Summary of Product Characteristics

1. Name of the Drug Product

Apalunix Tablet

2. Qualitative and Quantitative Composition

SN	Name of Materials	Specification	Quantity/ Tablet	Function
	ACTIVE SUBSTANCE:			
01	Apalutamide*	INN	60.000 mg	Active Material
	EXCIPIENTS:			
02	Hypromellose Acetate Succinate	USP-NF	15.000 mg	Binder
03	Sodium Starch Glycolate (Primojel)	BP	15.000 mg	Disintegrant
04	Croscarmellose Sodium	BP	12.000 mg	Disintegrant
05	Sodium Lauryl Sulphate	BP	3.000 mg	Solubilizer
06	Magnesium Stearate	BP	3.000 mg	Lubricant
07	Colloidal Anhydrous Silica (Aerosil 200)	BP	2.250 mg	Glidant
08	Microcrystalline Cellulose (Avicel PH 102)**	BP	189.750 mg	Diluent
	COATING MATERIALS:			
09	Opadry II White (85G68918)	Ph. Grade	7.875 mg	Coating Agent
10	Opadry II Yellow (85G52259)	Ph. Grade	2.625 mg	Coating Agent
11	Purified Water ***	USP	73.500 mg	Solvent

Note:

* Based on 100% potency

** Calculated amount of material

*** Solvent does not appear in the final product

3. Pharmaceutical Form

Film Coated Tablet

4. Clinical particulars

4.1 Therapeutic indications

Apalutamide is indicated:

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

- in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).

4.2 Posology and method of administration

Treatment with apalutamide should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer.

Posology

The recommended dose is 240 mg (four 60 mg tablets) as an oral single daily dose.

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

If a dose is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra tablets should not be taken to make up the missed dose.

If a ≥ Grade 3 toxicity or an intolerable adverse reaction is experienced by the patient, dosing should be held rather than permanently discontinuing treatment until symptoms improve to ≤ Grade 1 or original grade, then should be resumed at the same dose or a reduced dose (180 mg or 120 mg), if warranted. For the most common adverse reactions.

Special populations

Elderly

No dose adjustment is necessary for elderly patients.

Renal impairment

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

Caution is required in patients with severe renal impairment as apalutamide has not been studied in this patient population. If treatment is started, patients should be monitored for the adverse reactions and dose reduce as per Posology and method of administration.

Hepatic impairment

No dose adjustment is necessary for patients with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively).

Apalutamide is not recommended in patients with severe hepatic impairment as there are no data in this patient population and apalutamide is primarily hepatically eliminated.

Paediatric population

There is no relevant use of apalutamide in the paediatric population.

Method of administration

Oral use.

The tablets should be swallowed whole and can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Women who are or may become pregnant

4.4 Special warnings and precautions for use

Seizure

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

In two randomised studies (SPARTAN and TITAN), seizure occurred in 0.4% of patients receiving apalutamide and in 0.2% of patients treated with placebo. These studies excluded patients with a history of seizure or predisposing factors for seizure.

There is no clinical experience in re-administering Apalutamide to patients who experienced a seizure.

Falls and fractures

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

Ischaemic heart disease

Ischaemic heart disease, including events leading to death, occurred in patients treated with apalutamide. The majority of patients had cardiac risk factors. Patients should be monitored for signs and symptoms of ischaemic heart disease and management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidaemia should be optimised as per standard of care.

Concomitant use with other medicinal products

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

Co-administration of apalutamide with warfarin and coumarin-like anticoagulants should be avoided. If Apalutamide is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

Recent cardiovascular disease

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

appropriate, after initiating Apalutamide for these conditions according to established treatment guidelines.

Androgen deprivation therapy may prolong the QT interval

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

4.5 Interaction with other medicinal products and other forms of interaction

The elimination of apalutamide and formation of its active metabolite, N-desmethyl apalutamide, is mediated by both CYP2C8 and CYP3A4 to a similar extent at steady-state. No clinically meaningful changes in their overall exposure is expected as a result of drug interaction with inhibitors or inducers of CYP2C8 or CYP3A4. Apalutamide is an inducer of enzymes and transporters and may lead to an increase in elimination of many commonly used medicinal products.

