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Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer

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ABSTRACT

BACKGROUND

Injectable luteinizing hormone–releasing hormone agonists (e.g., leuprolide) are the standard agents for achieving androgen deprivation for prostate cancer despite the initial testosterone surge and delay in therapeutic effect. The efficacy and safety of relugolix, an oral gonadotropin-releasing hormone antagonist, as compared with those of leuprolide are not known.

METHODS

In this phase 3 trial, we randomly assigned patients with advanced prostate cancer, in a 2:1 ratio, to receive relugolix (120 mg orally once daily) or leuprolide (injections every 3 months) for 48 weeks. The primary end point was sustained testosterone suppression to castrate levels (<50 ng per deciliter) through 48 weeks. Secondary end points included noninferiority with respect to the primary end point, castrate levels of testosterone on day 4, and profound castrate levels (<20 ng per deciliter) on day 15. Testosterone recovery was evaluated in a subgroup of patients.

RESULTS

A total of 622 patients received relugolix and 308 received leuprolide. Of men who received relugolix, 96.7% (95% confidence interval [CI], 94.9 to 97.9) maintained castration through 48 weeks, as compared with 88.8% (95% CI, 84.6 to 91.8) of men receiving leuprolide. The difference of 7.9 percentage points (95% CI, 4.1 to 11.8) showed noninferiority and superiority of relugolix ($P<0.001$ for superiority). All other key secondary end points showed superiority of relugolix over leuprolide ($P<0.001$). The percentage of patients with castrate levels of testosterone on day 4 was 56.0% with relugolix and 0% with leuprolide. In the subgroup of 184 patients followed for testosterone recovery, the mean testosterone levels 90 days after treatment discontinuation were 288.4 ng per deciliter in the relugolix group and 58.6 ng per deciliter in the leuprolide group. Among all the patients, the incidence of major adverse cardiovascular events was 2.9% in the relugolix group and 6.2% in the leuprolide group (hazard ratio, 0.46; 95% CI, 0.24 to 0.88).

CONCLUSIONS

In this trial involving men with advanced prostate cancer, relugolix achieved rapid, sustained suppression of testosterone levels that was superior to that with leuprolide, with a 54% lower risk of major adverse cardiovascular events. (Funded by Myovant Sciences; HERO ClinicalTrials.gov number, NCT03085095.)

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Long-acting injectable luteinizing hormone–releasing hormone (LHRH) agonists are commonly used as androgen-deprivation therapy to achieve castrate levels of testosterone in the treatment of advanced prostate cancer. LHRH agonists cause an initial testosterone surge that may result in a clinical flare of symptoms such as bone pain, obstructive urinary symptoms, or, rarely, ureteral obstruction or spinal cord compression.[1,2] Desensitization and down-regulation of the luteinizing hormone–gonadal axis occur over a period of weeks, resulting in delayed suppression of testosterone levels.[3,4] Hence, most guidelines recommend adding an antiandrogen agent for the first few weeks after initiation of an LHRH agonist.[5,6] In addition, LHRH agonists do not fully suppress follicle-stimulating hormone (FSH), a potential mitogenic growth factor for prostate-cancer cells.[7,8]

The gonadotropin-releasing hormone (GnRH) antagonist degarelix is approved as a depot injection for androgen-deprivation therapy and achieves suppression of both luteinizing hormone and FSH through an inhibitory effect on pituitary GnRH receptors. Degarelix results in rapid testosterone suppression without an initial testosterone surge but has not achieved widespread clinical use. Possible reasons for this low use in clinical practice include the need for monthly injections and an incidence of injection-site reactions approaching 40%.[9-11]

Relugolix was developed as an oral, highly selective, GnRH antagonist that is given once daily with an effective half-life of 25 hours. Relugolix rapidly inhibits pituitary release of luteinizing hormone and FSH and has been shown to lower testosterone levels in multiple phase 1 and phase 2 studies.[9,12-14] The goals of the phase 3 HERO trial were to evaluate the efficacy and safety of oral relugolix (at a dose of 120 mg once daily) as compared with leuprolide in men with advanced prostate cancer.

