ERLYAND ®

apalutamide

DATA SHEET

1. PRODUCT NAME

ERLYAND apalutamide 60 mg film-coated tablet bottle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ERLYAND 60 mg tablets contain 60 mg of apalutamide.

For a full list of excipients, see **section 6.1** List of excipients.

3. PHARMACEUTICAL FORM

ERLYAND is supplied as slightly yellowish green to greyish green, oblong-shaped, film-coated tablets, debossed with “AR 60” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ERLYAND (apalutamide) is indicated for the treatment of patients with:

- metastatic castration-sensitive prostate cancer (mCSPC) or
- non-metastatic, castration-resistant prostate cancer (nmCRPC) (see **section 5.1 Clinical trials**).

4.2 Dose and method of administration

Dose in adults

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

Patients should concurrently receive a gonadotropin-releasing hormone (GnRH) analogue, unless they have had a bilateral orchiectomy.

Method of administration

ERLYAND should be administered orally once daily, with or without food. The tablets should be swallowed whole.

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.

Alternative Method of Administration

For patients who have difficulty swallowing tablets whole, the recommended dose of ERLYAND tablets may be mixed with 120 mL of applesauce. Do not crush the tablets. Stir applesauce upon introduction of whole tablets as well as at 15 minutes and 30 minutes afterwards until tablets are dispersed (well mixed with no chunks remaining). Using a spoon, swallow the mixture right away. Rinse the mixture container with 60 mL of water and immediately drink the contents. Repeat the rinse with 60 mL of water one more time to ensure the whole dose is taken. The mixture should be consumed within one hour of preparation. see **section 5.2 Pharmacokinetic Properties**

Dosage adjustment

Adverse effects

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

Hepatic insufficiency

No dosage adjustment is necessary for patients with baseline mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

No data are available in patients with severe hepatic impairment (Child-Pugh class C), see **section 5.2 Special populations**.

Renal insufficiency

No dosage adjustment is necessary for patients with mild to moderate renal impairment.

No data are available in patients with severe renal impairment or end-stage renal disease (eGFR $\leq$ 29 mL/min/1.73m^2), see **section 5.2 Special populations**.

Use in the elderly

No dosage adjustment is necessary based on patient age (see **sections 4.4 Special warnings and precautions for use** and **5.2 Special populations**).

Paediatric use

The safety and efficacy of ERLYAND in patients aged less than 18 years have not been established (see **section 4.4 Special warnings and precautions for use**).

4.3 Contraindications

ERLYAND is contraindicated in women who are or may become pregnant, see **section 4.6 Use in pregnancy**.

4.4 Special warnings and precautions for use

Falls and Fractures

Evaluate patients for fracture and fall risk and manage according to established treatment guidelines, including consideration of bone-targeted agents.

ERLYAND adds to the increased risk of osteopenia and osteoporosis associated with prolonged ADT therapy, which may contribute to the increased risk of fall and injury. Falls and fall-related injuries (including non-pathological fractures) occurred in patients receiving ERLYAND in the registrational study, and one patient died due to a skull fracture after a fall. Fall and fall-related injuries occurred more commonly in patients over 75 years of age. See **section 4.8 Description of selected adverse events**.

Seizure

Permanently discontinue ERLYAND in patients who develop a seizure during treatment. Advise patients of the risk of developing a seizure while receiving ERLYAND and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. It is unknown whether anti-epileptic medications will prevent seizures with ERLYAND. There is no clinical experience in re-administering ERLYAND to patients who experienced a seizure.

In two randomised studies, SPARTAN and TITAN, five patients (0.4%) treated with ERLYAND and two patients (0.2%) treated with placebo experienced a seizure. In these studies, patients with a history of seizure or predisposing factors for seizure were excluded. See **sections 4.8 Description of selected adverse events** and **4.7 Effects on ability to drive and use machines**.

Hypothyroidism

Initiation or adjustment of thyroid replacement therapy may be required. As levothyroxine exposure may be reduced when it is co-administered with apalutamide, evaluate for loss of levothyroxine efficacy and need for dose adjustment (see **section 4.5 Effects of ERLYAND on other medicines**).

Hypothyroidism occurred in patients receiving ERLYAND in the registrational study, based on elevation of thyroid-stimulating hormone (TSH). Hypothyroidism occurred more commonly in patients who were already receiving thyroid replacement therapy, and in patients > 75 years of age (see **section 4.8 Description of selected adverse events).**

Severe Cutaneous Adverse Reactions (SCAR)

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

Interstitial Lung Disease (ILD)

Postmarketing cases of ILD, including fatal cases, have been observed in patients treated with anti-androgens, including apalutamide. In case of acute onset and/or unexplained worsening of pulmonary symptoms, treatment with apalutamide should be interrupted pending further investigation of these symptoms. If ILD is diagnosed, apalutamide should be discontinued and further treatment with anti-androgens should be withheld (see **section 4.8 Undesirable effects – Postmarketing data**).

Cardiac effects

Ischaemic heart disease (IHD) and ischaemic cerebrovascular disorders

Ischaemic heart disease and ischaemic cerebrovascular disorders, including events leading to death, occurred in patients treated with ERLYAND. Patients with a cardiac history should be assessed for active cardiac disease before starting treatment with ERLYAND. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidaemia. The safety of ERLYAND has not been characterised in patients with recent (within 6 months) significant cardiovascular disease (including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial/venous thromboembolic events, clinically significant ventricular arrhythmias and uncontrolled hypertension), as these patients were excluded from the registrational trial.

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

In the SPARTAN study, with a median exposure of 32.9 months for ERLYAND and 11.5 months for placebo, ischaemic cerebrovascular disorders occurred in 4% of patients treated with ERLYAND and 1% of patients treated with placebo (see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). In the TITAN study, ischaemic cerebrovascular disorders occurred in a similar proportion of patients in the ERLYAND (1.5%) and placebo (1.5%) groups. Across the SPARTAN and TITAN studies, 2 patients (0.2%) treated with ERLYAND and no patients treated with placebo died from an ischaemic cerebrovascular disorder.

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

Adverse events indicative of ischaemic heart disease and cardiac failure were reported more frequently in patients treated with ERLYAND in the registrational study, including 3 fatal myocardial infarctions (see section **4.8 Description of selected adverse events)**.

QT interval prolongation

In patients with a history of QT prolongation, who are taking concomitant medications that may prolong the QT interval, or who have other risk factors for torsades de pointes, consider electrocardiogram (ECG) and electrolyte monitoring.

In a dedicated QT study in patients with CRPC taking ERLYAND 240 mg once daily plus ADT, based on the longest QTcF change at any time for each patient at steady-state, the mean maximum QTcF change from baseline (ΔQTcF) was 20.2 msec (upper 90% CI bound 23.7 msec). Pharmacokinetic and pharmacodynamic analysis showed a concentration-dependent increase in QTcF with apalutamide and N-desmethyl apalutamide. See **section 5.1 Pharmacodynamic effects**.

