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The Oral Gonadotropin-releasing Hormone Receptor Antagonist Relugolix as Neoadjuvant/Adjuvant Androgen Deprivation Therapy to External Beam Radiotherapy in Patients with Localised Intermediate-risk Prostate Cancer: A Randomised, Open-label, Parallel-group Phase 2 Trial

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Abstract

Background: External beam radiotherapy (EBRT) with neoadjuvant/adjuvant androgen deprivation therapy (ADT) is an established treatment option to prolong survival for patients with intermediate- and high-risk prostate cancer (PCa). Relugolix, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist, was evaluated in this clinical setting in comparison with degarelix, an injectable GnRH antagonist.
Objective: To evaluate the safety and efficacy of relugolix to achieve and maintain castration.
Design, setting, and participants: A phase 2 open-label study was conducted in 103 intermediate-risk PCa patients undergoing primary EBRT and neoadjuvant/adjuvant ADT between June 2014 and December 2015.
Intervention: Patients randomly assigned (3:2) to 24-wk treatment with either daily oral relugolix or 4-wk subcutaneous depot degarelix (reference control).
Outcome measurements and statistical analysis: The primary endpoint was the rate of effective castration (testosterone $<$1.73 nmol/l) in relugolix patients between 4 and 24 wk of treatment. Secondary endpoints included rate of profound castration (testosterone $<$0.7 nmol/l), prostate-specific antigen (PSA) levels, prostate volume, quality of life (QoL) assessed using the Aging Males' Symptoms scale, and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (30-item EORTC core questionnaire [EORTC QLQ-C30] and 25-item EORTC prostate cancer module [EORTC QLQ-PR25]) questionnaires, and safety. No formal statistical comparisons with degarelix were planned.
Results and limitations: Castration rates during treatment were 95% and 82% with relugolix and 89% and 68% with degarelix for 1.73 and 0.7 nmol/l thresholds, respec-

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tively. Median time to castration in the relugolix arm was 4 d. During treatment, PSA levels and prostate volumes were reduced in both groups. Three months after discontinuing treatment, 52% of men on relugolix and 16% on degarelix experienced testosterone recovery (statistical significance of differences not tested). Mean and median QoL scores improved following treatment discontinuation. The most common adverse event was hot flush (relugolix 57%; degarelix 61%). Lack of blinding was a potential limitation.
Conclusions: Relugolix achieved testosterone suppression to castrate levels within days and maintained it over 24 wk with a safety profile consistent with its mechanism of action.
Patient summary: Oral once-daily relugolix may be a novel oral alternative to injectable androgen deprivation therapies.

1. Introduction

Androgen deprivation therapy (ADT) with radiotherapy is an appropriate treatment option for most men with newly diagnosed intermediate- and high-risk prostate cancer (PCa) [1]. While the timing and duration of neoadjuvant/adjuvant ADT have not been defined fully, based on evidence from several large studies [2–5], European and American clinical practice guidelines suggest that 4–6 mo of ADT may be sufficient for patients with intermediate-risk disease, whereas patients with high-risk advanced localised disease are more likely to benefit from prolonged neoadjuvant/adjuvant treatment of 18–36 mo [6–10]. Meta-analyses have shown benefit from both short and long courses of ADT [11,12].

Established ADT options are gonadotropin-releasing hormone (GnRH) analogues administered subcutaneously or intramuscularly in a depot formulation. While effective in achieving castration, GnRH agonists are associated with potential worsening of genitourinary and other symptoms due to a testosterone flare within 14 d of initial injection, which may be symptomatic in advanced PCa, requiring additional use of an antiandrogen [13,14]. Historically, injectable GnRH agonists were developed because neither oral small molecules nor peptide antagonists with the requisite safety and efficacy to block the GnRH pathway could be identified [15]. Degarelix, an approved once-monthly injectable GnRH receptor antagonist, can rapidly reduce testosterone levels without the initial testosterone surge, and has been suggested to delay the time to the castration-resistant disease state [16–19]. However, this GnRH antagonist requires monthly high-volume injections that are commonly associated with injection-site reactions [20].

