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ADIS DRUG EVALUATION

Relugolix: A Review in Advanced Prostate Cancer

Matt Shirley[1]

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Abstract

Relugolix (Orgovyx®), an orally active nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist that provides rapid testosterone suppression, is indicated in the USA for the treatment of advanced prostate cancer and in the EU for advanced hormone-sensitive prostate cancer. In the pivotal phase III HERO trial in men with advanced prostate cancer, once-daily oral relugolix (with a loading dose on day 1) led to a sustained castration rate over 48 weeks of treatment of > 90%, a rate that was non-inferior to that provided by intramuscular leuprolide depot every 3 months (with an exploratory analysis further indicating the superiority of relugolix over leuprolide). Relugolix was generally well tolerated, having an adverse event profile that is consistent with testosterone suppression. Furthermore, there is evidence that relugolix may be associated with a lower risk of major adverse cardiac events compared with leuprolide. With the ability to provide the rapid testosterone suppression (with no initial surge in testosterone upon treatment initiation) combined with the benefits of oral administration and potentially improved cardiac safety, relugolix presents a valuable treatment option for men with advanced prostate cancer where androgen deprivation therapy is indicated.

Plain Language Summary

Androgen deprivation therapy (ADT), a key component of prostate cancer treatment, reduces testosterone production to slow disease progression. Relugolix (Orgovyx®), from a class of drugs known as gonadotropin-releasing hormone (GnRH) receptor antagonists, is approved for the treatment of advanced prostate cancer. Whereas some ADT agents (i.e. GnRH agonists) produce an initial surge in testosterone levels (with the potential to cause a flare in disease symptoms), GnRH receptor antagonists, of which relugolix is the first available as an oral medication, provide rapid testosterone suppression with no initial surge. In a key clinical trial in men with advanced prostate cancer, once-daily relugolix provided sustained castration in > 90% of patients, with a sustained castration rate that was non-inferior to that of a comparator agent (leuprolide) administered by intramuscular injection every 3 months. Relugolix was generally well tolerated and may be associated with a lower risk of major adverse cardiac events than leuprolide. Providing rapid and sustained testosterone suppression, combined with the benefits of oral administration and potentially improved cardiac safety, relugolix presents a valuable treatment option for ADT in men with advanced prostate cancer.

Digital Features for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.21721880.

Relugolix: clinical considerations in advanced prostate cancer

The first approved oral GnRH receptor antagonist; administered once daily
Provides rapid and sustained testosterone suppression
Most adverse events (e.g. hot flush) are consistent with testosterone suppression
Based on a descriptive analysis without formal adjudication, has a reduced risk of major adverse cardiac events compared with leuprolide

The manuscript was reviewed by: *K. Araki*, Department of Medical Oncology, Gunma Prefectural Cancer Center, Gunma, Japan; *B. A. Siddiqui*, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

✉ Matt Shirley
demail@springer.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

1 Introduction

Androgen deprivation therapy (ADT), which involves the inhibition of testosterone production, is a key component of standard-of-care treatment for locally advanced, recurrent or metastatic prostate cancer [1–4]. Additionally, antiandrogen agents can be used in ADT to block the effects of testosterone on prostate cancer cells. Most commonly, ADT involves the use of a gonadotropin-releasing hormone (GnRH) agonist [also known as luteinizing-releasing hormone (LHRH) agonists] (e.g., goserelin, histrelin, leuprolide, triptorelin), either alone or in combination with external beam radiation therapy or other systemic therapeutic agents [1–4]. Although effective as ADT, the initiation of GnRH agonist therapy is associated with an initial acute (1–3-week) surge in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone [5]. While the clinical significance of a surge in testosterone levels (including the potential for tumor flare with a worsening of symptoms) remains debated [6], an antiandrogen agent (e.g., bicalutamide, flutamide, nilutamide) may be necessary during the initial period of GnRH agonist treatment to counter the effects of a testosterone surge in some patients [1].

In contrast to GnRH agonists, GnRH receptor antagonists, which represent a separate class of ADT agents, are not associated with a testosterone surge upon treatment initiation [7]. The two currently available GnRH antagonists indicated for the treatment of advanced prostate cancer are degarelix [8], a synthetic linear decapeptide amide which is administered by subcutaneous injection, and relugolix (Orgovyx®) [9, 10], which was developed as an orally active nonpeptide GnRH receptor antagonist agent and is the subject of this article.

