# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

ALPALAT (Apalutamide Tablets 60 mg)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains, Apalutamide 60 mg.

## 3. PHARMACEUTICAL FORM

White colored, Oval shaped, biconvex, film coated tablets debossed with "60" on one side and "HA" on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Apalutamide tablets is indicated for the treatment of patients with

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nm CRPC)

### 4.2 Posology and method of Administration

This medicinal product should be prescribed by an appropriate healthcare professional. Posology

The recommended dose of Apalutamide tablets is 240 mg administered orally once daily. Swallow the tablets whole. Do not crush or split tablets. Apalutamide tablets can be taken with or without food. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

Dosage of Apalutamide

For patients who have difficulty swallowing tablets whole, the recommended dose of Apalutamide tablets may be mixed in applesauce.

1. Mix whole Apalutamide tablets in 4 ounces (120 mL) of applesauce by stirring. Do not crush or split the tablets.
2. Wait 15 minutes, stir the mixture.

3. Wait another 15 minutes, stir the mixture until tablets are dispersed (well mixed with no chunks remaining).
4. Using a spoon, swallow the mixture right away
5. Rinse the container with 2 ounces (60 mL) of water and immediately drink the contents. Repeat the rinse with 2 ounces (60 mL) of water a second time to ensure the whole dose is taken.

Consume the mixture within one hour of preparation. Do not store Apalutamide tablets that is mixed with applesauce.

**4.3 Contraindications**

None

**4.4 Special warnings and special precautions for use**

Cerebrovascular and Ischemic Cardiovascular events:

Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving Apalutamide Tablets. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of Apalutamide tablets for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 3.7% of patients treated with Apalutamide tablets and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with Apalutamide tablets and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with Apalutamide Tablets, and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with Apalutamide tablets and 1% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with Apalutamide Tablets and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with Apalutamide tablets, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event. 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.

Fractures

Fractures occurred in patients receiving Apalutamide tablets. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with Apalutamide tablets and in 7% of patients treated with placebo. Grade 3–4 fractures occurred in 2.7% of patients treated with Apalutamide tablets and in 0.8% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with Apalutamide tablets. Routine bone density assessment and treatment of osteoporosis with bone targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with Apalutamide tablets and in 6% of patients treated with placebo. Grade 3–4 fractures were similar in both arms at 1.5%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with Apalutamide tablets. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Falls

Falls occurred in patients receiving Apalutamide tablets with increased frequency in the elderly. Evaluate patients for fall risk. In a randomized study (SPARTAN), falls occurred in 16% of patients treated with Apalutamide tablets compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

Seizure

Seizure occurred in patients receiving Apalutamide tablets. Permanently discontinue Apalutamide tablets in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with Apalutamide tablets. Advise patients of the risk of developing a seizure while receiving Apalutamide tablets and of engaging in any activity where sudden loss of

consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with Apalutamide tablets and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 650 days after initiation of Apalutamide tablets. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering Apalutamide tablets to patients who experienced a seizure

Severe Cutaneous Adverse Reactions

Fatal and life threatening cases of severe cutaneous adverse reactions (SCARs), including Stevens- Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), occurred in patients receiving Apalutamide tablets . Monitor
patients for the development of SCARs. Advise patients of the signs and symptoms of SCARs (e.g.,aprodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy). If a SCAR is suspected, interrupt Apalutamide tablets until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, or for other grade 4 skin reactions, permanently discontinue Apalutamide tablets.

Embryo-Fetal Toxicity

The safety and efficacy of Apalutamide tablets have not been established in females. Based on findings from animals and its mechanism of action, Apalutamide tablets can cause fetal harm and loss of pregnancy when administered to a pregnant female. in an animal reproduction study,
oral administration of Apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥ 2 times the human clinical exposure (AUC) at the recommended dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of Apalutamide tablets.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effect of Other drugs on Apalutamide

tablets Strong CYP2C8 or CYP3A4

Inhibitors

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady- state exposure of the active moieties (sum of unbound Apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the Apalutamide tablets dose based on tolerability. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of Apalutamide tablets on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates Apalutamide tablets is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of

CYP2C9 in humans. Concomitant use of Apalutamide tablets 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 activity if medication is continued. Concomitant administration of Apalutamide tablets with medications that are substrates of UDP glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with Apalutamide tablets and evaluate for loss of activity.

P-gp, BCRP or OATP1B1 Substrates

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. At steady- state, Apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate). Concomitant use of Apalutamide tablets 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 Apalutamide tablets and evaluate for loss of activity if medication is continued.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

*Risk Summary*

The safety and efficacy of Apalutamide tablets have not been established in females. Based on findings from animals and its mechanism of action, Apalutamide tablets can cause fetal harm and loss of pregnancy when administered to a pregnant female. There are no available data on Apalutamide tablets use in pregnant women to inform a drug-associated risk. In an animal reproduction study, oral administration of Apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥ 2 times the human clinical exposure (AUC) at the recommended dose.

