Relugolix, an oral gonadotropin-releasing hormone antagonist for the treatment of prostate cancer

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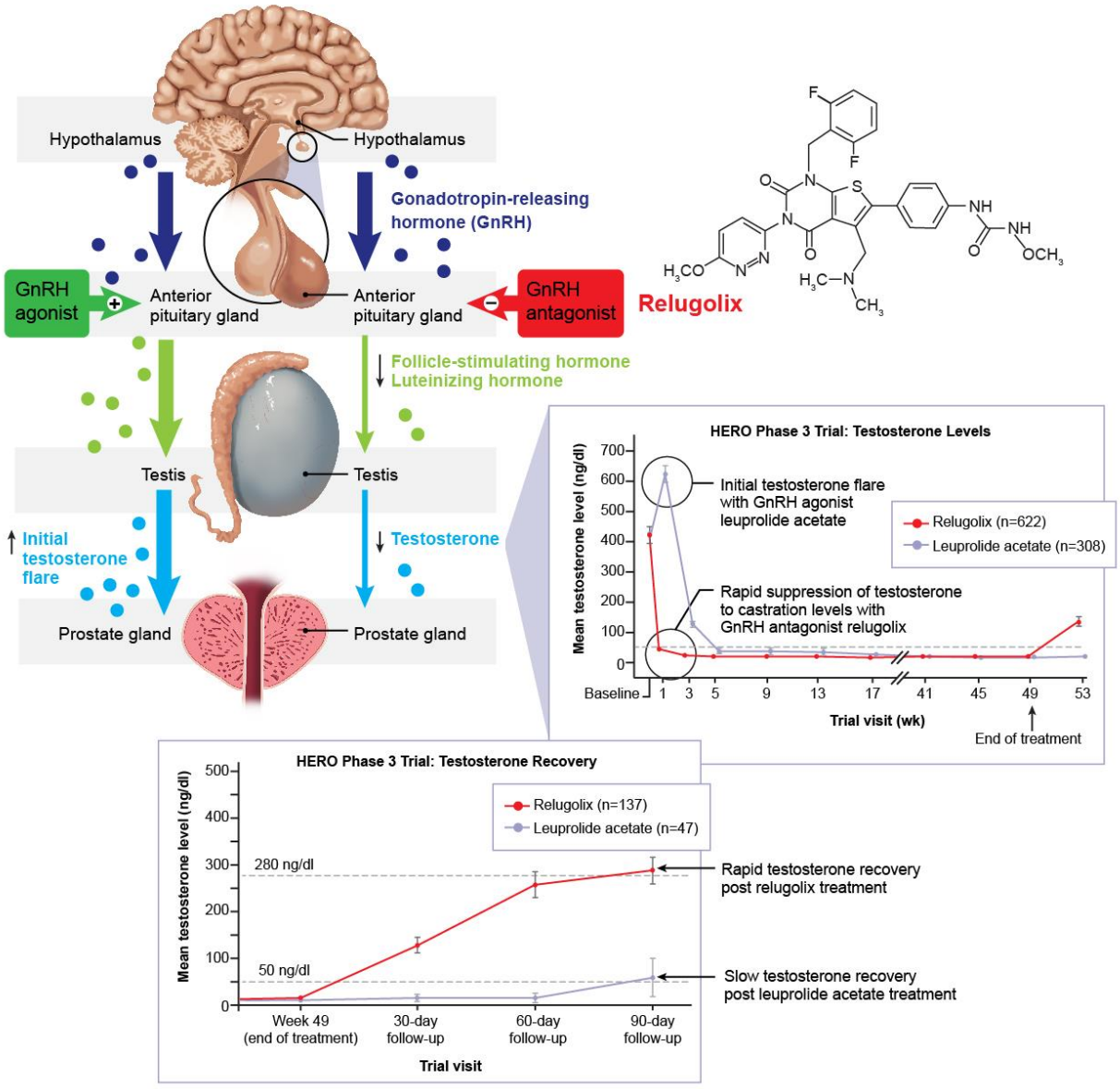
Graphical abstract



Abstract

Androgen deprivation therapy using gonadotropin-releasing hormone (GnRH) analogues is standard treatment for intermediate and advanced prostate cancer, but results in an initial testosterone flare, and increased metabolic and cardiovascular risks. In the HERO phase 3 trial, relugolix was superior to leuprolide acetate at rapidly reducing testosterone and continuously suppressing testosterone, with faster post-treatment recovery of testosterone levels. The GnRH antagonist relugolix is able to reduce serum testosterone levels in men with prostate cancer without inducing testosterone flare. Relugolix was associated with a 54% lower incidence of major adverse cardiovascular events than leuprolide acetate. As the first oral GnRH antagonist approved for the treatment of advanced prostate cancer, relugolix offers a new treatment option.

Keywords <3-10; currently 10>: relugolix, prostate cancer, testosterone, GnRH antagonist, gonadotropin-releasing hormone, androgen deprivation therapy

Lay Abstract

The male sex hormone testosterone promotes the growth of prostate cancer cells. Some drug treatments for prostate cancer like GnRH receptor agonists and antagonists work to reduce the production of testosterone. However, GnRH receptor agonists like leuprolide acetate can increase testosterone levels at first, before reducing it, and this temporary increase can cause side effects like bone pain. Drugs of this type have also been linked to a higher risk of heart attacks, strokes, and death. Relugolix works a different way, it is a GnRH receptor antagonist that reduces testosterone without an initial increase. A clinical study showed that relugolix reduced testosterone levels more quickly than leuprolide acetate, a commonly used injectable drug for the treatment of prostate cancer. After stopping treatment, levels of testosterone in the blood returned to normal faster in men who received relugolix than in men who received leuprolide acetate. Men who received relugolix had a lower incidence of heart attacks, strokes, and death compared to men who received leuprolide acetate. The US Food and Drug Administration approved relugolix as the first oral, once-daily GnRH receptor antagonist for the treatment of advanced prostate cancer, offering men a new treatment option.

Introduction

Prostate cancer represents a significant worldwide health burden: it is the most common cancer diagnosed in men and the second most common cause of cancer-related death in men [1], with 1.28 million new cases and over 350,000 deaths due to prostate cancer reported globally in 2018 [2]. There has been a 3.7-fold increase in the number of cases of prostate cancer over the past 30 years with an almost 2-fold increase in the incidence rate [3]. This change likely reflects trends of an aging population and more cancer screening as well as the increased use of life-prolonging therapies.

Treatment of prostate cancer depends on many different factors, including age, clinical features, and progression of disease. Management strategies for men with localized disease at an early stage include active surveillance, radical prostatectomy, and/or radiation therapy [4]. Hormonal therapy is given in addition to radiotherapy in localized or locally advanced disease and is the main treatment option for prostate cancer that has advanced—either by recurrence after localized treatment or by metastasis outside of the prostate [4].