Potential for other medicinal products to affect apalutamide exposures

Medicinal products that inhibit CYP2C8

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

Medicinal products that inhibit CYP3A4

CYP3A4 plays a role in the elimination of apalutamide and in the formation of its active metabolite. In a drug-drug interaction study, the C_{max} of apalutamide decreased by 22% while AUC was similar following co-administration of Apalutamide as a 240 mg single dose with itraconazole (strong CYP3A4 inhibitor). For the active moieties (sum of apalutamide plus the potency adjusted active metabolite), C_{max} decreased by 22% while AUC was again similar. No initial dose adjustment is necessary when Apalutamide is co-administered with a strong inhibitor of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) however, a reduction of the Apalutamide dose based on tolerability should be considered. Mild or moderate inhibitors of CYP3A4 are not expected to affect the exposure of apalutamide.

Medicinal products that induce CYP3A4 or CYP2C8

The effects of CYP3A4 or CYP2C8 inducers on the pharmacokinetics of apalutamide have not been evaluated *in vivo*. Based on the drug-drug interaction study results with strong CYP3A4 inhibitor or strong CYP2C8 inhibitor, CYP3A4 or CYP2C8 inducers are not expected to have clinically relevant effects on the pharmacokinetics of apalutamide and the active moieties therefore no dose adjustment is necessary when Apalutamide is co-administered with inducers of CYP3A4 or CYP2C8.

Potential for apalutamide to affect exposures to other medicinal products

Apalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites.

Drug metabolising enzymes

In vitro studies showed that apalutamide and N-desmethyl apalutamide are moderate to strong CYP3A4 and CYP2B6 inducers, are moderate inhibitors of CYP2B6 and CYP2C8, and weak inhibitors of CYP2C9, CYP2C19, and CYP3A4. Apalutamide and N-desmethyl apalutamide do not affect CYP1A2 and CYP2D6 at therapeutically relevant concentrations. The effect of apalutamide on CYP2B6 substrates has not been evaluated *in vivo* and the net effect is presently unknown. When substrates of CYP2B6 (e.g., efavirenz) are administered with Apalutamide, monitoring for an adverse reaction and evaluation for loss of efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations.

In humans, apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9. In a drug-drug interaction study using a cocktail approach, co-administration of apalutamide with single oral doses of sensitive CYP substrates resulted in a 92% decrease in the AUC of midazolam (CYP3A4 substrate), 85% decrease in the AUC of omeprazole (CYP2C19 substrate), and 46% decrease in the AUC of S-warfarin (CYP2C9 substrate). Apalutamide did not cause clinically meaningful changes in exposure to the CYP2C8 substrate. Concomitant use of Apalutamide with medicinal products that are primarily metabolised by CYP3A4 (e.g., darunavir, felodipine, midazolam, simvastatin), CYP2C19 (e.g., diazepam, omeprazole), or CYP2C9 (e.g., warfarin, phenytoin) can result in lower exposure to these medicinal products. Substitution for these medicinal products is recommended when possible or evaluation for loss of efficacy should be performed if the medicinal product is continued. If given with warfarin, INR should be monitored during Apalutamide treatment.

Induction of CYP3A4 by apalutamide suggests that UDP-glucuronosyl transferase (UGT) may also be induced via activation of the nuclear pregnane X receptor (PXR). Concomitant administration of Apalutamide with medicinal products that are substrates of UGT (e.g., levothyroxine, valproic acid) can result in lower exposure to these medicinal products. When substrates of UGT are co-administered with Apalutamide, evaluation for loss of efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations.

Drug transporters

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. A drug-drug interaction study using a cocktail approach showed that co-administration of apalutamide with single oral doses of sensitive transporter substrates resulted in a 30% decrease in the AUC of fexofenadine (P-gp substrate) and 41% decrease in the AUC of rosuvastatin (BCRP/OATP1B1 substrate) but had no impact on C_{max}. Concomitant use of Apalutamide with medicinal products that are substrates of P-gp (e.g., colchicine, dabigatran etexilate, digoxin), BCRP or OATP1B1 (e.g., lapatinib, methotrexate, rosuvastatin, repaglinide) can result in lower exposure of these medicinal products. When substrates of P-gp, BCRP or OATP1B1 are co-administered with Apalutamide, evaluation for loss of efficacy of the substrate should be

performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations.

