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ORIGINAL RESEARCH ARTICLE

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

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Abstract

Background The single-arm, open-label, multicenter, phase II Apa-RP study evaluates the biochemical recurrence (confirmed prostate-specific antigen [PSA] > 0.2 ng/mL)-free rate in patients with high-risk localized prostate cancer (HR-LPC) after radical prostatectomy following adjuvant apalutamide and androgen-deprivation therapy. In this substudy, relugolix, an oral gonadotropin-releasing hormone antagonist, was evaluated in combination with apalutamide.

Objective The aim of this study was to evaluate whether the approved standard maintenance dose of relugolix in combination with apalutamide sustains castrate testosterone levels (< 50 ng/dL).

Patients and Methods Twelve patients with HR-LPC who met all the main study criteria were included in the substudy. Patients received relugolix monotherapy for 2 weeks (loading dose [360 mg] at Day − 14 then 120 mg/day daily until Day − 1), then daily relugolix (120 mg) with apalutamide (240 mg) from Day 1 to Day 28. Endpoints were rate of maintained castration (testosterone < 50 ng/dL) through Day 28 (primary) and safety (secondary).

Results All 12 patients received relugolix and apalutamide and achieved castrate testosterone levels after 2-week relugolix monotherapy (median testosterone 348.5 ng/dL and 8.7 ng/dL at Days − 14 and − 1). All 11 patients who had testosterone measured at Day 28 maintained castrate testosterone (median 10.0 ng/dL) without relugolix dose adjustment. Treatment-emergent adverse events (TEAEs) occurred in nine patients during relugolix monotherapy and in eight patients during relugolix + apalutamide coadministration. Hot flush was the most common TEAE reported, in six and four patients, respectively.

Conclusions Relugolix administered at approved standard doses concurrently with apalutamide was effective in maintaining castrate testosterone levels in HR-LPC without new safety signals.

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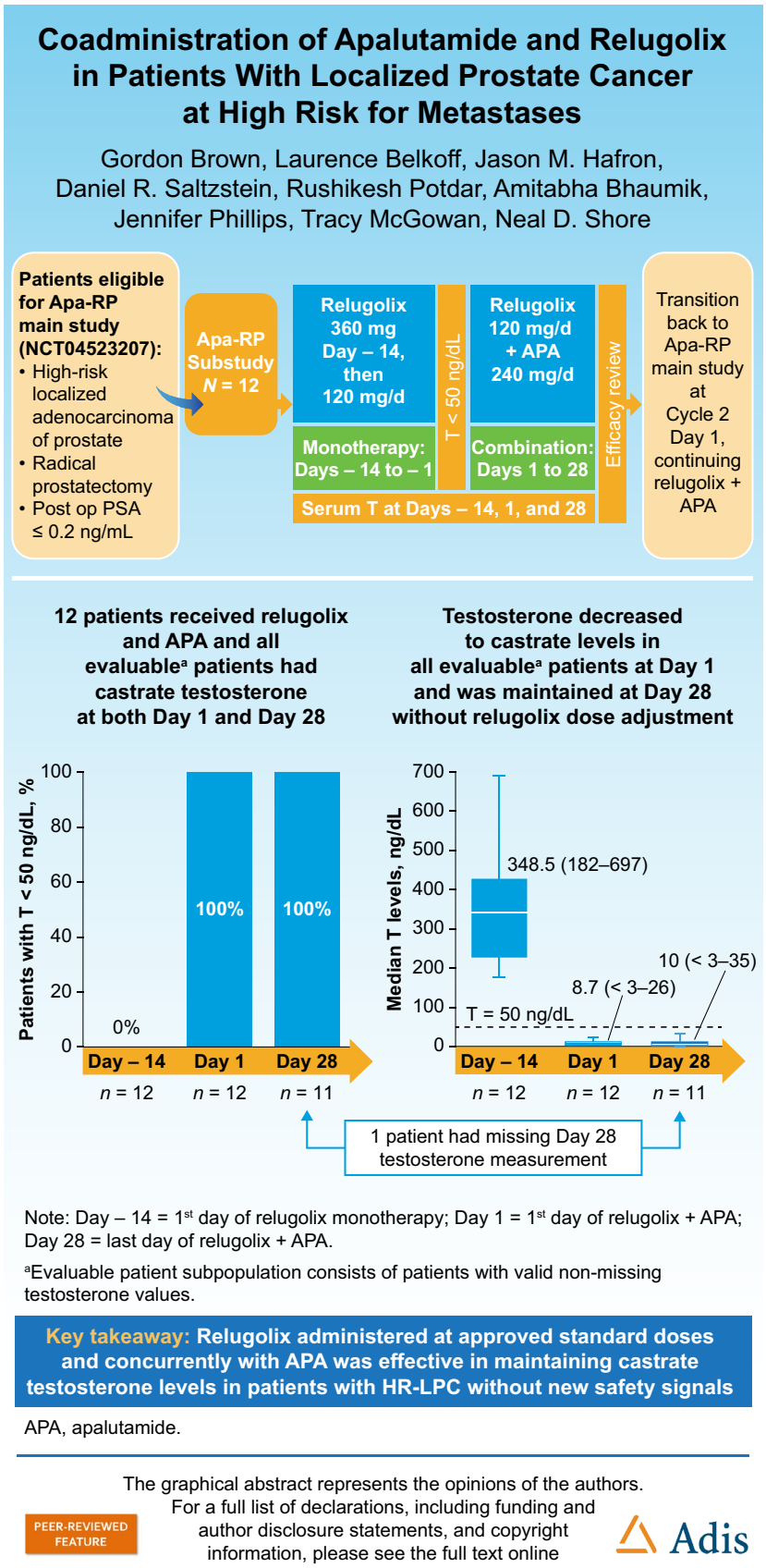
Graphical abstract