Data

*Animal Data*

In a pilot embryo-fetal developmental toxicity study in rats, Apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout and after the period of organogenesis (gestational days 6–20). Findings included embryo-fetal lethality (resorptions) at doses ≥50 mg/kg/day, decreased fetal anogenital distance, misshapen pituitary gland, and skeletal variations (unossified phalanges, supernumerary short thoracolumbar rib(s), and small, incomplete ossification, and/or misshapen hyoid bone) at ≥25 mg/kg/day. A dose of 100 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 2, 4 and 6 times, respectively, the AUC in patients**.**

Lactation

*Risk Summary*

The safety and efficacy of Apalutamide tablets have not been established in females. There are no data on the presence of Apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

Females and Males of Reproductive

Potential Contraception

*Males*

Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of Apalutamide

Tablets.

Infertility

*Males*

Based on animal studies, Apalutamide tablets may impair fertility in males of reproductive potential.

Pediatric use

Safety and effectiveness of Apalutamide tablets in pediatric patients have not been established. Geriatric use

Of the 1327 patients who received Apalutamide tablets in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over. No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with Apalutamide tablets (n=1073), Grade 3–4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65–74 years, and 49% of patients 75 years or older. Falls in patients receiving Apalutamide tablets with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65–74 years, and 19% of patients 75 years or older.

## 4.7 Effects on ability to drive and use machines

Not available

## 4.8 Undesirable effects

The following are discussed in more detail in other sections of the labelling:

Cerebrovascular and Ischemic Cardiovascular Events.

Fractur
es.

Falls.

Seizure.

Severe Cutaneous Adverse Reactions

(SCARs). Clinical Trail Experience:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse reactions (≥ 10%) that occurred more frequently in the Apalutamide tablets -treated patients (≥ 2% over placebo) from

the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

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 Apalutamide tablets 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 Apalutamide tablets and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (1.9%) who were treated with Apalutamide tablets died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio- respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). Apalutamide tablets was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2.3%). Adverse reactions leading to dose interruption or reduction of Apalutamide tablets occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of Apalutamide tablets -treated patients and 20% in patients receiving placebo. Table 1 shows adverse reactions occurring in ≥10% on the Apalutamide tablets arm in TITAN that occurred with a

≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the Apalutamide tablets arm compared to placebo.

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

| System/Organ class<br>adverse reaction | Apalutamide tablets<br>N=524 | | Placebo<br>N=527 | |
|---|---|---|---|---|
| | All Grades % | Grade 3-4% | All Grades % | Grade 3-4% |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Arthralgia* | 17 | 0.4 | 15 | 0.9 |
| **Skin and Subcutaneous tissue disorders** | | | | |
| Rash† | 28 | 6 | 9 | 0.6 |
| Pruritus | 11 | 0.2 | 4.6 | 0.2 |
| **Vascular Disorders** | | | | |
| Hot Flush | 23 | 0 | 16 | 0 |
| Hypertension | 18 | 8 | 16 | 9 |

*Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3.

†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.

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with Apalutamide tablets included diarrhea (9% versus 6% on placebo), muscle spasm (3.1% versus 1.9% on placebo), dysgeusia (3.2% versus 0.6% on placebo), and hypothyroidism (3.6% versus 0.6% on placebo).

**Table 2: Laboratory Abnormalities Occurring in ≥ 15% of Apalutamide tablets -Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in TITAN (mCSPC)**

| Apalutamide Tablets N=524 | | | Placebo N=527 | |
|---|---|---|---|---|
| **Laboratory Abnormality** | **All Grades %** | **Grade 3-4%** | **All Grades %** | **Grade 3-4%** |
| **Hematology** | | | | |
| White blood cell decreased | 27 | 0.4 | 19 | 0.6 |
| **Chemistry** | | | | |
| Hypertriglyceridemia* | 17 | 2.5 | 12 | 2.3 |

*Does not reflect fasting values

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either Apalutamide tablets at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 33 months (range: 0.1 to 75 months) in patients who received Apalutamide tablets and 11 months (range: 0.1 to 37 months) in patients who received placebo. Twenty-four patients (3%) who were treated with Apalutamide tablets died from adverse reactions. The reasons for death with ≥ 2 patients included infection (n=7), myocardial infarction (n=3), cerebrovascular event (n=2), and unknown reason (n=3). Apalutamide tablets was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3.2%). Adverse reactions leading to dose interruption or reduction of Apalutamide tablets occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of Apalutamide tablets -treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (3.4%) in the Apalutamide tablets arm and urinary retention (3.8%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the Apalutamide tablets arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients,

and more frequently (>5%) in the Apalutamide tablets arm compared to placebo.