Use in hepatic impairment

See **section 4.2 Dose and Method of Administration Dosage adjustment in Hepatic insufficiency**

Use in renal impairment

See **section 4.2 Dose and Method of Administration Dosage adjustment in Renal insufficiency**

Use in the elderly

Of the 1327 patients who received ERLYAND 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. In patients aged ≥75 years, the incidence of severe (grade 3 or higher) adverse events was 52% in the ERLYAND arm and 38% in the placebo arm. Falls, fall-related injuries and hypothyroidism occurred more frequently in patients older than 75 years, and all patients who died from adverse reactions were over 75 years of age.

No overall differences in effectiveness between older patients and younger patients were observed.

See **section 4.2 Dose and Method of Administration Dosage adjustment Use in the elderly.**

Paediatric use

The safety and efficacy of ERLYAND in patients aged less than 18 years have not been established. No data are available (see **section 4.2 Dose and Method of Administration**).

4.5 Interactions with other medicines and other forms of interactions

Effects of other medicines on ERLYAND

CYP2C8 inhibitors

Apalutamide C_{max} decreased by 21% while AUC increased by 68% following co-administration of ERLYAND as a 240 mg single dose with gemfibrozil (a strong CYP2C8 inhibitor). Gemfibrozil is predicted to increase the steady-state apalutamide C_{max} 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 C_{max} increased by 19% and AUC by 23%.

No initial dose adjustment is necessary however, reduce the ERLYAND dose based on tolerability [see **section 4.2 Adverse effects**]. Mild or moderate inhibitors of CYP2C8 are not expected to affect the exposure of apalutamide.

CYP3A4 inhibitors

Apalutamide C_{max} decreased by 22% while AUC was similar following co-administration of ERLYAND as a 240 mg single dose with itraconazole (a strong CYP3A4 inhibitor). Ketoconazole (a strong CYP3A4 inhibitor) is predicted to increase the steady-state apalutamide C_{max} by 38% and AUC by 51%. For the active moieties, the predicted steady-state C_{max} increased by 23% and AUC by 28%.

No initial dose adjustment is necessary however, reduce the ERLYAND dose based on tolerability (see **section 4.2 Adverse effects**). Mild or moderate inhibitors of CYP3A4 are not expected to affect the exposure of apalutamide.

CYP3A4/CYP2C8 inducers

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

Acid lowering agents

Apalutamide is not ionisable under relevant physiological pH conditions, therefore acid lowering agents (e.g. proton pump inhibitors, H_2-receptor antagonists, antacids) 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.

Effects of ERLYAND on other medicines

Effect of ERLYAND on drug metabolising enzymes

CYP enzymes

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

In humans, ERLYAND is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9. Co-administration of ERLYAND 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). ERLYAND did not cause clinically meaningful changes in exposure to pioglitazone (a CYP2C8 substrate).

Concomitant use of ERLYAND with medications that are primarily metabolised 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 Normalised Ratio (INR) during ERLYAND treatment.

UGT

Apalutamide may induce UDP-glucuronosyl transferase (UGT).

Concomitant administration of ERLYAND 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 ERLYAND and evaluate for loss of efficacy (see **Section 4.4 Hypothyroidism**).

Effect of apalutamide on drug transporters

P-gp, BCRP and OATP1B1

Apaluatmide 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. Co-administration of ERLYAND 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_{max}.

Concomitant use of ERLYAND 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 ERLYAND and evaluate for loss of efficacy if medication is continued.

OCT2, OAT1, OAT3 and MATEs

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 OAT3 substrates.

Gonadotropin-releasing hormone (GnRH) analogue

In metastatic castration-sensitive prostate cancer (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.

Effects on Laboratory Tests

See **section 4.8 Undesirable effects.**

Laboratory test interference

Falsely elevated digoxin plasma level results with the chemiluminescent microparticle immunoassay (CMIA) have been identified in patients treated with apalutamide, independently of being treated with digoxin. Therefore, results of digoxin plasma levels obtained by CMIA should be interpreted with caution and confirmed by another type of assay before taking any action with digoxin doses.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy - Category D

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

ERLYAND may be harmful to a developing foetus. 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 ERLYAND.

Breast-feeding

ERLYAND is not indicated for use in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed infant, or the effect on milk production.

Fertility

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

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 (0.5 times the human exposure based on AUC) and ≥ 2.5 mg/kg/day in dogs (0.5 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 (0.5 times the human exposure based on AUC). Effects on male rats were reversible after 8 weeks from the last apalutamide administration.

4.7 Effect on ability to drive and use machinery

No studies on the effects of ERLYAND on the ability to drive or use machines have been performed. Patients with a history of seizures or other predisposing factors should be advised of the risk of driving or operating machines (see **section 4.4 Special warnings and precautions for use - Seizure).**

4.8 Undesirable effects

Because clinical trials are conducted under widely varying conditions, adverse event 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.

In studies of patients with mCSPC or nmCRPC who were using a GnRH analog, or were previously treated with orchiectomy, ERLYAND was administered at a dose of 240 mg daily.

Overall, 8 patients (1%) who were treated with ERLYAND died from adverse events. The reasons for death were infection (n=4), myocardial infarction (n=3), and cerebral haemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse event of cardiopulmonary arrest (n=1). ERLYAND was discontinued due to adverse events in 11% of patients, most commonly from rash (3%). Adverse events leading to dose interruption or reduction of ERLYAND occurred in 33% of patients; the most common (>1%) were rash, diarrhoea, fatigue, nausea, vomiting, hypertension, and haematuria. Serious adverse events occurred in 25% of ERLYAND -treated patients and 23% in patients receiving placebo. The most common serious adverse events (>2%) were fracture (3%) in the ERLYAND arm and urinary retention (4%) in the placebo arm.

Table 1 shows adverse events commonly (≥1/100 to <1/10) occurring in the ERLYAND arm in clinical studies that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLYAND arm compared to placebo.

Table 1: Adverse events in the clinical studies that commonly occurred in ERLYAND-treated patients, and with at least a 2% absolute increase in frequency compared to placebo.

	ERLYAND N=1327		**Placebo N=925**	
System/Organ Class	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Adverse event	**%**	**%**	**%**	**%**
General disorders and administration site conditions				
Fatigue[1,2]	26.2	1.1	18.7	0.8
Vascular disorders				
Hypertension	22.4	12.1	17.6	10.3
Hot flush	17.7	0	13.0	0
Cardiac disorders				
Ischemic heart disease[7]	4.0	1.7	2.1	1.1
Skin and subcutaneous tissue disorders				
Skin rash[3]	25.9	5.7	7.7	0.5
Pruritus[2]	8.1	0.2	3.2	0.1

Gastrointestinal disorders				
Diarrhoea	16.3	0.7	10.1	0.3
Nausea	18	0	16	0
Nervous system disorders				
Dysgeusia	5.6	0	1	0
Ischaemic cerebrovascular disorders[9]	3.0	1.2	1.3	0.4
Seizure	0.4	0.1	0.2	0
Injury, poisoning and procedural complications				
Fall[2]	13.1	1.5	8.0	0.8
Fracture[4]	10.5	2.3	5.7	0.9
Musculoskeletal and connective tissue disorders				
Arthralgia[2]	17.1	0.2	12.0	0.5
Muscle spasm	3.8	0	1.8	0
Investigations				
Weight decreased[2]	12.7	1.0	5.6	0.6
Endocrine disorders				
Hypothyroidism[8]	7.8	0	1.5	0
Metabolism and nutrition disorders				
Decreased appetite[5]	12	0.1	9	0
Peripheral oedema[6]	11	0	9	0
Hypercholesterolemia	5.7	0.2	1.1	0
Hypertriglyceridemia	3.7	0.8	1.1	0.3