Based on *in vitro* data, inhibition of organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3) and multidrug and toxin extrusions (MATEs) by apalutamide and its N-desmethyl metabolite cannot be excluded. No *in vitro* inhibition of organic anion transporter 1 (OAT1) was observed.

GnRH Analog

In mHSPC subjects receiving leuprolide acetate (a GnRH analog), co-administration with apalutamide had no apparent effect on the steady-state exposure of leuprolide.

Medicinal products which prolong the QT interval

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Apalutamide with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g., quinidine, disopyramide) or class III (e.g., amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics (e.g. haloperidol), etc. should be carefully evaluated.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

It is not known whether apalutamide or its metabolites are present in semen. Apalutamide may be harmful to a developing foetus. For patients having sex with female partners of reproductive potential, a condom should be used along with another highly effective contraceptive method during treatment and for 3 months after the last dose of Apalutamide.

Pregnancy

Apalutamide is contraindicated in women who are or may become pregnant. Based on its mechanism of action, Apalutamide may cause foetal harm when administered during pregnancy. There are no data available from the use of Apalutamide in pregnant women. Animal reproductive studies have not been conducted with Apalutamide.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Apalutamide has no or negligible influence on the ability to drive and use machines. However, seizures have been reported in patients taking Apalutamide. Patients should be advised of this risk in regards to driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are fatigue (26%), skin rash (26% of any grade and 6% Grade 3 or 4), hypertension (22%), hot flush (18%), arthralgia (17%), diarrhoea (16%), fall (13%), and weight decreased (13%). Other important adverse reactions include fractures (11%) and hypothyroidism (8%).

Tabulated list of adverse reactions

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions identified in clinical studies

System organ class	Adverse reaction and frequency
Endocrine disorders	common: hypothyroidism*
Metabolism and nutrition disorders	common: hypercholesterolaemia, hypertriglyceridaemia
Nervous system disorders	common: dysgeusia
	uncommon: seizure[#]
Cardiac disorders	common: ischaemic heart disease[§]
	not known: QT prolongation
Vascular disorders	very common: hot flush, hypertension
Gastrointestinal disorders	very common: diarrhoea
Skin and subcutaneous tissue disorders	very common: skin rash**
	common: pruritus
Musculoskeletal and connective tissue disorders	very common: fracture[+], arthralgia
	common: muscle spasm
General disorders and administration site conditions	very common: fatigue
Investigations	very common: weight decreased
Injury, poisoning and procedural complications	very common: fall

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

[#] Includes tongue biting

** See "Skin rash" under "Description of selected adverse reactions"

[+] 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. See below.

[§] 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 ischaemia.

Description of selected adverse reactions

Skin rash

Skin rash associated with apalutamide was most commonly described as macular or maculo-papular. Skin rash included rash, rash maculo-papular, rash generalised, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular. Adverse reactions of skin rash were reported for 26% of patients treated with apalutamide. Grade 3 skin rashes (defined as covering > 30% body surface area [BSA]) were reported with apalutamide treatment in 6% of patients.

The median days to onset of skin rash was 83 days. Seventy-eight percent of patients had resolution of rash with a median of 78 days to resolution. Medicinal products utilised included topical corticosteroids, oral anti-histamines, and 19% of patients received systemic corticosteroids. Among patients with skin rash, dose interruption occurred in 28% and dose reduction occurred in 14%. Skin rash recurred in 59% of patients who had dose interruption. Skin rash led to apalutamide treatment discontinuation in 7% of patients who experienced skin rash.

Falls and fractures

In Study ARN-509-003, fracture was reported for 11.7% of patients treated with apalutamide and 6.5% of patients treated with placebo. Half of the patients experienced a fall within 7 days before the fracture event in both treatment groups. Falls were reported for 15.6% of patients treated with apalutamide *versus* 9.0% of patients treated with placebo.