**Table 3: Adverse Reactions in SPARTAN (nmCRPC)**

| **Apalutamide Tablets N=803** | | | **Placebo N=398** | |
|---|---|---|---|---|
| **System/Organ Class Adverse reaction** | **All Grades %** | **Grade 3-4 %** | **All Grades %** | **Grade 3-4 %** |
| **General disorders and administration site conditions** | | | | |
| Fatigue*† | 39 | 1.4 | 28 | 0.3 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Arthralgia † | 16 | 0 | 8 | 0 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash ‡ | 25 | 5.2 | 6 | 0.3 |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite § | 12 | 0.1 | 9 | 0 |
| Peripheral edema¶ | 11 | 0 | 9 | 0 |
| **Injury, poisoning and Procedural complications** | | | | |
| Fall† | 16 | 1.7 | 9 | 0.8 |
| Fracture # | 12 | 2.7 | 7 | 0.8 |
| **Investigations** | | | | |
| Weight decreased † | 16 | 1.1 | 6 | 0.3 |
| **Vascular disorders** | | | | |
| Hypertension | 25 | 14 | 20 | 12 |
| Hot flush | 14 | 0 | 9 | 0 |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 20 | 1.1 | 15 | 0.5 |
| Nausea | 18 | 0 | 16 | 0 |

* Includes fatigue and asthenia

† Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

‡ 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.

§ Includes appetite disorder, decreased appetite, early satiety, and Hypophagia

¶ Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

# 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, and tibia fracture.

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with Apalutamide tablets included hypothyroidism (8% versus 2% on placebo), pruritus (6% versus 1.5% on placebo), and heart failure (2.2% versus 1% on placebo).

**Table 4: Laboratory Abnormalities Occurring in ≥ 15% of Apalutamide tablets -Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN (nmCRPC)**

| | **Apalutamide tablets (N=803)** | | **Placebo (N=398)** | |
|---|---|---|---|---|
| **Laboratory Abnormality** | **All Grades %** | **Grade 3-4 %** | **All Grades %** | **Grade 3-4 %** |
| **Hematology** | | | | |
| Anemia | 70 | 0.4 | 64 | 0.5 |
| Leukopenia | 47 | 0.3 | 29 | 0 |
| Lmphopenia | 41 | 1.8 | 21 | 1.6 |
| **Chemistry** | | | | |
| Hypercholesterolemia* | 76 | 0.1 | 46 | 0 |
| Hyperglycemia* | 70 | 2 | 59 | 1.0 |
| Hypertriglyceridemia* | 67 | 1.6 | 49 | 0.8 |
| Hyperkalemia | 32 | 1.9 | 22 | 0.5 |

*Does not reflect fasting values Rash

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, rash associated with Apalutamide tablets was most commonly described as macular or maculo papular. Adverse reactions of rash were reported for 26% of patients treated with Apalutamide tablets versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering
> 30% body surface area [BSA]) were reported with Apalutamide tablets treatment (6%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of Apalutamide tablets treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of Apalutamide tablets.

Hypothyroidism

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, hypothyroidism was reported for 8% of patients treated with Apalutamide tablets and 1.5% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with Apalutamide tablets and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 4.9% of patients treated with Apalutamide tablets. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

**Post-Marketing Experience**

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

*Respiratory, Thoracic and Mediastinal Disorders:* interstitial lung disease

*Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).

**Reporting of suspected adverse reactions**

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

## 4.9 Overdose

There is no known specific antidote for Apalutamide overdose. In the event of an overdose, stop Apalutamide tablets, undertake general supportive measures until clinical toxicity has been diminished or resolved.

# 5. CLINICAL PHARMACOLOGY

## 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group*: Anti-

Neoplastic agent *ATC code:* L02BB05

Mechanism of Action:

Apalutamide is an Androgen Receptor (AR) inhibitor that binds directly to the ligand binding domain of the AR. Apalutamide inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription. A major metabolite, N-desmethyl apalutamide, is a less potent inhibitor of AR, and exhibited one-third the activity of Apalutamide in an in vitro transcriptional reporter assay. Apalutamide administration caused decreased tumor cell proliferation and increased apoptosis leading to decreased tumor volume in mouse xenograft models of prostate cancer.

**Pharmacodynamics effects**

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 patients 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.

## 5.2 Pharmacokinetic properties

Apalutamide pharmacokinetic parameters are presented as the mean [standard deviation (SD)] unless otherwise specified. Apalutamide Cmax and area under the concentration curve (AUC) increased proportionally following repeated once-daily dosing of 30 to 480 mg (0.125 to 2 times the recommended dosage). Following administration of the recommended dosage, Apalutamide steady-state was achieved after 4 weeks and the mean accumulation ratio was approximately 5- fold. Apalutamide Cmax was 6.0 mcg/mL (1.7) and AUC was 100 mcg·h/mL (32) at steady-state. 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. The auto-induction effect likely reached its maximum at the recommended dosage because exposure of Apalutamide across the dose range of 30 to 480 mg is dose-proportional.

The major active metabolite N-desmethyl Apalutamide C max was 5.9 mcg/mL (1.0) and AUC was 124 mcg·h/mL (23) at steady-state after the recommended dosage. N-desmethyl Apalutamide was characterized by a flat concentration-time profile at steadystate with a mean peak to-trough ratio of 1.27. Mean AUC metabolite/parent drug ratio for N-desmethyl Apalutamide following repeat-dose administration was 1.3. Based on systemic exposure, relative potency, and pharmacokinetic properties, N-desmethyl Apalutamide likely contributed to the clinical activity of apalutamide.