Methods

Trial Design and Oversight

The HERO trial is a multinational, randomized, open-label, phase 3 trial. Patients were enrolled at 155 centers and randomly assigned in a 2:1 ratio to receive either relugolix (120 mg once daily after a single oral loading dose of 360 mg) or leuprolide acetate (22.5 mg [or 11.25 mg in Japan and Taiwan] by injection every 3 months) for 48 weeks. Randomization was stratified according to geographic region (North and South America, Europe, and Asia–Pacific region), the presence or absence of metastatic disease, and age (≤75 and >75 years). Testosterone values for the primary end-point analysis were measured at a blinded central laboratory. In the context of rising prostate-specific antigen (PSA) levels or disease progression despite castration, patients were encouraged to remain in the trial and, if indicated, could receive enzalutamide or docetaxel after the confirmation of PSA progression defined according to Prostate Cancer Clinical Trials Working Group 3 criteria.[15] Testosterone recovery after discontinuation of the trial drug was to be evaluated in a subgroup of approximately 150 patients.

The trial was approved by the institutional review board or independent ethics committee at each center and was conducted 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. All the patients provided written informed consent. The steering committee and the sponsor (Myovant Sciences) jointly designed the trial and reviewed the data with the participation of the authors. Five of the authors wrote the first draft of the manuscript, with professional medical writing assistance funded by Myovant Sciences, and all the authors contributed to subsequent drafts. The authors had full access to the data and assume responsibility for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org).

Patients

Patients were eligible if they were 18 years of age or older, had histologically or cytologically confirmed adenocarcinoma of the prostate, and were candidates for at least 1 year of continuous androgen-deprivation therapy. Eligible patients could have one of three 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 are provided in the trial protocol.

TRIAL END POINTS AND ASSESSMENTS

The primary end point was the sustained castration rate, defined as the cumulative probability of testosterone suppression to less than 50 ng per deciliter during receipt of trial treatment from day 29 through 48 weeks. Key secondary end points for hierarchical testing included noninferiority of relugolix to leuprolide with respect to sustained castration rate with a noninferiority margin of –10 percentage points. If noninferiority was shown, testing for superiority could then be performed.[16] Other key secondary end points included the cumulative probability of testosterone suppression to less than 50 ng per deciliter on day 4 and day 15, the percentage of patients with a PSA response (>50% decrease) at day 15 with confirmation at day 29,[17] the profound castration rate (defined as the cumulative probability of testosterone suppression to <20 ng per deciliter) on day 15, and the FSH level at the end of week 24. Analysis of the key secondary end point of castration resistance–free survival is ongoing and is not reported here. A list of secondary end points is provided in Table S2 in the Supplementary Appendix, available at NEJM.org.

Serum testosterone levels were determined with the use of a validated liquid chromatography–tandem mass spectrometry method sensitive to 2 ng per deciliter. Safety was assessed through clinical laboratory tests, vital-sign measurements, electrocardiography, and reporting of adverse events (assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03). Analysis of additional exploratory end points that are listed in the trial protocol is ongoing.

STATISTICAL ANALYSIS

To calculate the sample size required for the primary efficacy end point of this trial, the cumulative probabilities of sustained testosterone suppression at the end of week 48 were assumed to be 94% for relugolix and 96% for leuprolide, with a dropout rate of 15%. In the relugolix group, 610 enrolled patients were determined to provide approximately 90% power to rule out a fixed probability of sustained testosterone suppression of 90% or less at a two-sided type I error rate of 0.05. For the noninferiority analysis with a noninferiority margin of –10 percentage points and a two-sided type I error rate of 0.05, a total of approximately 915 enrolled patients (610 in the relugolix group and 305 in the leuprolide group) were determined to yield at least 99% power in declaring the noninferiority of relugolix as compared with leuprolide.

This response rate for the primary end point was to be estimated for each treatment group with the use of the Kaplan–Meier method. Patients who did not have testosterone levels of less than 50 ng per deciliter at day 29 or who had any testosterone level of 50 ng or more per deciliter at any subsequent visit were determined to have an event of ineffective castration according to the statistical analysis plan. Data for patients who discontinued treatment before a testosterone level of 50 ng or more per deciliter was observed were censored at the last testosterone assessment before discontinuation.

