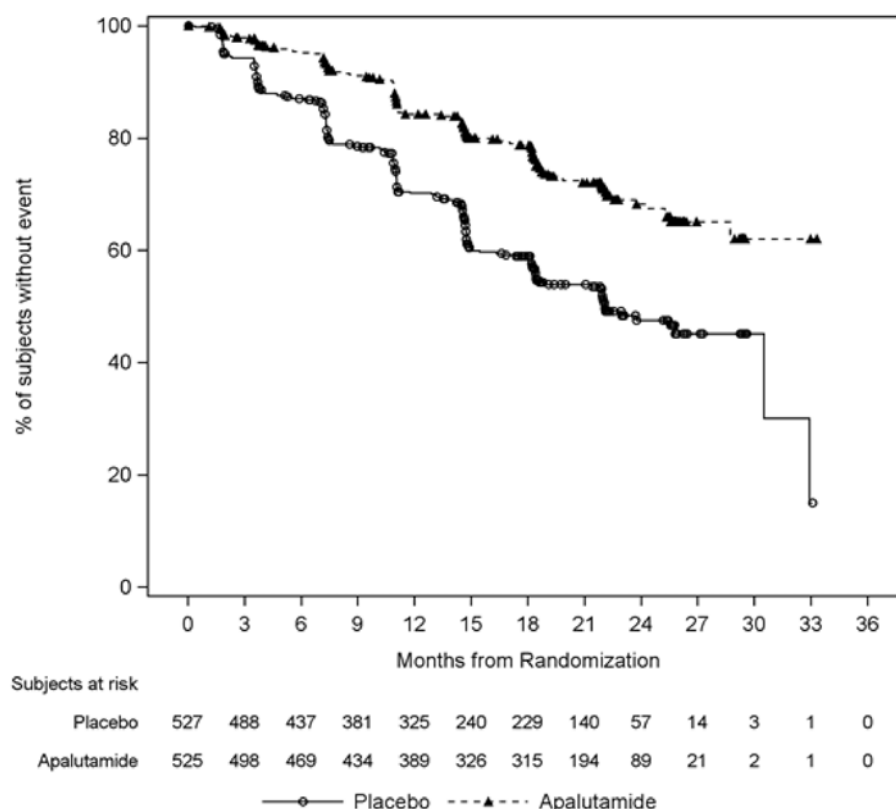
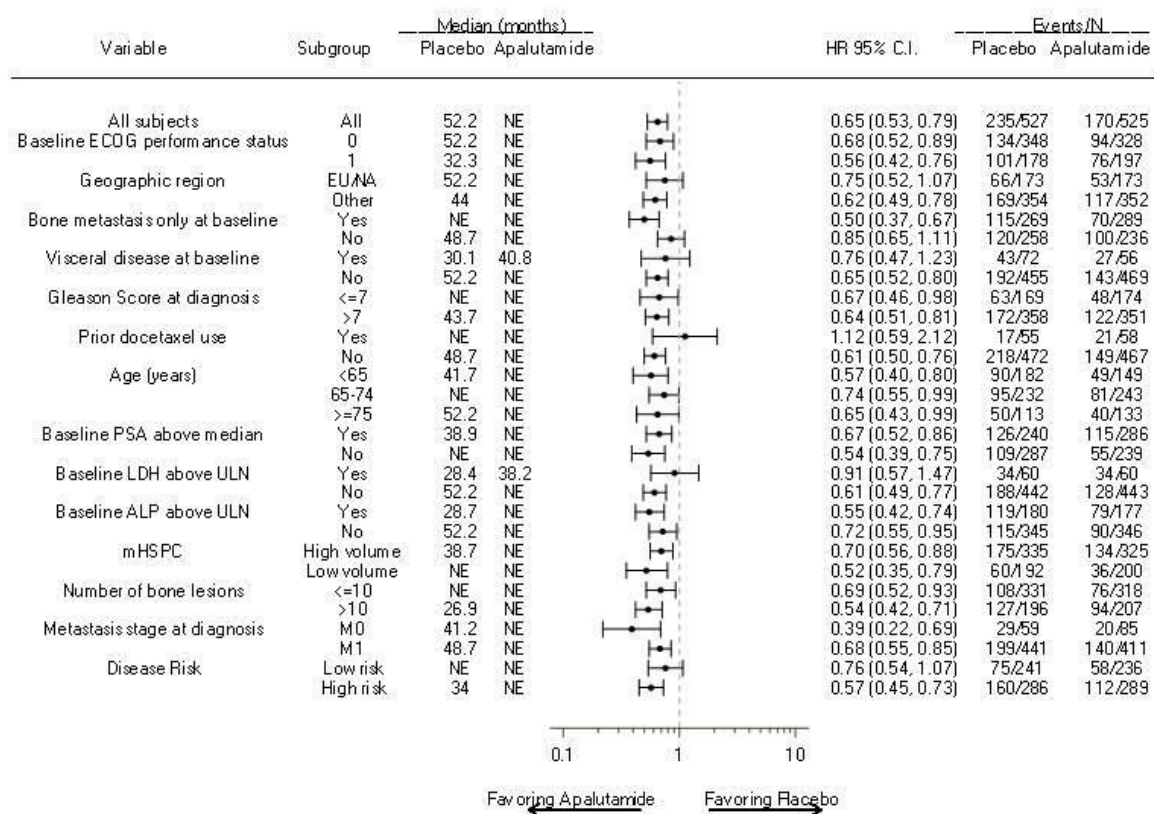