Absorption

Mean absolute oral bioavailability was approximately 100%. Median time to achieve peak plasma concentration (tmax ) was 2 hours (range: 1 to 5 hours). Oral administration of four 60 mg Apalutamide tablets dispersed in applesauce resulted in no clinically relevant changes in Cmax and AUC when compared to administration of four intact 60 mg tablets under fasting condition.

Effect of Food

Administration of Apalutamide to healthy subjects under fasting conditions and with a high-fat meal (approximately 500 to 600 fat calories, 250 carbohydrate calories, and 150 protein calories) resulted in no clinically relevant changes in Cmax and AUC. Median time to reach t max was delayed approximately 2 hours

with food.

Distribution

The mean apparent volume of distribution at steady-state of Apalutamide was approximately 276

L. Apalutamide was 96% and N-desmethyl Apalutamide was 95% bound to plasma proteins with no concentration dependency.

Elimination

The CL/F of Apalutamide was 1.3 L/h after single dosing and increased to 2.0 L/h at steady-state after once-daily dosing likely due to CYP3A4 auto-induction. The mean effective half-life for Apalutamide in patients was approximately 3 days at steady-state.

Metabolism

Metabolism is the main route of elimination of apalutamide. Apalutamide is primarily metabolized by CYP2C8 and CYP3A4 to form active metabolite, N-desmethyl apalutamide. The contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but changes to 40% and 37%, respectively at steady-state. Apalutamide represented 45% and N-desmethyl Apalutamide represented 44% of the total AUC following a single oral administration of radiolabeled Apalutamide 240 mg.

Excretion

Up to 70 days following a single oral administration of radiolabeled apalutamide, 65% of the dose 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).

Specific Populations

No clinically significant differences in the pharmacokinetics of Apalutamide or N-desmethyl Apalutamide were observed based on age (18–94 years), race (Black, non- Japanese Asian, Japanese), mild to moderate (eGFR 30–89 mL/min/1.73 m , estimated by the modification of diet in renal disease [MDRD] equation) renal impairment, or mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment. The effect of severe renal impairment or end stage renal disease (eGFR ≤29 mL/min/1.73 m , MDRD) or severe hepatic impairment (Child-Pugh C) on apalutamide pharmacokinetics is unknown.

Drug Interactions

*Effect of Other Drugs on* Apalutamide
tablets. Strong CYP2C8 inhibitors
Apalutamide Cmax decreased by 21% while AUC increased by 68% following coadministration of Apalutamide Tablets as a 240 mg single dose with gemfibrozil (a strong CYP2C8 inhibitor). Gemfibrozil is predicted to increase the steady-state Apalutamide Cmax by 32% and AUC by 44%. For the active moieties (sum of unbound Apalutamide plus the potency-adjusted unbound N-desmethyl apalutamide), the predicted steady-state Cmax increased by 19% and AUC by 23%. Strong CYP3A4 inhibitors Apalutamide C max decreased by 22% while AUC was similar following co-administration of Apalutamide Tablets as a 240 mg single dose with itraconazole (a strong CYP3A4 inhibitor). Ketoconazole (a strong CYP3A4 inhibitor) is predicted to increase the single-dose Apalutamide AUC by 24% but have no impact on Cmax . Ketoconazole is predicted to increase the steady-state Apalutamide Cmax by 38% and AUC by 51%. For the active moieties, the predicted steady-state Cmax increased by 23% and AUC by 28%.

<u>CYP3A4/CYP2C8 inducers:</u>

Rifampin (a strong CYP3A4 and moderate CYP2C8 inducer) is predicted to decrease the steady- state Apalutamide Cmax by 25% and AUC by 34%. For the active moieties, the predicted steady-state Cmax decreased by 15% and AUC by 19%.

Acid lowering agents;

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

<u>Drugs affecting transporters;</u>

In vitro, Apalutamide and N-desmethyl Apalutamide 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.

<u>Effect of Apalutamide tablets on Other</u>

Drugs CYP substrates

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. Co-administration of Apalutamide tablets with single oral doses of sensitive CYP substrates resulted in a 92% decrease in the AUC of midazolam (a CYP3A4 substrate), 85% decrease in the AUC of omeprazole (a CYP2C19 substrate), and 46% decrease in the AUC of S-warfarin (a CYP2C9 substrate). Apalutamide tablets did not cause clinically significant changes in exposure to a CYP2C8 substrate.

P-gp, BCRP and OATP1B1 substrates

Co-administration of Apalutamide tablets with single oral doses of transporter substrates resulted in a 30% decrease in the AUC of fexofenadine (a P-gp substrate) and 41% decrease in the AUC of rosuvastatin (a BCRP/OATP1B1 substrate) but had no impact on C .

UGT substrates

Apalutamide may induce UGT. Concomitant administration of Apalutamide tablets with medications that are substrates of UGT may result in lower exposure to these medications.

OCT2, OAT1, OAT3 and MATEs substrates

In vitro, Apalutamide and N-desmethyl Apalutamide inhibit organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3) and multidrug and toxin extrusions (MATEs), and do not inhibit organic anion transporter 1. Apalutamide is not predicted to cause clinically significant changes in exposure to an OAT3 substrate.