The efficacy and safety analyses were conducted in all randomly assigned patients who took at least one dose of trial treatment. Additional details regarding the trial design and analysis methods, including a prespecified sensitivity analysis, are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From April 2017 through October 2018, a total of 1327 patients were screened for eligibility, and 934 patients underwent randomization (Fig. S1). A total of 622 patients received relugolix and 308 received leuprolide. The characteristics of the patients at baseline were well balanced between the treatment groups (Table 1). Approximately half (50.2%) of the men enrolled had biochemical recurrence after definitive treatment for prostate cancer; approximately one third (28.9%) of the patients were enrolled in North America, and 11.5% were from Japan. The mean PSA level at baseline was higher in the relugolix group (104.2 ng per milliliter) than in the leuprolide group (68.6 ng per milliliter); the median PSA values were similar in the two groups (11.7 and 9.4 ng per milliliter, respectively). More than 90% of the patients had at least one cardiovascular risk factor across the three main categories assessed, which included lifestyle risk factors such as tobacco use and obesity, cardiovascular risk fac-

tors such as diabetes and hypertension, and a history of a major adverse cardiovascular event. The percentage of patients with these risk factors was similar in the two treatment groups. Treatment adherence (defined as the percentage of expected doses actually taken) was more than 99% in both groups. In the relugolix group, 90.2% of the patients completed 48 weeks of treatment, as compared with 89.0% in the leuprolide group. The median follow-up time in both groups, including the 30-day safety follow-up period for adverse events, was 52 weeks.

EFFICACY

Sustained testosterone suppression below castrate levels (<50 ng per deciliter) from day 29 through 48 weeks was achieved in 96.7% of the patients in the relugolix group (95% confidence interval [CI], 94.9 to 97.9) (Fig. 1A). The leuprolide group had a sustained castration rate of 88.8% (95% CI,

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Relugolix (N=622)	Leuprolide (N=308)	Total (N=930)
Median age (range) — yr	72 (48–91)	71 (47–97)	71 (47–97)
Age category — no. (%)			
≤75 yr	444 (71.4)	220 (71.4)	664 (71.4)
>75 yr	178 (28.6)	88 (28.6)	266 (28.6)
Geographic region — no. (%)			
North and South America	216 (34.7)	106 (34.4)	322 (34.6)
North America	182 (29.3)	87 (28.2)	269 (28.9)
Europe	247 (39.7)	122 (39.6)	369 (39.7)
Asia–Pacific region	159 (25.6)	80 (26.0)	239 (25.7)
Presence of metastatic disease — no. (%)	198 (31.8)	97 (31.5)	295 (31.7)
Clinical disease presentation — no. (%)			
Evidence of biochemical or clinical relapse after local primary intervention with curative intent†	309 (49.7)	158 (51.3)	467 (50.2)
Newly diagnosed androgen-sensitive metastatic disease	141 (22.7)	70 (22.7)	211 (22.7)
Advanced localized disease not suitable for primary surgical intervention with curative intent	172 (27.7)	80 (26.0)	252 (27.1)
Gleason score — no. (%)‡			
2–4	0	1 (0.3)	1 (0.1)
5–6	98 (15.8)	46 (14.9)	144 (15.5)
7	237 (38.1)	122 (39.6)	359 (38.6)
8–10	267 (42.9)	134 (43.5)	401 (43.1)
Missing data	20 (3.2)	5 (1.6)	25 (2.7)
ECOG performance status — no. (%)§			
0	548 (88.1)	271 (88.0)	819 (88.1)
1	74 (11.9)	36 (11.7)	110 (11.8)
3¶	0	1 (0.3)	1 (0.1)
Previous androgen-deprivation therapy — no. (%)	81 (13.0)	30 (9.7)	111 (11.9)
Previous radiotherapy — no. (%)	190 (30.5)	92 (29.9)	282 (30.3)
PSA level — ng/ml			
Mean	104.2±416.0	68.6±244.0	92.4±368.3
Median	11.7	9.4	10.8
Testosterone level — ng/dl	436.1±159.0	410.0±149.1	427.5±156.2

Table 1. (Continued.)