Historical overview of metastatic prostate cancer therapy

The link between total serum testosterone levels and prostate cancer was established in the 1940s, when Huggins and Hodges showed that men with symptomatic metastatic prostate cancer benefited from testosterone suppression [5]. Understanding testosterone synthesis and signaling became vitally important for developing medical strategies for prostate cancer treatment. Testosterone is produced by Leydig cells in the testes following stimulation from luteinizing hormone (LH) [6]. Testosterone production is regulated by the hypothalamic-pituitary axis, whereby the hypothalamus releases gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone–releasing hormone (LHRH), to activate pituitary secretion of LH and follicle-stimulating hormone (FSH). LH is then responsible for stimulation of subsequent testosterone production.

Historically, androgen deprivation therapy (ADT) for the treatment of prostate cancer focused on surgical castration (orchiectomy) or the use of estrogens to decrease testosterone levels. Negative side effects of orchiectomy include psychological problems, loss of libido, decreased muscle mass, osteoporosis, hot flashes, and cognitive decline [7]. Additionally, estrogens cause gynecomastia; studies showed the association of the most commonly used estrogen, diethylstilbestrol, with increased

mortality due to cardiovascular causes, leading to the development of alternative treatment options [8-10].

In prostate cancer cells, excess activation of the androgen signaling pathway in response to testosterone and dihydrotestosterone results in uncontrolled proliferation [5]. As a result, treatment methods focused on targeting the androgen receptor, using either steroidal (cyproterone acetate) or nonsteroidal (bicalutamide, flutamide, nilutamide) inhibitors. However, these androgen receptor inhibitors are also associated with adverse effects, including abdominal pain, nausea, vomiting, gynecomastia, and hepatic toxicity [11-13].

Focus began to shift to upstream targets in the testosterone synthesis pathway, namely GnRH, the hormone that governs testosterone production. GnRH is a decapeptide synthesized in the hypothalamus, where it is subsequently secreted and acts on gonadotroph cells in the pituitary through the GnRH receptor. The mechanism of action of GnRH agonists relies on the desensitization of the pituitary (Figure 1). Specifically, in preclinical mice models, when the pituitary is exposed to prolonged stimulation by a homologous GnRH ligand, it is not uncommon to see a refractory period in pituitary cells. According to this line of thinking, prolonged activation by a GnRH agonist results in the pituitary becoming desensitized to GnRH stimulation, so that it no longer releases LH and FSH. This strategy turned out to be effective, with initial experiments in mice showing a decrease in LH serum levels following 6 days of infusion of a GnRH agonist [14, 15].

Following the discovery of the structure of GnRH and the first treatment of a cancer patient in the early 1980s with a GnRH agonist (leuprolide acetate), endocrine therapy using GnRH agonists (i.e., goserelin) gained support as an effective alternative treatment option to surgical castration for advanced prostate cancer [16]. Phase 3 trials were performed in men with metastatic disease. In the UK, orchiectomy was compared with goserelin in 358 men [17], with no significant difference found in overall survival. A further study combined the results from two trials comparing orchiectomy with combined therapy using goserelin and flutamide [18]. The results suggested near equivalence, with a possible small benefit of combined therapy for men presenting with low tumor burden. Subsequently, the use of GnRH agonists with and without antiandrogens became the gold standard of treatment for advanced prostate cancer for more than 20 years [4].

Treatment with GnRH agonists has been associated with several adverse effects. Initial treatment with a GnRH agonist results in an initial testosterone flare followed by a substantial decrease in LH, FSH, and

testosterone levels. This flare may cause acute effects, including skeletal pain, spinal cord compression, and ureteral obstruction [19]. To help mitigate secondary effects, the use of antiandrogens is recommended, but these drugs come with their own negative side effects and additional cost [20]. Longer-term side effects of GnRH agonists are similar to those of orchiectomy (see above) but with the addition of metabolic changes [21] and cardiovascular complications [22]. In 2010, in light of these cardiovascular events, the US Food and Drug Administration (FDA) began a panel review on the safety of GnRH agonists. Their findings led to the addition of warnings for all GnRH agonists regarding an increased risk of diabetes and certain cardiovascular diseases [23]. Over the past two decades, GnRH agonists have been used in the context of radiotherapy for intermediate- and high-risk disease, as well as for intermittent therapy for prostate-specific antigen (PSA)-only recurrence following local therapy [24-31]. Although the duration of GnRH agonist treatment in these studies with radiotherapy has been well defined, there have been wide variations and delays in testosterone recovery [32, 33], which may relate to the duration of GnRH agonist therapy, type of depot preparation given, patient age, and pre-treatment testosterone levels.

Gonadotropin-releasing hormone antagonists

An alternative strategy for ADT is inhibition of LH and FSH release using a GnRH antagonist. GnRH antagonists competitively inhibit GnRH receptor signaling, which blocks the signal for release of LH and FSH from the pituitary, and consequently of testosterone from the testes (Figure 1) [34]. Depending on the characteristics of the antagonist, this effect could be immediate, in contrast to that of GnRH agonists. One of the main benefits of using an GnRH antagonist is that because there is no stimulation of the GnRH receptor, there should be no initial flare of LH, FSH, and testosterone [19]. Another potential advantage of using a GnRH antagonist is the more predictable and timely recovery of testosterone levels after cessation of ADT in comparison with agonists, since there is no desensitization of the pituitary signaling with GnRH antagonists [35].

Initial difficulties with solubility led to delays in development, but the first GnRH antagonist, abarelix, was approved for prostate cancer treatment in 2003 [36]. Abarelix showed clinical efficacy for chemical castration, with rapid (3 days) effects on serum testosterone levels [37, 38]; however, due to the risk of immediate-onset allergic reactions, it was voluntarily removed from the market in the USA [39-41]. The second GnRH antagonist to be approved for prostate cancer treatment was degarelix in 2008 [42]. Unlike its predecessor, degarelix has no association with systemic allergies [43-45]. Degarelix is an

injectable peptide, given once every 28 days, that has been shown to effectively reduce testosterone levels without the initial flare associated with GnRH agonists [45]. In the clinical setting, treatment with degarelix was able to rapidly elicit castration levels of testosterone (<50 ng/dl) [46, 47]. However, injection-site reactions are common (35%–44%), and together with the burden of monthly injections when compared to the dosing interval of 3 months or more for sustained-release formulations of leuprolide acetate, clinical uptake of degarelix has been limited [42, 48].

All peptide-based agonists and antagonists are susceptible to gastrointestinal peptidase degradation, making oral administration unsuitable due to very low bioavailability [49, 50]. Therefore, the majority of ADT treatment options (leuprolide acetate, goserelin, histrelin, degarelix) rely on the use of subcutaneous or intramuscular injections given at 1-, 3-, or 6-month intervals [51], which are associated with specific adverse effects related to this mode of administration [52, 53].