Note: Day – 14 = 1st day of relugolix monotherapy; Day 1 = 1st day of relugolix + APA; Day 28 = last day of relugolix + APA.

[a]Evaluable patient subpopulation consists of patients with valid non-missing testosterone values.

Key takeaway: Relugolix administered at approved standard doses and concurrently with APA was effective in maintaining castrate testosterone levels in patients with HR-LPC without new safety signals

APA, apalutamide.

Plain Language Summary

The Apa-RP study evaluates the combination of apalutamide with drugs that lower male sex hormones for reducing the risk of prostate cancer recurrence. Patients in this study had their prostate gland surgically removed and were at high risk for disease recurrence. Relugolix, a newly approved oral drug for advanced prostate cancer, lowers blood testosterone (the primary male sex hormone) and, in combination with apalutamide, may reduce the risk of prostate cancer recurrence. The Apa-RP substudy goal was to test whether relugolix lowers blood testosterone and maintains these low levels when administered with apalutamide. Researchers looked at the testosterone levels of 12 patients with early prostate cancer who received standard doses of relugolix alone for 2 weeks followed by apalutamide and relugolix for an additional 28 days. Testosterone was measured before and after 2 weeks of relugolix treatment, and then again 28 days after apalutamide was added. All 12 substudy patients achieved low testosterone levels (< 50 ng/dL) after 2 weeks of relugolix treatment. Testosterone was measured at Day 28 of relugolix + apalutamide treatment in 11 patients, all of whom maintained low testosterone without adjustment of their relugolix dose. Adverse effects were consistent with those previously reported for each drug when administered alone. All 12 patients completed the substudy and moved onto the main study, the longer-term results of which will be reported in the future. In summary, relugolix administered at the same time as apalutamide was effective in maintaining low testosterone levels in patients with prostate cancer, without any new safety concerns.

Key Points

Relugolix at a standard dose maintained castrate levels of testosterone when coadministered with apalutamide.

Safety profiles of apalutamide and relugolix were similar to those reported previously for each drug.

1 Introduction

Localized prostate cancer (LPC) accounts for approximately 80% of PCs in the United States [1, 2], and an estimated 15–50% of patients with LPC are at high risk for recurrence [3, 4]. Treatment options for patients with high-risk (HR) LPC who are at high risk for local or distant recurrence include radical prostatectomy (RP) or radiation therapy (RT), alone or in combination with systemic therapies [5]. Recurrence occurs in up to 75% of high-risk patients who have undergone RP or RP/lymphadenectomy [6, 7]. Studies supporting adjuvant treatments with systemic therapies, such as gonadotropin-releasing hormone (GnRH) agonists or antagonists and androgen receptor (AR) signaling inhibitors, are limited, with a paucity of phase III trials [5, 6]. The combination of local therapies with systemic androgen-deprivation therapy (ADT) has been shown to benefit patients with node-positive PC [6]. Neoadjuvant abiraterone acetate plus prednisone added to ADT has been shown to suppress the androgen axis and thus improve pathologic outcomes in patients with HR-LPC undergoing RP [8]. More options for treatments with proven efficacy in high-risk disease, especially post RP, are an unmet clinical need.

Apalutamide is an orally available AR inhibitor that selectively blocks androgen-induced AR activation, prevents nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription [9]. Apalutamide decreases prostate cell proliferation, increases cell death in tumors [9], and, in combination with ADT, was approved by the US Food and Drug Administration for the treatment of nonmetastatic castration-resistant PC in 2018 and metastatic castration-sensitive PC in 2019 [10]. Apalutamide is currently being evaluated for the treatment of HR-LPC in two phase III studies, with RP and RT (PROTEUS and ATLAS, respectively) [11, 12].

