Impact of Concomitant Prostate Cancer Medications on Efficacy and Safety of Relugolix Versus Leuprolide in Men With Advanced Prostate Cancer

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Abstract

To characterize the impact of concomitant prostate cancer treatments with use of relugolix in advanced prostate cancer, a subgroup and pharmacokinetic/pharmacodynamic analyses of the HERO study was undertaken. Treatment with relugolix was associated with similar efficacy and safety profiles with and without concomitant enzalutamide or docetaxel. Standard-of-care use of relugolix in combination with these agents is supported by these data.

Background: To characterize the impact of concomitant prostate cancer treatments with the use of relugolix, the oral GnRH receptor antagonist, in advanced prostate cancer, a subgroup and pharmacokinetic/pharmacodynamic analyses of the HERO study was undertaken. **Patients and Methods:** Overall, 934 patients were randomized 2:1 to receive relugolix 120 mg orally once daily or leuprolide injections every 12 weeks for 48 weeks. In the setting of rising PSA, patients could receive enzalutamide or docetaxel 2 months after study initiation. Assessments included sustained testosterone suppression to castrate levels (<50 ng/dL) through 48 weeks and safety parameters. Subgroups analyzed included patients with or without concomitant enzalutamide or docetaxel. A sensitivity analysis of the primary endpoint was performed excluding patients who received concomitant therapies that may affect testosterone. Pharmacokinetic/pharmacodynamic analyses of 20 participants in the relugolix treatment group assessed the net effect of enzalutamide on exposure to relugolix. **Results:** Overall, 125 patients (13.4%) took concomitant therapies that could impact testosterone levels. Enzalutamide (n = 23) was the most frequently used therapy in the relugolix (2.7%) and leuprolide groups (1.9%). Docetaxel (n = 13) was used by 1.3% and 1.6% of patients in the relugolix and leuprolide groups, respectively. All other relevant concomitant therapy were used in <1% of population. Sensitivity analysis showed concomitant therapy did not impact the testosterone levels. Castration rates were similar with and without concomitant use of enzalutamide or docetaxel. No clinically relevant differences in adverse events were observed between subgroups in either treatment group. No differences in relugolix C_{trough} or testosterone concentrations were observed, suggesting that any induction or inhibition properties of enzalutamide on relugolix metabolism result in a neutral net effect on relugolix exposure and testosterone suppression. **Conclusion:** Treatment with relugolix was associated with similar efficacy and safety profiles with and without concomitant enzalutamide or docetaxel. Standard-of-care use of relugolix in combination with these agents is supported by these data.

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. Key Take Home Messages

- Drug exposures in patients who received relugolix with concomitant administration of enzalutamide or docetaxel were similar to those with relugolix alone.
- Treatment with relugolix was associated with a similar safety profiles in a subgroup of men who received concomitant administration of enzalutamide or docetaxel to those observed in patients not receiving those concomitant treatments, with rates of serious adverse events generally more frequent in patients taking combination therapy in both treatment groups likely reflecting the more advanced disease and the safety profile of added therapies.
- Men who received concomitant administration of enzalutamide or docetaxel demonstrated similar testosterone suppression to patients on relugolix alone.

Introduction

Androgen deprivation therapy (ADT) is a cornerstone of prostate cancer treatment and is usually given with gonadotropin-releasing hormone (GnRH) analogues.[1-7] Combination therapy is commonly prescribed in advanced prostate cancer as complementary treatment regimens are believed to induce prostate cancer cell susceptibilities and enhance cancer cell death.[8] Previous clinical trials have demonstrated that ADT combined with other agents lead to improved outcomes versus monotherapy, including ADT combinations with docetaxel, enzalutamide, apalutamide, darolutamide, and abiraterone.[9-16]

Relugolix is an oral, highly selective, nonpeptide GnRH receptor antagonist that is given once daily with an effective half-life of 25 hours.[17-21] In the phase 3 HERO study, relugolix demonstrated suppression of testosterone to castrate levels in 96.7% of patients, which was superior to leuprolide. Relugolix was well tolerated and had a 54% lower risk of major adverse cardiovascular events relative to leuprolide.[22] Consequently, relugolix has been approved in the European Union for the treatment of adult patients with hormone-sensitive advanced prostate cancer[23] as well as in the United States for the treatment of adult patients with advanced prostate cancer.[17]

The absorption of relugolix after oral administration is primarily mediated by P-gp, a transporter that contributes to the active apical efflux of substrates from within enterocytes into the intestinal lumen, limiting intestinal absorption of orally administered drugs.[24] The P-gp-mediated efflux of relugolix is thought to be responsible for limiting the overall extent of absorption (absolute bioavailability of 11.6%) and governing absorption-mediated drug interactions. Inducers or inhibitors of P-gp have been shown to decrease or increase the exposure to relugolix, respectively.