Relugolix is approved in the USA for the treatment of advanced prostate cancer [9] and in the EU for advanced hormone-sensitive prostate cancer [10]. This article reviews the clinical data relating to the efficacy and tolerability of relugolix during use in this indication and summarizes the pharmacological properties of the drug.

2 Pharmacodynamic Properties of Relugolix

Relugolix is a nonpeptide, small molecule potent GnRH receptor antagonist which acts through competitive inhibition, competing with native GnRH for binding of the GnRH receptor in the anterior pituitary gland [9–11]. Oral administration of relugolix leads to potent and continuous suppression of the hypothalamic-pituitary-gonadal axis [9–11]. Upon initiation of relugolix treatment, LH and FSH concentrations rapidly decline [9, 10, 12], leading to reduced testosterone levels (Sect. 4). In contrast to what can occur with the use of GnRH agonists, no initial increases in FSH, LH, and testosterone levels are observed upon initiation of relugolix treatment [10, 12].

The effects of relugolix treatment on pituitary hormone levels are reversible [11], with FSH and LH levels returning to physiologic concentrations following relugolix discontinuation [9, 10]. Testosterone levels may also recover to baseline or normal levels after treatment discontinuation (Sect. 4).

3 Pharmacokinetic Properties of Relugolix

Relugolix is a substrate for P-glycoprotein (P-gp), and intestinal P-gp efflux is believed to contribute to the drug's limited bioavailability (mean absolute bioavailability = 12%) [13, 14]. Exposure to relugolix is decreased by approximately 20% when taken with a high-calorie high-fat meal, but the effect is not considered to be clinically meaningful and the drug can be taken without regard to food [9, 10]. Relugolix is rapidly absorbed following oral administration, with an initial concentration peak observed approximately 0.5 h post dose [13, 14]. Multiple subsequent absorption peaks follow, with a peak plasma concentration observed at a median time of 2.25 h. Although relugolix absorption is primarily mediated by intestinal P-gp, at higher doses a greater proportion of drug absorption occurs through passive diffusion [10]. Exposure to relugolix is approximately dose proportional over the dose range of 80 to 360 mg [9, 10]. With a loading dose of 360 mg on day 1 followed by once-daily administration of relugolix 120 mg, steady-state plasma concentrations are achieved by day 7 with an approximate twofold accumulation. Approximately 70% of relugolix is bound to plasma proteins, primarily albumin. The drug has a mean blood-to-plasma ratio of 0.78 [9, 10], indicating limited distribution into red blood cells [13]. Relugolix has an estimated volume of distribution at steady state of 3900 L, indicating wide distribution to tissues [9, 10].

Relugolix concentrations decline in a multiphasic manner, with an initial rapid decline followed by a slower phase of decline and a long terminal elimination phase [13, 14]. The drug has a mean effective half-life of 25 h and a mean terminal elimination half-life of 60.8 h [9, 10]. While unchanged drug is the primary drug-related component in plasma, elimination of relugolix primarily involves metabolism, mainly via CYP3A4/5 (45%) and CYP2C8 (37%), based on in vitro studies [13, 14]. Additionally, unabsorbed drug is metabolized by intestinal microflora. After administration of a single radiolabeled dose of relugolix, approximately 80.6% and 4.1% of the dose was recovered in feces and urine, respectively. Approximately 2.2% was excreted in urine as unchanged drug, representing approximately 19% of the total absorbed drug.

3.1 Potential Drug Interactions

In a drug interaction study, the co-administration of relugolix and erythromycin (a P-gp and moderate CYP3A inhibitor) was associated with increased exposure to relugolix, resulting from the inhibition of intestinal P-gp by erythromycin leading to increased relugolix oral bioavailability [9, 10]. Therefore, due to an increased risk of adverse events associated with relugolix, the co-administration of relugolix and oral P-gp inhibitors should be avoided (Sect. 6). If co-administration cannot be avoided, relugolix should be taken first and dosing should be separated by ≥ 6 h; alternatively, relugolix treatment can be interrupted for up to 2 weeks if a short course of a P-gp inhibitor is required [9, 10].