Ischaemic heart disease

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

Hypothyroidism

Hypothyroidism was reported for 8% of patients treated with apalutamide and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. There were no grade 3 or 4 adverse events. Hypothyroidism occurred in 30% of patients already receiving thyroid replacement therapy in the apalutamide arm and in 3% of patients in the placebo arm. In patients not receiving thyroid replacement therapy, hypothyroidism occurred in 7% of patients treated with apalutamide and in 2% of patients treated with placebo. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Ireland

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, anti-androgens.

ATC code: L02BB05

Mechanism of action

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

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. At steady-state, the maximum mean QTcF change from baseline was 12.4 ms (2-sided 90% upper CI: 16.0 ms). An exposure-QT analysis suggested a concentration-dependent increase in QTcF for apalutamide and its active metabolite.

Clinical efficacy and safety

The efficacy and safety of apalutamide has been established in two Phase 3 randomised, placebo-controlled studies, Study ARN-509-003 (nmCRPC) and 56021927PCR3002 (mHSPC).

TITAN: Metastatic Hormone-sensitive Prostate Cancer (mHSPC)

TITAN was a randomised, double-blind, placebo-controlled, multinational, multicenter clinical trial in which 1052 patients with mHSPC were randomised (1:1) to receive either apalutamide orally at a dose of 240 mg once daily (N = 525) or placebo once daily (N = 527). All patients were required to have at least one bone metastasis on Technetium ^{99m} bone scan. Patients were excluded if the site of metastases was limited to either the lymph nodes or viscera (e.g., liver or lung). All patients in the TITAN trial received concomitant GnRH analog or had prior bilateral

orchiectomy. Around 11% of patients received prior treatment with docetaxel (maximum of 6 cycles, last dose ≤2 months prior to randomisation and maintained response prior to randomisation). The exclusion criteria included known brain metastases; prior treatment with other next generation anti-androgens (eg, enzalutamide), CYP17 inhibitors (eg, abiraterone acetate), immunotherapy (eg, sipuleucel-T), radiopharmaceutical agents or other treatments for prostate cancer; or history of seizure or condition that may predispose to seizure. Patients were stratified by Gleason score at diagnosis, prior docetaxel use, and region of the world. Patients with both high- and low-volume mHSPC were eligible for the study. High-volume disease was defined as either visceral metastases and at least 1 bone lesion or at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis. Low-volume disease was defined as the presence of bone lesion(s) not meeting the definition of high-volume.

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 7 or higher (92%). Sixty-eight percent (68%) of patients received prior treatment with a first-generation anti-androgen in the non-metastatic setting. Although criteria for castration resistance were not determined at baseline, 94% of patients demonstrated a decrease in prostate specific antigen (PSA) from initiation of androgen deprivation therapy (ADT) to first dose of apalutamide or placebo. 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. Among the patients who discontinued study treatment (N = 271 for placebo and N = 170 for Apalutamide), the most common reason for discontinuation in both arms was disease progression. A greater proportion (73%) of patients treated with placebo received subsequent anti-cancer therapy compared to patients treated with Apalutamide (54%).

The major efficacy outcome measures of the study were overall survival (OS) and radiographic progression-free survival (rPFS). Efficacy results of TITAN are summarised in Table 2 and Figures 1 and 2.

Table 2: Summary of Efficacy Results – Intent-to-treat mHSPC Population (TITAN)

Endpoint	**Apalutamide N=525**	**Placebo N=527**
Overall Survival		
Deaths (%)	83 (16%)	117 (22%)
Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[a]	0.671 (0.507, 0.890)	
p-value[b]	0.0053	
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)[a]	0.484 (0.391, 0.600)	
p-value[b]	<.0001	

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors active treatment.
[b] 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).
NE=Not Estimable

A statistically significant improvement in OS and rPFS was demonstrated in patients randomised to receive Apalutamide compared with patients randomised to receive placebo. Consistent improvement in rPFS was observed across patient subgroups including high- or low-volume disease, prior docetaxel use (yes or no), age (< 65, ≥65, or ≥75 years old), baseline PSA above median (yes or no), and number of bone lesions (≤10 or >10).