Given the importance of combination therapy in the management of men with advanced prostate cancer, an understanding of potential synergies and drug-drug interactions for key therapies is imperative. Therefore, an assessment of the available clinical safety, efficacy and drug concentration data in patients who received relugolix in combination with enzalutamide or docetaxel from HERO was undertaken.

Patients and Methods

The HERO study was designed to evaluate relugolix in men with advanced prostate cancer and details of design have been previously published (Clinical Trial ID: NCT03085095).[22] In HERO, patients were randomized 2:1 to receive relugolix 120 mg once daily after a loading dose of 360 mg or leuprolide acetate injections every 12 weeks for 48 weeks.

Bicalutamide use was allowed after study initiation to protect against the consequences of the initial testosterone surge.

Addition of enzalutamide or docetaxel was allowed in case of a confirmed PSA progression as defined by the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria[25] or other disease progression in the setting of testosterone suppression to castration levels (< 50 ng/dL). Enzalutamide (160 mg administered orally once daily) or docetaxel (75 mg/m^2 intravenous given in 21 day cycles) were to be dosed as per approved label. Abiraterone acetate was not allowed due to its testosterone lowering capacity, thus interfering with the primary endpoint of the trial. Other therapies that were allowed and could impact testosterone levels included bicalutamide, megestrol, cyproterone, finasteride, goserelin, ketoconazole, medroxyprogesterone, caffeine, chlorphenamine, dihydrocodeine, methylephedrine, paracetamol, degarelix, flutamide, and glycyrrhiza glabra.

For all study participants included in the final analysis dataset, treatment with relugolix was initiated as monotherapy. Patients were instructed to take their study medication while at home once daily, in the morning, at approximately the same time each day, on an empty stomach. During in-clinic visits, the time of administration of relugolix, the blood sample collection times for determination of relugolix predose (trough) plasma concentrations and testosterone serum concentrations were recorded.

Eligibility requirements included men 18 years of age or older with histologically or cytologically confirmed adenocarcinoma of the prostate. Patients needed to be candidates for at least 1 year of continuous androgen-deprivation therapy. Eligible men had one of 3 clinical disease presentations: evidence of biochemical (PSA) or clinical relapse after local primary intervention with curative intent, newly diagnosed hormone-sensitive metastatic disease, or advanced localized disease unlikely to be cured by local primary intervention with curative intent. Patients with major adverse cardiovascular events within 6 months before trial initiation were excluded. Additional inclusion and exclusion criteria can be found in Shore et al.[22]

The trial was approved by the institutional review board or independent ethics committee at each center. Study conduct proceeded in accordance with the requirements of the regulatory authorities of each country and with the provisions of the Declaration of Helsinki and the good clinical practice guidelines of the International Council for Harmonisation. Written informed consent was provided by all patients enrolled in the study prior to any study-related procedures being performed.

Efficacy and Safety Assessments

Assessments included sustained testosterone suppression to castrate levels (<50 ng/dL) from day 29 through 48 weeks. Subgroups analyzed retrospectively included patients with or

without concomitant enzalutamide or docetaxel, the two most commonly utilized advanced prostate cancer concomitant medications during the study. Additionally, a prospectively-defined sensitivity analysis of the primary endpoint was performed excluding patients who received concomitant therapies that may affect testosterone levels.

Efficacy and sensitivity analyses were done in the HERO study primary analysis population,[22] whereas the safety and pharmacokinetic/pharmacodynamics analyses were done in the final analysis population. The final analysis population included additional patients, including additional men with metastatic disease, that were enrolled for the castration resistance-free analysis; efficacy analyses were not prospectively conducted in the final analysis population.

Pharmacokinetic and Pharmacodynamics Analysis With Concomitant Enzalutamide

In a subset of patients (n = 20) whose disease progressed during the study, enzalutamide was prescribed in accordance with prostate cancer treatment guidelines. These patients received combination treatment with enzalutamide and relugolix for a mean of 113.1 days (18.0-266.0 days).

Enzalutamide was taken continuously once initiated during the study with the exception of 2 patients who discontinued then restarted 160 mg enzalutamide after periods of 5 or 34 days, respectively. Additionally, all subjects received a 160-mg dose of enzalutamide for the entire duration of combination treatment with the exception of 2 patients who underwent enzalutamide dose reductions in accordance with prescribing information as recommended for the management of safety and tolerability.

Summary statistics (mean, median, CV%, range) for relugolix trough (predose) and testosterone concentrations were calculated for the specified categories and associated definitions. (1) Relugolix alone: the last relugolix C_{trough} or testosterone concentration available prior to initiation of treatment with enzalutamide. (2) Relugolix + enzalutamide: the C_{trough} or testosterone concentration available after the first 30 days of treatment with enzalutamide (ie, after reaching steady state for enzalutamide).