Characteristic	Relugolix (N=622)	Leuprolide (N=308)	Total (N=930)
FSH level — IU/liter‖	16.3±12.8	16.7±14.5	16.4±13.4
Cardiovascular risk factors — no. (%)**	570 (91.6)	290 (94.2)	860 (92.5)
Lifestyle risk factors††	422 (67.8)	202 (65.6)	624 (67.1)
Cardiovascular or cerebrovascular risk factors‡‡	488 (78.5)	254 (82.5)	742 (79.8)
History of MACE§§	84 (13.5)	45 (14.6)	129 (13.9)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. FSH denotes follicle-stimulating hormone, MACE major adverse cardiovascular event, and PSA prostate-specific antigen.
† Biochemical relapse was defined by a rising PSA level.
‡ Gleason scores range from 2 to 10, with higher scores indicating a worse prognosis.
§ Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with higher scores reflecting greater disability.
¶ One patient in the leuprolide group had a surgical vascular procedure on his leg and was given an ECOG score of 3 at screening because of the use of crutches. By the baseline day 1 visit, the patient no longer used crutches, and his ECOG score had improved to 0.
‖ The normal range of FSH values for adults is 1.5 to 12.4 IU per liter.
** Patients with multiple risk factors were counted only once.
†† Lifestyle risk factors included tobacco smoking (current or past), heavy alcohol use, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 30.
‡‡ Cardiovascular or cerebrovascular risk factors included prespecified event terms in the MACE query and a manual search of known risk factors, including hypertension; dyslipidemia; diabetes; a history of myocardial infarction or cardiovascular disease; a history of stroke, transient ischemic attack, or cerebral hemorrhage; peripheral arterial disease; atrial fibrillation and other arrhythmias; heart-valve disease; chronic obstructive pulmonary disease; chronic kidney disease; chronic liver disease; carotid-artery stenosis or occlusion; venous thromboembolic events; and heart failure.
§§ Search criteria included "myocardial infarction" (broad standardized *Medical Dictionary for Regulatory Activities* [MedDRA] query) and "central nervous system hemorrhages and cerebrovascular conditions" (broad standardized MedDRA query).

84.6 to 91.8), and the sustained castration rate in the relugolix group was determined to be noninferior to that in the leuprolide group (between-group difference, 7.9 percentage points; 95% CI, 4.1 to 11.8). The lower boundary of the 95% confidence interval for the between-group difference was above zero, which showed the superiority of relugolix over leuprolide (P<0.001) (Fig. 1A). The results of the primary end-point and noninferiority analyses were consistent across a broad range of subgroups (Fig. S2). The results of the Kaplan–Meier analysis for sustained castration rate are provided in Table S1.

All key secondary end points showed superiority of relugolix over leuprolide (P<0.001) (Table 2). These end points included the cumulative probability of castration on day 4 (56.0% vs. 0%) and on day 15 (98.7% vs. 12.0%) and of testosterone suppression to profound castrate levels (<20 ng per deciliter) on day 15 (78.4% vs. 1.0%). The percentage of patients with a confirmed PSA response at day 15 was 79.4% with relugolix and 19.8% with leuprolide (P<0.001). Waterfall plots for the maximal decrease in the PSA level in the first 29 days are provided in Figure S3. FSH suppression was greater with relugolix than with leuprolide at all available time points, with FSH levels in the leuprolide group increasing after day 29 until the end of the trial (Fig. S4A). At the end of week 24, mean FSH levels were 1.72 IU per liter in the relugolix group and 5.95 IU per liter in the leuprolide group (P<0.001). Luteinizing hormone levels during the trial are provided in Figure S4B.

Testosterone suppression to castrate levels occurred rapidly in the relugolix group, with a mean testosterone level on day 4 of 38 ng per deciliter. Testosterone was then maintained at castrate levels throughout the treatment period (Fig. 1B). In contrast, a surge in testosterone levels from baseline resulted in a mean testosterone level of 625 ng per deciliter at day 4 in the leuprolide group before decreasing to castrate levels at day 29 and remaining at castrate levels thereafter. Mean testosterone levels at 90 days after treatment discontinuation in the testosterone recovery subgroup (184 patients) were 288.4 ng per deciliter in the relugolix group and 58.6 ng per deciliter in the leu-