Relugolix (TAK-385) is an investigational, highly selective, orally active, nonpeptide GnRH receptor antagonist [15,21]. As a potent oral agent, relugolix has the potential to eliminate the need for injections while rapidly decreasing testosterone and prostate-specific antigen (PSA) levels. In a phase 1 study in healthy men, once-daily relugolix was effective in lowering testosterone to below castration levels (1.73 nmol/l or <50 ng/dl) [22]. Subsequent research defined the efficacious dose range for further development as 80–160 mg daily with a single loading dose of 320 mg to achieve a rapid testosterone-lowering response [22]. Finally, the half-life of 36–65 h [22] suggests that testosterone recovery after short-term or intermittent ADT should be more rapid with relugolix than with depot formulations of GnRH analogues. The safety of relugolix in these earlier studies has been consistent with other ADT options [14,22].

The primary objective of this phase 2 study was to evaluate whether relugolix results in rapid and sustained testosterone suppression in men with intermediate-risk PCa who require 6 mo of neoadjuvant/adjuvant ADT in conjunction with external beam radiotherapy (EBRT). Secondary objectives included evaluation of the effects of relugolix on the kinetics of testosterone suppression and recovery, PSA levels, prostate volume, quality of life (QoL), and safety/tolerability. A degarelix arm was included in the study to serve as a contemporary ADT benchmark for qualitative comparisons. A second phase 2 study evaluating relugolix in men with advanced PCa and including a leuprolide arm for qualitative comparison (ClinicalTrials.gov identifier NCT02083185) will be reported in a subsequent publication.

2. Patients and methods

2.1. Patients

Eligible patients had histologically confirmed, localised, intermediate-risk prostate adenocarcinoma with indication for 24 wk of neoadjuvant/adjuvant ADT to EBRT. High-risk patients were also considered for inclusion if, based on physician judgement, they were deemed likely to benefit from 6 mo of ADT. A complete list of eligibility criteria is provided in the Supplementary material (Methods) and Supplementary Table 1. A total of 103 patients were enrolled in the USA (18 sites) and UK (five sites).

This study was approved by two central institutional review boards and conducted in accordance with the Declaration of Helsinki (2013 revision) and Good Clinical Practice guidelines. All patients provided written informed consent.

2.2. Study design and treatments

This was a phase 2 randomised, open-label, parallel-group study conducted between June 2014 and December 2015 (ClinicalTrials.gov identifier NCT02135445). The trial was not blinded. Patients were randomised in a 3:2 ratio to

Table 1 – Patient demographics and baseline characteristics.

Characteristic	Relugolix 120 mg QD(*N* = 65)	Degarelix 80 mg Q4W (*N* = 38)
Race, *n* (%)		
White	58 (89)	31 (82)
Black or African American	7 (11)	7 (18)
Median (IQR) age (yr)	71.0 (67–73)	70.5 (67–75)
ECOG PS 0/1, [a] *n* (%)	60 (92)/4 (6)	33 (87)/4 (11)
Median (IQR) time since initial diagnosis (yr)	0.2 (0.1–0.3)	0.1 (0.1–0.2)
Gleason score, [b] *n* (%)		
6	5 (8)	2 (5)
7	40 (62)	26 (68)
8	5 (8)	3 (8)
9	2 (3)	2 (5)
Primary tumour (T), *n* (%)		
Not available	11 (17)	8 (21)
T1	21 (32)	12 (32)
T2	6 (9)	5 (13)
T2a	12 (18)	3 (8)
T2b	7 (11)	1 (3)
T2c	7 (11)	7 (18)
T3	1 (2)	1 (3)
TX	0	1 (3)
Regional lymph nodes (N), *n* (%)		
N0	39 (60)	19 (50)
NX [c]	26 (40)	19 (50)
PSA (μg/l)		
Mean (SD)	9.4 (6.0)	14.6 (21.0)
Median (IQR)	7.3 (4.8–12.9)	7.3 (5.5–11.2)

ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; PSA = prostate-specific antigen; QD = once daily; Q4W = once every 4 wk; SD = standard deviation.
[a] ECOG PS was missing for one patient in each group.
[b] Total Gleason score was missing for 13 and five patients in the relugolix and degarelix groups, respectively.
[c] NX includes unknown, not available, and missing regional lymph node data.

receive 24 wk of either oral relugolix (loading dose of 320 mg on day 1 and 120 mg daily thereafter) or degarelix as a subcutaneous depot injection (loading dose of 240 mg on day 1, and then 80 mg every 4 wk). Patients were randomised sequentially by study centre. No stratification was implemented in the computer-generated randomisation schedule. Unique randomisation numbers were assigned to patients using a centralised interactive voice/web response system. The inclusion of degarelix provided a contemporary GnRH antagonist benchmark for relugolix, using the same assays and assessments. EBRT was initiated after 12–16 wk of ADT, as per each clinical site's standard of care.