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 steadystate exposure of leuprolide.

**Preclinical safety data**

In a 2-year carcinogenicity study in male rats, Apalutamide was administered by oral gavage at doses of 5, 15 and 50 mg/kg/day. Apalutamide increased the incidence of Leydig interstitial cell adenoma in the testes at doses ≥ 5 mg/kg/day (0.2 times the human exposure based on AUC). The findings in the testes are considered to be related to the pharmacological activity of apalutamide. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Oral administration of Apalutamide to male rasH2 transgenic mice for 6 months did not result in increased incidence of neoplasms at doses up to 30 mg/kg/day.

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

In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), atrophy of the prostate gland and seminal vesicles, aspermia/hypospermia, tubular ndegeneration and/or hyperplasia or hypertrophy of the interstitial cells 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, increased abnormal sperm morphology, lower 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 (0.8 times the human exposure based on AUC). A reduced number of live fetuses due to increased pre- and/or post-implantation loss was observed following 4 weeks of 150 mg/kg/day administration (5.7 times the human exposure based on AUC). Effects on male rats were reversible after 8 weeks from the last Apalutamide administration.

**CLINICAL STUDIES:**

The efficacy and safety of Apalutamide tablets was established in two randomized placebo controlled clinical trials.

TITAN (NCT02489318): Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN was a randomized, double-blind, placebo-controlled, multinational, clinical trial in which 1052 patients with mCSPC were randomized (1:1) to receive either Apalutamide tablets orally at a dose of 240 mg once daily (N=525) or placebo once daily (N=527). All patients in the TITAN trial received concomitant GnRH analog or had prior bilateral orchiectomy. Patients were stratified by Gleason score at diagnosis, prior docetaxel use, and region of the world. Patients with both high- and low-volume mCSPC were eligible for the study. High volume of disease was defined as metastases involving the viscera with 1 bone lesion or the presence of 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bones.

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 patients were 75 years of age or older. The racial distribution was 68% Caucasian, 22% Asian, and 2% Black. Sixty-three percent (63%) of patients had high-volume disease and 37% had low-volume disease. Sixteen percent (16%) of patients had prior surgery, radiotherapy of the prostate or both. A majority of patients had a Gleason score of 8 or higher (67%). Sixty-eight percent (68%) of patients received prior treatment with an anti-androgen (bicalutamide, flutamide, or nilutamide).

All patients except one in the placebo group, had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry.

The major efficacy outcome measures of the study were overall survival (OS) and radiographic progression-free survival (rPFS). Radiographic progression-free survival was based on investigator assessment and was defined as time from randomization to radiographic disease progression or death. Radiographic disease progression was defined by identification of 2 or more new bone lesions on a bone scan with confirmation (Prostate Cancer Working Group 2 criteria) and/or progression in soft tissue disease.

A statistically significant improvement in OS and rPFS was demonstrated in

patients randomized to receive Apalutamide tablets compared with patients randomized to receive placebo. The results for OS are based upon a prespecified interim efficacy analysis. An updated OS analysis was conducted at the time of final study analysis when 405 deaths were observed. The median follow-up time was 44 months. Thirty-nine percent of patients in the placebo arm crossed over to receive Apalutamide tablets**.** Efficacy results of TITAN are summarized in Table 5 and Figures 1 and 2.

**Table 5: Efficacy Results from the TITAN Study**

| **Endpoint** | **Apalutamide tablets (N=525)** | **Placebo (N=527)** |
|---|---|---|
| **Primary Overall Survival*** | | |
| Deaths (%) | 83 (16%) | 117 (22%) |
| Median, months (95% CI) † | NE (NE, NE) | NE (NE, NE) |
| Hazard Ratio (95% CI) ‡ | 0.67 (0.51,0.89) | |
| p-value§ | 0.0053 | |
| **Updated Overall Survival** | | |
| Deaths (%) | 170 (32%) | 235 (45%) |
| Median, months (95% CI) † | NE (NE, NE) | 52 (42, NE) |
| Hazard Ratio (95% CI) ‡ | 0.65 (0.53,0.79) | |
| **Radiographic Progression-free Survival** | | |
| Disease progression or death (%) | 134 (26%) | 231 (44%) |
| Median, months (95% CI) † | NE (NE,NE) | 22.1 (18,33) |
| Hazard Ratio (95% CI) ‡ | 0.48 (0.39,0.60) | |
| p-value§ | <0.0001 | |

*Interim analysis is based on 50% of the number of events planned for the final analysis. Allocated alpha = 0.01.

† NE=Not Estimable

‡ Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Apalutamide tablets.

§ 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).

Consistent improvement in rPFS was observed across the following patient 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 patient subgroups: disease volume (high vs low) and Gleason score at diagnosis (≤7 vs. >7). Treatment with Apalutamide tablets resulted in a statistically significant delay in the initiation of cytotoxic chemotherapy (HR = 0.39, 95% CI = 0.27, 0.56; p < 0.0001).