The use of oral hormonal therapies in prostate cancer has been common, although they are generally given in addition to a GnRH agonist. Drugs include both nonsteroidal (bicalutamide, flutamide, nilutamide) and steroidal (cyproterone acetate) antiandrogens, oral estrogens such as stilbestrol, and ancillary treatments such as corticosteroids and tamoxifen. More recently, second-generation endocrine therapy with abiraterone or enzalutamide has become the standard of care in castration-resistant prostate cancer (CRPC), and compliance with oral medication has been shown to be high (over 90% mean medication possession ratio) [54-57]. This suggests that, if available, oral therapy may be a reliable alternative to injection to achieve initial testosterone suppression.

Clinically relevant serum testosterone levels in prostate cancer

The definition of medical castration as a testosterone level <50 ng/dl is based on older assays that were less sensitive than present-day techniques. We now know that bilateral orchiectomy frequently reduces serum testosterone levels to <20 ng/dl. Although the 50 ng/dl threshold is still used today in trials as the value for medical castration, there is evidence that lower levels of testosterone (<32 ng/dl) result in better prostate cancer survival, minimizing potential development of castration resistance [58]. In a recent study by Klotz et al, the authors found that serum testosterone levels below 20 ng/dl were correlated with greater survival and longer duration of response to androgen deprivation [59]. An earlier retrospective study also found that lower testosterone levels during the first 6 months of treatment correlated to longer survival [60]. Serum testosterone has also been suggested as a potential predictor for the time to development of CRPC, with nadir testosterone during ADT correlating with a delay in

CRPC development [59, 61]. For these reasons, the European Association of Urology (EAU) now suggests 20 ng/dl to be a more appropriate threshold than 50 ng/dl [62].

Following termination of ADT, testosterone levels should return to normal. However, the time to return to normal levels can vary depending on the drug given and duration of treatment. There is also a small percentage of men whose testosterone levels do not return to normal. Men with prolonged periods of low testosterone may suffer from a variety of effects, including erectile dysfunction, decrease in sexual desire and arousal, and metabolic syndrome [63]. Several studies have shown that after discontinuation of treatment with GnRH agonists (leuprolide acetate or goserelin), recovery can take 12–24 months, and that normalization only occurs in 80%–90% of men for those receiving less than 12 months of ADT [35, 64]. For men receiving longer-term ADT, recovery of serum testosterone levels to baseline was less than 50% [64].

Cardiovascular disease and ADT

Cardiovascular disease (CVD) is the second most common cause of death in men with prostate cancer [65, 66]. Over the past 15 years, several studies have suggested a link between ADT and an increased risk of cardiovascular events (CVEs) [67-70], but the underlying mechanism has yet to be explained. In one large study, the authors found that the risk for CVD within the first 6 months of treatment with a GnRH agonist increased and persisted during the entire year [71]. A meta-analysis of pooled data from six trials comparing GnRH agonists and the GnRH antagonist degarelix found that among men with pre-existing CVD, those receiving a GnRH antagonist had a 56% lower risk of CVEs within the first year when compared to those receiving GnRH agonists [72]. In two publications by Margel et al., the authors found that men being treated with a GnRH agonist had significantly more CVEs and cerebrovascular events compared to those given a GnRH antagonist (20% vs. 7%) [73, 74]. Several studies have implicated a GnRH receptor–dependent pathophysiology that may explain the increased risk of CVEs for men undergoing GnRH agonist treatment [72, 75-77]. Studies examining immune cells have shown that atherosclerosis progression can promote the emergence of T helper cells within plaques [78]. T cells expressing GnRH receptors may become activated in the presence of GnRH agonists. It has been postulated that these activated T cells could then expand and cause atherosclerotic plaques to become destabilized [76].

Introduction to relugolix

Relugolix (initially known as TAK-385) is a highly selective, orally active, nonpeptide GnRH antagonist (Figure 2). Early tests found high affinity of another nonpeptide GnRH antagonist, sufugolix, for binding to the human GnRH receptor in both the presence and absence of fetal bovine serum (half maximal inhibitory concentration [IC50] = 0.1 nM and 1.6 nM respectively), but with CYP3A4 inhibition (36%) and possible drug-drug interactions [79]. In comparative studies between relugolix and sufugolix performed in male cynomolgus monkeys, when relugolix was given as a single oral dose it showed a similar suppressive effect and a 10-fold lower minimum effective dose than that of sufugolix [79, 80]. Binding was also superior for relugolix with or without fetal bovine serum (IC50 = 0.08 nM and 0.33 nM respectively), with no drug-drug interactions (0% CYP3A4 inhibition) [79]. Studies on human GnRH receptor knock-in mice also showed that twice-daily treatments with relugolix for 4 weeks at 20 mg/kg body weight significantly decreased the weights of the testes and ventral prostate. The effect on decreased ventral prostate weight was also seen with relugolix doses of 3 mg/kg body weight. The effect was shown to be reversible, as serum testosterone levels and ventral prostate weight returned to untreated levels within 14 days after cessation of treatment [81].

To determine a safe and effective dose range, a phase 1 clinical study was conducted in healthy men (age 18–75 years). Participants received a range of doses (20–360 mg) either as a single dose or once daily for 14 or 28 days (2 or 4 weeks), with or without initial loading doses, and testosterone levels were measured to determine effective castration [82]. Effective castration was defined as having serum testosterone concentrations <1.73 nmol/l (<50 ng/dl) at all scheduled visits. It was also noted if men achieved a more profound castration level, defined as serum testosterone levels <0.69 nmol/l (<20 ng/dl). Pharmacokinetic evaluation showed that relugolix is readily absorbed following oral administration, with a median time to maximum plasma concentration (T_{max}) of 1.01 to 1.59 hours post dose. This absorption was dose-dependent and showed an approximate 2-fold accumulation over a 2-week dosing period. The T_{max} did not change with continuous dosing. Plasma concentrations of relugolix decreased with a mean disposition half-life of 36 to 65 hours following administration of relugolix within the tested 20–180 mg once daily dose range [82].

Men who received either 60, 80, or 160 mg relugolix once daily for 28 days showed the most promising results. In the cohort receiving 160 mg once daily, relugolix was able to reduce mean testosterone serum levels to castration concentration (<50 ng/dl) by day 7, with 100% of the cohort having castration

levels by day 28. Men who received daily doses of either 20 mg or 40 mg with a loading dose of ≥320 mg achieved castration levels within 3 days of treatment; however, testosterone levels did not remain low after day 4. Those receiving either 60 or 80 mg/day showed castration levels in >70% of men by day 28. Furthermore, in 75% of men receiving 160 mg relugolix, serum concentration levels fell below 20 ng/dl by day 28. FSH and LH serum concentrations were also reduced, with FSH levels falling below 90% of baseline values. Recovery of serum testosterone was monitored for 28 days following completion of dosing. Recovery was dose-dependent, with recovery to baseline by day 28 in 60% (160 mg/day group) to 100% (40 mg/day plus loading dose group) of men.