The protocol did not specify the use of adjunctive medications such as calcium and vitamin D, but these could have been given at the clinician's discretion.

Patients were evaluated on days 1, 2, and 4 during week 1; once in each of weeks 2, 3, and 5; every 4 wk thereafter during the 24-wk treatment period; and for 12 wk after treatment discontinuation. Serum testosterone concentrations were assayed using a conventional immunoassay at screening, and subsequently using liquid

Table 2 – Castration rates for patients who received at least one dose of treatment.

	Relugolix 120 mg QD (*N* = 65)	Degarelix 80 mg Q4W (*N* = 38)
Castration rate [a] over 24 wk		
n (%)	62 (95)	34 (89)
90% CI [b] (one sided, lower bound)	90.0	
95% CI [b] (two sided)	87.1–99.0	75.2–97.1
Profound castration rate [c] over 24 wk		
n (%)	53 (82)	26 (68)
90% CI [b] (one sided, lower bound)	73.9	56.9
95% CI [b] (two sided)	70.0–90.1	51.3–82.5

CI = confidence interval; QD = once daily; Q4W = once every 4 wk.
[a] Castration rate was defined as the estimated proportion of patients with testosterone concentrations <1.73 nmol/l (50 ng/dl) at all scheduled visits from 4 through 24 wk.
[b] The 90% one-sided and the 95% two-sided CIs were calculated using exact method.
[c] Rate of profound castration was defined as the estimated proportion of patients with testosterone concentrations <0.7 nmol/l (<20 ng/dl) at all scheduled visits from week 13, day 1 through to week 25, day 1.

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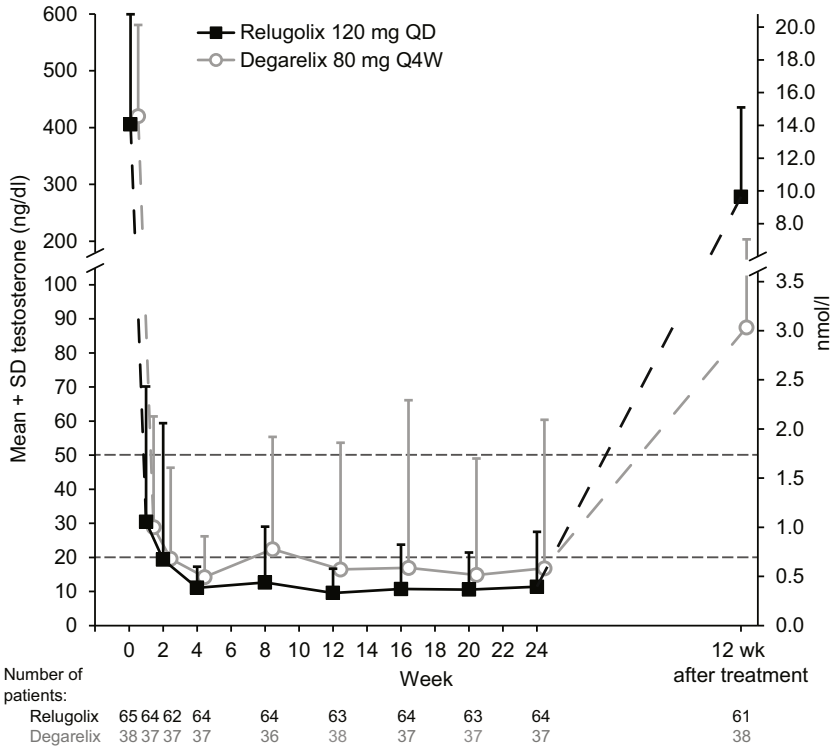