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

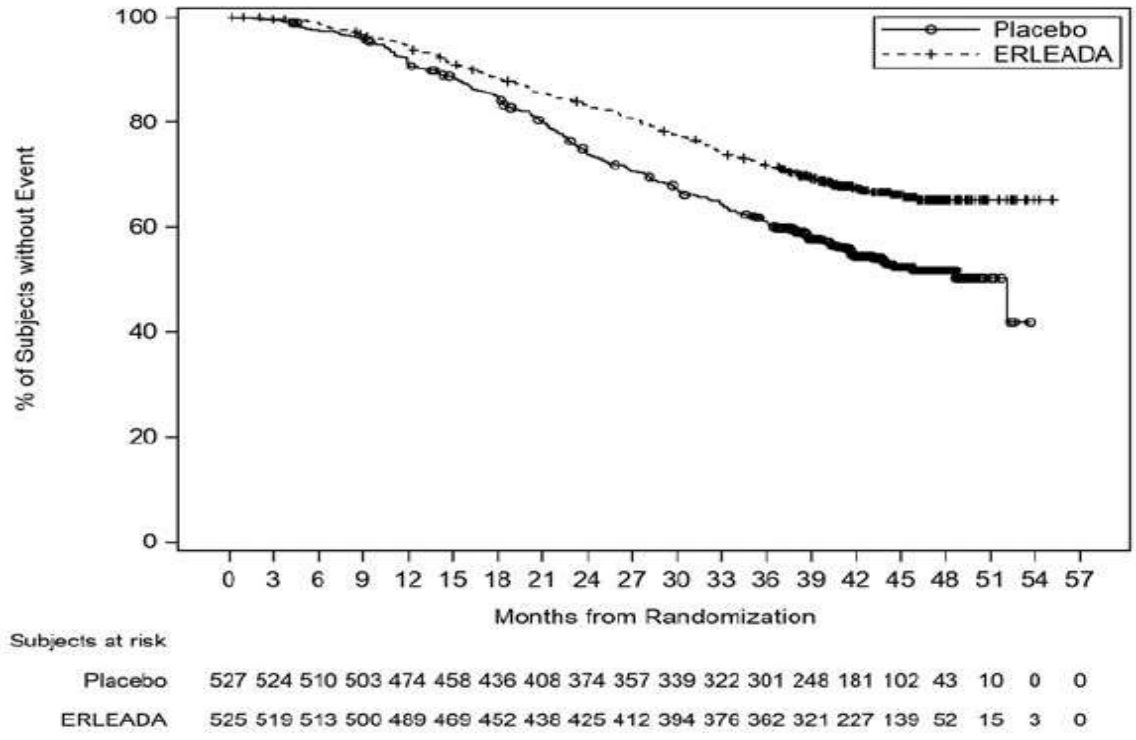
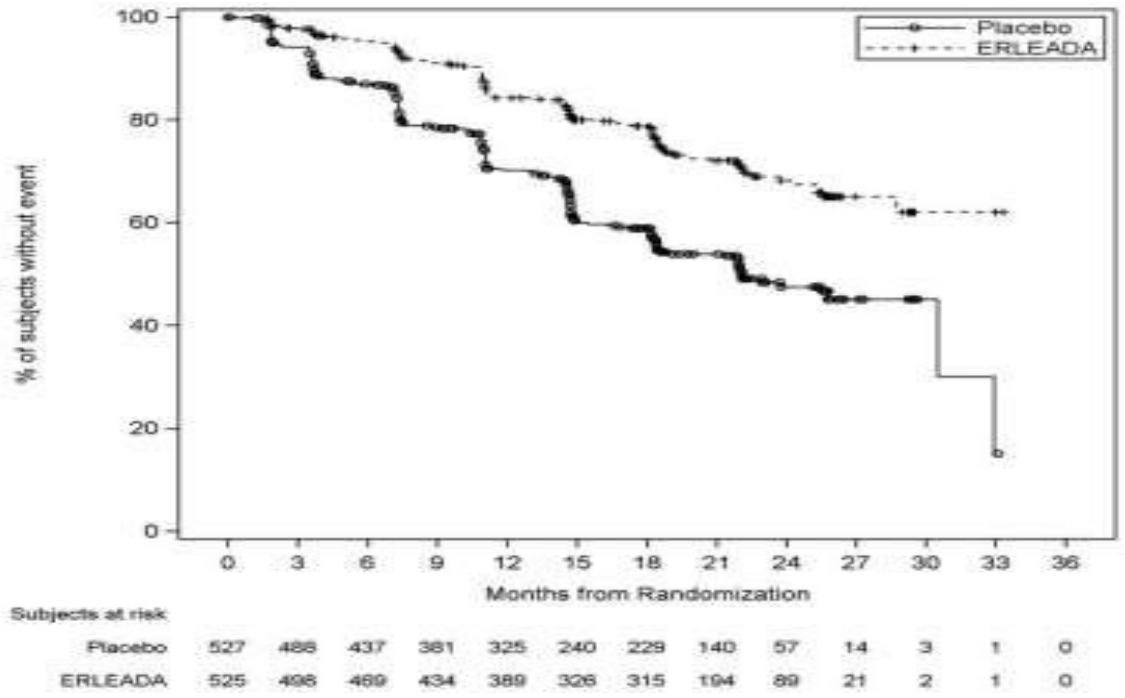