In early studies, AEs in patients treated with relugolix were similar to those seen with other ADT options [82, 83], a notable exception being that there were no signs of histamine release with relugolix, a common issue with GnRH agonists/antagonists [45, 84-86]. In addition, because relugolix is orally administered once daily, there are no injection-related adverse events (AEs).

Clinical efficacy

Phase 2 trial

In order to determine safety and efficacy, relugolix was tested in a phase 2 open-label, randomized, parallel-group study [87]. A total of 103 men with histologically confirmed, localized, intermediate-risk prostate adenocarcinoma with an indication for 24-week neoadjuvant/adjuvant ADT to external beam radiation therapy (EBRT) were enrolled in both the US and UK. Candidates were excluded if they had prior or current use of any GnRH analogue or androgen receptor antagonist as first-line hormone therapy. Results from the phase I trial showed a single loading dose of 320 mg and daily subsequent doses 80–160 mg to be effective at achieving rapid and sustained castration [82]. As such, men were randomized in a 3:2 ratio to a 24-week regimen of oral relugolix (320 mg loading dose on day 1 and 120 mg once daily thereafter) or degarelix as a subcutaneous depot injection (240 mg loading dose on day 1, then 80 mg every 4 weeks). EBRT was given 12 to 16 weeks after ADT treatment had begun.

The primary endpoint of the study was the rate of effective (conventional) castration (serum testosterone <50 ng/dl) between 4 and 24 weeks at all scheduled visits. Profound castration as defined in the phase 1 study (<20 ng/dl) was also noted. To verify downstream-signaling antagonism of the GnRH receptor, measurements of LH and FSH were also performed. Secondary endpoints included PSA response at 12 weeks, PSA nadir during treatment and follow-up, prostate volume 8 to 12 weeks after treatment, time to achieve effective castration, and time to testosterone recovery (defined as return to

baseline or to >9.8 nmol/l or >280 ng/dl). Additionally, changes to quality of life were measured using the European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C30 and EORTC-QLQ-PR25 questionnaires and the Aging Males' Symptoms (AMS) scale, and safety measures were recorded.

Relugolix achieved the primary endpoint of conventional castration throughout the duration of the study. The median time to castration was 4 days, with 95% of men reaching conventional castration levels by week 24 (95% CI: 87.1%–99.0%) (Figure 3); 82% of men receiving relugolix showed profound castration (95% CI: 70.0%–90.1%). For men receiving degarelix, 89% (95% CI: 75.2%–97.1%) of men reached conventional castration levels by week 24, with 68% (95% CI: 51.3%–82.5%) showing profound castration. Recovery of testosterone levels after discontinuing treatment was rapid with relugolix, with 56% of men recovering to baseline or >9.8 nmol/l (>280 ng/dl) within 12 weeks, compared to 16% in the degarelix group.

Relugolix was equivalent or superior to degarelix for most secondary endpoints. At 8 to 12 weeks after initiation of treatment, the median prostate volume levels had decreased from baseline by 26% for relugolix and 29% for degarelix. By 12 weeks, reduction of PSA levels by ≥50% had occurred in >97% of men treated for both treatment arms. Furthermore, 55% of men treated with relugolix had PSA level decreases of ≥90% at this time, compared with 47% of those treated with degarelix. Median PSA levels remained low after discontinuation of treatment: <90% from baseline 12 weeks after discontinuation.

From baseline to week 24, FSH levels decreased by 88% with relugolix and LH levels by 98%. These results were similar in men receiving degarelix, in whom FSH levels decreased by 90% and LH levels by 98%. This effect was transient, as both LH and FSH returned to baseline levels for both groups within 12 weeks after discontinuation of treatment.

Global health status and AMS scores were both negatively impacted by treatments with relugolix (−7.7 and 14.6% respectively) and degarelix (−6.8 and 40.5% respectively). Following discontinuation, sexual activity scores and hormonal treatment–related symptoms improved for both treatment groups, although more rapidly in the relugolix group [87].

Phase 3 trial: HERO

In order to evaluate the efficacy and safety of relugolix in comparison with a GnRH agonist (leuprolide acetate), a phase 3, open-label, multinational, randomized study (the HERO trial) was conducted [88]. A total of 930 adult men were enrolled in the study across 155 centers. Eligible men must have had either histologically or cytologically confirmed adenocarcinoma of the prostate and been a candidate for at

least 1 year of continuous ADT. The patient could also 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. Men were excluded if they had any major adverse CVEs (e.g., myocardial infarction, unstable angina, unstable symptomatic ischemic heart disease) within 6 months of the beginning of the trial. Men could not have received any form of ADT within 3 months prior to baseline. Men were also excluded if they had uncontrolled hypertension, active conduction system abnormalities, or metastases to the brain per clinical evaluation.

The men were randomized in a 2:1 ratio to receive either relugolix (n=622) or leuprolide acetate (n=308). They were given either a 120-mg once daily oral dose of relugolix following an initial loading dose of 360 mg or 22.5 mg of leuprolide acetate by injection every 3 months (with the exception of men in Japan and Taiwan, who received leuprolide acetate injections of 11.25 mg as per the local prescribing information).The primary endpoint of the trial was the sustained castration rate, defined as cumulative probability of testosterone suppression to <50 ng/dl during receipt of trial treatment from day 29 through 49 weeks. The secondary endpoints included assessing non-inferiority of relugolix to leuprolide acetate with respect to sustained castration rate with a noninferiority margin of −0.10, with a follow-up test for superiority if found non-inferior. Other key secondary endpoints included cumulative probability of testosterone suppression to <50 ng/dl (conventional castration) at day 4 and day 15, the percentage of men with PSA response (>50% decrease) at day 15 with confirmation at day 29, the profound castration rate (<20 ng/dl) on day 15, and the FSH level at the end of week 24. Lifestyle risk factors assessed included tobacco and alcohol use and obesity; cardiovascular risk factors were prespecified event terms and included hypertension, dyslipidemia, and diabetes.

Patient characteristics were similar across both treatment groups, with median ages of 71 years (leuprolide acetate) and 72 years (relugolix), and approximately 50% had evidence of biochemical relapse after definitive treatment for prostate cancer. Men were evenly distributed geographically, with approximately 29% from North America, 39% from Europe, and 25% from Asia Pacific. More than 90% of men had at least one cardiovascular risk factor across three main categories: lifestyle, cardiovascular, or history of a non-fatal myocardial infarction or stroke.