Fig. 1 – Mean testosterone levels through week 24 and after treatment discontinuation. Mean (+SD) testosterone levels are presented over time, including during treatment (24 wk) and during 12 wk of follow-up after study drug discontinuation. Note the break in the *y* axis and different scaling of values <100 versus >200 ng/dl. Data for the two treatment arms are staggered along the *x* axis for legibility. The dotted lines indicate a castration threshold of 1.73 nmol/l (50 ng/dl) or 0.7 nmol/l (20 ng/dl). The week-2 assessment in one patient in the relugolix group is omitted from this figure as the value was 10 times the upper limit of normal and is believed to be a technical error. All other data from this patient are included in the analysis. QD = once daily; Q4W = once every 4 wk; SD = standard deviation.

chromatography-tandem mass spectrometry (LC-MS/MS). Serum PSA assays were performed by a central facility (LabCorp). Prostate volume was measured using transrectal ultrasound or magnetic resonance imaging at baseline and at the next imaging assessment 8–12 wk after initiating ADT. QoL was assessed via the 30-item European Organisation for Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30) [23], the 25-item EORTC prostate cancer module (EORTC QLQ-PR25) [24], and the Aging Males' Symptoms (AMS) scale [25]. QoL assessments were completed at screening; at baseline; after 4, 12, and 24 wk of treatment; 4 wk after treatment discontinuation; and at the end-of-study visit (36 wk after starting the study; 12 wk off treatment). Treatment compliance was measured by a patient-reported daily diary using a handheld electronic device.

2.3. Outcomes

The primary endpoint was the rate of effective castration, between 4 wk and 24 wk of treatment, defined as the estimated proportion of patients with testosterone concentrations <1.73 nmol/l (<50 ng/dl) at all scheduled visits. A lower (profound) castration threshold was defined as testosterone levels <0.7 nmol/l (<20 ng/dl). Secondary endpoints included PSA response at 12 wk and PSA nadir during treatment and follow-up, prostate volume 8–12 wk after treatment, and the time to achieve effective castration and testosterone recovery (recovery was defined as the return of testosterone values to baseline or to >9.8 nmol/l [>280 ng/dl]), changes in QoL during and after treatment, and safety measures. Such measures included the incidence and severity of treatment-emergent adverse events (AEs), and changes in vital signs, laboratory studies, and electrocardiograms (ECGs). Additional assessments included ophthalmology examinations, bone densitometry, and serum/urinary biomarkers of bone turnover and phospholipidosis.

2.4. Statistical analysis

Assuming a 95% effective castration rate (<1.73 nmol/l or 50 ng/dl) with relugolix treatment, 60 evaluable patients provided >91% as the lower bound of a one-sided 90% confidence interval (CI). The sample size for the degarelix arm was based on historical estimates of castration rate using 80-mg 4-wk depot dosing of >95% [26], and no more than two patients were expected to fail the defined successful castration endpoint. A total of 100 patients were planned to be enrolled into the study. In addition to the one-sided 90% CI for the primary endpoint, two-sided 95% CIs were calculated for the primary endpoint and the secondary endpoint of profound castration. No formal statistical differences were sought or hypothesised between relugolix and degarelix.

Changes in PSA, prostate volume, and testosterone levels were summarised over time. Changes in QoL values over time were analysed using linear mixed models. Time to castration and time to testosterone recovery were analysed using the Kaplan–Meier method. The safety population, defined as all patients who received one or more doses of either study drug, was used for all safety and efficacy analyses.

3. Results

A total of 103 patients were enrolled in this study. Sixty-three of the 65 patients (97%) randomised to relugolix and all 38 patients randomised to degarelix completed the 24-wk treatment period and the 12-wk follow-up period. Two patients in the relugolix arm did not complete the study: one due to patient withdrawal and the other due to loss to follow-up. All patients were included in efficacy and safety analyses (Supplementary Fig. 1).

Patient demographics and baseline characteristics (Table 1) and EBRT treatment details (Supplementary Table 2) were similar between treatment groups. Most patients had intermediate-risk disease; however, two patients in each group with Gleason 9 PCa and one patient in each group with T3 disease were allowed per protocol based on investigator discretion despite higher-risk disease. Overall, 18 patients had missing Gleason scores that the contract research monitoring team was unable to document at the enrolling sites. Median compliance with study drug, as measured with the electronic patient diary, was >98% in both arms.