In another drug interaction study, the co-administration of relugolix with rifampicin (a P-gp and strong CYP3A inducer) was associated with decreased relugolix exposure, resulting from decreased relugolix oral bioavailability and increased CYP3A-mediated relugolix metabolism [9, 10]. Therefore, given the potential for the interaction to reduce relugolix therapeutic effects, the co-administration of relugolix and combined P-gp and strong CYP3A inducers should be avoided; if co-administration cannot be avoided, the relugolix dose should be increased to 240 mg once daily (returning to the 120-mg once-daily dose after discontinuation of the combined P-gp and strong CYP3A inducer) [9, 10].

4 Therapeutic Efficacy of Relugolix

Following the demonstration in phase I [15, 16] and phase II [17–19] trials of the ability of relugolix to lower testosterone levels, its efficacy was compared with that of leuprolide in the multinational, randomized, open-label, phase III HERO trial in men with advanced prostate cancer (Fig. 1) [12]. In HERO, 934 men (≥ 18 years of age) with histologically or cytologically confirmed prostate cancer were randomized 2:1 to receive oral relugolix 120 mg once daily (after a single oral loading dose of 360 mg) or intramuscular leuprolide 22.5 mg (or 11.25 mg in Japan and Taiwan, in accordance with local prescribing information) depot every 3 months for 48 weeks. Randomization was stratified based on geographical region (North and South America, Europe, Asia-Pacific region), the presence of metastatic disease (yes or no), and age (≤ 75 years or > 75 years) [12]. Eligible patients were candidates for at least 1 year of continuous ADT and could have one of three clinical disease state presentations: evidence of biochemical relapse [i.e. rising prostate-specific antigen (PSA)] or clinical relapse following local primary intervention with curative intent (representing 50.2% of the randomized population); newly diagnosed androgen-sensitive metastatic disease (22.7%); or advanced localized disease not suitable for local primary intervention with curative intent (27.1%) [12]. Patients with myocardial infarction, unstable symptomatic ischemic heart disease, cerebrovascular events or any significant cardiac condition within 6 months prior to the trial were excluded [12].

The primary endpoint of the trial was the sustained castration rate (defined as the cumulative probability of testosterone suppression to < 50 ng/dL, estimated using the Kaplan–Meier method) from day 29 through 48 weeks [12]. Under the trial protocol, the primary endpoint was evaluated under two criteria to support assessment requirements for different regulatory authorities (Table 1). For Evaluation Criterion 1, the primary endpoint was considered to be met if the lower bound of the 95% confidence interval

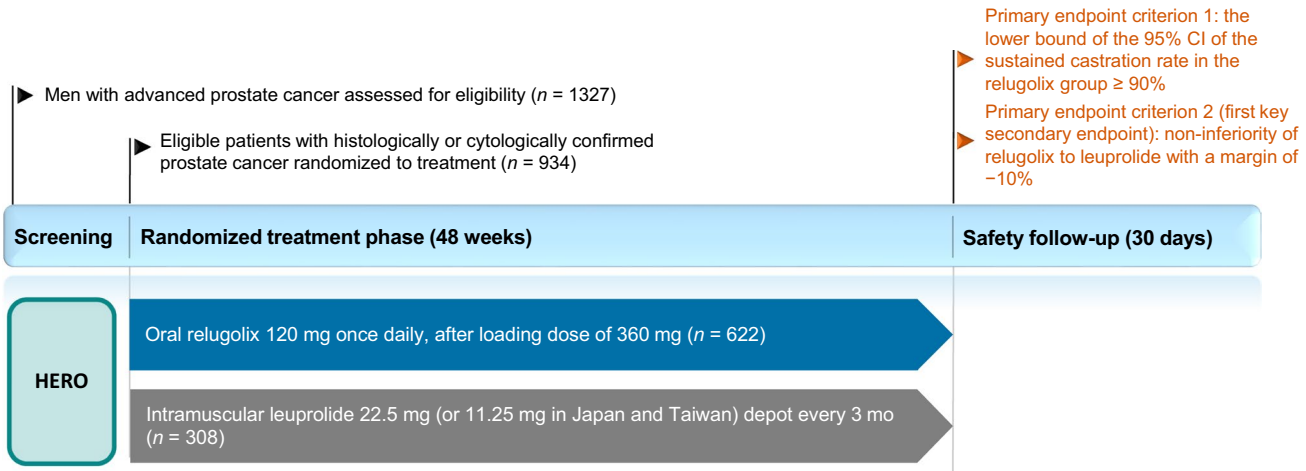

Fig. 1 Trial design of the randomized, open-label, active-controlled phase III HERO trial in patients with advanced prostate cancer [12]. The primary endpoint of the trial was the sustained castration rate (defined as the cumulative probability of testosterone suppression to < 50 ng/dL) from day 29 through 48 weeks. Efficacy results are reported in the animated figure (available online). *BGD* between-group difference, *mo* months, *pts* patients