**Figure 2: Kaplan-Meier Plot of Radiographic progression-Free Survival Intent-to-treat mCSPC Population (TITAN)**




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Placebo** | 527 | 488 | 437 | 381 | 325 | 240 | 229 | 140 | 57 | 14 | 3 | 1 | 0 |
| **Apalutamide Tablets** | 525 | 498 | 469 | 434 | 389 | 326 | 315 | 194 | 89 | 21 | 2 | 1 | 0 |

SPARTAN (NCT01946204): Non-metastatic, Castration-resistant Prostate Cancer (nmCRPC) SPARTAN was a multicenter, double-blind, randomized (2:1), placebo-controlled clinical trial in which 1207 patients with nmCRPC were randomized (2:1) to receive either Apalutamide tablets orally at a dose of 240 mg once daily (N=806) or placebo once daily (N=401). All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchiectomy. Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time(PSADT), the use of bone- sparing agents, and locoregional disease. Patients were required to have a PSADT ≤ 10 months and confirmation of non-metastatic disease by blinded independent central review (BICR). PSA results were blinded and were not used for treatment discontinuation. Patients randomized to either arm discontinued treatment for radiographic disease progression confirmed by BICR, locoregional-only progression, initiation of new treatment, unacceptable toxicity, or withdrawal. 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 patients were 80 years of age or older. The racial distribution was 66% Caucasian, 12% Asian, and 6% Black. Seventy-seven percent (77%) of patients in both treatment arms had prior surgery or radiotherapy of the prostate. A majority of patients had a Gleason score of 7 or higher (78%). Fifteen percent (15%) of patients had <2 cm pelvic lymph nodes at study entry. Seventy-three percent (73%) of patients received prior treatment with an anti-androgen; 69% of patients received bicalutamide and 10% of patients received flutamide. All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry. The major efficacy outcome measure of the study was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first. Additional efficacy endpoints were time to metastasis (TTM), progression-free survival (PFS) which also includes locoregional progression, time to symptomatic progression, overall survival (OS), and time to initiation of cytotoxic chemotherapy A statistically significant improvement in MFS and OS was demonstrated in patients randomized to receive Apalutamide tablets compared with patients randomized to receive placebo. The major efficacy outcome (MFS) was supported by improvements in TTM and PFS. The final analysis of OS and time to initiation of cytotoxic chemotherapy was conducted 32 months after the analysis of MFS, TTM and PFS. The efficacy results from SPARTAN are summarized in Table 6 and Figures 3 and 4.

**Table 6: Efficacy Results from the SPARTAN Study**

| **Endpoint** | **Apalutamide Tablets (N=806)** | **Placebo (N=401)** |
|---|---|---|
| **Metastasis Free Survival** *,†,‡ | | |
| Number of Events (%) | 184 (23%) | 194 (48%) |
| Median, months (95% CI) § | 40.5 (NE, NE) | 16.2 (15, 18) |
| Hazard Ratio (95% CI) | 0.28 (0.23, 0.35) | |
| p-value* | <0.0001 | |
| **Time to Metastasis** *,† | | |

| | | |
|---|---|---|
| Number of Events (%) | 175 (22%) | 191 (48%) |
| Median, months (95% CI) § | 40.5 (NE, NE) | 16.6 (15, 18) |
| Hazard Ratio (95% CI) | 0.28 (0.23, 0.34) | |
| p-value* | <0.0001 | |
| **Progression-Free Survival***,† | | |
| Number of Events (%) | 200 (25%) | 204 (51%) |
| Median, months (95% CI) § | 40.5 (NE, NE) | 14.7 (14, 18) |
| Hazard Ratio (95% CI) | 0.28 (0.23, 0.36) | |
| p-value* | <0.0001 | |

| **Overall Survival** | | |
|---|---|---|
| Number of Events (%) | 274 (34%) | 154 (38%) |
| Median, months (95% CI) § | 73.9 (61, NE) | 59.9 (53, NE) |
| Hazard Ratio (95% CI) | 0.78 (0.64, 0.96) | |
| p-value* | 0.0161 | |

*All analyses stratified by PSA doubling time, bone-sparing agent use, and Locoregional disease status.

