Supplementary Material

Coadministration of Apalutamide and Relugolix in Patients With Localized Prostate Cancer at High Risk for Metastases

Targeted Oncology

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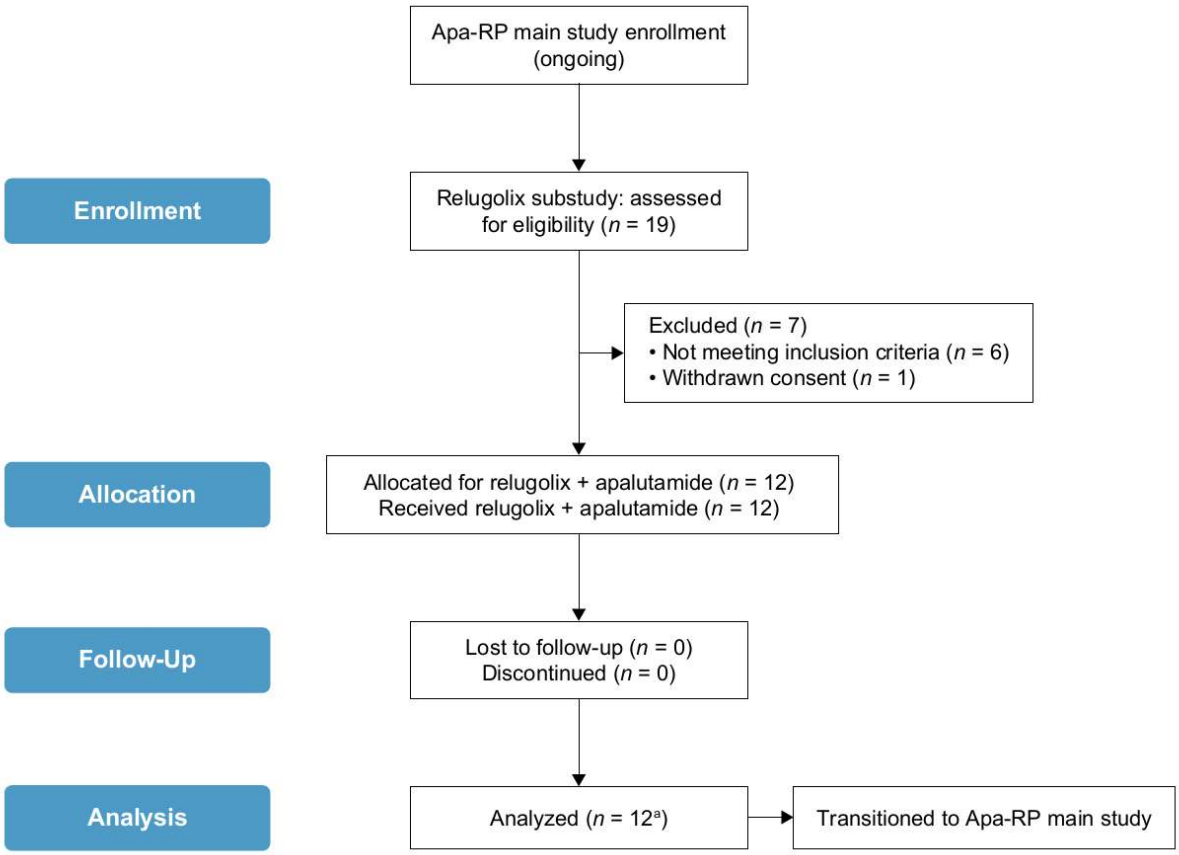
Supplementary Fig. 1 CONSORT diagram for the substudy



[a]One patient had missing testosterone measurement at Day 28

Supplementary Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Patient	• Male, age ≥18 years • Candidate for RP or status post RP • Eligible to receive substudy intervention between Day 29 and Day 90 post RP • Post RP PSA of ≤0.2 ng/mL • Adequate organ function (hepatic, renal, hematologic, and cerebral) • ECOG PS of 0 or 1 • Histologically confirmed adenocarcinoma of the prostate	• Any condition for which participation would not be in the best interest of the participant or that could limit, or confound, the protocol-specified assessments • Allergy or hypersensitivity to apalutamide or excipients, unable or unwilling to take ADT
History	• Recovered from RP procedure and has had no worsening in cardiac risk in the perioperative period • High risk[a] for recurrent PC	• Soft tissue/bone metastasis or metastasis in distant lymph nodes • Bilateral orchiectomy • Seizure or any condition that may predispose to seizure or treatment with drugs known to lower the seizure threshold within 4 weeks prior to starting treatment with apalutamide • Psoriasis, neurodermatitis, acneiform rashes, or any dermatological condition that in the opinion of the investigator may predispose to confounding with the evaluation and management of rash related to substudy intervention • Malignancies other than prostate cancer[c]

		• Any of the following within 12 months prior to baseline: severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, uncontrolled hypertension, long QT, arterial or venous thromboembolic events, or clinically significant ventricular arrhythmias
Concomitant therapies	• Receiving no other treatment for PC	• Taking any disallowed therapies or chronic need for prohibited medications • Received an investigational intervention ≤4 weeks before the planned first dose of substudy intervention
Consent	• Completed informed consent form and able to fully comply with all required procedures, restrictions, and prohibitions • Able to take apalutamide per ERLEADA USPI and able to receive ADT for up to 1 year • Willing to wear a condom when engaging in any activity that allows for passage of ejaculate to another person[b] • Willing to agree not to donate sperm for the purpose of reproduction during the substudy and for a minimum 90 days after receiving the last dose of substudy intervention	• Plans to father a child while enrolled in this substudy or within 12 weeks after the last dose of substudy intervention