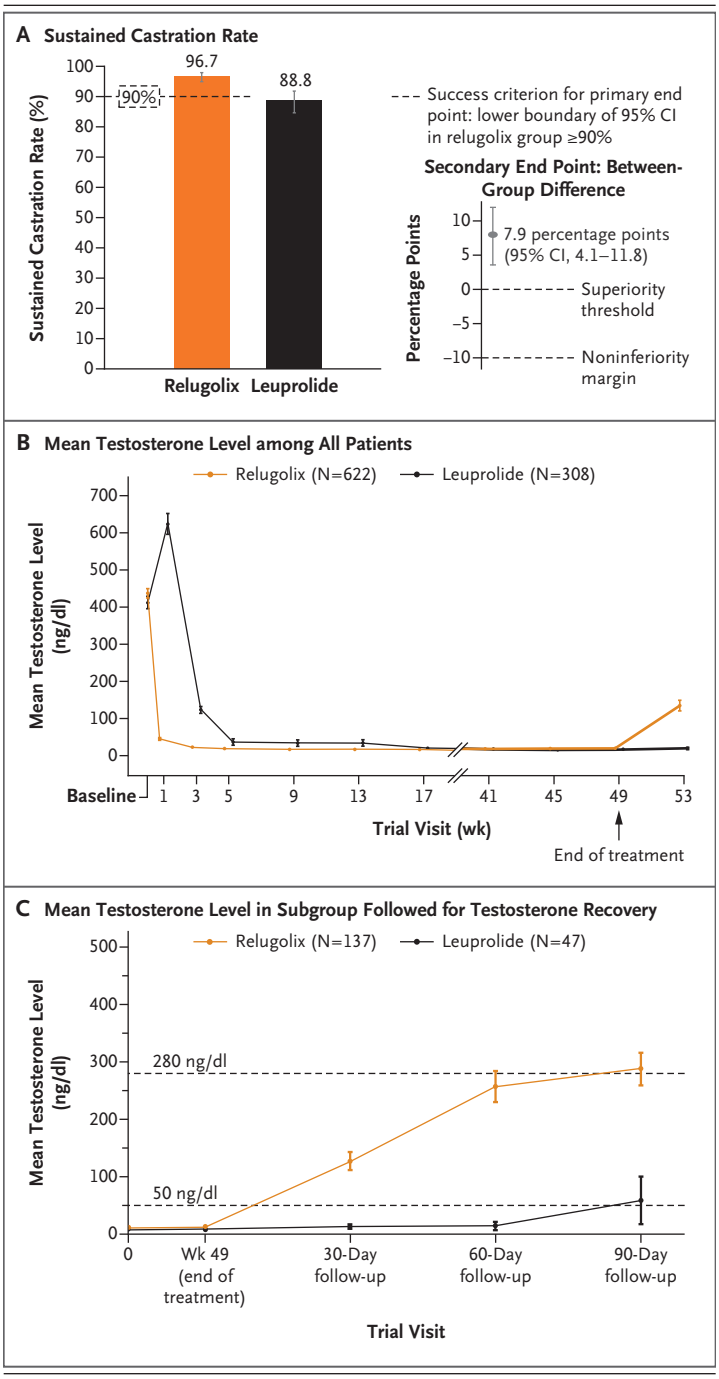

Figure 1. Efficacy Assessments.

Panel A depicts the sustained castration rate (defined as the cumulative probability of testosterone suppression to <50 ng per deciliter through 48 weeks) in the relugolix and leuprolide groups. The criterion for success with respect to the primary end point was a lower boundary of the 95% confidence interval in the relugolix group of 90% or higher; the lower boundary was 94.9%, so this criterion was met. The criterion for the secondary end point of noninferiority to leuprolide was also met, with the lower boundary of the 95% confidence interval for the difference between the relugolix group and the leuprolide group above the noninferiority margin of –10 percentage points. If noninferiority was shown, testing for superiority was permitted; superiority was shown because the lower boundary of the 95% confidence interval for the between-group difference was above zero. Panel B depicts mean testosterone levels over time, including testosterone recovery 30 days after discontinuation of trial treatment at the end of week 48. Panel C depicts the mean testosterone levels in the cohort of 184 patients followed for testosterone recovery 90 days after discontinuation of trial treatment at the end of week 48. The I bars indicate 95% confidence intervals.

prolide group (Fig. 1C). The percentage of patients with testosterone recovery to at least 280 ng per deciliter (the lower limit of the normal range) at 90 days was 54% in the relugolix group and 3% in the leuprolide group (nominal P=0.002).