[1] Includes fatigue and asthenia

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

[3] Includes 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, dermatitis and rash vesicular

[4] 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

[5] Includes appetite disorder, decreased appetite, early satiety, and hypophagia

[6] Includes peripheral oedema, generalised oedema, oedema, oedema genital, penile oedema, peripheral swelling, scrotal oedema, lymphoedema, swelling, and localised oedema

[7] 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

[8] Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine decreased, autoimmune thyroiditis, thyroxine free decreased, tri-iodothyronine decreased

[9] Includes transient ischaemic attack, cerebrovascular accident, cerebrovascular disorder, ischaemic 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 for the SPARTAN study with a median exposure of 32.9 months for ERLYAND and 11.5 months for placebo

Table 2: Laboratory abnormalities occurring in ≥15% of ERLYAND-treated patients and at a higher incidence than placebo (between arm difference >5% all grades) in SPARTAN,

	ERLYAND N=803		**Placebo N=398**	
Laboratory Abnormality	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Haematology				

Anaemia	70	0.4	64	0.5
Leukopenia	47	0.3	29	0
Lymphopenia	41	2	21	2
Chemistry				
Hypercholesterolaemia[1]	76	0.1	46	0
Hyperglycaemia[1]	70	2	59	1
Hypertriglyceridemia[1]	67	2	49	0.8
Hyperkalaemia	32	2	22	0.5

[1] Does not reflect fasting values

Description of selected adverse events

Falls and Fractures

In SPARTAN, a randomised study of patients with nmCRPC, falls were reported for 16% of subjects treated with ERLYAND versus 9% of subjects treated with placebo and were not associated with loss of consciousness or seizure. Non-pathological fracture was reported for 12% of subjects treated with ERLYAND and 7% of subjects treated with placebo. In half of these cases in both arms, a fall had occurred in the proceeding 7 days. Severity was grade 3-4 in 3% of patients treated with ERLYAND and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLYAND. Routine bone density assessment and treatment of osteoporosis with bone targeted agents were not performed in the SPARTAN study. In TITAN, a randomised study of patients with mCSPC, nonpathological fractures occurred in 6% of patients treated with ERLYAND and in 5% of patients treated with placebo. See **section 4.4 Special warnings and precautions for use.**

Seizure

In the SPARTAN study, two patients (0.2%) treated with ERLYAND experienced a seizure versus none in the placebo arm. Seizure occurred from 354 to 475 days after initiation of ERLYAND. 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 from the study. See **section 4.4 Special warnings and precautions for use**.

Hypothyroidism

In the combined data of two randomised, placebo-controlled studies, hypothyroidism was reported for 8% of subjects treated with ERLYAND and 2% of subjects treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. The median onset was Day 113. There were no grade 3 or 4 adverse events.

In patients who were already receiving thyroid replacement therapy, hypothyroidism occurred in 30% of subjects in the apalutamide arm and in 3% of subjects in the placebo arm. In subjects not previously receiving thyroid replacement therapy, hypothyroidism occurred in 7% of subjects treated with apalutamide and in 2% of subjects treated with placebo.

Thyroid replacement therapy was initiated in 7% of patients treated with ERLYAND. In patients who discontinued ERLYAND and had a reported event of hypothyroidism (n=14), the event resolved in 5 patients (36%). In patients who discontinued ERLYAND and had increased laboratory values for TSH (>5.5 mIU/L) (n=45), TSH levels returned to normal in 27 patients (60%). Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted. See **sections 4.4 Special warnings and precautions for use and 4.5 Effect of ERLYAND on drug metabolising enzymes.**

Skin Rash

In the combined data of two randomised, placebo-controlled clinical studies, skin rash associated with ERLYAND was most commonly described as macular or maculo-papular. Adverse events of

skin rash were reported for 26% of subjects treated with ERLYAND versus 8% of subjects treated with placebo. Grade 3 skin rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLYAND treatment (6%) versus placebo (0.5%). There were no reported events of drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) in clinical trials.

The onset of skin rash occurred at a median of 83 days of ERLYAND treatment and resolved in 78% of patients, within a median of 78 days from onset (range: 2 to 709 days). Rash was commonly managed with oral antihistamines, topical corticosteroids and 19% of subjects received systemic corticosteroids. Rash led to dose interruption in 28%, dose reduction in 14% and treatment discontinuation in 7% of cases. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLYAND.

Post marketing data

Adverse events identified during post-marketing experience with frequency category estimated from spontaneous reporting rates. The frequencies are provided according to the following convention:

Very common ≥ 1/10

Common ≥ 1/100 and < 1/10

Uncommon ≥ 1/1,000 and < 1/100

Rare ≥ 1/10,000 and < 1/1,000

Very rare < 1/10,000

Not known Cannot be estimated from the available data

System Organ Class: **Metabolism and nutrition disorders**

Decreased appetite Uncommon

System Organ Class: **Nervous system disorders**

Restless Legs Syndrome very rare

System Organ Class: **Respiratory, thoracic and mediastinal disorders**

Interstitial lung disease[a] Uncommon

System Organ Class: **Skin and subcutaneous tissue disorders**

Drug reaction with eosinophilia and systemic symptoms[a,b] Rare

Toxic epidermal necrolysis[a,b] Rare

Steven-Johnson syndrome [a,b] Rare

[a] The adverse reaction was not identified from clinical trials and the frequency was not known. Frequency is calculated by "Rule of 3."

[b] See section 4.4 Special Warnings and Precautions for Use

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Treatment

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Apalutamide is an orally administered, 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. A major metabolite, N-desmethyl apalutamide, exhibited one-third the *in vitro* activity of apalutamide in an *in vitro* transcriptional reporter assay. In mouse models of prostate cancer, apalutamide administration causes decreased tumour cell proliferation and increased apoptosis leading to tumour growth inhibition and regression.

Pharmacodynamic effects

Prostate Specific Antigen (PSA) Reduction

Apalutamide 240 mg daily in addition to ADT in patients with mCSPC (TITAN) reduced PSA to undetectable levels (<0.2 ng/mL) in 68% of patients compared to 32% of patients taking ADT alone. Median time to undetectable PSA for patients receiving apalutamide in combination with ADT was 1.9 months. Apalutamide in combination with ADT led to a ≥ 50% PSA reduction from baseline at any time in 90% of patients compared to 55% of patients taking ADT alone.

Apalutamide 240 mg daily in addition to ADT in patients with nmCRPC (SPARTAN) reduced PSA to undetectable levels (<0.2 ng/mL) in 38% of patients compared to no patients (0%) taking ADT alone. Median time to undetectable PSA for patients receiving apalutamide in combination with ADT was 2.8 months. Apalutamide in combination with ADT led to a ≥ 50% PSA reduction from baseline at any time in 90% of patients compared to 2.2% of patients taking ADT alone.