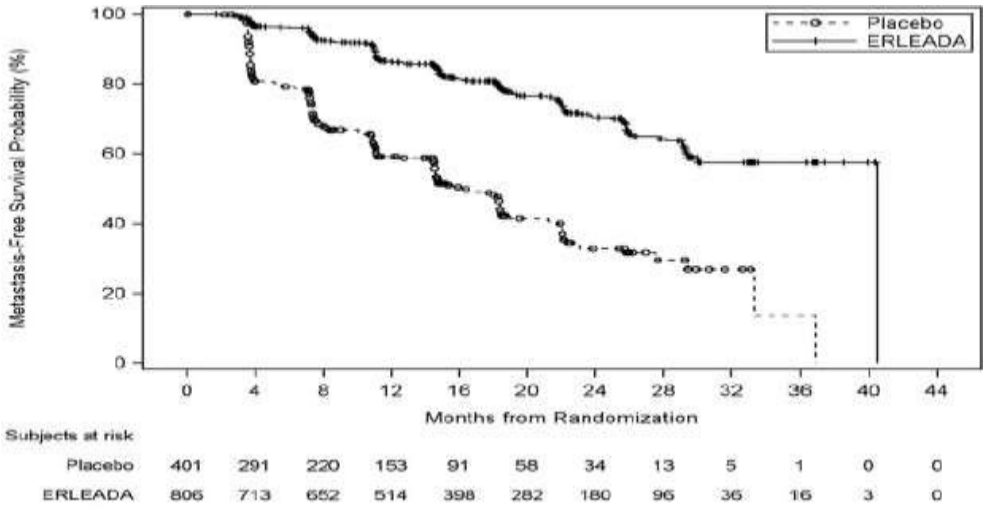
†Confirmed responses assessed by BICR.

‡Locoregional-only progression is observed in 2.4% of patients overall.

§NE=Not Estimable

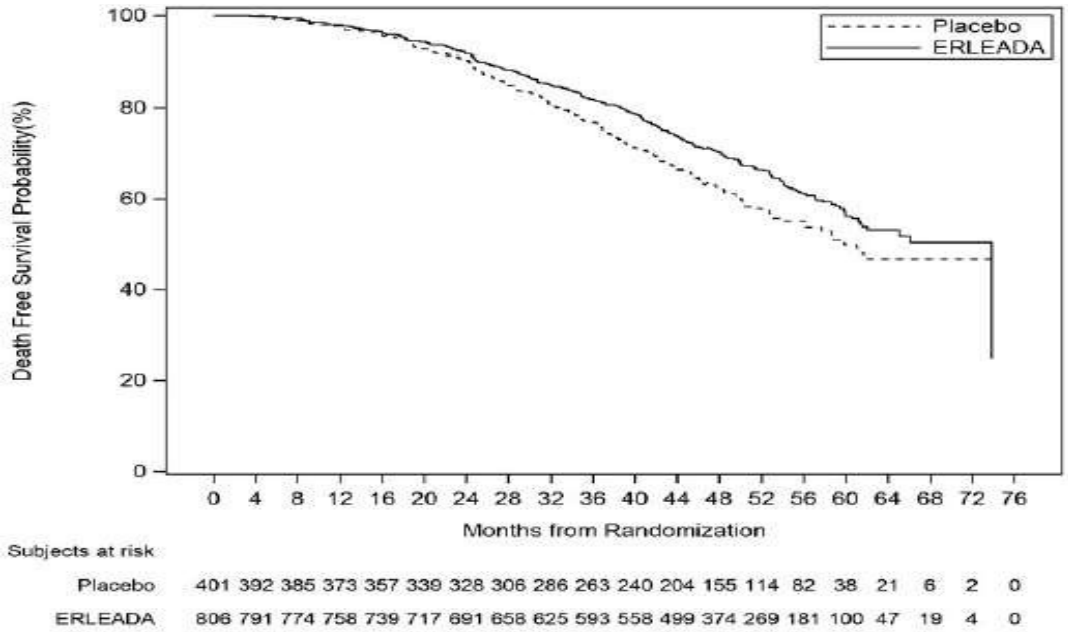
Consistent results for MFS were observed across patient subgroups including PSADT (≤ 6 months or > 6 months), use of a prior bone-sparing agent (yes or no), and locoregional disease (N0 or N1). Treatment with Apalutamide tablets resulted in a statistically significant delay in the initiation of cytotoxic chemotherapy [HR = 0.63 (95% CI:0.49, 0.81), p=0.0002].

**Figure 3: Kaplan-Meier Metastasis-Free Survival (MFS) Curve in SPARTAN (nmCRPC)**




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

**Figure 4: Kaplan-Meier Overall Survival (OS) Curve in SPARTAN (nmCRPC)**




## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients:

**List of Excipients**

Apalutamide, microcrystalline cellulose, Silicified microcrvstalline cellulose, Colloidal anhydrous silica, Hydroxypropvl methylcellulose-acetate succinate, Croscarmellose sodium, Magnesium stearate and Opadry-II White.

***Coating material composition:***

Polyvinyl alcohol, Talc, Titanium dioxide, Macrogol/Peg.

### 6.2 Incompatibilities

Not Applicable

### 6.3 Shelf life

24 Months

### 6.4 Special precautions for storage

Stored below 30° C

### 6.5 Nature and contents of pack's

120's HDPE Container

### 6.6 Instructions for use, handling and disposal

Not applicable.

## 7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

**Marketing Authorization Holder**

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Jadcherla Mandal, Mahabubnagar
District, Pincode 509301, Telangana
state, India.

## 8. Marketing Authorization Number

CTD12614/27172

## 9. Date of first authorization/Renewal of the Authorization

17-01-2026

## 10. Date of revision of the text

17-01-2026