Relugolix is an oral GnRH receptor antagonist that rapidly inhibits pituitary release of luteinizing hormone and follicle-stimulating hormone and has been shown to lower testosterone levels [13–15]. Relugolix was recently approved for treating patients with advanced PC based on results from the HERO study [16]. While relugolix is currently being evaluated in combination with other PC drugs, including apalutamide [17], the results have not yet been reported and there is a need to understand the effect of this combination on testosterone suppression.

Relugolix is metabolized through multiple pathways, including cytochrome P450 (CYP) 3A, and is a substrate of CYP2C8 and P-glycoprotein (P-gp) [16]. Intestinal P-gp efflux is the primary determinant of absorption and oral bioavailability of relugolix [16]. Apalutamide is a strong inducer of CYP3A4 and a weak inducer of P-gp, as well as a moderate inhibitor of CYP2C9 [10]. The relugolix label recommends avoiding coadministration with combined P-gp and strong CYP3A inducers or, if unavoidable, to double the relugolix dose from 120 to 240 mg once daily [16]. However, no clinically significant differences in the pharmacokinetics of relugolix were observed when it was coadministered with other strong CYP3A inhibitors, such as voriconazole or enzalutamide [16]. Thus, it was hypothesized that relugolix administered concurrently with apalutamide should be able to maintain castrate levels of testosterone without modification of its dose.

The Apa-RP study (NCT04523207) is a single-arm, open-label, multicenter, phase II study evaluating the biochemical recurrence-free rate in patients with HR-LPC following RP who receive apalutamide with ADT. The primary hypothesis

of the Apa-RP substudy is that castrate levels of serum testosterone (< 50 ng/dL) achieved following relugolix will be maintained after coadministration of relugolix with apalutamide 240 mg once daily, without the need to increase the maintenance dose of relugolix.

2 Patients and Methods

2.1 Study Design

The study design of the main study of apalutamide and ADT (Apa-RP) has been reported [18] and is described briefly above. The substudy was single arm and open label (Fig. 1) and enrolled 12 patients with HR-LPC from six community-based urology practices following an amendment of the original protocol on 20 April 2021. Eligibility criteria were the same as for the main study. Patients who were treatment naive, had no evidence of metastatic disease prior to substudy entry, were within 90 days post RP, and had prostate-specific antigen (PSA) ≤ 0.2 ng/mL at substudy entry were included. Patients had histologically confirmed adenocarcinoma of the prostate categorized as high risk for recurrent PC, which was defined as PSA ≥ 20 ng/mL or Gleason score (GS) ≥ 8 (≥ 9 in any core, or GS ≥ 8 [4 + 4 or 5 + 3] in > 80% of two cores, or GS = 8 [4 + 4 or 5 + 3] in one core with ≥ 5 other cores of GS ≥ 7). Reasons for exclusion from participation included history or presence of soft tissue/bone metastasis or metastasis in distant lymph nodes, history of bilateral orchiectomy, history of seizure or any condition or medication that may predispose to seizure, or major cardiovascular events within 12 months prior to baseline. Electronic Supplementary Table 1 provides a complete list of inclusion and exclusion criteria. All patients successfully completing the substudy were planned to transition to the main Apa-RP study, in which they would continue on relugolix + apalutamide. No pharmacokinetic assessments were planned in the substudy.

2.2 Treatment

Patients received a loading dose of oral relugolix (360 mg) on Day − 14 followed by 2 weeks of 120 mg daily relugolix monotherapy, after which they were confirmed to have serum testosterone < 50 ng/dL, and then apalutamide (240 mg once daily) combined with relugolix (120 mg once daily) was administered for 28 days.

2.3 Efficacy Analysis

Efficacy assessments included serum testosterone measured at baseline (Day − 14; the first day of relugolix monotherapy), on the first day of apalutamide and relugolix coadministration (Day 1), and on Day 28 of apalutamide and relugolix coadministration. Testosterone < 50 ng/dL was considered castrate level [5]. The primary endpoint was the percentage of patients maintaining testosterone levels < 50 ng/dL through Day 28, and the secondary endpoint was safety.

2.4 Safety Analysis

Treatment-emergent adverse events (TEAEs) were evaluated from Days − 14 to 28 and were summarized for relugolix monotherapy and relugolix + apalutamide treatment periods. TEAEs were defined as any AE occurring at or after the initial administration of substudy intervention.

2.5 Statistical Analysis

The percentage of patients with testosterone < 50 ng/dL through Day 28 was summarized descriptively. The protocol dictated that the substudy would be considered negative if two or more participants had testosterone ≥ 50 ng/dL on Day 28. TEAEs were summarized descriptively. Events related to and associated with the recovery from the preplanned RP were not assessed.