As shown in Table 2, both relugolix and degarelix were associated with high rates of effective castration, with conventional castration rates of 95% and 89%, respectively. A sensitivity analysis including only patients with intermediate-risk disease yielded similar results (Supplementary Table 3). The profound castration rates for the lower threshold of 0.7 nmol/l (20 ng/dl) were 82% in the relugolix group and 68% in the degarelix group. Mean testosterone levels across 24 wk of treatment and 12 wk of follow-up after discontinuation of treatment are reported in Fig. 1 and Supplementary Table 4. The time to castration was rapid in both groups, at a median of 4 d in the relugolix group and 3 d in the degarelix group.

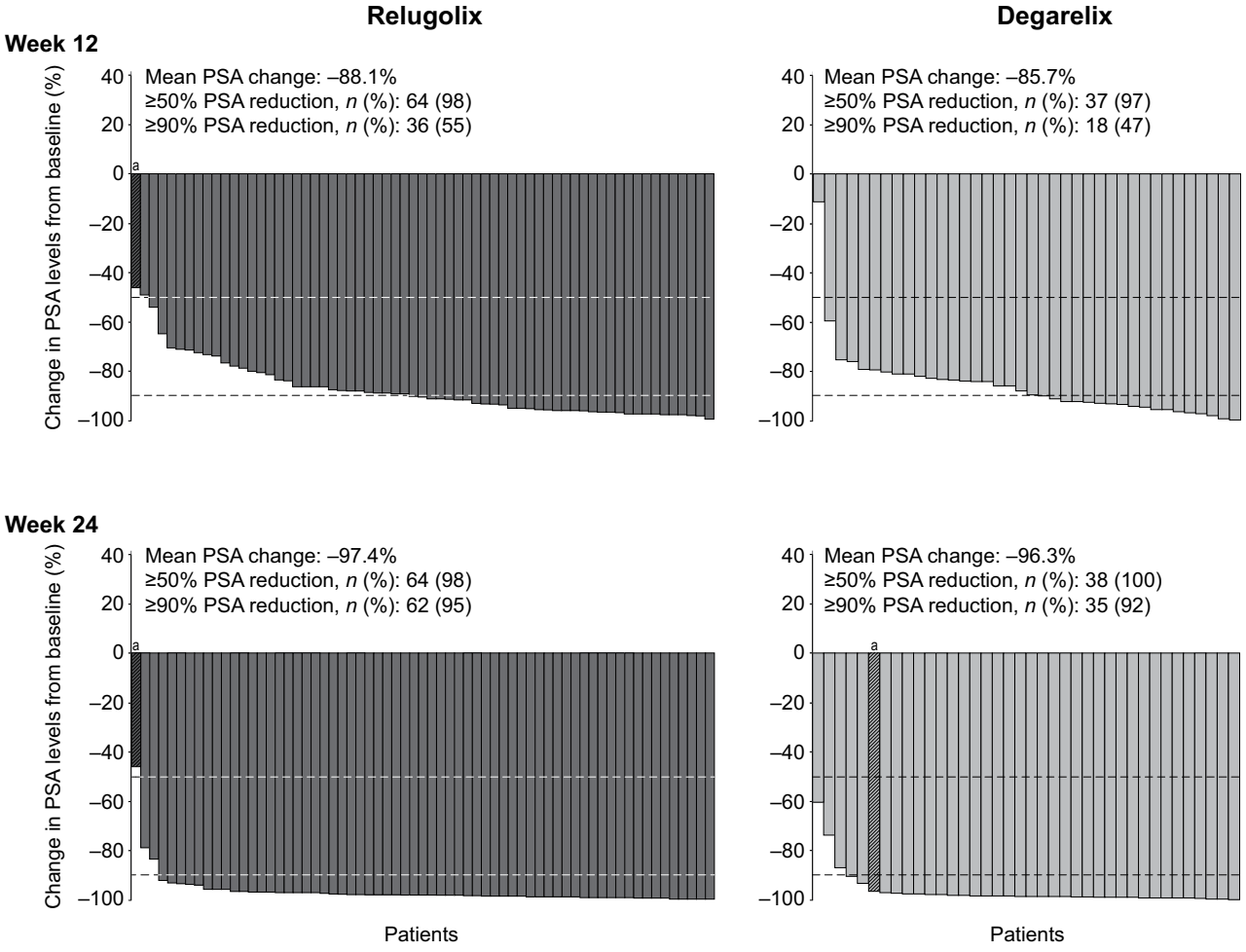

Fig. 2 – Individual PSA responses of patients in the relugolix and degarelix groups. Waterfall plots of reduction in PSA percentage for individual patients at week 12 (neoadjuvant) and week 24 (neoadjuvant/adjuvant/EBRT) for relugolix and degarelix, as well as associated PSA50 and PSA90 responses. Dotted lines indicate the PSA50 and PSA90 thresholds, respectively. EBRT = external beam radiotherapy; PSA = prostate-specific antigen; PSA50 = reduction in PSA by ≥50%; PSA90 = reduction in PSA by ≥90%. [a] Last observation carried forward.

Following discontinuation of relugolix treatment at 24 wk, testosterone levels recovered rapidly within 12 wk; recovery to baseline or >9.8 nmol/l (280 ng/dl) occurred in 52% of patients. In the degarelix group, median testosterone remained well below 1.73 nmol/l (<50 ng/dl) following discontinuation, with only 16% of patients meeting the protocol-specified definition of testosterone recovery to baseline or >9.8 nmol/l. The time to testosterone recovery is depicted in Supplementary Fig. 2.

In both groups, the median prostate volume decreased from baseline to 8–12 wk of treatment (relugolix 26% and degarelix 29%; Supplementary Table 5). Similarly, median PSA levels declined steadily through week 24 (Supplementary Table 6). Waterfall plots of individual PSA percentage reductions at weeks 12 and 24 are shown in Fig. 2. By 12 wk, the reduction in PSA by ≥50% in both groups was ≥97%, and the reduction in PSA by ≥90% was 55% and 47% in the relugolix and degarelix groups, respectively. Median PSA levels remained low after treatment discontinuation in both arms (Supplementary Table 4). Both luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels were suppressed on treatment with both relugolix and degarelix (Supplementary Table 4).