SAFETY

The overall incidence of adverse events was consistent across treatment groups (Table 3). Hot flash was the most common adverse event in both groups (54.3% in the relugolix group and 51.6% in the leuprolide group). Diarrhea was reported in a higher percentage of patients in the relugolix group (12.2%) than in the leuprolide group (6.8%). All cases of diarrhea were mild or moderate (grade 1 or grade 2), and no patient was withdrawn because of diarrhea. No substantial difference between treatment groups was observed in the incidence of increases in levels of hepatic aminotransferases that were at least 3 times the upper limit of the normal range (1.4% in the relugolix group and 1.3% in the leuprolide group).

Fatal events were reported for 1.1% of the patients in the relugolix group and 2.9% of those in the leuprolide group (Table 3). In a prespecified safety analysis, major adverse cardiovascular events were defined as nonfatal myocardial infarction, nonfatal stroke, and death from any cause. After 48 weeks of treatment, the incidence of major adverse cardiovascular events was 2.9% (exact 95% CI, 1.7 to 4.5) in the relugolix group and 6.2% (exact 95% CI, 3.8 to 9.5) in the leuprolide group. Kaplan–Meier estimates of the incidence rate were consistent with a 54% lower risk (hazard ratio, 0.46; 95% CI, 0.24 to 0.88) in the relugolix group than in the leuprolide group (Fig. 2). In the subgroup of patients with a reported medical history of these events, the incidence of major

Table 2. Key Secondary Efficacy End Points.

Secondary End Point	Relugolix (N=622)	Leuprolide (N=308)	P Value
Noninferiority analysis for sustained castration rates — %*	96.7	88.8	<0.001†
Cumulative probability of testosterone suppression to <50 ng/dl on day 4 — %	56.0	0	<0.001
Cumulative probability of testosterone suppression to <50 ng/dl on day 15 — %	98.7	12.0	<0.001
PSA response at day 15 followed by confirmation at day 29 — %‡	79.4	19.8	<0.001
Cumulative probability of profound testosterone suppression to <20 ng/dl on day 15 — %	78.4	1.0	<0.001
Mean FSH level at end of wk 24 — IU/liter	1.72	5.95	<0.001

* The sustained castration rate was defined as the cumulative probability of testosterone suppression to less than 50 ng per deciliter through 48 weeks.
† The between-group difference was 7.9 percentage points (95% confidence interval, 4.1 to 11.8). Because the lower boundary of the 95% confidence interval (4.1 percentage points) was higher than the noninferiority margin of –10 percentage points, noninferiority of relugolix as compared with leuprolide was shown. The P value is for the test of superiority of relugolix to leuprolide.
‡ A PSA response was defined as a decrease of more than 50% in the PSA level.

Table 3. Adverse Events.*

Event	Relugolix (N=622)		Leuprolide (N=308)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any adverse event — no. (%)	578 (92.9)	112 (18.0)	288 (93.5)	63 (20.5)
Serious adverse event — no. (%)	76 (12.2)	61 (9.8)	47 (15.3)	35 (11.4)
Fatal adverse event — no. (%)	7 (1.1)	—	9 (2.9)	—
MACE — no. (%)†	18 (2.9)	8 (1.3)	19 (6.2)	4 (1.3)
Without a history of MACE — no./total no. (%)	15/538 (2.8)	—	11/263 (4.2)	—
With a history of MACE — no./total no. (%)	3/84 (3.6)	—	8/45 (17.8)	—
Adverse events that occurred in >10% of patients in either group — no. (%)				
Hot flash	338 (54.3)	4 (0.6)	159 (51.6)	0
Fatigue	134 (21.5)	2 (0.3)	57 (18.5)	0
Constipation	76 (12.2)	0	30 (9.7)	0
Diarrhea	76 (12.2)	0	21 (6.8)	0
Arthralgia	75 (12.1)	2 (0.3)	28 (9.1)	0
Hypertension	49 (7.9)	10 (1.6)	36 (11.7)	2 (0.6)

* Shown are the number of patients with an event, rather than the number of events. Adverse events were evaluated with the use of MedDRA, version 22.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
† Search criteria included "myocardial infarction" (broad standardized MedDRA query), "central nervous system hemorrhages and cerebrovascular conditions" (broad standardized MedDRA query), and deaths from any cause.

adverse cardiovascular events during receipt of the trial drug was 3.6% (3 of 84 patients) in the relugolix group and 17.8% (8 of 45 patients) in the leuprolide group, which indicates that the odds of having an event were 4.8 times as high with leuprolide as with relugolix (Table 3). The cumulative incidence of major adverse cardiovascular events over the 48-week treatment period is shown in Figure 2.