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of apalutamide have not been fully characterised.

Effect on $GABA_A$-gated chloride channel

$GABA_A$ inhibition is an off-target activity of both apalutamide and N-desmethyl apalutamide. This is considered the mechanism for the seizures/convulsions observed at high doses in toxicology studies in animals.

Effect on QT/QTc interval and cardiac electrophysiology

Apalutamide and N-desmethyl apalutamide inhibit the hERG K+ channel with an IC_{50} below steady-state C_{max} at the recommended dose. In a dedicated QT study in men with CRPC administered apalutamide 240 mg once daily plus ADT, based on the longest QTcF change at any time for each patient at steady-state, the mean maximum QTcF change from baseline (ΔQTcF) was 20.2 msec (upper 90% CI bound 23.7 msec). Pharmacokinetic and pharmacodynamic analysis showed a concentration-dependent increase in QTcF with apalutamide and N-desmethyl apalutamide. See **section 4.4 Special warnings and precautions for use**.

Clinical trials

The efficacy of ERLYAND was established in two randomised placebo-controlled multicentre Phase 3 clinical studies of subjects with mCSPC (TITAN) or nmCRPC (SPARTAN). All subjects in these studies received concomitant GnRH analogue or had prior bilateral orchiectomy.

TITAN: Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN (56021927PCR3002) was a randomised, double-blind, placebo-controlled, multinational, multicentre clinical trial in which 1052 subjects with mCSPC were randomised (1:1) to receive either ERLYAND 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 analogue 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 of subjects had high-volume disease and 37% had low-volume disease. Sixteen percent 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 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 ERLYAND), 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 ERLYAND (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 3 and Figures 1 and 2.

Table 3: Summary of Efficacy Results – Intent-to-treat mCSPC Population (TITAN)

Endpoint	ERLYAND N=525	Placebo N=527
Primary Overall Survival[a]		
Deaths (%)	83 (16%)	117 (22%)
Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[b]	0.671 (0.507, 0.890)	
p-value[c]	0.0053	
Updated Overall Survival[d]		
Deaths (%)	170 (32%)	235 (45%)
Median, months (95% CI)	NE (NE, NE)	52 (42, NE)
Hazard ratio (95% CI)[b]	0.651 (0.534, 0.793)	
p-value[c]	<0.0001	
Overall Survival by IPCW		
Median, months (95% CI)	NE	40
Hazard ratio (95% CI)	0.520 (0.423, 0.639)	
Radiographic Progression-free Survival		
Disease progression or death (%)	134 (26%)	231 (44%)
Median, months (95% CI)	NE (NE, NE)	22.08 (18.46, 32.92)
Hazard ratio (95% CI)[b]	0.484 (0.391, 0.600)	

p-value[c]	<0.0001

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

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

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

[d] Median follow up time of 44 months

NE=Not Estimable

IPCW=Inverse pProbability of cCensoring wWeighting analysis

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

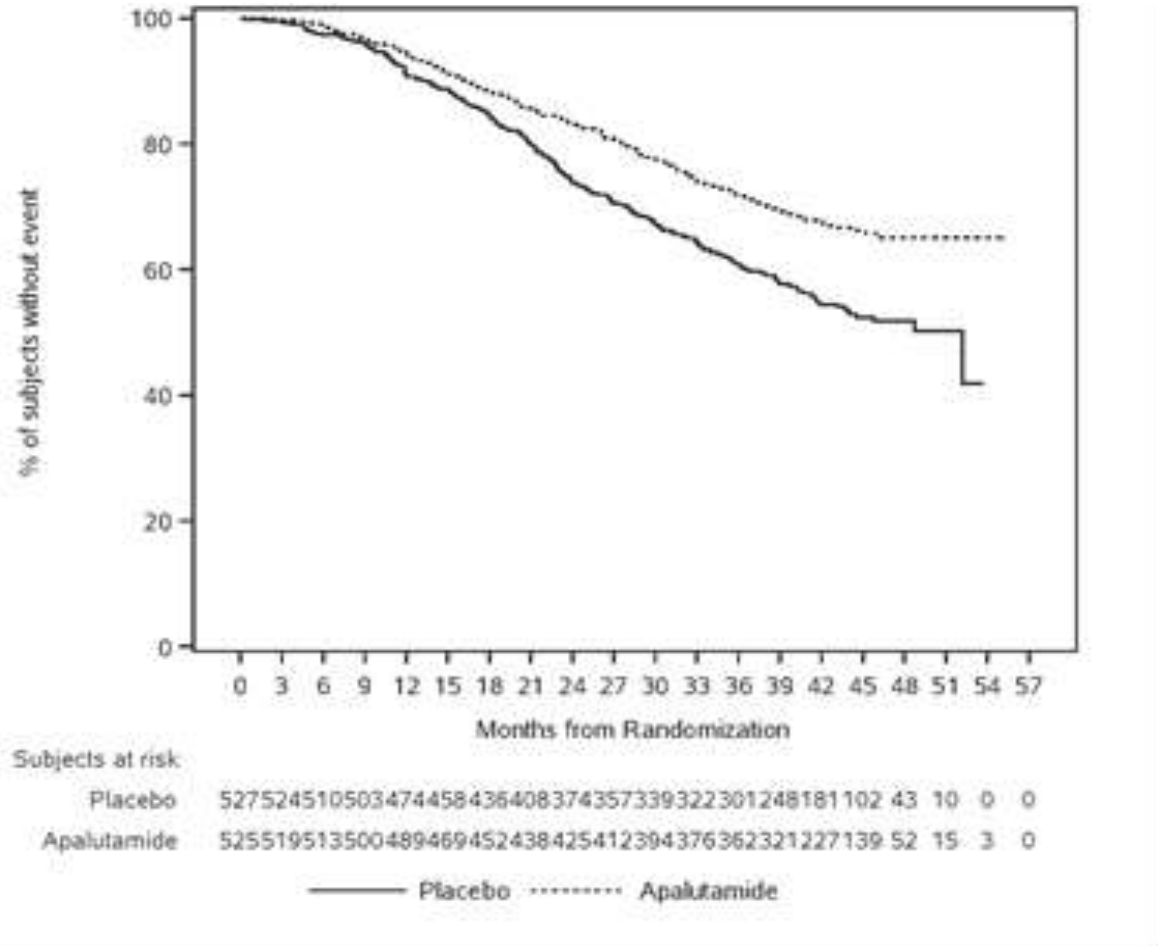
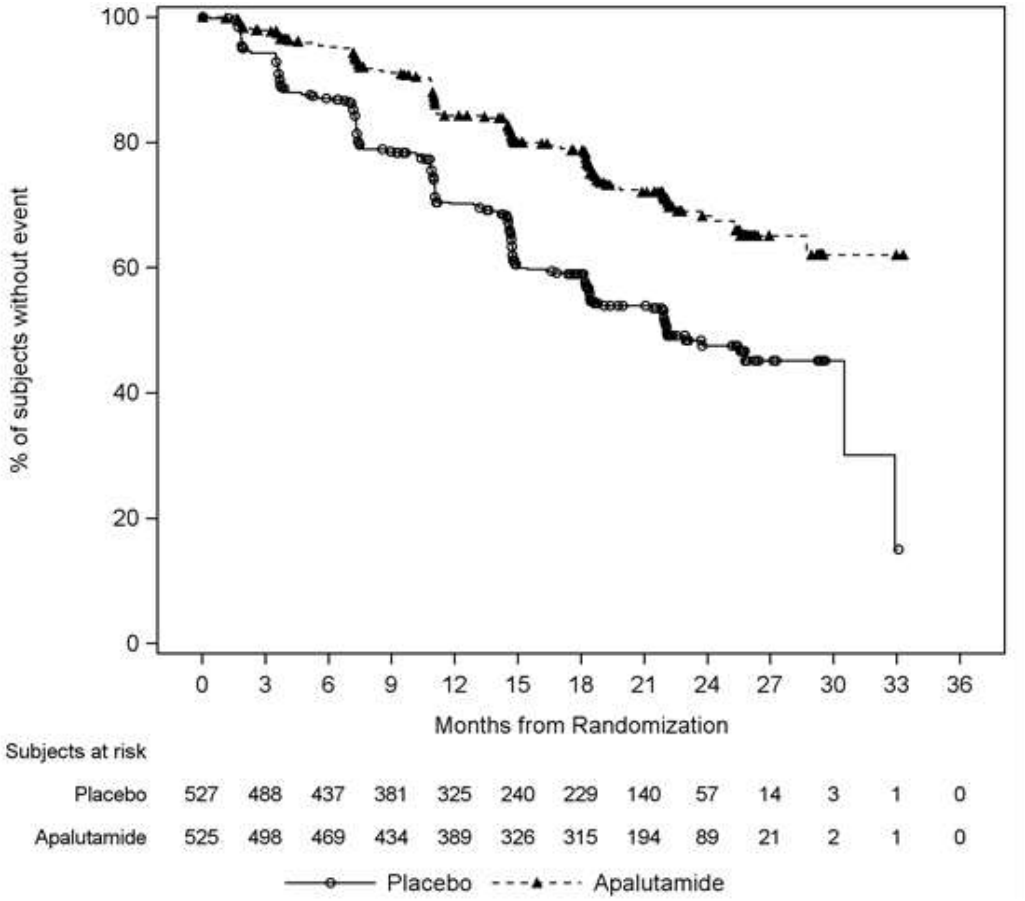