Global health status, as assessed by EORTC-QLQ-C30, and sexual activity and hormonal treatment-related symptoms, as assessed by the EORTC-QLQ-PR25, were negatively affected during treatment in both groups (Table 3). Within 12 wk after treatment discontinuation, sexual activity scores improved by a mean of 12.1 for relugolix and 6.6 for degarelix (median 8.3 and 0.0, respectively) and hormonal treatment-related symptoms changed by a mean of –5.0 and –1.2 (median −5.6 and 0.0), respectively.

Similarly, AMS total and subscale scores (sexual, psychological, and somatic) worsened during treatment in both groups (Table 3 and Supplementary Table 7). After treatment discontinuation, the mean percentage change in AMS total scores was –15% in the relugolix group and –2.9% in the degarelix group. Median percentage changes were consistent (–16% and –3.9%, respectively). Similar patterns were observed in the subscale scores (Supplementary Table 7).

At least one AE was reported by most patients in both groups (relugolix 86%; degarelix 97%), although severe (grade 3 or higher) AEs were infrequent (relugolix 2%; degarelix 11%). The most common AE in both groups was hot flush (relugolix 57%; degarelix 61%). Except for findings of increased alanine aminotransferase (13%) and injection-site erythema (11%) in the degarelix group, the overall AE profile was similar between relugolix and degarelix (Table 4). There were no differences between groups in ophthalmology findings, laboratory findings, ECGs, or biomarkers of bone turnover, bone density, or phospholipidosis. No patients in either group discontinued treatment due to AEs.

4. Discussion

In this phase 2 study of intermediate-risk PCa patients, adding neoadjuvant/adjuvant relugolix to EBRT resulted in a 95% rate of sustained castration. While the study was not designed or powered to make formal statistical comparisons between

Table 3 – Change in quality of life during treatment (24 wk) and during recovery (12 wk) as measured by the EORTC QLQ-C30 Global health/QoL scale, the EORTC QLQ-PR25 Sexual Activity and Hormone Treatment-related Symptoms scales, and the AMS Total score.