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

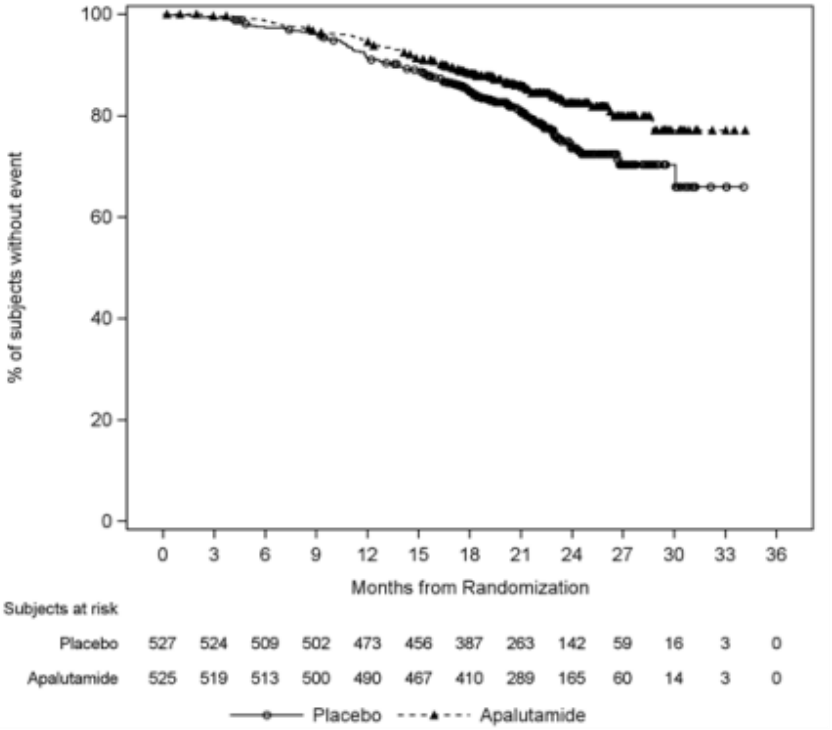
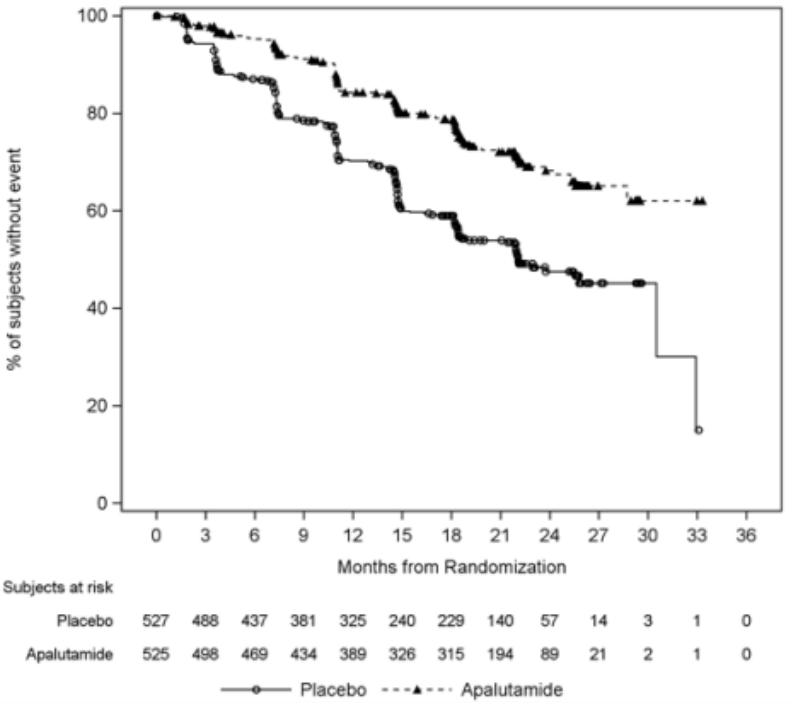


Figure 2: Kaplan-Meier Plot of Radiographic Progression-Free Survival (rPFS); Intent-to-treat mHSPC Population (TITAN)



Treatment with Apalutamide statistically significantly delayed the initiation of cytotoxic chemotherapy (HR = 0.391, 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.