(CI) for the cumulative probability of sustained testosterone suppression in the relugolix group was ≥ 90%. The first key secondary endpoint, which was assigned as Evaluation Criterion 2 of the primary endpoint to support EMA and Japanese regulatory assessment, was the non-inferiority of relugolix to leuprolide based on the sustained castration rate, with a prespecified non-inferiority margin of −10%. Other key secondary endpoints are detailed in Table 1, with the primary and key secondary endpoints all evaluated using a hierarchical testing process [12].

In total, 622 patients received relugolix and 308 received leuprolide and were analyzed for efficacy [12]. With the exception of PSA level at baseline (mean, 104.2 ng/mL in the relugolix group vs 68.6 ng/mL in the leuprolide group; median, 11.7 vs 9.4 ng/mL), patient demographics and clinical characteristics at baseline were well balanced between the two treatment groups [12].

The HERO trial met its primary endpoint, with sustained castration observed in 96.7% (95% CI 94.9–97.9) of patients in the relugolix group (Table 1) [12]. Furthermore, the sustained castration rate for relugolix was found to be non-inferior to that for leuprolide [88.5% (95% CI 84.6–91.8)] (Table 1). After the demonstration of the non-inferiority, an additional analysis was performed which found that the sustained castration rate for relugolix was superior to that for the leuprolide depot (Table 1) [12]; however, given that this analysis was not part of the prespecified hierarchical testing, it can only be considered exploratory and would require further investigation for any potential confirmation [13].

High sustained castration rates (> 90%) were observed among relugolix recipients across a range of patient subgroups, including ones based on geographical region, the presence or absence of metastatic disease, age (≤ 75 years or > 75 years), clinical disease state presentation, Gleason score at study entry (< 8 or ≥ 8), and baseline PSA level (< 20 ng/mL or ≥ 20 ng/mL) [12]. Analyses across the subgroups with regard to the non-inferiority of relugolix versus leuprolide were also generally consistent with results for the overall population.

Relugolix also demonstrated superior efficacy to leuprolide for key secondary endpoints, including the cumulative probability of testosterone suppression to castrate levels (< 50 ng/dL) on day 4 and on day 15, PSA response (> 50% decrease) at day 15 with confirmation at day 29, the cumulative probability of testosterone suppression to profound

Table 1 Efficacy of relugolix in the phase III HERO trial in adults with advanced prostate cancer [12]

Endpoint[a]	Oral relugolix 120 mg once daily[b] ($n = 622$)	IM leuprolide depot 22.5 mg q3mo[c] ($n = 308$)	Between-group difference
Sustained castration rate [% (95% CI)][d]	96.7 (94.9–97.9)[e]	88.8 (84.6–91.8)	7.9 (4.1–11.8)[f]
Testosterone suppression to < 50 ng/dL on day 4 (%)[g]	56.0*	0	
Testosterone suppression to < 50 ng/dL on day 15 (%)[g]	98.7*	12.0	
PSA response[h] at day 15 (%)	79.4*	19.8	
Profound testosterone suppression to < 20 ng/dL on day 15 (%)[g]	78.4*	1.0	
Mean FSH level at end of week 24 (IU/L)	1.72*	5.95	

FSH follicle-stimulating hormone, *IM* intramuscular, *PSA* prostate-specific antigen, *q3mo* every 3 months

*$p < 0.001$ vs IM leuprolide depot

[a]Endpoints are listed in hierarchical order according to the statistical analysis plan. Additional key secondary endpoints (following the mean FSH level at the end of week 24) were castration resistance-free survival in patients with metastatic cancer and in patients with or without metastatic cancer (not assessed in the primary analysis but rather when ≈ 390 patients with metastatic cancer had completed 48 weeks of study treatment), and the cumulative probability of testosterone recovery to 280 ng/dL 90 days after completing 48 weeks of treatment in a subset of ≈ 150 patients with no plan to start alternative androgen deprivation therapy within the following 12 weeks (or within 24 weeks following the last injection of IM leuprolide depot)