Figure 2: Kaplan-Meier Plot of Radiographic Progression-Free Survival (rPFS); Intent-to-treat mCSPC Population (TITAN)



Subgroup analysis in patients who had used docetaxel before did not show a statistically significant improvement in overall survival with ERLEDA compared to placebo (median overall survival NE vs NE; HR = 1.12; 95% CI: 0.59-2.12).

Figure 3: Forest Plot of Overall Survival Defined by Baseline Clinical Disease Characteristics; Intent-to-treat Population (Study 56021927PCR3002)



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 significant detrimental effects to overall health-related quality of life, as measured by the FACT-P total score change from baseline, with the addition of ERLEADA to ADT. The addition of ERLEADA to ADT did not worsen the FACT-P item level score for fatigue or patient reported bother due to side effects.

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

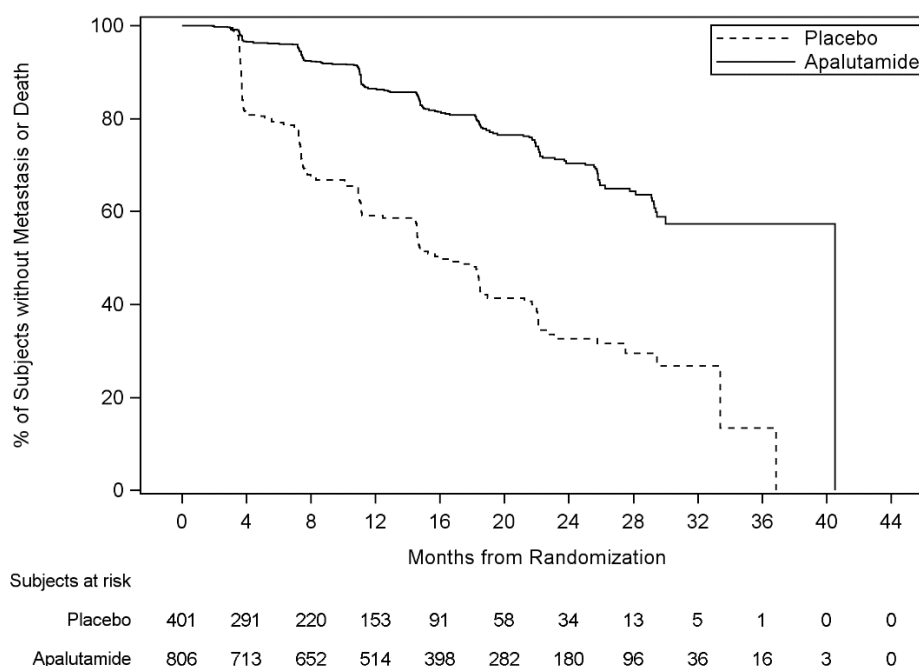
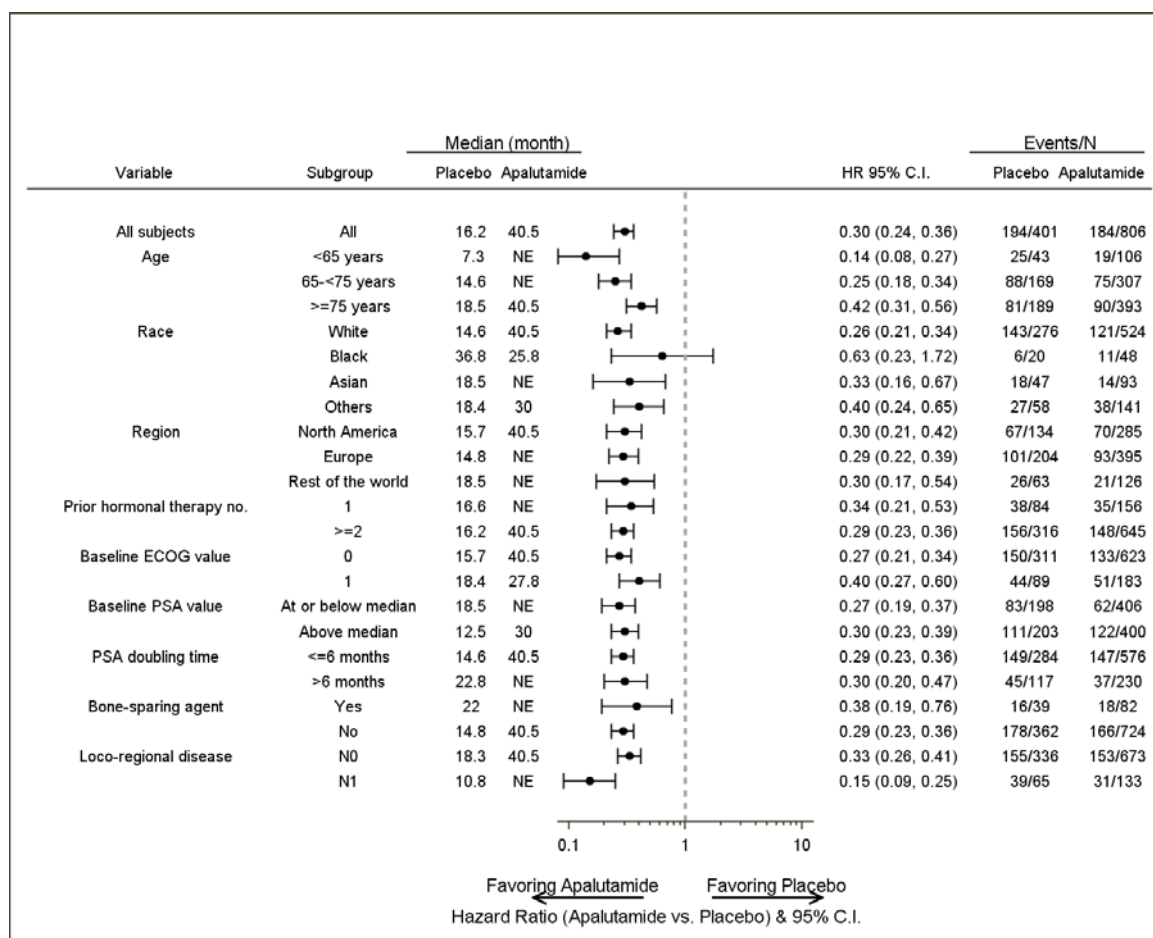


Figure 5: Metastasis-free Survival by Subgroups in SPARTAN



- 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) < 0.0001 ^d
Overall Survival (OS)	NR	39.0	0.70 (0.47-1.04) 0.0742
Time to Initiation of Cytotoxic Chemotherapy	NR	NR	0.44 (0.29-0.66) < 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) 0.0161
Time to Symptomatic Progression	NR	NR	0.57 (0.44-0.73) < 0.0001 ^c
Time to Initiation of Cytotoxic Chemotherapy	NR	NR	0.63 (0.49-0.81) 0.0002