Results

Patients

The use of concomitant medication overall and use of enzalutamide or docetaxel during HERO study for the primary analysis population and final analysis population is summarized in Table 1. Enzalutamide was the most frequently used therapy in the relugolix group (primary: 2.7%; final: 2.8%), with similar use in the leuprolide group (primary: 1.9%; final: 2.5%). Docetaxel was used by a generally similar percentage of men in the relugolix (primary: 1.3%; final: 2.4%) and leuprolide (primary: 1.6%; final: 3.1%) groups, respectively. In the final analysis population, mean (SD) duration for enzalutamide was 13.9 (10.4) weeks in the relugolix group and 14.0 (10.9) weeks in the leuprolide group. Mean (SD) duration for docetaxel was 7.0 (5.7) 21-day cycles in the relugolix group and 10.2 (11.0) 21-day cycles in the leuprolide group. Median (range) duration for enzalutamide was 12.9 (2.6-38.0) weeks in the relugolix group and 15.7 (0.3-33.7) weeks in the leuprolide group. Median (range) duration for docetaxel was 5.0 (1.0-9.0) 21-day cycles in the relugolix group and 4.0 (1.0-5.0) 21-day cycles in the leuprolide group. All other relevant concomitant therapies were used in <1% of the population, except for bicalutamide, which was used in 26.6% of patients in the leuprolide group, primarily for flare protection, and 1.0% in the relugolix group. Median duration for bicalutamide was 13.1 and 4.0 weeks for relugolix and leuprolide groups, respectively. Baseline characteristics were generally similar for men who took enzalutamide or docetaxel to those who did not, with the exception that a higher percentage of men who received concomitant therapy entering the study with metastatic disease (Table 2).

Efficacy

Sustained castration rates utilizing Kaplan-Meier estimated cumulative probability of testosterone values <50 ng/dL through 48 weeks for the concomitant enzalutamide or docetaxel subgroup are shown in Figure 1. Castration rates were similar with and without concomitant use of enzalutamide or docetaxel. Sustained testosterone suppression below castrate levels (<50 ng per deciliter) from day 29 through 48 weeks in patients who received concomitant enzalutamide or docetaxel was achieved in 95.8% of the men in the relugolix group and 90.9% in men in the leuprolide group. Castration rates were 96.7% and 88.7% for the subgroup of men who did not receive enzalutamide or docetaxel in the relugolix and leuprolide groups, respectively.

Table 3 summarizes the results concomitant medication sensitivity analysis of Kaplan-Meier estimates for sustained castration rate. The estimated castration rates for the sensitivity analysis excluding patients who received concomitant therapies that may affect testosterone levels, such as ENZ and first-generation anti-androgens was 96.9% (95% CI: 95.0%, 98.1%) for relugolix for 48 weeks compared with 89.6% (95% CI: 84.6%, 93.0%) for leuprolide (between group difference, 7.3 percentage points; 95% CI: 2.9%, 11.7%) (Table 3).

Safety

Frequencies of adverse events (AEs) overall were similar between relugolix and leuprolide in patients with or without concomitant use of ENZ or DOC (Table 4). Hot flash was the most common adverse event in both groups (relugolix: with ENZ, 65.0%; with DOC, 70.6%; overall, 53.8%; leuprolide: with ENZ, 44.4%; with DOC, 45.5%; overall, 51.0%). Diarrhea was reported in a higher percentage of patients in the relugolix group (with ENZ, 10.0%; with DOC, 11.8%; overall, 11.4%) than in the leuprolide group (with ENZ, 0%; with DOC, 9.1%; overall, 6.4%). All cases of diarrhea were mild or moderate in intensity (grade 1 or grade 2), and no patient was withdrawn because of diarrhea. Adverse events that started after 30 days postinitiation of enzalutamide or docetaxel were not clinically meaningful (Table S1> and Table S2).