DISCUSSION

This globally conducted, prospective, phase 3 trial involving men with advanced prostate cancer

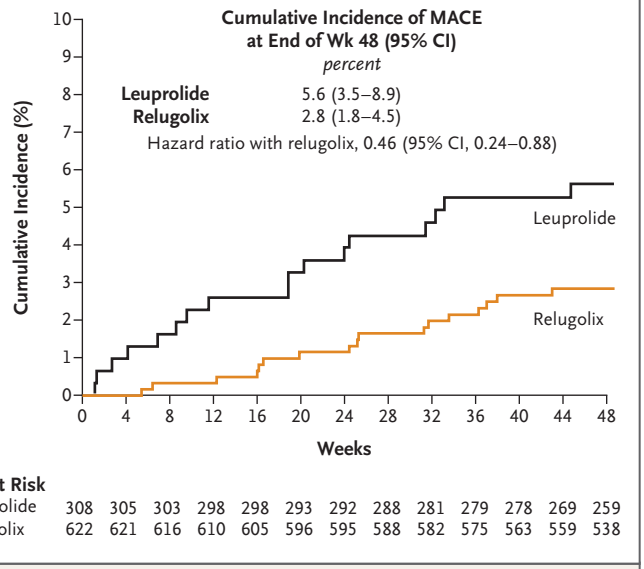

Figure 2. Cumulative Incidence of Major Adverse Cardiovascular Events (MACE).

Kaplan–Meier curves show the cumulative incidence of MACE in the relugolix group and the leuprolide group through 48 weeks of treatment. The hazard ratio was based on a Cox regression model.

evaluated the ability of an oral GnRH antagonist, relugolix, as compared with the depot-injection mainstay LHRH agonist, leuprolide, to achieve androgen deprivation. Treatment with relugolix resulted in a 96.7% response rate, defined as men achieving sustained testosterone suppression to castrate levels through 48 weeks of treatment. The sustained castration rate of relugolix was statistically superior to that of leuprolide. High response rates in the relugolix group were observed across the subgroups analyzed.

Since the discovery of the GnRH pathway by Schally et al. in 1971,[18] LHRH agonists have become the standard treatment for men with advanced prostate cancer. The development of safe and effective GnRH antagonists has proved to be difficult[19]; hence, LHRH agonists were developed. When administered on a long-term basis, LHRH agonists desensitize the pituitary receptor and suppress the production of luteinizing hormone and testosterone, thus blocking the pulsatile secretion of GnRH by the hypothalamus. At the time of first administration, and to a lesser extent on repeat administration, LHRH agonists result in an acute rise in luteinizing hormone, FSH, and testosterone and delayed testosterone suppression. The clinical implications of this acute testosterone surge are still debated, as is the value of antiandrogen pretreatment.[20,21] Furthermore, long-term administration of LHRH agonists fails to suppress FSH, the significance of which is undetermined.[8,10] Less well explored is the possibility that LHRH agonists may stimulate extrapituitary receptors, such as those expressed in the heart, prostate, and bladder.[22]

Injectable peptide and oral nonpeptide antagonists directly and rapidly suppress both luteinizing hormone and FSH, as well as testosterone, although safety concerns such as injection-site and hypersensitivity reactions have limited their use.[1,10,12,19,23,24] Degarelix, which is administered by injection, is the only commercially available GnRH antagonist.[11]