NR = Not reached

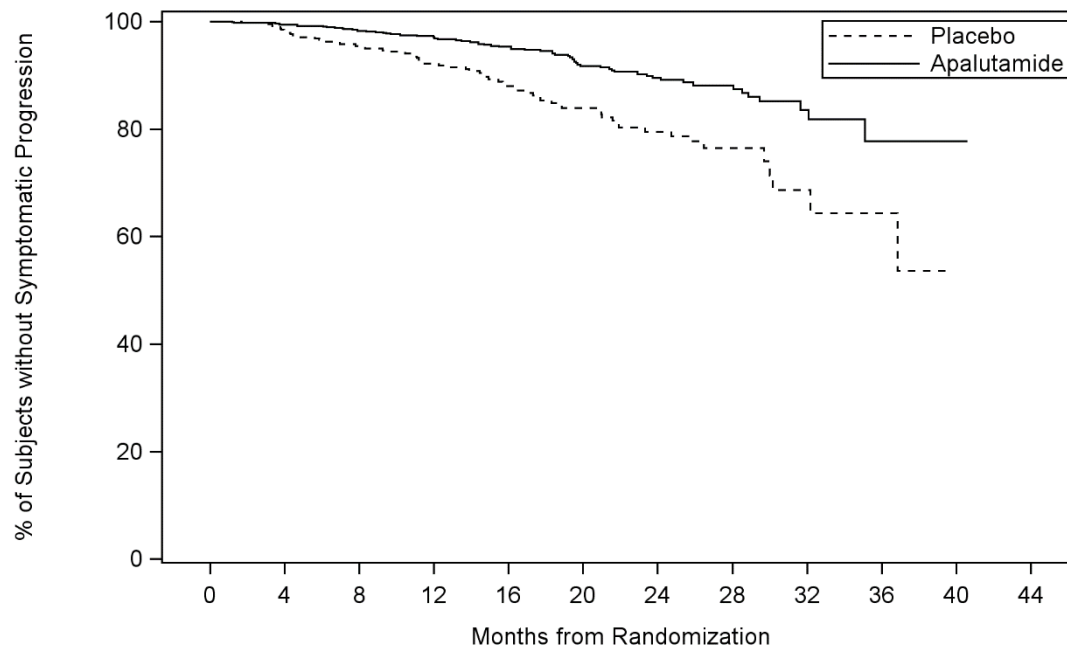
a. Median follow-up time of 52.0 months

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).

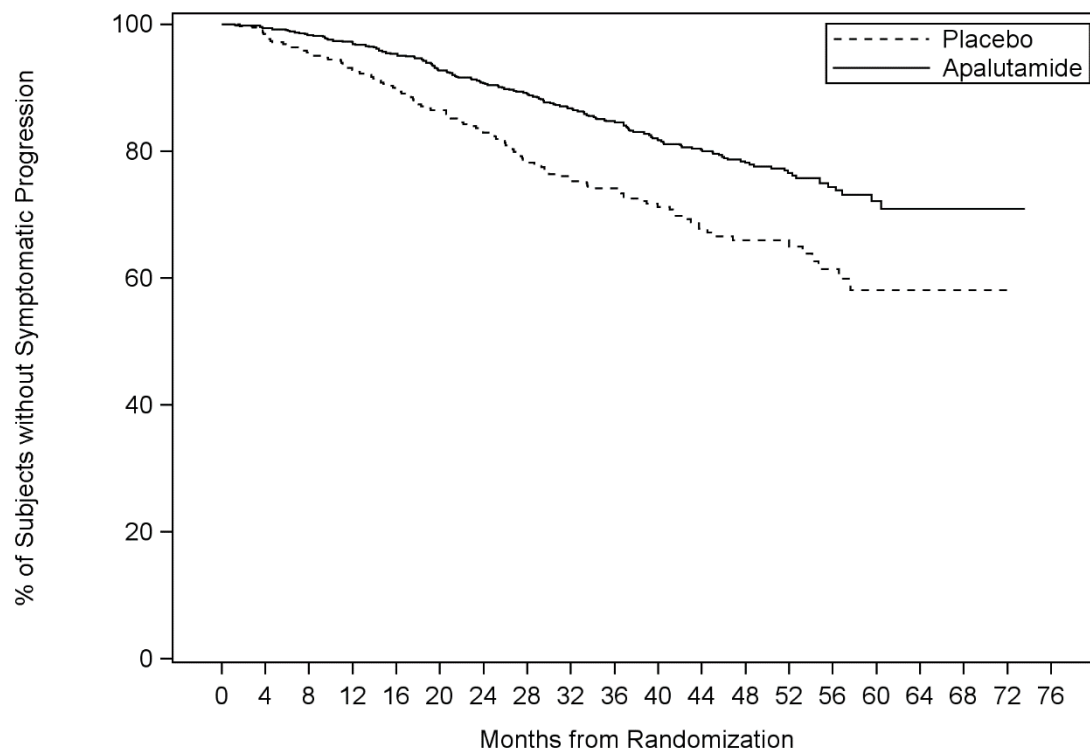
Figure 6: Kaplan-Meier Plot of Time to Symptomatic Progression; Intent-to-treat Population in SPARTAN at Interim Analysis