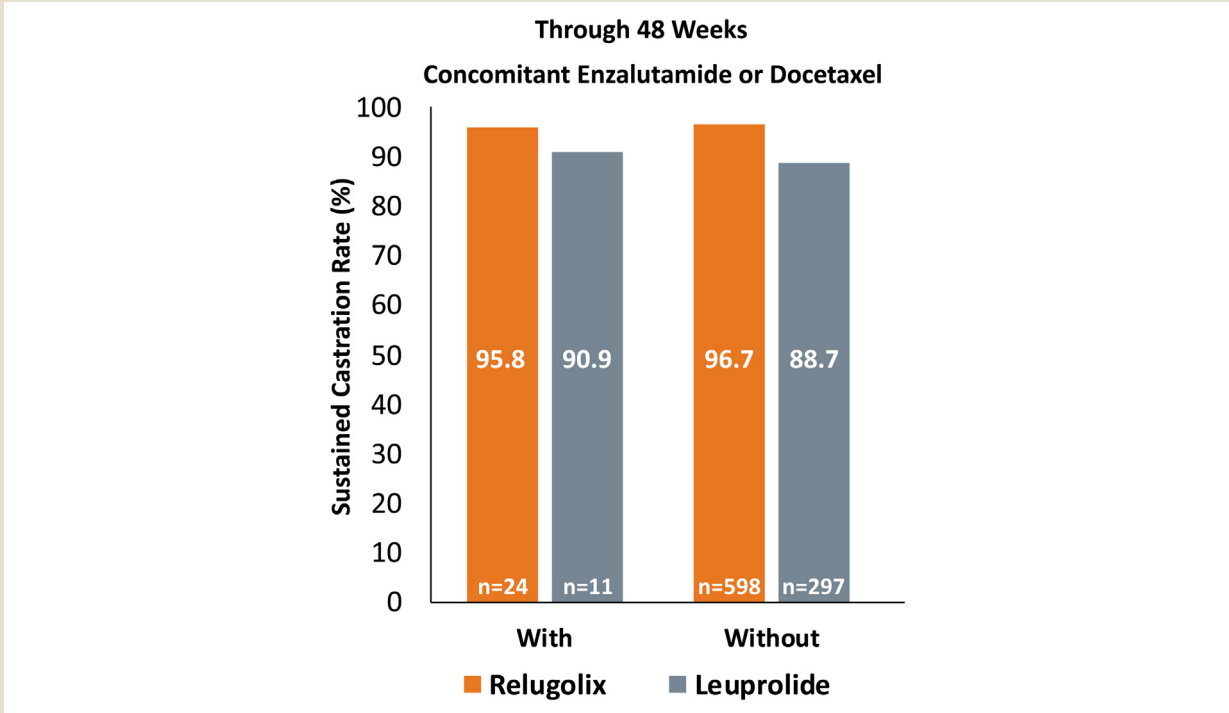
Grade 3 or higher AE frequencies were similar between relugolix and leuprolide in patients with or without concomitant use of ENZ or DOC (with enzalutamide/docetaxel: 37.5% in the relugolix group and 36.4% in the leuprolide group; without enzalutamide/docetaxel: 17.2% in the relugolix group and 19.9% in the leuprolide group;). Concomitant therapy with enzalutamide or docetaxel was associated in higher frequency of serious and fatal AEs in both treatment groups, although patient numbers are too small to make any definitive conclusions.

Table 1 Use of Concomitant Medication Overall and Use of Enzalutamide or Docetaxel During HERO Study (Primary Analysis Population and Final Analysis Population)

	Primary Analysis Population			Final Analysis Population		
	Relugolix (N = 622)	Leuprolide (N = 308)	Total (N = 930)	Relugolix (N = 717)	Leuprolide (N = 357)	Total (N = 1074)
Patients taking therapy that may affect testosterone levels[a]	31 (5.0%)	94 (30.5%)	125 (13.4%)	39 (5.4%)	117 (32.8%)	156 (14.5%)
Enzalutamide	17 (2.7%)	6 (1.9%)	23 (2.5%)	20 (2.8%)	9 (2.5%)	29 (2.7%)
Docetaxel	8 (1.3%)	5 (1.6%)	13 (1.4%)	17 (2.4%)	11 (3.1%)	28 (2.6%)

Percentages are based on the total number of patients in the modified intent-to-treat population for each treatment group or total.
[a] Therapies included bicalutamide, enzalutamide, megestrol, docetaxel, cyproterone, finasteride, goserelin, ketoconazole, medroxyprogesterone, caffeine, chlorphenamine, dihydrocodeine, methylephedrine, paracetamol, degarelix, flutamide, and glycyrrhiza glabra.

Figure 1 Sustained castration rates (Kaplan-Meier Estimated cumulative probability of testosterone values <50 ng/dL through 48 weeks; primary analysis population)



Pharmacokinetic and Pharmacodynamic Analysis With Enzalutamide

Relugolix and testosterone concentrations for relugolix alone and in combination with enzalutamide, in a subgroup of men from the phase 3 HERO study are shown in Table 5. During treatment with relugolix alone and combination therapy with enzalutamide >30 days, mean (SD) relugolix trough concentrations were 9.56 (8.9638) and 10.18 (5.1381) ng/mL, respectively. Corresponding values for testosterone predose concentrations were 10.08 (8.075) and 15.72 (8.338) ng/dL, respectively, demonstrating sustained therapeutic suppression of testosterone concentrations during combination therapy with relugolix and enzalutamide. The geometric mean ratio (GMR; enzalutamide + relugolix/relugolix alone) for relugolix trough concentrations for combination therapy with enzalutamide was 1.286. Although relugolix trough concentrations were slightly higher during combination treatment with enzalutamide, the observed increase is considered not to be clinically meaningful. With respect to testosterone, corresponding value was 1.641. Although testosterone predose concentrations were up to 1.6-fold higher during combination treatment of relugolix and enzalutamide, as shown by the actual mean (SD) values, testosterone concentrations were maintained in the therapeutic range and importantly, well below castration levels of testosterone.