[b]After a single oral loading dose of 360 mg

[c]11.25-mg dose used for patients in Japan or Taiwan, in accordance with local prescribing information

[d]Primary endpoint; defined as the cumulative probability of testosterone suppression to < 50 ng/dL from day 29 through 48 weeks. Under the trial protocol, the primary endpoint was evaluated under two criteria to support different regulatory authorities

[e]Primary endpoint Evaluation Criterion 1 was met, with the lower bound of the 95% CI for the sustained castration rate in the relugolix group being ≥ 90%

[f]The between-group difference (7.9 percentage points) met the prespecified non-inferiority margin of −10% (first key secondary endpoint, or Evaluation Criterion 2 of the primary endpoint for EMA and Japanese regulatory assessment). Additionally, with the lower bound of the 95% CI being > 0, statistical superiority of relugolix over leuprolide was determined ($p < 0.001$; exploratory analysis)

[g]Data are the cumulative probability

[h]A decrease of > 50% from level at baseline

castrate levels (< 20 ng/dL) on day 15, and mean FSH level at the end of week 24 (Table 1) [12].

In a further key secondary endpoint, testosterone recovery was investigated in a subgroup of patients ($n = 184$) [12]. Formal testing of this endpoint was not performed since an endpoint (castration resistance-free survival) which was higher in the hierarchical testing process (albeit not assessed at the primary analysis; Table 1) was not met [14]. However, based on an exploratory analysis (conducted at the time of the primary analysis), 54% of relugolix recipients versus 3% of leuprolide recipients had testosterone recovery to ≥ 280 ng/dL (i.e. the lower limit of normal) 90 days after completing 48 weeks of treatment (nominal $p = 0.002$) [12]. Mean testosterone levels at this timepoint in the respective groups were 288.4 ng/dL and 58.6 ng/dL [12].

5 Tolerability of Relugolix

This section focuses on data from the pivotal phase III HERO trial (Sect. 4) [12]; data from earlier clinical trials in men with prostate cancer are generally consistent with the findings from HERO [15, 18, 19].

Relugolix was generally well tolerated in men with prostate cancer, with most adverse events being consistent with physiologic effects of testosterone suppression [12]. In HERO, 90.2% and 89.0% of patients in the relugolix and leuprolide groups, respectively, completed 48 weeks of treatment; treatment adherence (defined as the percentage of expected doses actually taken) was > 99% in both groups. Hot flush was the most commonly reported adverse event in both the relugolix (54.3%) and leuprolide (51.6%) groups; other adverse events occurring in > 10% of patients in either group included fatigue, constipation, diarrhea, arthralgia, and hypertension (Fig. 2). Most adverse events were of grade 1 or 2 severity [12]. Common (incidence ≥ 15%) laboratory abnormalities in the relugolix group included increased glucose (44%), increased triglycerides (35%), decreased hemoglobin (28%), increased alanine aminotransferase (ALT; 27%), and increased aspartate aminotransferase (AST; 18%) [9]. ALT/AST increases to ≥ 3 times the upper limit of normal occurred in 1.4% of relugolix recipients versus 1.3% of leuprolide recipients [12]. In the relugolix and leuprolide groups, respectively, 18.0% versus 20.5% of patients experienced grade 3 or 4 adverse events, 12.2% versus 15.3% experienced serious adverse events and 1.1% (seven patients) versus 2.9% (nine patients) experienced an adverse event resulting in death.

In a prespecified (albeit descriptive) analysis, the incidence of unadjudicated major adverse cardiac events (MACE; defined as nonfatal myocardial infarction, nonfatal stroke, or death from any cause) was determined in the two groups [12]. After 48 weeks of study drug treatment, 2.9% (exact 95% CI 1.7–4.5) of patients in the relugolix group and 6.2% (exact 95% CI 3.8–9.5) of patients in the leuprolide group had experienced a MACE, representing a 54% reduction in the risk of MACE (hazard ratio = 0.46; 95% CI 0.24–0.88) for relugolix versus leuprolide based on post-hoc Kaplan-Meier estimates. In the subgroup of patients with a documented history of MACE at study entry, 3 of 84 (3.6%) patients in the relugolix group versus 8 of 45 (17.8%) patients in the leuprolide group experienced a MACE during study drug treatment [12].