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



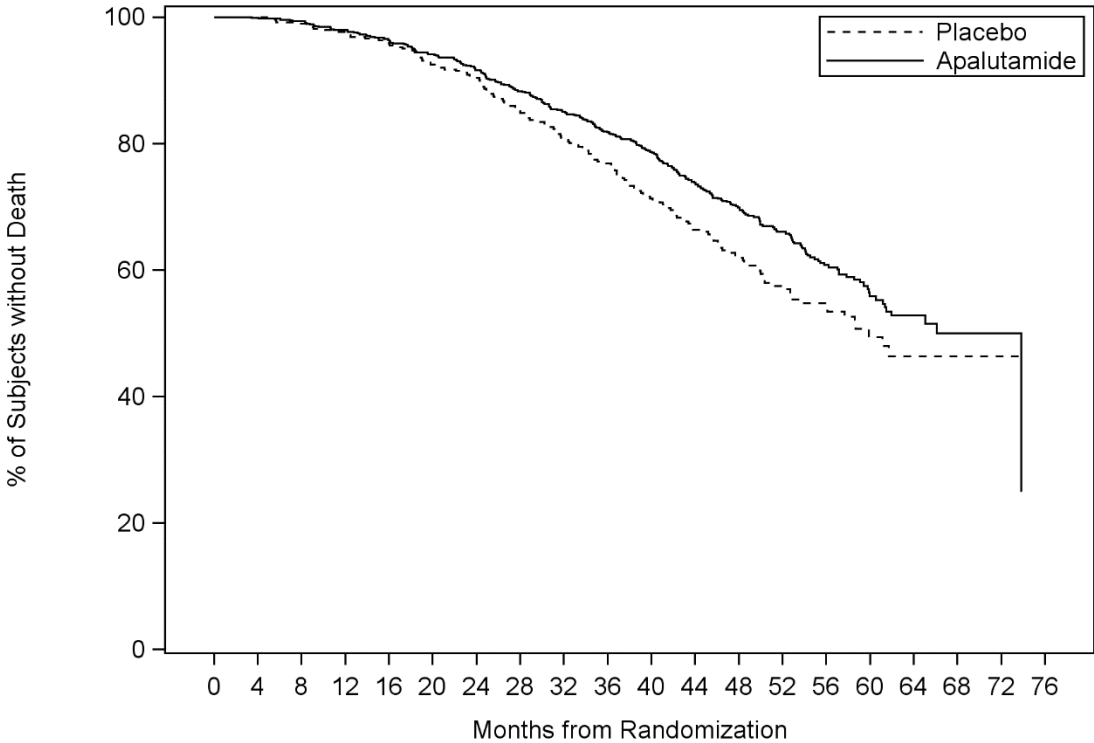
Subjects at risk

Placebo	401	377	355	331	308	279	253	223	206	185	158	126	90	66	45	17	11	5	1	0
Apalutamide	806	771	749	721	693	658	620	589	553	520	476	413	286	206	132	65	22	6	1	0

At the interim analysis, with median follow-up time of 20.3 months, the OS was longer for ERLEADA than placebo with a hazard ratio (HR) of 0.700 (95% CI: 0.472, 1.038). The p-value was 0.0742 which did not meet the pre-specified value for statistical significance. 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