Table 2 Baseline Characteristics (Primary Analysis Population and Final Analysis Population)

	Primary Analysis Population				Final Analysis Population			
	With ENZ/DOC		Without ENZ/DOC		With ENZ/DOC		Without ENZ/DOC	
	Relugolix (N = 24)	Leuprolide (N = 11)	Relugolix (N = 598)	Leuprolide (N = 297)	Relugolix (N = 36)	Leuprolide (N = 20)	Relugolix (N = 681)	Leuprolide (N = 337)
Age category								
≤75 years	18 (75.0%)	9 (81.8%)	426 (71.2%)	211 (71.0%)	28 (77.8%)	17 (85.0%)	481 (70.6%)	237 (70.3%)
>75 years	6 (25.0%)	2 (18.2%)	172 (28.8%)	86 (29.0%)	8 (22.2%)	3 (15.0%)	200 (29.4%)	100 (29.7%)
Age, years								
Median	71.5	69.0	72.0	71.0	69.0	69.0	72.0	71.0
Min, Max	54, 87	58, 79	48, 91	47, 97	52, 87	57, 85	48, 91	47, 97
Geographic region								
North America	8 (33.3%)	1 (9.1%)	174 (29.1%)	86 (29.0%)	13 (36.1%)	4 (20.0%)	195 (28.6%)	98 (29.1%)
South America	1 (4.2%)	0	33 (5.5%)	19 (6.4%)	2 (5.6%)	1 (5.0%)	43 (6.3%)	23 (6.8%)
Europe	7 (29.2%)	9 (81.8%)	240 (40.1%)	113 (38.0%)	11 (30.6%)	12 (60.0%)	260 (38.2%)	123 (36.5%)
Asia	7 (29.2%)	1 (9.1%)	118 (19.7%)	69 (23.2%)	9 (25.0%)	3 (15.0%)	146 (21.4%)	83 (24.6%)
Rest of world	1 (4.2%)	0	33 (5.5%)	10 (3.4%)	1 (2.8%)	0	37 (5.4%)	10 (3.0%)
Disease stage at study entry								
Metastatic	22 (91.7%)	10 (90.9%)	176 (29.4%)	87 (29.3%)	34 (94.4%)	19 (95.0%)	256 (37.6%)	125 (37.1%)
Locally advanced	2 (8.3%)	1 (9.1%)	187 (31.3%)	94 (31.6%)	2 (5.6%)	1 (5.0%)	190 (27.9%)	95 (28.2%)
Localized	0	0	178 (29.8%)	82 (27.6%)	0	0	178 (26.1%)	83 (24.6%)
Clinical disease state presentation								
Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent	5 (20.8%)	2 (18.2%)	304 (50.8%)	156 (52.5%)	7 (19.4%)	3 (15.0%)	317 (46.5%)	164 (48.7%)
Newly diagnosed androgen-sensitive metastatic disease	18 (75.0%)	9 (81.8%)	123 (20.6%)	61 (20.5%)	28 (77.8%)	17 (85.0%)	191 (28.0%)	92 (27.3%)
Advanced localized disease not suitable for primary surgical intervention with curative intent	1 (4.2%)	0	171 (28.6%)	80 (26.9%)	1 (2.8%)	0	173 (25.4%)	81 (24.0%)
ECOG Performance Status								
0	21 (87.5%)	8 (72.7%)	527 (88.1%)	263 (88.6%)	31 (86.1%)	15 (75.0%)	588 (86.3%)	292 (86.6%)
1	3 (12.5%)	3 (27.3%)	71 (11.9%)	33 (11.1%)	5 (13.9%)	5 (25.0%)	93 (13.7%)	44 (13.1%)
3	0	0	0	1 (0.3%)	0	0	0	1 (0.3%)
Mean testosterone level (SD), ng/dL	384.2 (184.7)	386.3 (128.9)	438.2 (157.7)	410.9 (149.9)	401.2 (174.4)	411.0 (180.7)	438.3 (160.7)	408.9 (150.7)

Table 3 Sensitivity Analysis of Kaplan-Meier Estimates for Sustained Castration Rate (Primary Analysis Population)

	Relugolix				Leuprolide			
	No. at Risk[a]	Cumulative No. With Testosterone ≥ 50 ng/dL[b]	Censored	Cumulative Probability[c]	No. at Risk[a]	Cumulative No. With Testosterone ≥ 50 ng/dL[b]	Censored	Cumulative Probability[c]
Concomitant medication sensitivity analysis								
mITT population	622				308			
Day 1	591	0	31	100.0%	214	0	94	100.0%
Day 337	0	17	574	96.9%	0	22	192	89.6%
95% CI at Day 337[d]				(95.0%, 98.1%)				(84.6%, 93.0%)
Difference from leuprolide at Day 337				7.3%				
95% CI for difference from leuprolide at Day 337[e]				(2.9%, 11.7%)				
P-value[f]				.0001				
Hazard ratio to leuprolide (95% CI)[g]				.27 (0.14, .50)				