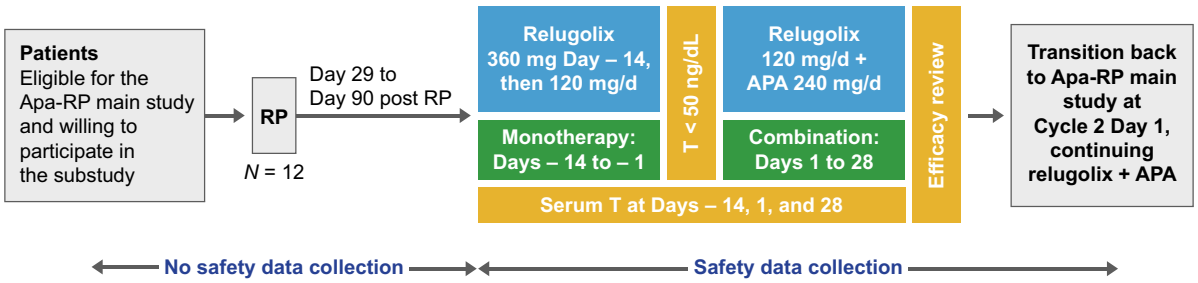


Fig. 1 Schematic overview of the substudy. *APA*, apalutamide, *RP* radical prostatectomy, *T* testosterone

3 Results

The substudy clinical data cut-off was 7 March 2022. The Apa-RP substudy enrolled 12 patients (median age 68 years) (Table 1). Median PSA at the time of initial diagnosis prior to RP was 7.4 (4.2–26.2) ng/dL. All 12 patients received one or more doses of apalutamide. The patient flow diagram is shown in Electronic Supplementary Fig. 1. No patients discontinued during the substudy period. All 12 patients received concomitant medication, most commonly lipid-modifying agents and analgesics (9 [75%] and 8 [67%], respectively) (see Electronic Supplementary Table 2).

All 12 patients achieved castrate testosterone levels after 2-week relugolix monotherapy (Fig. 2a). One patient inadvertently did not have testosterone measured at Day 28, but all 11 patients with available measurements maintained castrate testosterone levels at the end of apalutamide and relugolix coadministration without requiring adjustment of the relugolix dose. At baseline (Day − 14), median (range) serum testosterone was 348.5 (182–697) ng/dL; it decreased to 8.7 (< 3–26) ng/dL after 2 weeks of relugolix monotherapy and was 10.0 (< 3–35) ng/dL at Day 28 of apalutamide and relugolix coadministration (Fig. 2b).

TEAEs were reported in 9 (75%) patients while they were receiving relugolix monotherapy and in 8 (67%) patients while receiving relugolix + apalutamide treatment (Table 2), and were consistent with the known safety profiles of apalutamide and relugolix. All TEAEs were grade 1 or 2 (Electronic Supplementary Table 3). The most common TEAE was hot flush, which was grade 1, and occurred in 6 (50%) and 4 (33%) patients in the relugolix and relugolix + apalutamide treatment phases, respectively (Electronic Supplementary Table 3). Rash occurred in one (8.3%) patient treated with relugolix + apalutamide (Electronic Supplementary Table 3). No new safety signals were observed. No patients interrupted treatment, reduced their dose, or discontinued treatment due to TEAEs during the substudy period. All 12 patients transitioned to the main Apa-RP study and continued receiving relugolix + apalutamide. Efficacy and safety outcomes in these patients with longer follow-up will be reported together with the full cohort of the main study.

4 Discussion

Recent research efforts to develop oral ADT led to the approval of relugolix, a nonpeptide GnRH receptor antagonist, for advanced prostate cancer. Whether relugolix effectively suppresses testosterone when administered concurrently with apalutamide has not yet been established and the clinical relevance of potential drug–drug interaction has not been addressed. The HERO study, which included 17 patients who were coadministered enzalutamide, demonstrated that relugolix at standard doses (360 mg loading dose followed by 120 mg daily) was sufficiently potent to lower testosterone to castrate levels [19]. It was hypothesized that administration of relugolix with apalutamide (a strong CYP3A inhibitor) may not lead to a clinically significant interaction. The Apa-RP substudy aimed to assess whether patients receiving concomitant apalutamide and relugolix were able to maintain castrate testosterone levels (< 50 ng/dL) without the need to adjust the relugolix dosing regimen. All patients achieved castrate testosterone levels after 2 weeks of relugolix monotherapy, and all patients with available data were able to maintain castrate testosterone while receiving relugolix + apalutamide. The safety profile of relugolix + apalutamide was consistent with the known adverse effects of these drugs [19–23]. All TEAEs were low grade, including the most common TEAE of hot flush, and none resulted in treatment discontinuation. All patients transitioned to the main study and continued receiving relugolix + apalutamide.