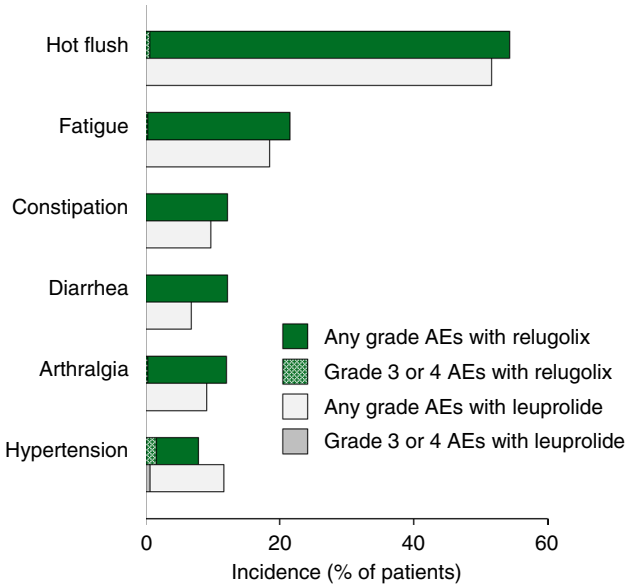

Fig. 2 Adverse events (AEs) occurring in > 10% of patients in either treatment group in the phase III HERO trial [12].

6 Dosage and Administration of Relugolix

Relugolix is approved in the USA for the treatment of advanced prostate cancer [9] and in the EU for advanced hormone-sensitive prostate cancer [10]. It is to be taken orally (tablets to be swallowed whole), and can be taken with or without food [9, 10]. Treatment should be initiated with a loading dose of relugolix 360 mg on the first day followed by relugolix 120 mg once daily, with the dose to be taken at approximately the same time each day. If treatment is interrupted for > 7 days, relugolix should be restarted with a 360-mg loading dose before re-continuing relugolix 120 mg once daily [9, 10].

No dose adjustment is required for patients with mild or moderate hepatic or renal impairment [9, 10], although

caution is warranted during use of relugolix 120 mg once daily in patients with severe renal impairment given an up to twofold increase in drug exposure in such patients [10]. The effects of severe hepatic impairment or end-stage renal disease on relugolix pharmacokinetics are unknown [9, 10]. Due to pharmacokinetic drug interactions (Sect. 3.1), relugolix should not be co-administered with oral P-gp inhibitors or with combined P-gp and strong CYP3A inducers [9, 10]; if co-administration cannot be avoided, dose modification is required (Sect. 3.1).

Local prescribing information should be consulted for full details regarding the use of relugolix, including further information on warnings and precautions, contraindications, use in special populations, and potential drug interactions.

7 Place of Relugolix in the Management of Advanced Prostate Cancer

ADT is a key component in the treatment of advanced prostate cancer [1–4], with relugolix being one of several possible options recommended in current National Comprehensive Cancer Network® (NCCN) guidelines when ADT is indicated [1]. Depending on the specific clinical setting, other options for ADT include orchiectomy, a GnRH agonist (alone or with a first-generation antiandrogen), or degarelix, with other agents (e.g., abiraterone, docetaxel) also included in select clinical settings [1]. While European treatment guidelines highlight the role of ADT in various clinical settings in the treatment of prostate cancer [2, 3], the guidelines do not provide recommendations on specific agents for ADT (although GnRH agonists or antagonists are preferred over orchiectomy because of the reversibility of their effects and the avoidance of the physical and psychologic distress that can occur with surgical castration [3]).

In the pivotal phase III HERO trial in men with advanced prostate cancer, once-daily oral relugolix provided sustained castration from day 29 through 48 weeks of treatment in > 90% of patients, with the effect consistent across a range of patient subgroups (Sect. 4). The sustained castration rate with relugolix was shown to be non-inferior to 3-monthly intramuscular leuprolide depot, with an exploratory analysis further indicating the superiority of relugolix to leuprolide depot. With the use of a loading dose on day 1 of treatment (Sect. 6) and rapid drug absorption (Sect. 3), and consistent with the mechanism of action of GnRH antagonism (Sect. 2), rapid testosterone suppression was observed with relugolix, with testosterone reaching castrate levels in 98.7% of patients at day 15 (compared with 12.0% of patients receiving leuprolide) (Table 1).