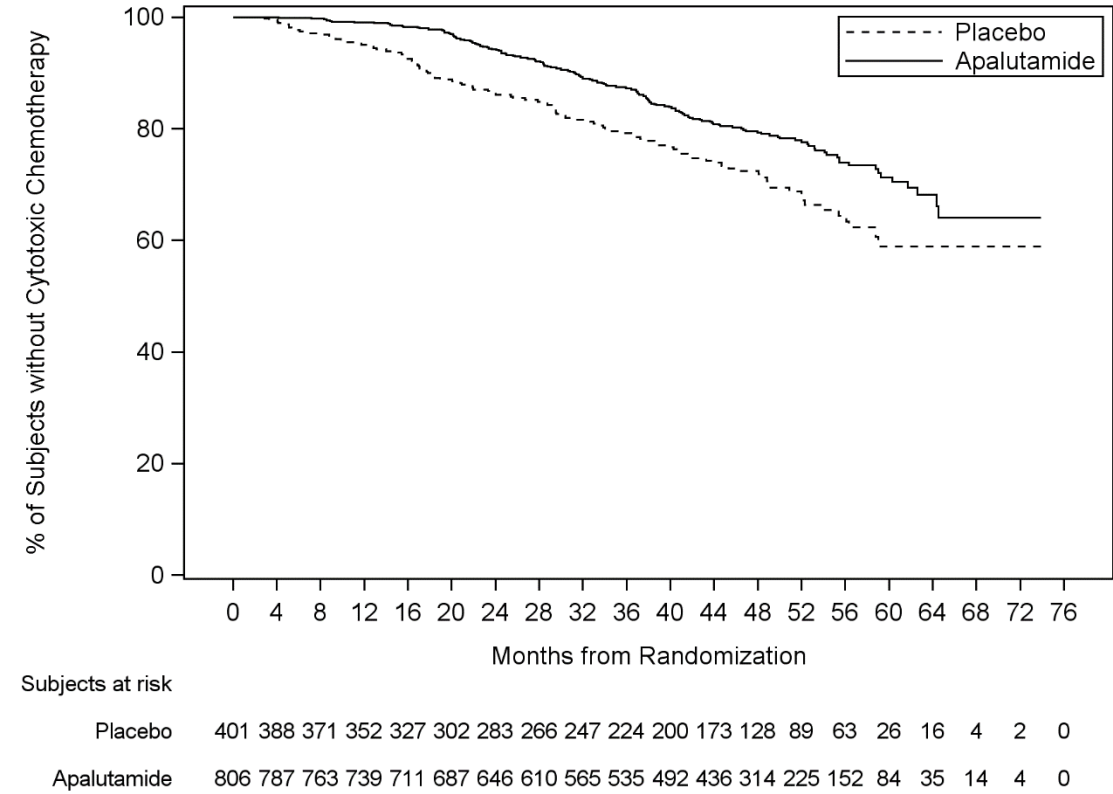
Subjects at risk

Placebo	401	392	385	373	358	339	328	306	286	263	240	204	156	114	82	38	21	6	2	0
Apalutamide	806	791	774	758	739	717	691	658	625	593	558	499	376	269	181	100	47	19	4	0