The recent National Comprehensive Cancer Network (NCCN) guidelines caution against using relugolix in combination with other commonly used agents in advanced PC because it has not been adequately studied [5]. The NCCN called for further investigations of relugolix dosing and drug–drug interactions to ensure proper dosing and safety.

Table 1 Baseline clinical and demographic characteristics

Characteristic	Overall population ($N = 12$)
Median age, years (range)	68 (50–74)
Median PSA (range) at initial diagnosis prior to RP, ng/dL	7.4 (4.2–26.2)
Gleason score	
7 (3 + 4)	1 (8.3)
8 (4 + 4)	2 (17)
9 (4 + 5)	8 (67)
10 (5 + 5)	1 (8.3)
Metastasis stage at diagnosis	
M0	11 (92)
Unknown	1 (8.3)
Nodal status at diagnosis	
N0	8 (67)
N1	2 (17)
NX	2 (17)
Tumor stage at diagnosis	
T1	3 (25)
T2	3 (25)
T3	6 (50)

Data are expressed as *n* (%) unless otherwise specified

RP radical prostatectomy, *PSA* prostate-specific antigen

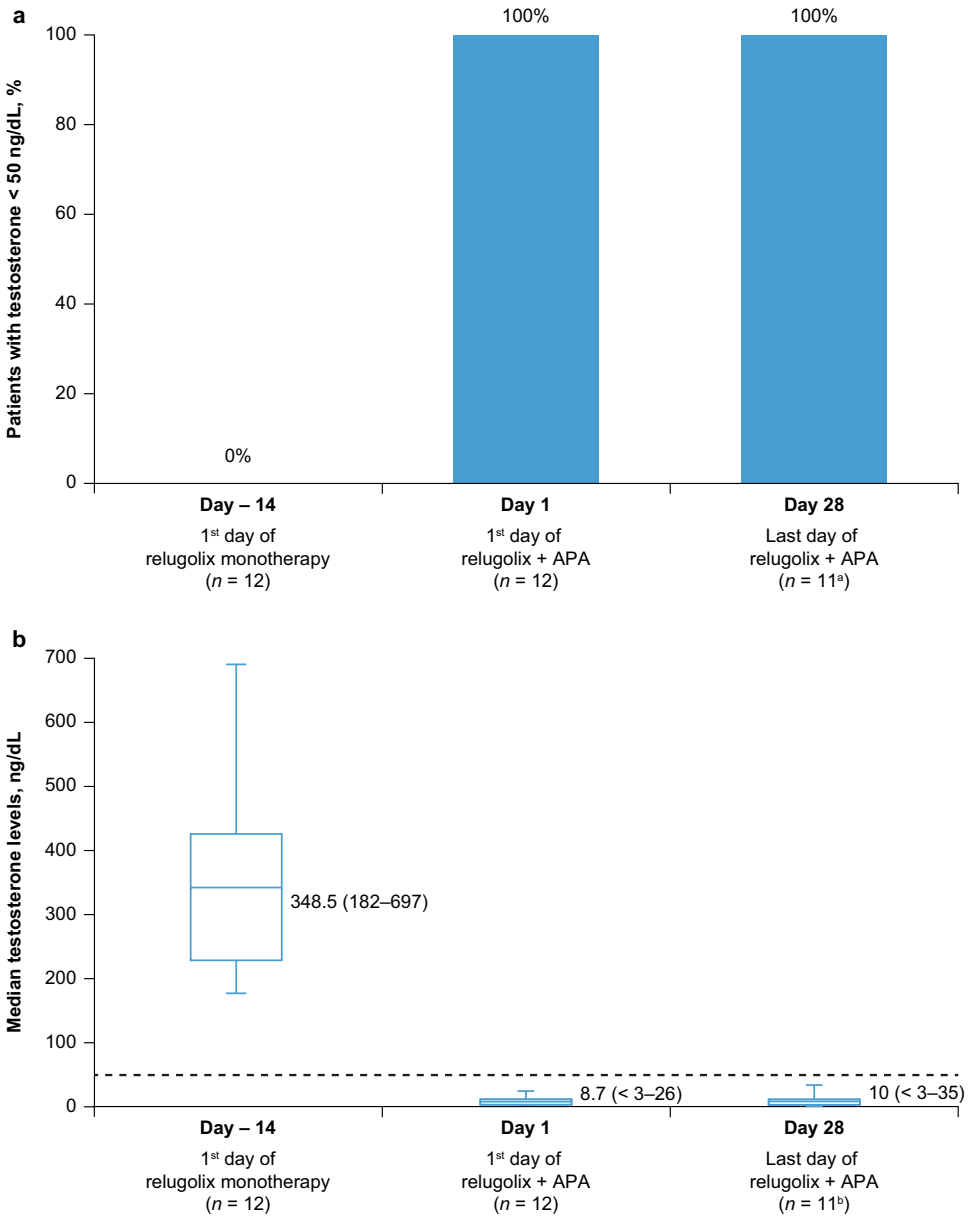


Fig. 2 Serum testosterone dynamics in the substudy from a subpopulation of evaluable patients with valid and non-missing testosterone values. Testosterone values collected as < 3.0 ng/dL or < 10 ng/dL were imputed to 2.9 ng/dL and 9.9 ng/dL, respectively, for median calculation. **a** Proportion of patients with castrate testosterone < 50 ng/dL at Days − 14, 1, and 28; **b** median testosterone levels (range) at Days − 14, 1, and 28; 50 ng/dL threshold, medians, interquartile ranges, and median ranges are shown. [a]One patient had missing Day 28 testosterone measurement. [b]One patient had missing Day 28 testosterone measurement. *APA* apalutamide

Table 2 Summary of treatment-emergent adverse events in the relugolix and relugolix + apalutamide treatment phases of the Apa-RP substudy

TEAE [*n* (%)]	Overall population (*N* = 12)	
	Relugolix monotherapy[a]	Relugolix + apalutamide[b]
Any	9 (75)	8 (67)
Serious[c]	0	0
Grade 3–4 TEAEs	0	0
TEAE leading to treatment discontinuation, treatment interruption, or treatment dose reduction	0	0
TEAE leading to death	0	0

TEAE treatment-emergent adverse event

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

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

[c]Excludes grade 5 adverse events

The guidelines also recommended ongoing monitoring for sustained suppression of testosterone (< 50 ng/dL) following relugolix due to uncertain patient compliance [5]. The relugolix prescribing information recommends doubling the relugolix dose from 120 to 240 mg once daily if coadministration with combined P-gp and strong CYP3A inducers is unavoidable [16].