Treatment adherence was over 99%, and approximately 90% of men completed the 48 weeks of treatment. Men were followed for a median of 52 weeks after the last treatment.

There was rapid response with relugolix treatment, resulting in a mean testosterone level of 38 ng/dl by day 4, whereas men treated with leuprolide acetate showed a testosterone flare (mean 625 ng/dl) that eventually decreased by day 29. Relugolix achieved castration levels of testosterone from day 29 through week 48 in 96.7% (95% CI: 94.9%–97.9%) of men (Figure 4). This proved to be both non-inferior and superior to leuprolide acetate, which achieved castration levels in 88.8% of men (95% CI: 84.6%–91.8%). Subgroup analysis on the primary endpoint showed relugolix to be superior to leuprolide acetate regardless of region (North America vs. other regions), presence or absence of metastatic disease, age, Gleason score, baseline PSA levels <20 ng/ml, and disease presentation (newly diagnosed androgen-sensitive metastatic disease and biochemical or clinical relapse).

Relugolix was also superior to leuprolide acetate on five secondary endpoints (Table 1). Probabilities of castration achieved by day 4 and day 29 were higher in the relugolix group (56.0% by day 4 and 98.7% by day 29) than in the leuprolide group (0.0% by day 4 and 12.0% by day 29). Probability of profound castration levels of testosterone was also higher in the relugolix group (78.4%) vs. the leuprolide acetate group (1.0%) on day 15. FSH levels were significantly lower at all time points (day 4, day 29, week 25 and week 49) for men receiving relugolix. The nadir FSH concentration was reached at day 29 for both treatment groups; however, FSH levels increased after day 29 for the leuprolide acetate group but remained suppressed for those receiving relugolix. At week 24, the mean concentration of FSH for men receiving relugolix was 1.72 IU/l, compared to 5.95 IU/l for men receiving leuprolide.

Another important indicator was the recovery of serum testosterone following treatment discontinuation, which was assessed in a subgroup of 184 men. For men receiving relugolix, 54% had testosterone levels recovered to the lower limit of normal range within 90 days of discontinuation of treatment, compared to only 3% of men receiving leuprolide acetate (Figure 4).

Safety

Safety and tolerability were assessed in the phase 2 (relugolix vs. degarelix) and phase 3 (relugolix vs. leuprolide acetate) trials. In the phase 2 trial, AEs were seen in both groups (86% for relugolix and 97% for degarelix). Most of these were considered mild. The most common reported adverse effect was hot flashes (57% for relugolix and 61% for degarelix) [87]. Several mild AEs were seen solely in the group treated with degarelix; these included injection-site erythema and increased alanine aminotransferase.

In the phase 3 HERO trial, similar AEs were reported in both treatment groups. These events were consistent with those for all ADTs and consisted primarily of hot flashes (50% of men) and fatigue (20%).

Mild diarrhea was higher with relugolix (12.2%) vs. leuprolide acetate (6.8%) but did not lead to any withdrawals. There were 7 (1.1%) deaths reported in the relugolix group and 9 (2.9%) in the leuprolide acetate group. Major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke, and all-cause mortality, were higher with leuprolide acetate treatment (6.2%) compared to relugolix (2.9%), yielding a 54% lower risk for these events with relugolix (hazard ratio vs. leuprolide acetate, 0.46; 95% CI: 0.24–0.88). Men with a pre-existing history of these events had an even greater difference in MACE if when treated with leuprolide acetate (17.8%) as compared to relugolix (3.6%).

In December of 2020, the FDA approved relugolix for the treatment of adult men with advanced prostate cancer, making it the first oral GnRH antagonist with this indication [89].

Current perspective

These clinical data suggest that relugolix, administered orally at a starting dose of 360 mg followed by once-daily 120 mg doses, is effective at reducing levels of serum testosterone to castration levels quickly and consistently throughout the treatment period. As with other GnRH antagonists, treatment with relugolix does not result in an initial flare in testosterone as seen with GnRH agonists, eliminating the need for concomitant antiandrogen therapy. The absence of a flare may avoid potentially related symptoms of bone pain and urinary retention.

Relugolix has been shown to be a fast and effective alternative for decreasing testosterone levels. Results from the phase 2 and phase 3 trials showed that relugolix was able to reduce testosterone to standard castration levels in over 95% of men and to profound castration (<20 ng/dl) in approximately 80% of men. When looking at the success of other hormonal modifiers (antiandrogens and GnRH agonists) to achieve testosterone levels <20 ng/dl, we see large variations depending on drug and dosing [38, 90-92]. In a study using the GnRH agonist leuprolide acetate, only 44% of men had levels below 20 ng/dl [58].

In the phase 3 trial, men receiving relugolix were more likely to have testosterone levels return to normal after 90 days than those receiving leuprolide acetate (54% vs. 3%). A similar finding was seen in the phase 2 study when men were treated with 6 months of relugolix. This improvement in return to normal levels can be useful for men receiving intermittent therapy, those receiving a short course of ADT, or those discontinuing therapy, as it would be expected to alleviate the burden of symptoms such

as fatigue, hot flushes, erectile dysfunction, impaired sexual desire and arousal, and metabolic changes [93].

In both the phase 2 and phase 3 studies, treatment with relugolix resulted in a decrease in FSH by nearly 90% from baseline levels. In the phase 3 study, the mean FSH level at the end of week 24 was 1.72 IU/l for men receiving relugolix vs. 5.95 IU/l for those receiving leuprolide acetate. A link has been found between FSH levels and the development of locally invasive prostate cancer and CRPC [94-96]. In one of these studies, it was found that a FSH level below 4.8 IU/l was associated with a longer time to CRPC [94]. It remains to be established whether relugolix therapy may impact rates of CRPC in clinical practice.

Men with metastatic disease treated with GnRH agonists usually develop resistance, with CRPC developing over time. Current guidelines suggest the use of therapies such as abiraterone plus prednisone, enzalutamide, and docetaxel [4]. However, a recent meta-analysis showed that switching men from a GnRH agonist to a GnRH antagonist resulted in a decrease in PSA in almost 30% of men [97]. This decrease may be a result of lower FSH levels, a characteristic shown with GnRH antagonists [98]. Treatment with GnRH agonists fails to suppress FSH over the long term, which may explain part of the success of switching to a GnRH antagonist [46]. Switching men from a GnRH agonist to relugolix may result in a decrease in PSA, given the ability of relugolix to maintain reduced FSH levels. However, there is currently a lack of data regarding the use of these agents in combination with chemotherapy. Primary ADT and chemotherapy have become the standard of care for metastatic hormone-sensitive prostate cancer and CRPC, supported by demonstrated improvements in overall survival vs. ADT alone for combination therapy of ADT plus docetaxel [99] and ADT plus the androgen receptor axis-targeted drug abiraterone [100].