Abbreviations: CI = confidence interval; mITT = modified intent-to-treat.
Sensitivity analysis was performed to consider patients who had received concomitant medications and herbal supplements that could possibly affect testosterone level as censored at day 1. Day 1 data are included to show sample size.
[a] Number of patients at risk.
[b] Cumulative number of patients with testosterone ≥ 50 ng/dL. For this analysis any patients with testosterone ≥ 50 ng/dL in the first 29 days were censored and not considered an event.
[c] Cumulative probability = Estimated probability of testosterone values < 50 ng/dL.
[d] The 95% CI in each treatment group was calculated by log-log transformation of survival function in each treatment group.
[e] The 95% CI for treatment difference was calculated by linear transformation of the difference in survival function.
[f] Unstratified test statistics via log-log transformation of the difference in survival function at a fixed time point were performed.
[g] Hazard ratio in comparison of relugolix to leuprolide was performed using Cox proportional hazard model.The noninferiority margin for the difference from leuprolide was −10%.

Table 4 Adverse Events for Patients With and Without Concomitant ENZ or DOC (Final Analysis Population)

	Relugolix						Leuprolide					
	With ENZ (N = 20)		With DOC (N = 17)		Overall Population (N = 717)		With ENZ (N = 9)		With DOC (N = 11)		Overall Population (N = 357)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Any AE	20 (100)	8 (40.0)	17 (100)	8 (47.1)	664 (92.6)	136 (19.0)	9 (100)	1 (11.1)	11 (100)	3 (27.3)	330 (92.4)	70 (19.6)
Serious AE	5 (25.0)		5 (29.4)		89 (12.4)		1 (11.1)		2 (18.2)		51 (14.3)	
AEs that occurred in >10% of patients in either group in the overall safety population												
Hot flash	13 (65.0)	0	12 (70.6)	0	386 (53.8)	4 (0.6)	4 (44.4)	0	5 (45.5)	0	182 (51.0)	0
Fatigue	8 (40.0)	0	6 (35.3)	0	158 (22.0)	4 (0.6)	3 (33.3)	0	5 (45.5)	0	68 (19.0)	0
Constipation	3 (15.0)	0	6 (35.3)	0	91 (12.7)	0	3 (33.3)	0	2 (18.2)	0	36 (10.1)	0
Diarrhea	2 (10.0)	0	2 (11.8)	0	82 (11.4)	0	0	0	1 (9.1)	0	23 (6.4)	0
Arthralgia	5 (25.0)	1 (5.0)	2 (11.8)	0	87 (12.1)	0	0	0	1 (9.1)	0	32 (9.0)	0
Hypertension	4 (20.0)	4 (15.0)	1 (5.9)	1 (5.9)	61 (8.5)	15 (2.1)	0	0	0	0	37 (10.4)	2 (0.6)

Abbreviations: AE = adverse event; DOC = docetaxel; ENZ = enzalutamide; ENZ/DOC = ENZ or DOC.
Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. MedDRA Version 22.0.

Table 5 Summary of Relugolix and Testosterone Concentrations for Relugolix Alone and in Combination With Enzalutamide in Phase 3 Study MVT-601-3201 (Final Analysis Population)

Statistics	Relugolix C_{trough} (ng/mL)		Testosterone (ng/dL)	
	Relugolix Alone (n = 20)	Relugolix + Enzalutamide[a] (n = 18)	Relugolix Alone (n =20)	Relugolix + Enzalutamide[a] (n = 18)
Mean (SD)	9.559 (8.9638)	10.167 (5.1381)	10.08 (8.075)	15.72 (8.338)
CV%	93.773	50.536	80.11	53.04
Geometric mean	7.117	9.153	8.43	13.83
Median	7.965	8.390	7.52	12.71
Min, max	1.86, 42.20	2.98, 25.80	3.4, 41.3	4.6, 36.4
GMR[b]	1.286		1.641	

[a] For assessment of the Relugolix + Enzalutamide group, data analyzed include the first the Ctrough or testosterone concentration available after at least 30 days of treatment with enzalutamide (ie, after reaching steady state for enzalutamide). Evaluable data were available from all but two subjects (18/20) who started enzalutamide less than 30 days prior to the last study visit on Week 49.
[b] Geometric Mean Ratio (GMR): Geometric Mean Relugolix + Enzalutamide/Relugolix Alone