Within the confines of the ongoing main Apa-RP study in community-based outpatient urology settings [18], additional visits for collecting pharmacokinetic samples from prostate cancer patients in this substudy were deemed not feasible. Despite the lack of formal pharmacokinetic assessments, it was not necessary for any substudy patients to double their relugolix dose to maintain castrate testosterone levels after the addition of apalutamide, suggesting a low probability of drug–drug interaction. Our results provide preliminary evidence that the standard dose of relugolix (120 mg) when taken once daily is sufficiently potent to consistently lower testosterone to castrate levels in the presence of apalutamide during the study duration. While other studies formally assessing the pharmacokinetics between apalutamide and relugolix are ongoing [24], our substudy provides the first evidence of the feasibility and efficacy of this combination.

No new safety signals were observed in this substudy compared with safety profiles of apalutamide and relugolix reported previously for each drug [19–23]. Similar to the findings in the HERO study, the most common AE was hot flush [19]. The incidence of skin rash during the short duration of the substudy was lower (8%) than previously reported in the SPARTAN and TITAN studies for advanced diseases (24–27%) [20–23]. Further information on patients who participated in the substudy, including long-term dermatological outcomes in these patients, will be available upon the completion of the main Apa-RP study. The safety and tolerability of relugolix + apalutamide are being investigated in an open-label study in patients with advanced PC for up to 1 year [17], and this may provide additional insights into this combination.

A limitation of this substudy was its open-label design and small sample size. Larger studies of relugolix and apalutamide are needed to confirm our observations. Despite the limitations, the substudy results are encouraging, and we look forward to future results on the combination of relugolix + apalutamide.

5 Conclusions

The results from this open-label, phase II evaluation of patients with HR-LPC post RP suggest that standard relugolix doses administered concurrently with apalutamide are effective at maintaining castrate levels of serum testosterone. In this study, the safety profile of relugolix + apalutamide was consistent with those previously reported for each drug.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-022-00932-8.

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Declarations

Funding This study was funded by Janssen US Medical Affairs. The sponsor was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript. The sponsor paid the open access fee.