In the phase 3 HERO trial, treatment with relugolix resulted in a significantly lower incidence of MACE when compared to the GnRH agonist leuprolide acetate (2.9% vs. 6.2%). This supports recent findings that GnRH antagonists may present a lower risk of CVEs compared with GnRH agonists [72-74]. As CVD is the second most common cause of death for men receiving ADT, management of CVE risk is an important element when choosing the most appropriate treatment protocol. Relugolix appears similar to degarelix (another GnRH antagonist) and superior to leuprolide acetate (a GnRH agonist) at lowering CVE risk associated with ADT. One explanation may be the decreased levels of FSH with relugolix compared to leuprolide acetate; FSH has been associated with proinflammatory effects and cardiometabolic changes, both of which may play a role in CVE, and high levels of FSH are associated

with cardiovascular side effects [75]. Finally, as the length of time on ADT increases with improved survival for advanced prostate cancer in men, and as more of these men are treated with additional hormonal agents including androgen receptor antagonists (which may also increase cardiovascular risks [101]), it will be essential to keep the baseline risk with ADT to a minimum.

Conclusion

Relugolix was demonstrated in the phase 2 and phase 3 trials to be effective at quickly reducing testosterone to conventional castration levels (<50 ng/dl) in almost all men and to profound castration levels (<20 ng/dl) for the majority of men. Along with the suppression of testosterone, PSA and FSH levels were also rapidly reduced. In the phase 3 HERO trial, the effect was significantly quicker than that of the comparator GnRH agonist leuprolide acetate. Reflecting its drug class, treatment with relugolix also did not produce any initial LH and testosterone flare, adverse effects typically associated with GnRH agonists. One important difference between relugolix and all other GnRH agonists and GnRH antagonists is that relugolix is given orally, eliminating the injection-site reactions commonly encountered with other GnRH analogues. Additionally, the reported 54% reduction in relative risk for MACE in the HERO trial with relugolix compared with leuprolide suggests that relugolix may be a preferable alternative to GnRH agonists, particularly for men with pre-existing cardiovascular risk factors.

It must be pointed out that medication taken orally does have its own challenges relating to patient adherence. Depending on the individual and their condition, oral treatment may result in lower adherence. A recent study showed that over one-third of patients with swallowing difficulties will skip an oral dose [102]. In addition, the study found that patients with swallowing difficulties will often not report this to their physician. Another element that may impact adherence is the cognitive state of the patient. In a recent study, it was shown that persons with cognitive impairments have lower medication adherence [103]. There is also an inherent uncertainty about patient adherence to daily consumption of oral cancer medications since adherence cannot be directly assessed, unlike with injections administered by a healthcare professional. Clinician communication may be of particular importance in ensuring patient adherence to treatment with relugolix, since patient satisfaction with clinician communication has been shown to improve adherence to oral cancer therapy [104]. These studies highlight the importance of tailoring treatment to best fit the patient. It will be important for physicians to consider the individual and their circumstances when choosing the most appropriate treatment.

Executive Summary

Mechanism of action

- Relugolix is a novel nonpeptide gonadotropin-releasing hormone (GnRH) antagonist.
- Relugolix quickly blocks GnRH receptors in the pituitary. This leads to decreased release of follicle-stimulating hormone and luteinizing hormone and subsequently less testosterone expression.

Administration and pharmacokinetics

- Relugolix is orally administered once daily.
- Relugolix is highly absorbable, with maximum plasma concentrations reached within 1 to 2 hours of dosing.
- Absorption does not decrease with repeated exposure, and the disposition half-life is 36 to 65 hours.

Clinical efficacy

- Results from the phase 3 HERO trial showed that relugolix was superior to the GnRH agonist leuprolide acetate at maintaining testosterone levels below 50 ng/dl over a 48-week period.
- Castration occurred quickly with relugolix, with a mean testosterone level on day 4 of 38 ng/dl, whereas leuprolide acetate caused an initial flare in testosterone (mean level of 625 ng/dl).
- Prostate-specific antigen levels responded more quickly with relugolix compared with leuprolide acetate.

Safety and tolerability

- The most common adverse events for relugolix in the phase 3 HERO trial were hot flashes and fatigue. These were also associated with leuprolide acetate and are common to androgen deprivation therapy.
- No histaminergic reactions occurred at any point during treatment with relugolix.
- Major adverse cardiovascular events were less frequent with relugolix compared to leuprolide acetate (2.9% vs. 6.2%, respectively).

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Reference annotation

*Reference 4 is of interest as it provides the recommended treatment protocols for prostate cancer.

*Reference 73 is of interest as it provides further evidence on the different impacts of GnRH agonists vs. antagonists on cardiovascular disease.

*Reference 74 is of interest as it provides further evidence on the different impacts of GnRH agonists vs. antagonists on cardiovascular disease.

**Reference 87 is of considerable interest as it is the phase 2 clinical trial with relugolix showing effectiveness in treating men with advanced prostate cancer

**Reference 88 is of considerable interest as it is the phase 3 clinical trial with relugolix for the treatment of advanced prostate cancer.

*Reference 98 is of interest as it presents the relationship between FSH and LH and cardiometabolic morbidities, which may explain the reduced incidence of MACE in patients receiving relugolix.