Discussion

This subgroup analysis from the HERO study evaluated the impact of concomitant enzalutamide and docetaxel on the efficacy and safety of relugolix treatment. In addition, an analysis was undertaken to evaluate the effect of enzalutamide on relugolix pharmacokinetics in a subgroup of men from the HERO study. Results from these analyses suggested that patients who received concomitant therapy had similar castration rates and safety outcomes relative to the overall population of the HERO study.[22] This substudy is crucial, considering that intensification of ADT with docetaxel and/or an AR pathway inhibitor (ie, enzalutamide, apalutamide, darolutamide, or abiraterone) is now standard of care treatment for patients with metastatic castration-sensitive prostate cancer, high-risk nonmetastatic (nmCRPC) and metastatic (mCRPC) castration-resistant prostate cancer.[3-4] It is thus important to confirm that the administration of relugolix can be safely continued when initiating docetaxel or one of the AR pathway inhibitors.

In the HERO study, treatment with relugolix resulted in a very high testosterone response rate, defined as men achieving sustained testosterone suppression to castrate levels through 48 weeks of treatment.[22] The sustained castration rate of relugolix was statistically superior to that of leuprolide. The safety profile of relugolix in men receiving concomitant enzalutamide/docetaxel was comparable to that observed in the overall population. As expected, cconcomitant therapy with enzalutamide or docetaxel generally resulted in higher frequency of serious and fatal AEs in both treatment groups, although patient numbers are small to make any definitive conclusions. In this analysis, there were not enough patients in these subgroups to evaluate CV-related AEs, where in the overall population relugolix demonstrated a 54% lower risk of major adverse cardiovascular events.[22]

A comprehensive series of nonclinical and clinical studies indicate that relugolix is a P-gp substrate which is the primary determinant of relugolix absorption and oral pharmacokinetics and that coadministration of drugs that inhibit or induce P-gp can effect relugolix oral exposures.[17] With the exception of apalutamide and enzalutamide (strong CYP3A inducers), none of the commonly prescribed prostate cancer drugs demonstrate potential to affect the oral pharmacokinetics of relugolix. Clinically, enzalutamide is a strong CYP3A inducer and moderate CYP2C9 and CYP2C19 inducer and, therefore, also has potential for induction of intestinal P-gp via activation and coregulation by the Pregnane-X-Receptor (PXR). Additionally, enzalutamide is a potent in vitro inhibitor of P-gp (IC_{50} 1.67 μM) at clinically relevant concentrations based on a 160 mg oral dose[26] and, as such, there is potential for mixed-mechanism pharmacokinetic interactions with intestinal P-gp (ie, net inhibition, induction, or no effect). Based on data presented in this analysis, no clinical meaningful differences in the pharmacokinetics of relugolix or in testosterone suppression were observed with co-administration of enzalutamide in the 20 patients receiving both drugs. The lack of effect of enzalutamide on relugolix trough concentrations may be attributed to the net-neutral effect of P-gp induction and inhibition by enzalutamide. Additionally, relugolix is not expected to cause clinically meaningful changes in pharmacokinetics of enzalutamide or docetaxel[26,27] Importantly, these analyses indicate that these drugs can be co-administered with the standard relugolix dosage (120-mg QD).

The current analysis is mainly limited to data with enzalutamide and docetaxel. Although abiraterone was commercially available at the time of the HERO trial, it was not allowed on study, considering that its mode of action would interfere with the primary endpoint of testosterone suppression. The main limitation of the paper is the relatively small number of patients available to make definitive conclusions on the efficacy and safety of relugolix combination regimens for men with advanced prostate cancer. There is currently limited data for relugolix with other concomitant medications and more research is needed to further enhance our overall understanding of the utility of these regimens. There is a clinical study that recently completed enrollment that will give us insight into relugolix combination therapy with abiraterone and apalutamide (NCT04666129). In addition, a study of apalutamide (adjuvant treatment) and ADT in participants who have undergone radical prostatectomy (RP) for nonmetastatic prostate cancer and who are at high risk for metastases showed that relugolix administered at approved standard doses concurrently with apalutamide was effective in maintaining castrate testosterone levels in patients with high-risk localized prostate cancer without new safety signals.[28]

In summary, men who received concomitant administration of enzalutamide or docetaxel demonstrated similar testosterone suppression to patients on relugolix alone. Overall incidence of adverse events was similar between relugolix and leuprolide in patients with or without concomitant therapy. Serious adverse events including death were generally more frequent in patients taking combination therapy in both treatment groups likely reflecting the more advanced disease and the safety profile of added therapies. Standard-of-care use of concomitant relugolix used in combination with these agents is supported by these data. Further prospective studies are justified combining relugolix with other systemic treatment options for advanced prostate cancer.