Conflict of interest Gordon Brown: Consultant/advisor, speakers' bureau, expert testimony: Astellas Pharma, Bayer, Janssen, Merck, and Pfizer; research funding: Janssen Biotech, Merck. Jason M. Hafron: Consultant/advisor: Astellas Pharma Inc., Dendreon Pharmaceuticals LLC, Janssen Biotech Inc., Myriad Genetic Laboratories, Myovant Sciences, Pfizer Inc., Promaxo, Lynx DX; meeting participant/lecturer: Astellas Pharma Inc., Amgen Inc., Bayer, Blue Earth Diagnostics, Dendreon Pharmaceuticals LLC, Janssen Biotech Inc., Lantheus, Merck & Co., Myriad Genetic Laboratories, Myovant Sciences, Pfizer Inc., Procept-Biorobotic, Progenics Pharmaceuticals, Inc., Tolmar Pharmaceuticals Inc., Urogen Pharma Inc. Neal D. Shore: Consultant/advisor: AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bayer, Boston Scientific, Bristol-Myers Squibb/Sanofi, Clarity Pharmaceuticals, CG Oncology, Clovis Oncology, Dendreon, Exact Imaging, Exact Sciences, FerGene, Ferring, Foundation Medicine, Genesis Cancer Care, Genzyme, InVitae, Janssen Scientific Affairs, Lantheus, Lilly, MDxHealth, Medivation/Astellas, Merck, Myovant Sciences, Myriad Genetics, Nymox, Pacific Edge Biotechnology, Pfizer, Phosphorus, Sanofi, Sema4, Sesen Bio, Specialty Networks, Peerview, Photocure, Propella Therapeutics, Telix Pharmaceuticals, Tempus, Tolmar, Urogen Pharma, Vaxiion; speakers' bureau: Astellas Pharma, AstraZeneca, Bayer, Janssen, Clovis Oncology, Foundation Medicine, Guardant Health, Merck, Pfizer; expert testimony: Ferring; research finding: AbbVie, Advantagene, Amgen, Aragon Pharmaceuticals, Astellas Pharma, AstraZeneca, Bayer, Boston Scientific, Bristol-Myers Squibb/Pfizer, CG Oncology, Clovis Oncology, Dendreon, DisperSol, Endocyte, Exact Imaging, Exelixis, Ferring, FKD Therapies, FORMA Therapeutics, Foundation Medicine, Genentech, Guardant Health, InVitae, ISTARI Oncology, Janssen, Jiangsu Yahong Meditech, MDxHealth, Medivation, Merck, MT Group, Myovant Sciences, Myriad Genetics, Novartis, Nymox, OncoCellMDx, Pacific Edge, Palette Life Sciences, Pfizer, Plexxikon, POINT Biopharma, Propella Therapeutics, RhoVac, Sanofi, Seattle Genetics, Sesen Bio, Steba Biotech, Theralase, Tolmar, Very, Urogen Pharma, Urotronic, US Biotest, Vaxiion, Zenflow. Rushikesh Potdar, Amitabha Bhaumik, Jennifer Phillips, and Tracy McGowan are employees of Janssen US Medical Affairs or Janssen Research & Development and may hold stock in Johnson & Johnson. Laurence Belkoff and Daniel R. Saltzstein have no conflicts of interest to declare.

Availability of Data and Material The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this

site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Code Availability Not applicable.

Ethics Approval Independent Ethics Committees or Institutional Review Boards at all participating institutions approved the Apa-RP study, which was conducted in accordance with International Council for Harmonisation guidelines for Good Clinical Practice and according to the principles of the Declaration of Helsinki.

Consent to Participate All patients provided written informed consent.

Consent to Publish Informed consent was obtained from all individual participants included in the study. No patient-identifying information is included in this article; therefore, consent to publish was not required.