The oral GnRH antagonist relugolix rapidly lowered testosterone to castrate levels by day 4 in this trial. In contrast, mean testosterone levels in the leuprolide group first surged to more than 600 ng per deciliter, then declined to castrate levels by day 29. Not only does treatment with relugolix avoid the risks of a surge in testosterone and the need for an antiandrogen to prevent the flare of symptoms,[1,2] but the rapid suppression of testosterone may also be beneficial for clinicians and patients when considering additional antineoplastic interventions such as radiation or chemotherapy. The literature suggests that the beneficial effects of radiation are dependent on androgen deprivation.[25,26]

One of the main advantages of the oral formulation is the higher percentage of patients with testosterone recovery within the normal range 90 days after discontinuation of treatment in the relugolix group than in the leuprolide group (54% vs. 3%). A similar finding was observed when testosterone recovery was assessed in patients treated with relugolix for 6 months or with monthly injections of degarelix.[14] The testosterone recovery that we observed with relugolix may have meaningful clinical relevance for men receiving intermittent therapy, those receiving a short course of androgen-deprivation therapy (as is commonly administered in the context of radiation therapy), or those who may want to discontinue treatment to recover from a serious and debilitating complication. Intermittent androgen-deprivation therapy that is monitored by means of PSA levels is a potential option for patients with prostate cancer, because studies have shown improved quality-of-life outcomes

with noninferior overall survival as compared with continuous therapy.[6,27,28] Relugolix resulted in rapid and sustained testosterone suppression in men with intermediate-risk localized disease who received 6 months of neoadjuvant or adjuvant androgen-deprivation therapy in conjunction with external-beam radiotherapy.[14]

A lower incidence of major adverse cardiovascular events was reported in the relugolix group than in the leuprolide group in a prespecified safety analysis, with a higher incidence of grade 1 or 2 diarrhea. After 48 weeks of treatment, the risk of major adverse cardiovascular events was 54% lower in the relugolix group than in the leuprolide group. Further subgroup analysis suggests that this difference may have been even greater in patients with preexisting cardiovascular risk factors. These cardiovascular findings are supported by a large meta-analysis that pooled data from six phase 3, prospective, randomized studies for which 2328 men were recruited between 2005 and 2012.[29] Among men with preexisting cardiovascular disease, the risk of cardiac events within 1 year after initiation of therapy was significantly lower among men treated with a GnRH antagonist than among those treated with LHRH agonists (hazard ratio, 0.44; 95% CI, 0.26 to 0.74; P=0.002).[29] A prospective phase 2 study showed an absolute risk reduction in major cardiovascular and cerebrovascular events at 12 months with the use of GnRH antagonists as compared with LHRH agonists.[30] The mechanism by which LHRH agonists increase the near-term risk of major adverse cardiovascular events is unclear, although it is speculated that LHRH agonists may promote plaque destabilization and rupture.[31,32]

The increased risk of cardiovascular events among men with prostate cancer treated with leuprolide is noteworthy, because death from cardiovascular causes is the leading cause of death in patients with prostate cancer and now accounts for 27 to 34% of deaths, given improved therapies for prostate cancer.[33,34] Approximately 30% of men with prostate cancer have known cardiovascular disease, and many more of these patients have risk factors, including obesity, diabetes, hypertension, and hyperlipidemia.[35] In the HERO trial, more than 90% of men had cardiovascular risk factors. Key baseline characteristics, including age, metastatic disease, a history of major adverse cardiovascular events, and other cardiovascular risk factors, were similar in the two treatment groups. Men with prostate cancer, depending on the presence of cardiovascular risk factors, are estimated to have a yearly incidence of major adverse cardiovascular events of approximately 2 to 3%,[36-38] similar to that observed in the relugolix group and two to three times lower than that observed in the leuprolide group. Prescribing information for LHRH agonists already contains warnings about increased risk of myocardial infarction, sudden cardiac death, and stroke.

Although other oral treatments are now commonly used for men with advanced and castration-resistant prostate cancer, concern remains about adherence to oral therapies. Treatment adherence with oral relugolix was more than 99% and similar to that of injectable leuprolide. These findings are consistent with reported real-world adherence rates for the oral androgen axis–directed therapies used in castration-resistant prostate cancer, which have shown adherence rates of 92 to 96%.[39,40]

In the HERO trial, the oral GnRH antagonist relugolix showed sustained testosterone suppression superior to that of leuprolide and a 54% lower risk of major adverse cardiovascular events than with leuprolide.

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