Figure 2: **Kaplan-Meier Plot of Radiographic Progression-Free Survival (rPFS); Intent-to-treat mCSPC Population (TITAN)**



Treatment with ERLYAND 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 ERLYAND to ADT. The addition of ERLYAND 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)

SPARTAN (Study ARN 509-003) was a multicentre, double-blind, randomised, placebo-controlled clinical trial in which 1207 subjects with nm-CRPC were randomised 2:1 to receive either ERLYAND orally at a dose of 240 mg once daily (n=806) or placebo once daily (n=401). All patients received a concomitant gonadotropin-releasing hormone (GnRH) analogue, or had a bilateral orchiectomy. Patients were required to have a PSADT ≤ 10 months and confirmation of non-metastatic disease by blinded independent central review (BICR). Patients with pelvic lymph nodes <2 cm in short axis (N1) located below the iliac bifurcation could enter the SPARTAN study. Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT; >6 months vs ≤ 6 months), the use of bone-sparing agents, and presence of locoregional disease. Systemic corticosteroids were not allowed at study entry. PSA results were blinded and were not used for treatment discontinuation. Subjects randomised to either arm discontinued treatment for disease progression confirmed by BICR, initiation of new treatment, unacceptable toxicity or withdrawal. Upon development of distant metastatic disease, subjects were offered abiraterone acetate 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. In the SPARTAN study, metastases were detected by technetium-99m bone scan, CT or MRI of the chest, abdomen and pelvis. Seventy-three percent (73%) of subjects had received prior treatment with a first-generation anti-androgen; 69% of subjects had received bicalutamide and 10% of subjects had received flutamide. All subjects enrolled had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) performance status score of 0 or 1 at study entry. Among the patients who discontinued study treatment (N = 279 for placebo and N = 314 for ERLYAND), a greater proportion (80%) of patients treated with placebo received subsequent therapy compared to patients treated with ERLYAND (56%). Locoregional-only progression occurred in 2% of patients overall.

The primary efficacy outcome was metastasis-free survival (MFS), defined as the time from randomisation 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, and overall survival (OS).

A statistically significant improvement in MFS was demonstrated in patients randomised to receive ERLYAND compared with patients randomised to receive placebo. Consistent results were observed across patient subgroups including PSADT (≤ 6 months or > 6 months), use of a prior bone-sparing agent (yes or no), and locoregional disease (N0 or N1). The major efficacy outcome was supported by statistically significant improvements in TTM, PFS, and time to symptomatic progression. In addition, overall survival (OS) and time to initiation of cytotoxic chemotherapy were also significantly improved. (see Table 4 for Interim Analysis and Table 5 for Final Analysis).

The efficacy results and the above supporting results from SPARTAN are summarised in Figure 3 to Figure 8 and Table 4 and Table 5.

Figure 3: Kaplan-Meier Metastasis-Free Survival (MFS) Curve in SPARTAN Study (ARN 509-003)

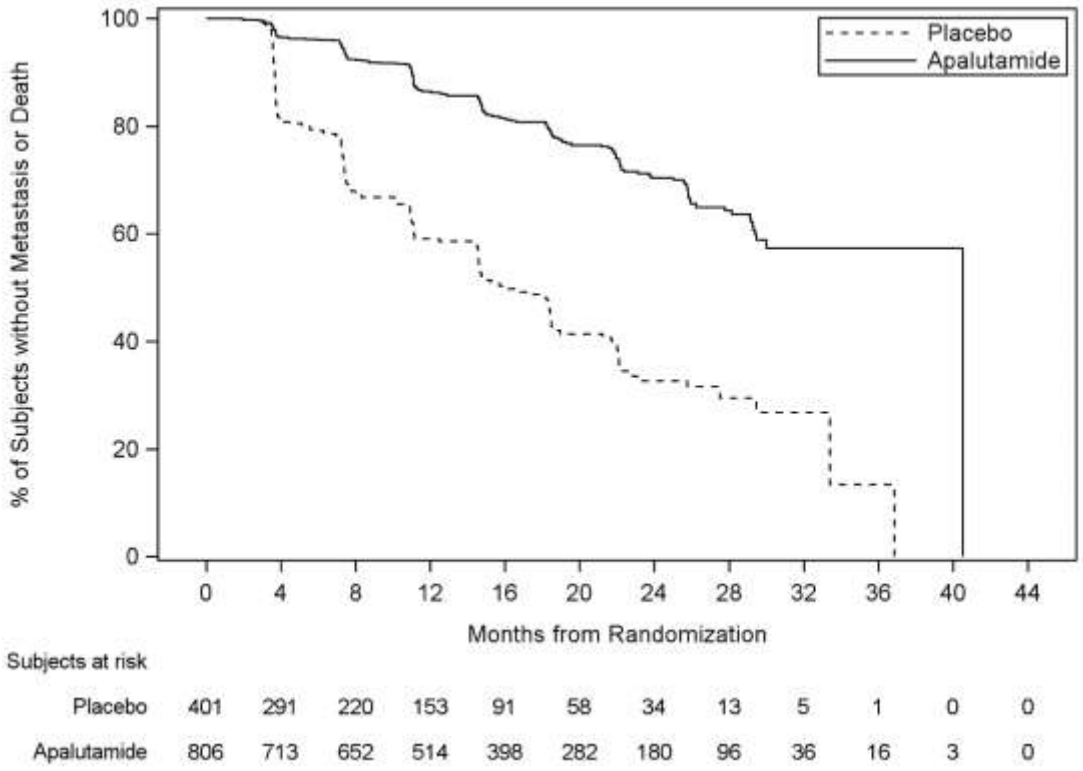


Table 4: Summary of Efficacy Analysis SPARTAN Study (ARN-509-003) at Interim Analysis[1]