Author Contributions All authors participated in the design and conduct of the study, had access to the data, drafted the manuscript with input from the sponsor (Janssen), reviewed and approved the manuscript before submission, made the decision to submit the manuscript for publication, and agreed to be accountable for all aspects of this work. Gordon Brown had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Siegel DA, O'Neil ME, Richards TB, Dowling NF, Weir HK. Prostate cancer incidence and survival, by stage and race/ethnicity—United States, 2001–2017. MMWR Morb Mortal Wkly Rep. 2020;69:1473–80. https://doi.org/10.15585/mmwr.mm6941a1.
2. Winter A, Sirri E, Jansen L, Wawroschek F, Kieschke J, Castro FA, et al. Comparison of prostate cancer survival in Germany and the USA: can differences be attributed to differences in stage distributions? BJU Int. 2017;119:550–9. https://doi.org/10.1111/bju.13537.
3. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol. 2010;28:1117–23. https://doi.org/10.1200/JCO.2009.26.0133.
4. D'Amico A, Altschuler M, Whittington R, Kao G, Malkowicz SB, Wein A. The use of clinical parameters in an interactive statistical package to predict pathological features associated with local failure after radical prostatectomy for prostate cancer. Clin Perform Qual Health Care. 1993;1:219–22.
5. National Comprehensive Cancer Network. Prostate cancer. Version 4.2022-May 10, 2022. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 12 Aug 2022.
6. Messing EM, Manola J, Yao J, Kiernan M, Crawford D, Wilding G, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol. 2006;7:472–9. https://doi.org/10.1016/S1470-2045(06)70700-8.
7. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 1999;281:1591–7. https://doi.org/10.1001/jama.281.17.1591.
8. McKay RR, Xie W, Ye H, Fennessy FM, Zhang Z, Lis R, et al. Results of a randomized phase II trial of intense androgen deprivation therapy prior to radical prostatectomy in men with high-risk localized prostate cancer. J Urol. 2021;206:80–7. https://doi.org/10.1097/JU.0000000000001702.
9. Clegg NJ, Wongvipat J, Joseph JD, Tran C, Ouk S, Dilhas A, et al. ARN-509: a novel antiandrogen for prostate cancer treatment. Cancer Res. 2012;72:1494–503. https://doi.org/10.1158/0008-5472.CAN-11-3948.
10. ERLEADA® (apalutamide) [Prescribing information]. Horsham: Janssen Pharmaceutical Companies; 2019.
11. Kibel AS, Gleave M, Brookman-May SD, Kim W, Evans CP, Efstathiou E, et al. PROTEUS: a randomized, double-blind, placebo (PBO)-controlled, phase 3 trial of apalutamide (APA) plus androgen deprivation therapy (ADT) versus PBO plus ADT prior to radical prostatectomy (RP) in patients (pts) with localized or locally advanced high-risk prostate cancer (PC). J Clin Oncol. 2022;40(Suppl 6):TPS285. https://doi.org/10.1200/JCO.2022.40.6_suppl.TPS285.
12. Sandler HM, Freedland SJ, Shore ND, Smith MR, Rosales RS, Brookman-May SD, et al. Patient (pt) population and radiation therapy (RT) type in the long-term phase 3 double-blind, placebo (PBO)-controlled ATLAS study of apalutamide (APA) added to androgen deprivation therapy (ADT) in high-risk localized or locally advanced prostate cancer (HRLPC). J Clin Oncol. 2022;40(Suppl 16):5084. https://doi.org/10.1200/JCO.2022.40.16_suppl.5084.
13. Dearnaley DP, Saltzstein DR, Sylvester JE, Karsh L, Mehlhaff BA, Pieczonka C, et al. The oral gonadotropin-releasing hormone receptor antagonist relugolix as neoadjuvant/adjuvant androgen deprivation therapy to external beam radiotherapy in patients with localised intermediate-risk prostate cancer: a randomised, open-label, parallel-group phase 2 trial. Eur Urol. 2020;78:184–92. https://doi.org/10.1016/j.eururo.2020.03.001.
14. MacLean DB, Shi H, Faessel HM, Saad F. Medical castration using the investigational oral GnRH antagonist TAK-385 (relugolix): phase 1 study in healthy males. J Clin Endocrinol Metab. 2015;100:4579–87. https://doi.org/10.1210/jc.2015-2770.
15. Suzuki H, Uemura H, Mizokami A, Hayashi N, Miyoshi Y, Nagamori S, et al. Phase I trial of TAK-385 in hormone treatment-naive Japanese patients with nonmetastatic prostate cancer. Cancer Med. 2019;8:5891–902. https://doi.org/10.1002/cam4.2442.
16. ORGOVYX (relugolix) [Prescribing information]. Brisbane: Myovant Sciences, Inc.; 2020.
17. De La Cerda J, Migoya E, Brown B, Lu S, Zohren F, Tutrone RF, et al. Relugolix in combination with abiraterone acetate, apalutamide, or docetaxel in men with advanced prostate cancer (aPC): a phase 1, three-part, open-label, parallel-cohort study. J Clin Oncol. 2022;40(Suppl 6):207. https://doi.org/10.1200/JCO.2022.40.6_suppl.TPS207.
18. Hafron JM, Saltzstein DR, Lacouture ME, Sutton J, Potdar R, Bhaumik A, et al. Society of Urologic Oncology 22nd Annual Meeting. Apa-RP: phase 2 study of apalutamide and androgen-deprivation therapy (ADT) in treatment-naive patients post-radical prostatectomy (RP) for nonmetastatic prostate cancer at high risk for metastases; 2021. https://suo-abstracts.secure-platform.com/a/gallery/rounds/12/details/1524. Accessed 17 Jun 2022.

19. Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med. 2020;382:2187–96. https://doi.org/10.1056/NEJMoa2004325.
20. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med. 2019;381:13–24. https://doi.org/10.1056/NEJMoa1903307.
21. Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. J Clin Oncol. 2021;39:2294–303. https://doi.org/10.1200/JCO.20.03488.
22. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378:1408–18. https://doi.org/10.1056/NEJMoa1715546.
23. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide and overall survival in prostate cancer. Eur Urol. 2021;79:150–8. https://doi.org/10.1016/j.eururo.2020.08.011.
24. ClinicalTrials.gov. Study of relugolix in men with metastatic castration-sensitive prostate cancer or non-metastatic or metastatic castration-resistant prostate cancer; 2020. https://clinicaltrials.gov/ct2/show/NCT04666129. Accessed 20 Jun 2022.