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

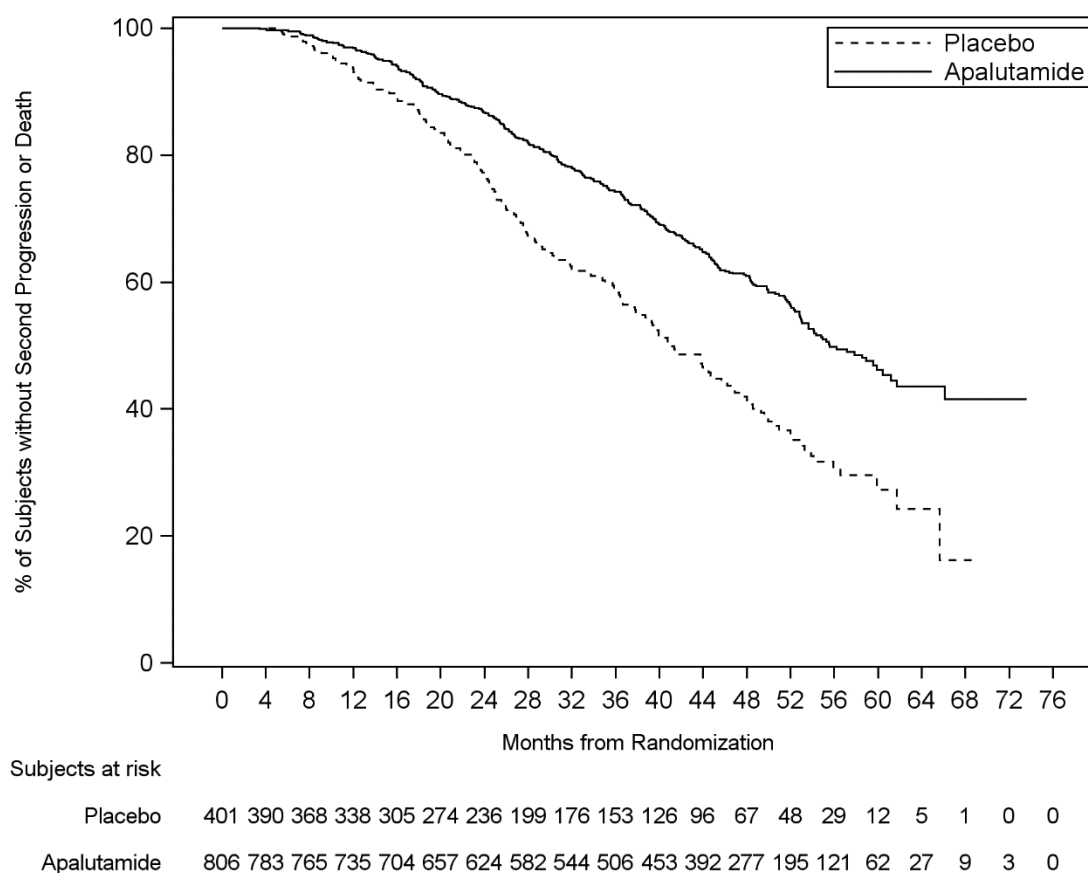


If eligible and without evidence of disease progression, subjects treated with placebo were given the opportunity to cross-over to treatment with ERLEADA at time of unblinding. After unblinding, 19% of the randomized placebo population crossed over to ERLEADA. Of all the randomized subjects, a greater 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 $\mu\text{g/mL}$ (28%) and 100 $\mu\text{g.h/mL}$ (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 $\mu\text{g/mL}$ (18%) and 124 $\mu\text{g.h/mL}$ (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 4) (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.