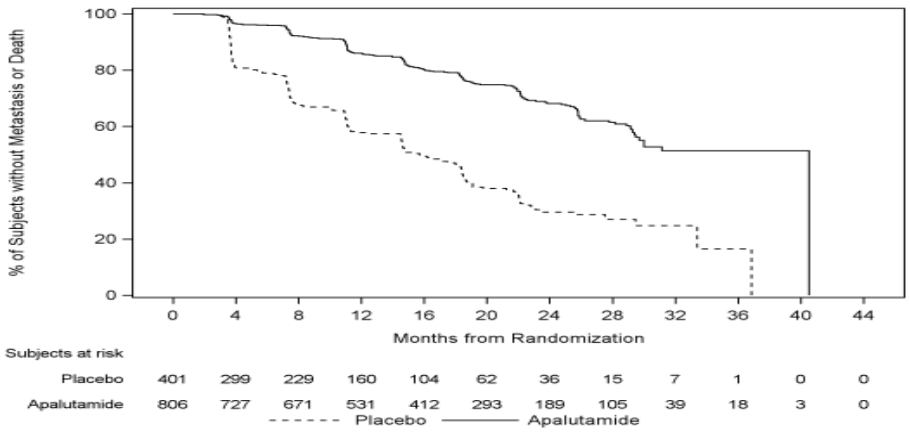
SPARTAN: Non-Metastatic Castration Resistant Prostate Cancer (nmCRPC)

A total of 1207 subjects with NM-CRPC were randomised 2:1 to receive either apalutamide orally at a dose of 240 mg once daily in combination with androgen deprivation therapy (ADT) (medical castration or prior surgical castration) or placebo with ADT in a multicenter, double-blind, clinical study (Study ARN-509-003). Subjects enrolled had a Prostate Specific Antigen (PSA) Doubling Time (PSADT) ≤ 10 months, considered to be at high risk of imminent metastatic disease and prostate cancer-specific death. All subjects who were not surgically castrated received ADT continuously throughout the study. PSA results were blinded and were not used for treatment discontinuation. Subjects randomised to either arm were to continue treatment until disease progression defined by blinded central imaging review (BICR), initiation of new treatment, unacceptable toxicity or withdrawal.

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. Seventy-three percent (73%) of subjects received prior treatment with a first generation anti-androgen; 69% of subjects received bicalutamide and 10% of subjects received flutamide. All subjects enrolled were confirmed to be non-metastatic by blinded central imaging review and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) performance status score of 0 or 1 at study entry.

Metastasis-free survival (MFS) was the primary endpoint, defined as the time from randomisation to the time of first evidence of BICR-confirmed bone or soft tissue distant metastasis or death due to any cause, whichever occurred first. Treatment with Apalutamide significantly improved MFS. Apalutamide decreased the relative risk of distant metastasis or death by 70% compared to placebo (HR = 0.30; 95% CI: 0.24, 0.36; p < 0.0001). The median MFS for Apalutamide was 41 months and was 16 months for placebo (see Figure 3). Consistent improvement in MFS with Apalutamide was observed for all pre-specified subgroups, including age, race, region of the world, nodal status, prior number of hormonal therapies, baseline PSA, PSA doubling time, baseline ECOG status and use of bone-sparing agents.

Figure 3: Kaplan-Meier metastasis-free survival (MFS) curve in Study ARN-509-003



Subjects treated with Apalutamide and ADT showed significant improvement over those treated with ADT alone for the following secondary endpoints of time to metastasis (HR = 0.28; 95% CI: 0.23, 0.34; p < 0.0001), progression-free survival (PFS) (HR = 0.30; 95% CI: 0.25, 0.36; p < 0.0001); time to symptomatic progression (HR = 0.45; 95% CI: 0.32, 0.63; p < 0.0001); and a trend for overall survival (OS) (HR = 0.70; 95% CI: 0.47 1.04; p = 0.0742).

Time to symptomatic progression was defined as time from randomization to development of a skeletal related event, pain/symptoms requiring initiation of a new systemic anti-cancer therapy, or loco-regional tumor progression requiring radiation/surgery. While the overall number of events was small, the difference between the two arms was sufficiently large to reach statistical significance. In the apalutamide arm 64 (7.9%) subjects developed symptomatic progression compared with 63 (16%) in the placebo arm, with a hazard ratio of 0.447 (95% CI: 0.315, 0.634), which met the pre-specified O'Brien Fleming type efficacy boundary for significance, p < 0.00008. The median time to symptomatic progression was not reached in either treatment group.