	EORTC QLQ-C30 Global health/QoL, mean (SD) change [a]		EORTC QLQ-PR25, mean (SD) change				Aging Males' Symptoms Total score, percentage change, mean (SD) [b]	
			Sexual activity [a]		Hormone treatment-related symptoms [b]			
	Relugolix 120 mg QD	Degarelix 80 mg Q4W	Relugolix 120 mg QD	Degarelix 80 mg Q4W	Relugolix 120 mg QD	Degarelix 80 mg Q4W	Relugolix 120 mg QD	Degarelix 80 mg Q4W
Baseline to week 24	–10.1 (18.9)	–7.5 (13.7)	–19.7 (29.4)	–11.8 (36.3)	13.4 (12.1)	12.9 (10.4)	43.6 (52.5)	48.2 (41.2)
Week 24 to week 36	2.3 (16.6)	0.7 (15.5)	12.1 (21.8)	6.6 (22.8)	–5.0 (10.3)	–1.2 (9.1)	–15.1 (24.4)	–2.9 (18.4)
Baseline to week 36 (EOS)	–7.7 (17.8)	–6.8 (16.0)	–7.3 (30.0)	–5.3 (34.7)	8.5 (11.3)	11.7 (10.2)	14.6 (30.0)	40.5 (35.4)

AMS = Aging Males' Symptoms scale; EORTC QLQ-C30 = 30-item European Organisation for Research and Treatment of Cancer core questionnaire; EORTC QLQ-PR25 = 25-item EORTC prostate cancer questionnaire; EOS = end of study; QD = once daily; QoL = quality of life; Q4W = once every 4 wk; SD = standard deviation.

[a] Higher scores of Global Health/QoL and Sexual Activity scales reflect better QoL, positive change indicates QoL improvement, and negative change indicates QoL worsening.

[b] Higher scores of Hormonal Treatment-related Symptoms scale and AMS Total reflect worse QoL, positive change indicates QoL worsening, and negative change indicates QoL improvement.

Table 4 – Most common (≥10%) all-cause and grade ≥3 treatment-emergent adverse events (safety population).

n (%)	Relugolix 120 mg QD (*N* = 65)		Degarelix 80 mg Q4W (*N* = 38)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Any AE [a]	56 (86)	1 (2)	37 (97)	4 (11)
Hot flush [b]	37 (57)	0	23 (61)	0
Fatigue	17 (26)	0	6 (16)	0
Diarrhoea	12 (18)	0	5 (13)	0
Cataract	10 (15)	0	7 (18)	0
Nocturia	9 (14)	0	5 (13)	0
Pollakiuria	8 (12)	0	6 (16)	0
Dysuria	5 (8)	0	6 (16)	0
Increased blood testosterone	2 (3)	0	4 (11)	0
Decreased urine flow	1 (2)	0	4 (11)	0
Increased ALT	0	0	5 (13)	0
Injection-site erythema	0	0	4 (11)	0
Bone fracture [c]	0	0	0	1 (3)
Paranasal sinus haematoma	0	0	0	1 (3)
Pleural effusion	0	0	0	1 (3)
Ulcerative oesophagitis	0	0	0	1 (3)
Pulmonary contusion	0	0	0	1 (3)
Road traffic accident	0	0	0	1 (3)
Diabetes mellitus	0	0	0	1 (3)
Malignant mesothelioma	0	0	0	1 (3)
Cold sweat	0	0	0	1 (3)
Headache	0	1 (2) [d]	0	0
Hypertension	0	1 (2) [d]	0	0

AE = adverse event; ALT = alanine aminotransferase; QD = once daily; Q4W = once every 4 wk.
[a] Concomitant medications to manage any AE were taken by 52% (34/65) of patients in the relugolix arm and 71% (27/38) in the degarelix arm. Calcium and/or vitamin D was taken by 32% (21/65) and 37% (14/38), respectively.
[b] Drugs to treat hot flushes were taken by 6% (4/65) of patients in the relugolix arm and 11% (4/38) in the degarelix arm.
[c] Bone fracture includes ankle, fibula, radius, ulna, jaw, rib, and facial bone fractures that occurred in a road traffic accident in a single patient.
[d] These events occurred in a single patient.

relugolix and degarelix, both drugs rapidly induced and maintained castration during the treatment period. Accordingly, effects on PSA response and prostate volume were consistent between relugolix and degarelix groups, as well as consistent with data previously reported with other GnRH analogues [26–28]. Both relugolix and degarelix yielded rapid reductions in testosterone not seen with GnRH receptor agonists, which are associated with an early testosterone flare. Furthermore, both LH and FSH are fully suppressed while on treatment with both relugolix and degarelix, whereas GnRH agonists do not fully suppress FSH [19].