Endpoint	ERLYAND (n=806) Median (months)	Placebo (n=401) Median (months)	HR (95% CI) p value[2]
Metastasis Free Survival (MFS)[3]	40.5	16.2	0.28 (0.23-0.35) < 0.0001
Time to Metastasis (TTM)[3]	40.5	16.6	0.27 (0.22-0.34) < 0.0001
Progression-free Survival (PFS)[3]	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[4]
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

1 Median follow-up time of 20.3 months

2 p value from stratified log-rank test

3 Assessed by BICR and unchanged for final analysis

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

Table 5: Summary of Efficacy Analysis (SPARTAN) at Final Analysis[1]

Endpoint	ERLYAND (N=806) Median (months)	Placebo (N=401) Median (months)	HR (95% CI) p value[2]
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[3]
Time to Initiation of Cytotoxic Chemotherapy	NR	NR	0.63 (0.49-0.81) 0.0002

NR = Not reached

1 Median follow-up time of 52.0 months

2 p value from stratified log-rank test

3 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 ERLYAND significantly decreased the risk of symptomatic progression by 55% compared with placebo (see Table 4 and Figure 4). The final analysis corroborated that treatment with ERLYAND decreased the risk of symptomatic progression by 43% compared with placebo. The observed p-value (0.00000356) crossed the Obrien-Fleming (OBF) efficacy boundary (p=0.00008) for significance. (see Table 4, 5 and Figure 4, 5) .

Figure 4: **Kaplan-Meier Plot of Time to Symptomatic Progression; Intent-to-treat Population in (SPARTAN) at Interim Analysis**

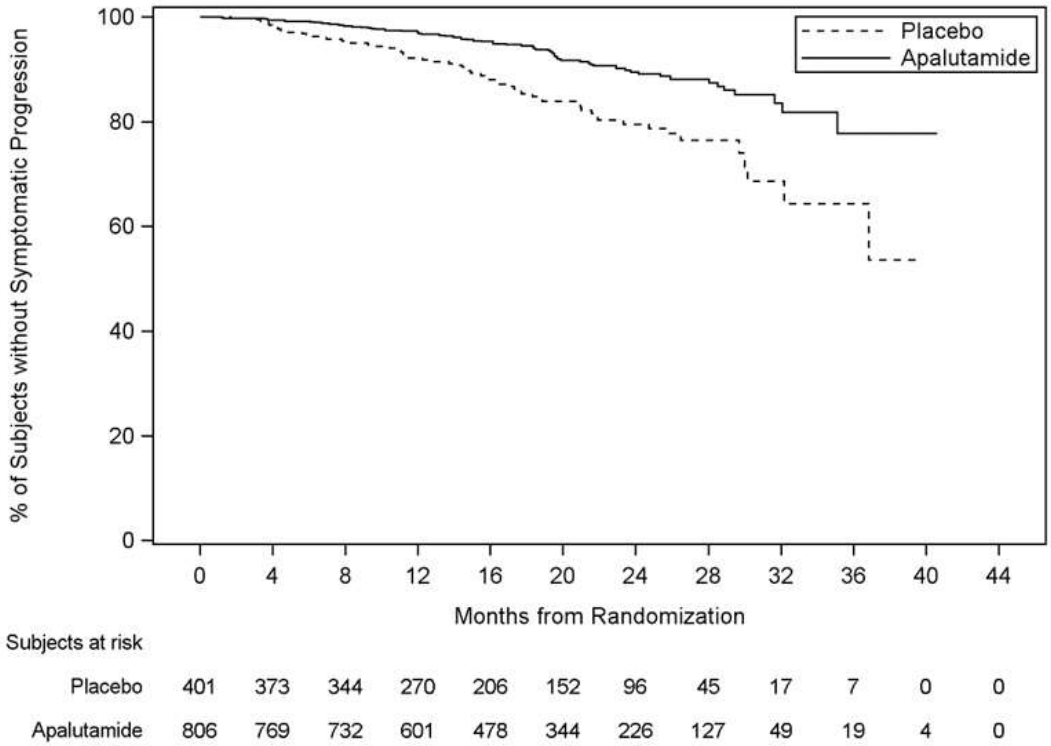
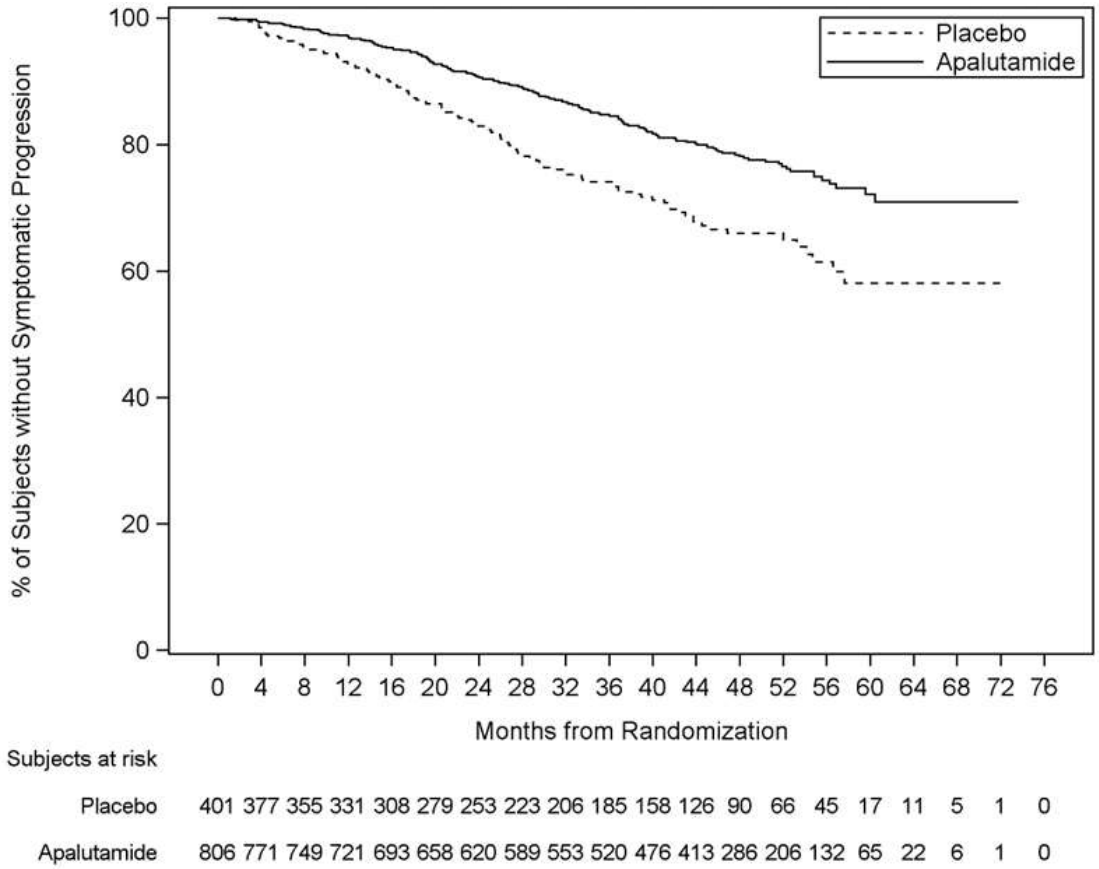
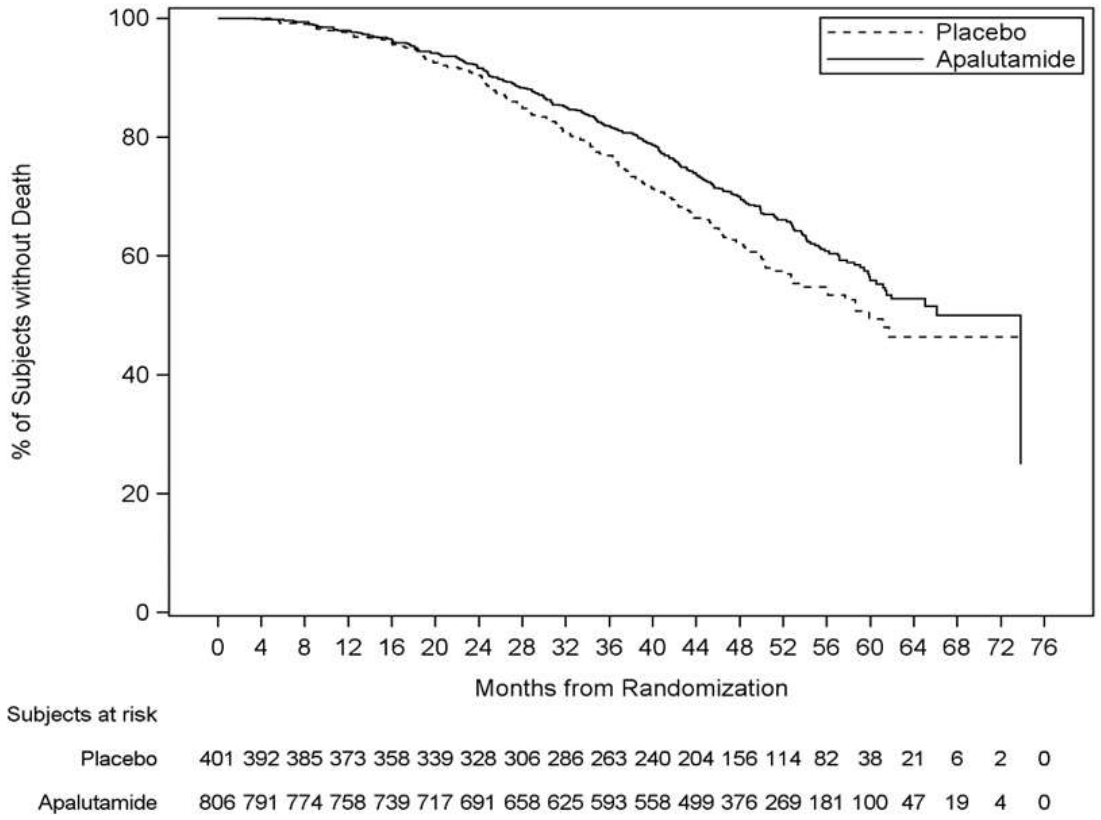