Clinical Practice Points

- In the phase 3 HERO study, relugolix, a once-daily, oral, highly selective, nonpeptide GnRH receptor antagonist, demonstrated suppression of testosterone to castrate levels in 96.7% of patients, which was superior to leuprolide.
- Relugolix was well tolerated and had a 54% lower risk of major adverse cardiovascular events relative to leuprolide.
- Given the importance of combination therapy in the management of men with advanced prostate cancer, an understanding of potential synergies and drug-drug interactions for key therapies is imperative.
- An assessment of the available clinical safety, efficacy and drug concentration data in patients who received relugolix in combination with enzalutamide or docetaxel from HERO was undertaken.
- Our results indicate that drug exposures in patients who received relugolix with concomitant administration of enzalutamide or docetaxel were similar to those with relugolix alone.
- Treatment with relugolix was associated with a similar efficacy and safety profiles in a subgroup of men who received concomitant administration of enzalutamide or docetaxel to those observed in patients not receiving those concomitant treatments.
- No commonly used oral prostate cancer agents, with the exception of apalutamide, require dose adjustment when coadministered with relugolix.
- Since apalutamide is a transporter and enzyme inducer that is expected to decrease the exposure to relugolix, the dose of relugolix should be doubled during concomitant use.
- Standard-of-care use of relugolix in combination with these agents is supported by these data.

Author Credit Statement

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Disclosure

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Supplemental Tables

Table S1 Adverse Events by the Timing of Initialization of Enzalutamide (Final Analysis Population)

Preferred Term	Relugolix Alone Prior to Enazalutamide (N = 20)	Within 30 Days of Relugolix+enzalutamide (N = 20)	After 30 Days of Relugolix+enzalutamide (N = 20)
No. of patients with at least one AE, n (%)	18 (90.0%)	7 (35.0%)	12 (60.0%)
Hot flush	13 (65.0%)	0	1 (5.0%)
Fatigue	7 (35.0%)	1 (5.0%)	2 (10.0%)
Arthralgia	4 (20.0%)	1 (5.0%)	0
Nausea	3 (15.0%)	0	1 (5.0%)
Pyrexia	3 (15.0%)	0	0
Abdominal pain	2 (10.0%)	0	0
Back pain	2 (10.0%)	0	0
Constipation	2 (10.0%)	0	1 (5.0%)
Depression	2 (10.0%)	0	2 (10.0%)
Diarrhoea	2 (10.0%)	0	0
Dizziness	2 (10.0%)	0	0
Hypertension	2 (10.0%)	1 (5.0%)	1 (5.0%)
Nocturia	2 (10.0%)	0	0
Transaminases increased	2 (10.0%)	0	0
Tumor pain	2 (10.0%)	0	0

Abbreviations: AE = adverse event; N = number of patients in the treatment group; n = number of patients with specified AE.
Patients with multiple events for a given preferred term are counted only once for each preferred term.
Events are sorted by decreasing frequency of preferred term in the relugolix group. Events that occurred in more than one patient in any category were included.
MedDRA Version 22.0.

Table S2 Adverse Events by the Timing of Initialization of Docetaxel (Final Analysis Population)

Preferred Term	Prior to Docetaxel Taken (N = 17)	After Docetaxel Taken Until Last Dose of Docetaxel (N = 17)	After Last Dose of Docetaxel (N = 17)
No. of patients with at least one AE, n (%)	15 (88.2%)	14 (82.4%)	8 (47.1%)
Hot flush	12 (70.6%)	0	1 (5.9%)
Blood alkaline phosphatase increased	3 (17.6%)	0	0
Arthralgia	2 (11.8%)	0	0
Constipation	2 (11.8%)	4 (23.5%)	2 (11.8%)
Fatigue	2 (11.8%)	6 (35.3%)	1 (5.9%)
Gynaecomastia	2 (11.8%)	1 (5.9%)	0
Insomnia	2 (11.8%)	0	0
Nocturia	2 (11.8%)	0	0
Urinary incontinence	2 (11.8%)	0	0
Weight increased	2 (11.8%)	1 (5.9%)	1 (5.9%)
Alanine aminotransferase increased	1 (5.9%)	1 (5.9%)	1 (5.9%)
Alopecia	1 (5.9%)	4 (23.5%)	0
Dizziness	1 (5.9%)	2 (11.8%)	0
Nausea	1 (5.9%)	6 (35.3%)	0
Asthenia	0	2 (11.8%)	0
Decreased appetite	0	2 (11.8%)	0
Dysgeusia	0	2 (11.8%)	0
Neutrophil count decreased	0	2 (11.8%)	0
White blood cell count decreased	0	2 (11.8%)	0

Abbreviations: AE = adverse event; N = number of patients in the treatment group; n = number of patients with specified AE.
Patients with multiple events for a given preferred term are counted only once for each preferred term.
Events are sorted by decreasing frequency of preferred term in the relugolix group. Events that occurred in more than 1 patient in any category were included.
MedDRA Version 22.0.