The rate of gonadotropin and testosterone recovery after treatment discontinuation was rapid with relugolix. These findings are consistent with its pharmacokinetic profile as a daily oral therapy. Fast testosterone recovery with relugolix was associated with a rapid improvement in a range of castration-related symptoms on QoL measures.

Previous data suggest that recovery from degarelix monthly depot injections can take >100 d; in this study, only 16% of degarelix patients had testosterone recovery 84 d after treatment discontinuation. Similar delayed recovery of testosterone has been reported using GnRH agonists, particularly with the 3-mo depot preparations [29,30].

The ability to personalise dosing strategies with a once-daily oral medication with reliable rapid return of testosterone and fast relief from symptoms related to ADT may be advantageous for patients who do not want injections, those receiving a specific duration of therapy, those with disease eligible for intermittent therapy, and elderly patients with comorbidities or acute intercurrent illnesses where fatigue and muscle wasting are problematic.

Both relugolix and degarelix were well tolerated in this study. Although the frequency and type of AEs were not compared between the treatment arms with formal statistical analyses, similar patterns of AEs were reported by patients in both groups, with hot flush and fatigue being the most common. No hepatic-related AEs occurred in either group that resulted in dose modification or treatment discontinuation. Several patients receiving degarelix had injection-site reactions, consistent with past observations with injectable GnRH analogues. With the exception of those local reactions, the incidence and pattern of AEs with relugolix were as expected for a GnRH receptor antagonist [31]. Overall, there were no unexpected safety findings, no evidence of any bone safety or ophthalmological findings, no evidence of drug-induced phospholipidosis, and no safety concerns identified that would limit treatment in most patients.

The lack of blinding in this study is a potential limitation. Although knowledge of treatment assignments is unlikely to have had a meaningful impact on testosterone levels or other pharmacodynamic endpoints, it could have influenced investigators' assessments of safety and patients' responses on QoL questionnaires.

Despite the high compliance reported for relugolix administration in this study (>98%), another potential limitation of the trial is that it may not reflect compliance and adherence in a real-world setting. Inconsistent dosing

carries the danger of ineffective therapeutic delivery and suboptimal treatment outcomes. Although compliance is more difficult to monitor with self-administered oral medications compared with injections administered by healthcare professionals, compliance can be monitored indirectly with testosterone or PSA levels. Novel strategies are being developed to improve adherence to oral oncology drugs [32]. Studies with longer-term follow-up are needed to further evaluate the clinical impact of more rapid testosterone recovery with relugolix, as well as long-term suppression of both FSH and LH. The phase 3 HERO trial investigating relugolix versus leuprolide over 48 wk is on-going in patients with advanced PCa (NCT03085095) and will evaluate whether relugolix can suppress testosterone through 48 wk in men with advanced PCa. This study will also evaluate whether relugolix can prolong the time to the castration-resistant PCa as compared with leuprolide acetate.

Recently released guidelines on the management of patients with localised intermediate-risk PCa recommend ADT with radiotherapy as a standard treatment option [33]. Considering the limitations of injectable GnRH agonists and GnRH receptor antagonists, there is an unmet need for a novel ADT in this treatment landscape. While other oral GnRH receptor antagonists are currently in development for women's health indications [34], to our knowledge, relugolix is the only such antagonist in clinical development for PCa.

5. Conclusions

In summary, 24-wk treatment with the oral GnRH receptor antagonist relugolix rapidly and effectively reduced and sustained testosterone to castration levels, while exhibiting a well-tolerated safety profile. A global phase 3 trial is on-going to further evaluate the efficacy and safety of relugolix in men with PCa.

***Author contributions*:** David P. Dearnaley had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Saad, Shi, Faessel, Lin, MacLean, Shore.
Acquisition of data: Saltzstein, Sylvester, Karsh, Pieczonka, Bailen, Shi, Ye, Faessel, Lin, MacLean.
Analysis and interpretation of data: Dearnaley, Saltzstein, Sylvester, Karsh, Pieczonka, Saad, Shi, Ye, Faessel, Lin, Zhu, MacLean, Shore.
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Appendix A. Supplementary data

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