Figure 5: **Kaplan-Meier Plot of Time to Symptomatic Progression; Intent-to-treat Population in (SPARTAN) at Final Analysis**



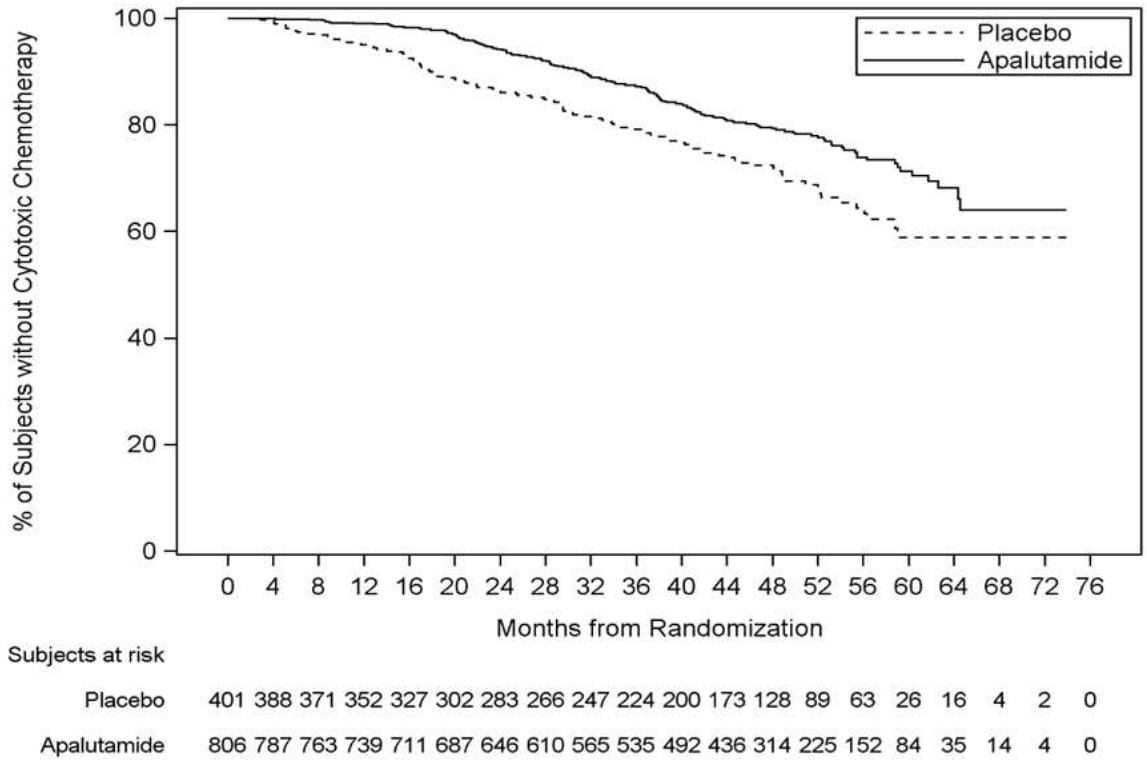
At the interim analysis, with median follow-up time of 20.3 months , the OS Overall survival was longer for ERLYAND than placebo with a hazard ratio (HR) of 0.700 (95% CI: 0.472, 1.038). The p-value was 0.0742 which did not meet the pre-specified value for statistical significance. At the final analysis, with median follow-up time of 52.0 months, results showed that treatment with ERLYAND 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 ERLYAND arm and 59.9 months for the placebo arm. The pre specified alpha boundary (p≤0.046) for this final analysis was crossed and statistical significance was achieved.