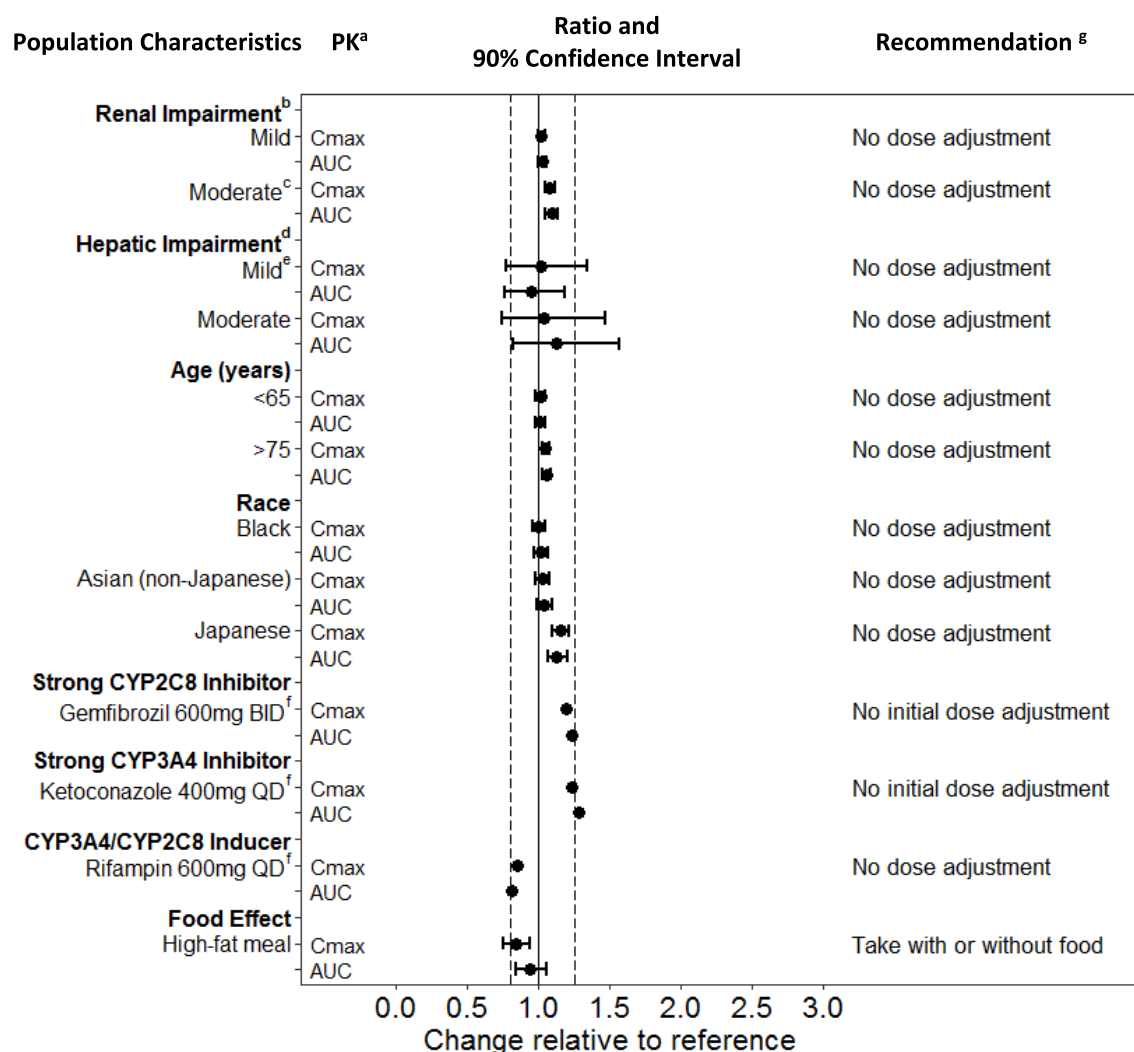
Elimination

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/1.73m²), mild (60-89 mL/min/1.73m²), moderate (30-59 mL/min/1.73m²)
- ^c Data included 2 subjects with severe renal impairment (≤ 29 mL/min/1.73m²)
- ^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 population 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/1.73m²) or moderate renal impairment (eGFR 30-59 mL/min/1.73m²), mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, age ranging from 18 to 94 years, or between different races.

The potential effect of severe renal impairment or end stage renal disease (eGFR ≤ 29 mL/min/1.73m²) have not been established due to insufficient data. 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. Results of a 24-month carcinogenicity study in the male rat are not yet available. 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 development toxicity study in the rat, early embryonic loss was seen at 50 and 100 mg/kg/day. In addition, a disturbance of the normal embryo-fetal development was observed ≥ 25 mg/kg/day (2.3 times the human exposure based on AUC), evidenced by a shortening of the mean anogenital distance, a misshapen (rounded) pituitary gland and some skeletal variations.

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

Shelf-life before opening: 24 months.

Shelf-life after opening: 6 weeks.

See expiry date on the outer pack.

Storage Conditions

Do not store above 30°C.

Keep out of the sight and reach of children.

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.

HOW SUPPLIED

Erleada film-coated (FC) tablets

Box, 1 bottle @ 120 tablets

Reg. No.: DK11910901617A1

HARUS DENGAN RESEP DOKTER

Manufacturing and primary packaging by Janssen Ortho LLC, Gurabo, Puerto Rico

Final batch release and secondary packaging by Janssen Cilag, S.p.A., Latina, Italy

Imported and distributed by PT Soho Industri Pharmasi

Jl. Pulogadung No. 6, Kawasan Industri Pulogadung,

Jakarta 13920 – Indonesia - (021) 460-5550

For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or (021) 2935-3935

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