In the apalutamide arm, 62 (7.7%) subjects died compared to 42 (10.5%) subjects in the placebo arm. The median survival for the apalutamide arm was not reached compared to 39.03 months with a 95% CI of (39.03, NE) for the placebo arm. Statistical significance was not reached in overall survival at the pre-specified interim analysis.

Post-progression survival (PFS-2, defined as the time to disease progression after first subsequent therapy or death) was longer for subjects treated with Apalutamide compared to those treated with placebo (HR = 0.489; 95%CI: 0.361, 0.662; p < 0.0001).

There were no statistically significant differences observed in the change from baseline analysis of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) for the total score or any of the subscales between subjects on Apalutamide added to ADT *versus* placebo with ADT.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Apalutamide in all subsets of the paediatric population in advanced prostate cancer.

5.2 Pharmacokinetic properties

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

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

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

Absorption

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

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

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

In vitro, apalutamide and its N-desmethyl metabolite are substrates for P-gp. 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.

Distribution

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

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

Biotransformation

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

Metabolism is the main route of elimination of apalutamide. It is metabolised primarily by CYP2C8 and CYP3A4 to form N-desmethyl apalutamide. Apalutamide and N-desmethyl apalutamide are further metabolised to form the inactive carboxylic acid metabolite by carboxylesterase. The contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but the level of contribution is expected to change at steady-state due to induction of CYP3A4 by apalutamide after repeat dose.

Elimination

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

The apparent oral clearance (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 patients is about 3 days at steady-state.

In vitro data indicate that apalutamide and its N-desmethyl metabolite are not substrates for BCRP, OATP1B1 or OATP1B3.

Special populations

The effects of renal impairment, hepatic impairment, age, race, and other extrinsic factors on the pharmacokinetics of apalutamide are summarised below.

Renal impairment

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

Hepatic impairment

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

Ethnicity and race

Based on population pharmacokinetic analysis, there were no clinically relevant differences in apalutamide pharmacokinetics between White (Caucasian or Hispanic or Latino; N=761), Black (of African heritage or African American; N=71), Asian (non-Japanese; N=58) and Japanese (N=58).

Age

Population pharmacokinetic analyses showed that age (range: 18 to 94 years) does not have a clinically meaningful influence on the pharmacokinetics of apalutamide.

5.3 Preclinical safety data

Apalutamide was negative for genotoxicity in a standard battery of *in vitro* and *in vivo* tests.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of apalutamide.

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 and dogs, atrophy, aspermia/hypospermia, degeneration and/or hyperplasia or hypertrophy in the reproductive system were observed at doses corresponding to exposures approximately equal to 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 doses corresponding to exposures approximately equal to the human exposure based on AUC. Effects on male rats were reversible after 8 weeks from the last apalutamide administration.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet contents:

Hypromellose Acetate Succinate
Sodium Starch Glycolate (Primojel)
Croscarmellose Sodium
Sodium Lauryl Sulphate
Magnesium Stearate
Colloidal Anhydrous Silica (Aerosil 200)
Microcrystalline Cellulose (Avicel PH 102)**

Coating Materials:

Opadry II White (85G68918)

Opadry II Yellow (85G52259)

Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a cool and dry place, away from light. Keep out of the reach of Children.

6.5 Nature and contents of container

Primary Packaging: HDPE Bottle

Secondary Packaging: Paper board carton

Pack size: 1 × 120’s Tablets in Box

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

CORPORATE OFFICE

Beacon Business Center

9/B/2, Toyenbee Circular Road, Motijheel, Dhaka- 1223, Bangladesh

Tel: +880-2-5716371-76,

Fax: 880-2-57165379

E-mail: beacon@beaconpharma.com.bd

Website: www. beaconpharma.com.bd

FACTORY

Bhaluka, Mymensingh, Bangladesh

8. Marketing authorization Number:

M.A No. 341-384-010

9. Date of first authorization/renewal of the authorization

08.08.2019/ 07.08.2024

10. Date of revision of the text

27.01.2020