Figure 6: Kaplan-Meier Plot of Time to Overall Survival (OS); Intent-to-treat Population in (SPARTAN) at Final Analysis



At the final analysis, treatment with ERLYAND 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 statisically significant improvement for ERLYAND versus placebo. The median time to the initiation of cytotoxic chemotherapy was not reached for either treatment arm.

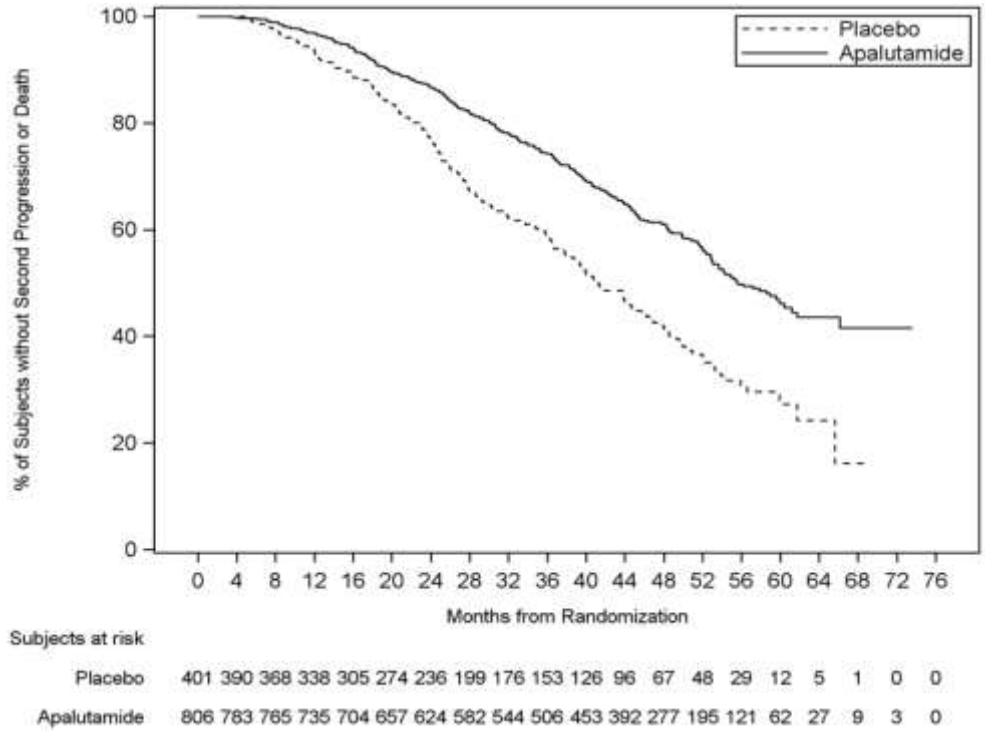
Figure 7: Kaplan-Meier Plot of Time to Initiation of Cytotoxic Chemotherapy: Intent-to-treat Population in (SPARTAN) at Final Analysis



If eligible and without evidence of disease progression, subjects treated with placebo were given the opportunity to cross-over to treatment with ERLYAND at time of unblinding. After unblinding, 19% of the randomized placebo population crossed over to ERLYAND. Of all the randomized subjects, a greater proportion of subjects in the placebo arm received subsequent therapy (285/401, 71%) compared with the ERLYAND 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 ERLYAND 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 ERLYAND versus placebo (HR=0.565; 95% CI: 0.471, 0.677; p<0.0001).

Figure 8: 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 ERLYAND to placebo and a small but not clinically meaningful difference in change from baseline in favour of ERLYAND observed in the analysis of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score and subscales.

5.2 Pharmacokinetic properties

Apalutamide pharmacokinetic parameters are presented as the mean (coefficient of variation; CV%) unless otherwise specified. Following repeat once-daily dosing, apalutamide exposure (C_{max} and AUC) increased in a dose-proportional manner across the dose range of 30 mg 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. At steady-state, apalutamide C_{max} was 6 µg/mL (28%) and AUC was 100 µg.h/mL (32%). 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 major active metabolite (N-desmethyl apalutamide) C_{max} and was 5.9 µg/mL (18%) and AUC was 124 µg.h/mL (19%). N-desmethyl apalutamide is characterised by a flat concentration-time profile at steady-state with a mean peak-to-trough ratio of 1.27. The 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 contributes to the clinical activity of apalutamide.

Absorption

Mean absolute oral bioavailability is approximately 100%. Median time to achieve peak plasma concentration (t_{max}) was 2 hours (range: 1 to 5 hours).

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.

Following oral administration of 4x60 mg apalutamide tablets dispersed in applesauce, Cmax and AUC were 28% and 5% higher, respectively, when compared to administration of 4 intact 60 mg tablets under fasting condition, see **section 4.2 Dosage and Method of Administration.**

Distribution

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

Apalutamide is 96% (and N-desmethyl apalutamide is 95%) bound to plasma proteins, with no concentration dependency. Studies in rodents and dogs indicate that apalutamide and N-desmethyl apalutamide can cross the blood brain barrier.

Metabolism

Metabolism is the main route of elimination of apalutamide. It is metabolised primarily by CYP2C8 and CYP3A4 to form N-desmethyl apalutamide. Apalutamide and N-desmethyl apalutamide are further metabolised by carboxylesterase to form an inactive carboxylic acid metabolite. 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 (45%), N-desmethyl apalutamide (44%), and an inactive carboxylic acid metabolite (3%) represented most of the total ^{14}C-AUC following a single oral administration of ^{14}C-labeled apalutamide 240 mg.

Elimination

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 faeces (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

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 renal impairment (eGFR 30-89 mL/min/1.73m^2, estimated by the modification of diet in renal disease [MDRD] equation) 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/1.73m^2) or severe hepatic impairment (Child-Pugh Class C) on apalutamide pharmacokinetics is unknown.

5.3 Preclinical safety data

Carcinogenicity

Apalutamide was not carcinogenic in a 6-month study in the male transgenic (Tg.rasH2) mouse.

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

Genotoxicity

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

In a developmental toxicity study in the rat, apalutamide affected pregnancy including survival. Effects on the external genitalia were observed though apalutamide was not teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal anhydrous silica
Croscarmellose sodium
Hypromellose acetate succinate
Magnesium stearate
Microcrystalline cellulose
Silicified microcrystalline cellulose

Film-coat

Opadry® II 85F210036 Green

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 mg tablets have a shelf-life of 3 years. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Keep out of the sight and reach of children. Store in the original container, protect from light and moisture.

6.5 Nature and contents of container

ERLYAND 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.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

17 October 2019

10. DATE OF REVISION OF THE TEXT

3 March 2026

Summary table of changes

Section changes	Summary of new information
4.5	Add new subsection about digoxin test interference