Relugolix was generally well tolerated in men with advanced prostate cancer, with most adverse events being of mild to moderate severity and consistent with the physiologic effects of testosterone suppression (Sect. 5). Furthermore, in line with the growing body of evidence suggesting that GnRH antagonists may have improved cardiovascular safety relative to GnRH agonists [20–23], relugolix was associated with a 54% reduction in the risk of MACE in HERO compared with leuprolide, based on a descriptive analysis (without formal adjudication) [12]. The relative cardiovascular safety of GnRH antagonists and agonists has yet to be conclusively resolved [24]. Indeed, the randomized phase III PRONOUNCE trial, which prospectively compared the cardiovascular safety of the GnRH antagonist degarelix with the GnRH agonist leuprolide, found no significant between-group difference in MACE (although it should be noted that the trial was terminated prematurely due to slower-than-projected enrolment and fewer-than-anticipated events) [24]. Nonetheless, given that cardiovascular disease represents a significant cause of mortality in the demographic affected by prostate cancer, a reduced risk of MACE could represent a clinically important consideration. Although patients with recent cardiac conditions were excluded from HERO (Sect. 4), > 90% of patients had at least one cardiovascular risk factor at baseline, including 13.9% of patients with a prior history of MACE [12].

Consistent with its oral route of administration, relugolix treatment was associated with diarrhea in a numerically higher proportion of patients in HERO than leuprolide treatment (Fig. 2); however, all cases were mild or moderate in severity and no cases led to withdrawal from the study [12]. On the other hand, the oral route of administration of relugolix avoids the potential for injection-site reactions [21], which can be a concern for injectable ADT agents such as degarelix [8, 25].

Another potential benefit of (once-daily) oral administration of relugolix is the likely added patient convenience, including the reduced requirement for clinic visits. On the other hand, concerns have been raised about the potential for reduced treatment adherence with an oral ADT agent and the negative effects that it could have on patient outcomes. NCCN guidelines suggest that ongoing monitoring of testosterone levels may be useful to confirm sustained testosterone suppression to castrate levels and an alternative option for ADT may be preferable if compliance with oral therapy is uncertain [1]. Adherence to treatment was high (> 99%) in both treatment groups in the HERO trial [12]. Furthermore, simulations using a semi-mechanistic population pharmacokinetic/pharmacodynamic model for relugolix, with the assumption of 100% adherence to the recommended dosing regimen for 40 days, predicted 97.3% and 85.5% of patients would have testosterone remaining at castrate levels upon temporary interruption of treatment for 7 days and 14 days, respectively [26]. Nonetheless, data

on long-term compliance with relugolix treatment in the real-world setting would be of interest.

Another area where future data will be of interest is on concomitant use of relugolix with other drugs commonly used in the treatment of patients with advanced prostate cancer. In this regard, an ongoing phase I clinical trial (NCT04666129) is assessing the safety and tolerability of relugolix as the ADT component in combination treatment with abiraterone, apalutamide or docetaxel. However, given the currently limited data on the use of relugolix in combination with androgen receptor inhibitors or with chemotherapy, NCCN treatment guidelines for prostate cancer do not recommend relugolix in combination with other therapies at this time [1].

Another area of interest for future study is on intermittent versus continuous relugolix treatment. Indeed, in the context of intermittent ADT for prostate cancer, the once-daily dosing, the rapid onset of action, and the apparent more rapid testosterone recovery associated with relugolix could potentially help facilitate more precise or targeted ADT [27]. The testosterone recovery observed with relugolix may have other clinically meaningful benefits, for example for men receiving a short course of ADT, or for men unable to tolerate adverse effects of testosterone suppression [12].

In conclusion, with the ability to provide the rapid testosterone suppression (with no initial surge in testosterone upon treatment initiation) combined with the benefits of oral administration and potentially improved cardiac safety, relugolix presents a valuable treatment option for men with advanced prostate cancer where ADT is indicated.

Data selection—Relugolix: 79 records identified	
Duplicates removed	1
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	36
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	15
Cited efficacy/tolerability articles	6
Cited articles not efficacy/tolerability	21
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were: prostate cancer, Orgovyx, relugolix, RVT 601, TAK-385. Records were limited to those in English language. Searches last updated 08 Dec 2022.	

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-022-00944-4.

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Declarations

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Ethics Approval, Consent to Participate, Consent to Publish, Availability of Data and Material, Code Availability Not applicable.

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