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Figures and tables

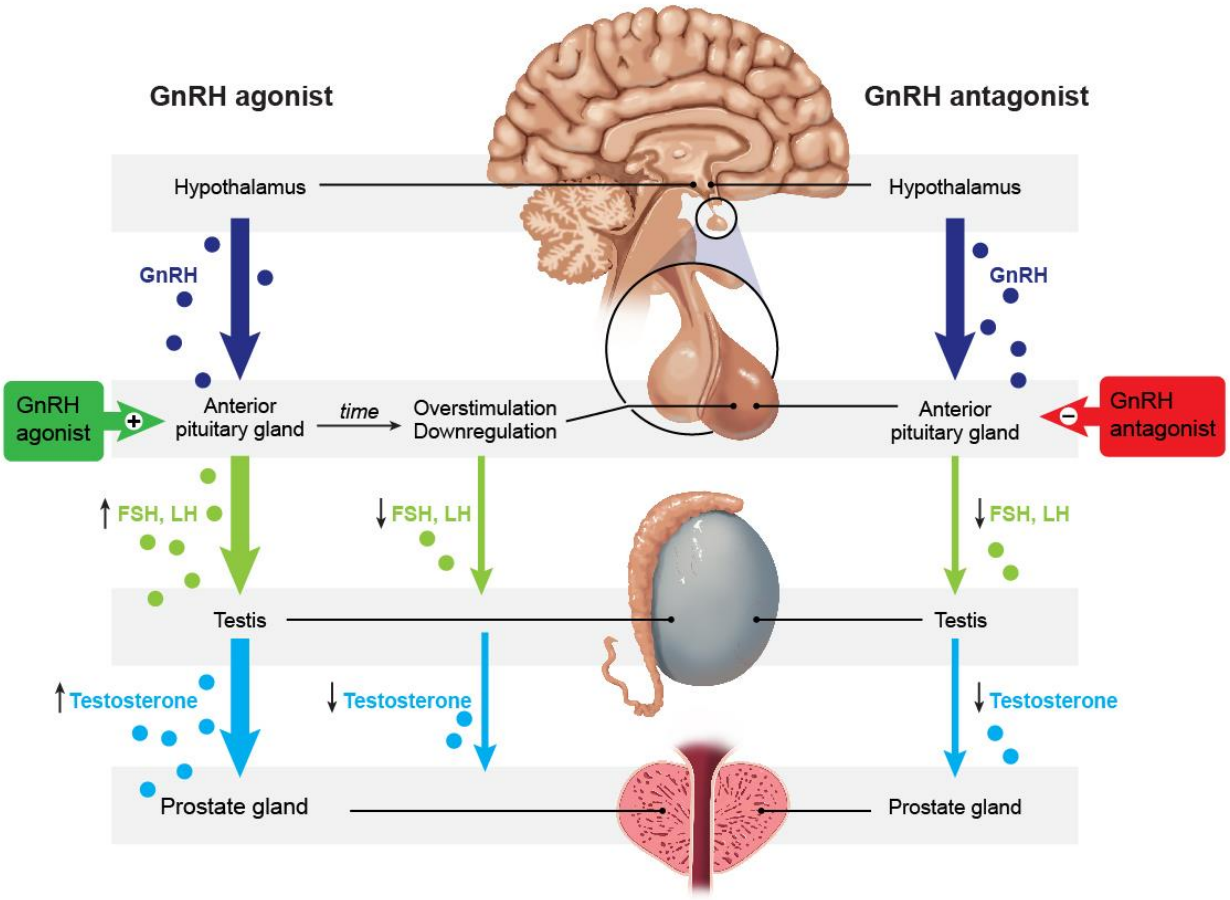

Figure 1. Signaling pathway and mechanisms of GnRH agonist/antagonist and subsequent inhibition of LH, FSH and testosterone [105, 106]

FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone

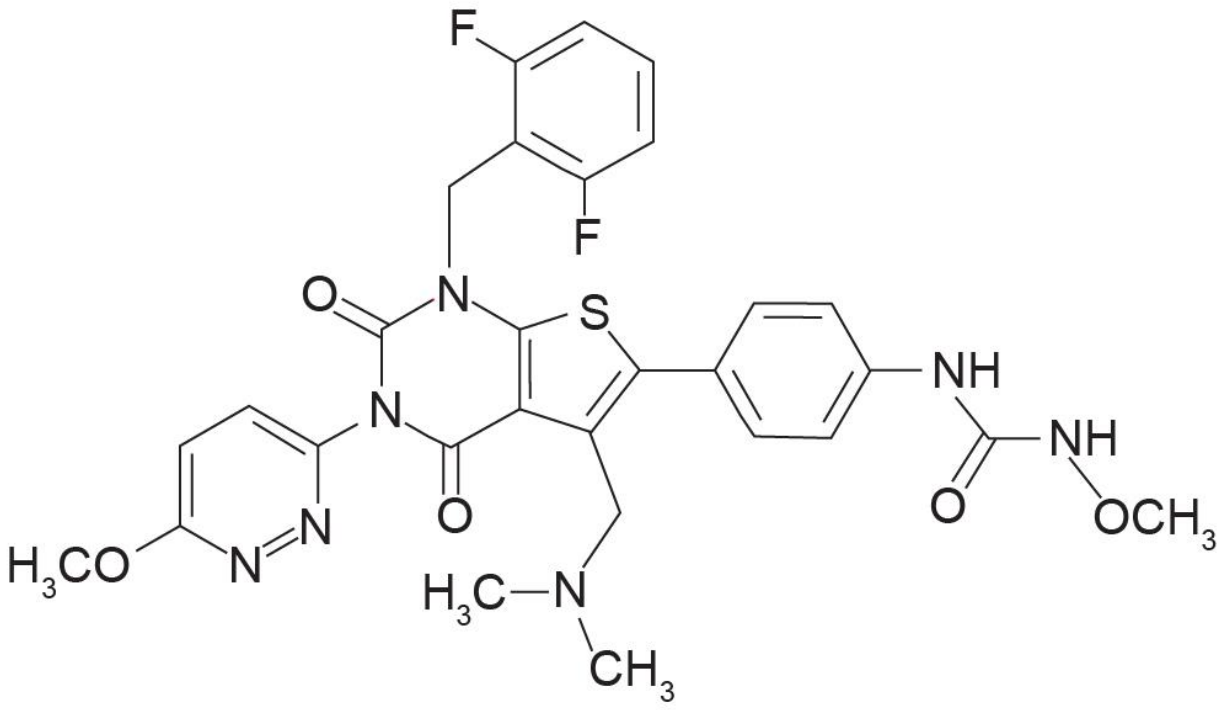

Figure 2. Chemical structure of relugolix [79]