[a]High risk can be defined based on prostate-specific antigen (PSA) alone or biopsy or RP specimen: PSA ≥20 ng/mL or Gleason score ≥9 in any biopsy core or Gleason score ≥8 (4 + 4 or 5 + 3) in >80% of 2 cores or Gleason score = 8 (4 + 4 or 5 + 3) in 1 core as long as 5 or more other cores with minimum Gleason score of 4 + 3 on biopsy. The determination of high risk may be based on pathology report of biopsy or equivalent criteria from RP

[b]Patients were to be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak

[c]The only allowed exceptions were non–muscle invasive bladder cancer or skin cancer (nonmelanoma or melanoma) treated within the last 24 months that is considered completely cured. Malignancies considered cured for more than 24 months were allowed

ADT androgen-deprivation therapy; *ECOG PS* Eastern Cooperative Oncology Group performance status; *PC* prostate cancer; *PSA* prostate-specific antigen; *RP* radical prostatectomy; *USPI* United States prescribing information

Supplementary Table 2 Concomitant medications[a] during substudy interventions (relugolix monotherapy and apalutamide plus relugolix treatment)

Concomitant medication, *n* (%)	Overall population, *N* = 12
Patients with ≥1 concomitant medication	12 (100.0)
Lipid-modifying agents	9 (75)
Analgesics	8 (67)
Agents acting on the renin-angiotensin system	6 (50)
Vitamins	6 (50)
Antihistamines for systemic use	5 (42)
Anti-inflammatory and antirheumatic products	5 (42)
Drugs for acid related disorders	5 (42)
Drugs for constipation	5 (42)
Urologicals	5 (42)
Corticosteroids for systemic use	4 (33)
Drugs used in diabetes	4 (33)
Antiepileptics	3 (25)
Beta-blocking agents	3 (25)
Mineral supplements	3 (25)
Antifungals for dermatological use	2 (17)
Antihypertensives	2 (17)
Diuretics	2 (17)
Drugs for obstructive airway diseases	2 (17)
Ophthalmologicals	2 (17)
Psychoanaleptics	2 (17)
Psycholeptics	2 (17)
Unspecified herbal and traditional medicine	2 (17)
All other therapeutic products	1 (8)
Antianemic preparations	1 (8)

Antibacterials for systemic use	1 (8)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	1 (8)
Antigout preparations	1 (8)
Calcium channel blockers	1 (8)
Cough and cold preparations	1 (8)
Emollients and protectives	1 (8)
Gynecological anti-infectives and antiseptics	1 (8)
Other alimentary tract and metabolism products	1 (8)
Other dermatological preparations	1 (8)
Vaccines	1 (8)

[a]Concomitant medications include those that are ongoing at the start of the first dose of relugolix treatment (Day –14) or those taken during the treatment period, from the date of first relugolix dose through 28 days after the start of apalutamide + relugolix treatment

Supplementary Table 3 Treatment-emergent adverse events (TEAEs) by system organ class and preferred term in the relugolix and apalutamide + relugolix treatment phases of the Apa-RP substudy

System organ class, *n* (%) Preferred term, *n* (%)	Overall population, *N* = 12									
	Relugolix monotherapy[a]					Relugolix + apalutamide[b]				
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4
Vascular disorders	6 (50)	6 (50)	0	0	0	5 (42)	4 (33)	1 (8.3)	0	0
Hot flush	6 (50)	6 (50)	0	0	0	4 (33)	4 (33)	0	0	0
Hypertension	0	0	0	0	0	1 (8.3)	0	1 (8.3)	0	0
Nervous system disorders	0	0	0	0	0	2 (17)	1 (8.3)	1 (8.3)	0	0
Headache	0	0	0	0	0	1 (8.3)	0	1 (8.3)	0	0
Hypoesthesias	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Restless leg syndrome	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Skin and subcutaneous tissue disorders	1 (8.3)	0	1 (8.3)	0	0	2 (16.7)	1 (8.3)	1 (8.3)	0	0
Dry skin	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Rash	1 (8.3)	0	1 (8.3)	0	0	1 (8.3)	0	1 (8.3)	0	0
General disorders and administration site conditions	4 (33)	4 (33)	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Chest discomfort	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0

Fatigue	4 (33)	4 (33)	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Metabolism and nutrition disorders										
Increased appetite	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0
	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Musculoskeletal/connective tissue										
disorders	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Back pain	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Psychiatric disorders	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Anxiety	0	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0
Gastrointestinal disorders	1 (8.3)	1 (8.3)	0	0	0	0	0	0	0	0
Diarrhea	1 (8.3)	1 (8.3)	0	0	0	0	0	0	0	0
Infections and infestations	1 (8.3)	0	1 (8.3)	0	0	0	0	0	0	0
Urinary tract infection	1 (8.3)	0	1 (8.3)	0	0	0	0	0	0	0

[a]TEAEs that occurred between Day –14 and Day –1

[b]TEAEs that occurred between Day 1 and Day 28