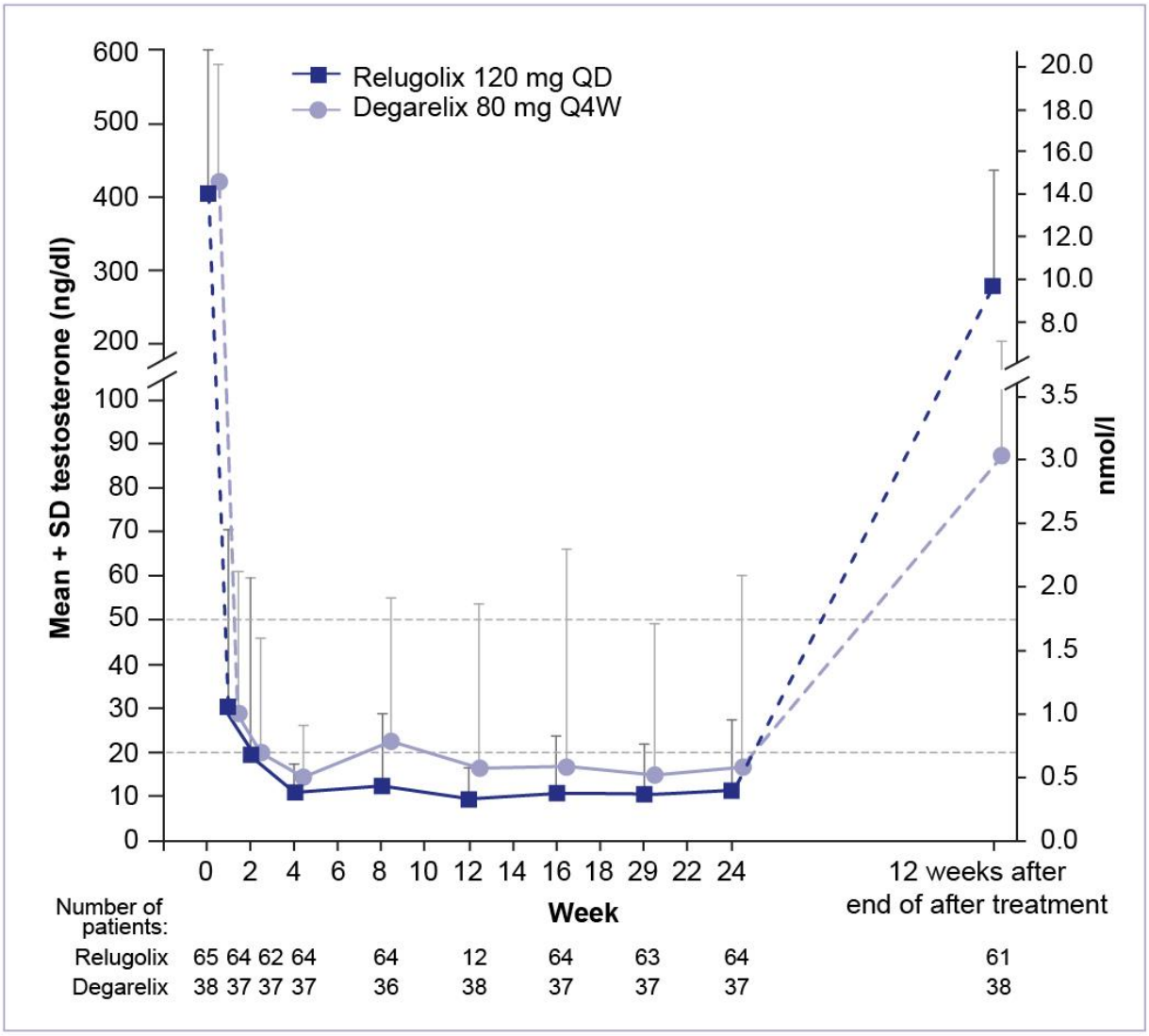

Figure 3. Mean testosterone levels over time during treatment with relugolix (320 mg loading dose and 120 mg once daily thereafter) or degarelix (loading dose 240 mg 80 mg every 4 weeks thereafter) and 12 weeks after discontinuation of treatment in the phase 2 trial [87].

Table 1. Key secondary efficacy endpoint results in HERO trial [88]

Secondary Endpoint	Relugolix (n=622)	Leuprolide acetate (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 week 24, IU/l	1.72	5.95	<0.001

FSH: follicle-stimulating hormone; IU: international unit; PSA: prostate-specific antigen

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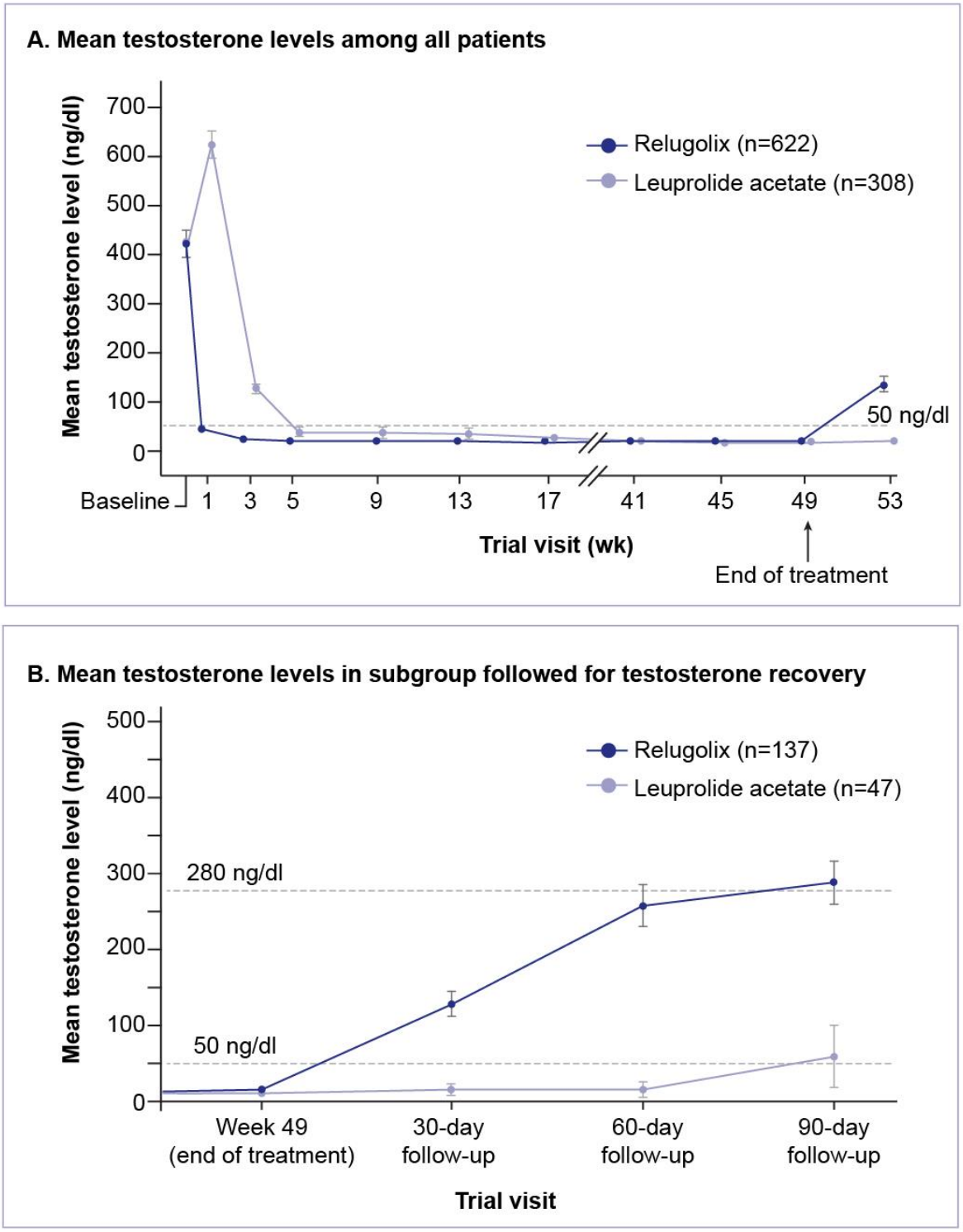

Figure 4. Mean testosterone levels during (A) 49 weeks of treatment and (B) 90 days after discontinuation with either relugolix or leuprolide acetate (HERO trial) [88].

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