CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

relugolix (Orgovyx)

Indication: For the treatment of adult patients with advanced prostate cancer

Sponsor: Sumitomo Pharma Canada, Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: May 2024
Report Length: 17 Pages

Single Technology

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that relugolix be reimbursed for the treatment of advanced prostate cancer in adult patients only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, open-label, parallel-group, multicentre trial (HERO, N = 934) demonstrated that treatment with relugolix resulted in the suppression of testosterone levels compared to leuprolide. The study was conducted in adult patients who were candidates for at least one year of continuous androgen deprivation therapy (ADT) for various stages of advanced prostate cancer including biochemical relapse, newly diagnosed androgen sensitive metastatic disease, and advanced localized disease not suitable for primary surgical intervention. Specifically, from day 29 through week 49, the proportion of patients who achieved sustained testosterone suppression was 96.7% (95% confidence interval (CI), 94.9 to 97.9%) for those treated with relugolix compared to 88.8 % (95% CI, 84.6 to 91.8) of those treated with leuprolide, thus meeting the primary study objective with a prespecified non-inferiority margin of -10% and demonstrating superiority (lower bound of 95% CI>0, p<0.0001). The mean difference (MD) in proportion of patients achieving sustained testosterone suppression at week 49 between the treatment groups was 7.9% (95% CI, 4.1% to 11.8%). Similarly, from day 29 through week 49, treatment with relugolix resulted in a higher proportion of patients achieving and maintaining profound castration levels of testosterone (< 20 ng/dL) (81.6%; 95% CI: 78.1%, 84.5%) compared with those treated with leuprolide (68.6%; 95% CI: 63.0%, 73.5%), a level of suppression considered to be more important by the clinical experts consulted by CADTH. However, the analysis for this outcome was outside the statistical hierarchy and was not adjusted for multiplicity.

pERC noted that the proportion of patients who experienced treatment-emergent adverse events in the HERO trial was similar for those treated with relugolix as those treated with leuprolide, and considered the harms manageable and in line with clinical expectations for the ADTs.

Patient-identified needs included availability of treatments that can extend life, improve quality of life, delay disease progression, reduce side effects, and that could be administered orally rather than by injection and potentially more easily accessed. pERC concluded that relugolix met some of the needs identified by patients, such as potentially delaying progression, being convenient to take and having manageable treatment side effects.

At the sponsor submitted price for relugolix and publicly listed price for other ADTs, relugolix ranged from being similar to or potentially less costly than other ADTs. While the phase III HERO trial showed relugolix is non-inferior compared to leuprolide acetate, comparative efficacy and safety of relugolix versus other ADTs could not be determined; therefore the total drug cost of relugolix should not exceed the total drug cost of other ADTs.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults (18 years or older) with histologically or cytologically confirmed PC who are not candidates for chemotherapy or surgical therapy soon after initiating ADT.	Evidence from the HERO trial demonstrated that treatment with relugolix resulted in clinical benefit in terms of testosterone suppression, compared with leuprolide, in patients with advanced PC	—
2. Patients should have good performance status.	Patients with an ECOG performance status of 0 or 1 were included in the HERO trial.	pERC agreed with the clinical experts that patients with ECOG PS 2 or 3 could potentially benefit from relugolix
Renewal		
3. Assessment for disease progression should be based on clinical, PSA, and radiographic evaluations at least every 3 to 6 months or per physician's discretion.	According to clinical expert input, in clinical practice, clinical and PSA assessments are conducted every 3 to 6 months.	—
Discontinuation		
4. Reimbursement of relugolix should continue until unacceptable toxicity.	Patients from the HERO trial discontinued treatment upon the development of unacceptable toxicity.	—
Prescribing		
5. Relugolix should be prescribed by a clinician with expertise in management of PC and ADT.	To ensure that relugolix is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. Relugolix pricing should be negotiated so that it does not exceed the drug program cost of treatment with the least costly ADT reimbursed for the treatment of advanced PC.	As relugolix is considered non-inferior compared to leuprolide acetate, but comparative efficacy and safety of relugolix versus other ADTs could not be determined, there is insufficient evidence to justify a cost premium for relugolix over the least expensive ADT reimbursed for advanced PC.	—
Feasibility of adoption		
7. The feasibility of adoption of relugolix must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; PC = prostate cancer; PSA = Prostate-specific antigen.

Discussion Points

- pERC considered the results of a sponsor-submitted indirect treatment comparison (ITC) comparing the efficacy and safety of relugolix versus other medical ADTs available in Canada. [redacted] However, the committee noted the heterogeneity in the data within the NMA networks and acknowledged the clinical experts' observation that profound castration levels would have been a better efficacy outcome for the Canadian context, and that the MACE assessment was performed too early and hence the outcome was non-informative. pERC noted that relugolix, similar to the administration of other ADTs in clinical practice, should be used with caution in patients with major adverse cardiovascular events.
- pERC noted that the HERO trial did not assess the effectiveness or safety of relugolix as part of an intensification therapy option or as neoadjuvant/adjuvant therapy to radiation therapy. The committee noted that the studies the sponsor submitted to fill the evidence gaps had several limitations (e.g., small phase I or phase II open-label studies, short duration, etc.) and insufficient evidence to draw definitive conclusions.
- pERC noted that despite relugolix's faster testosterone suppression and recovery profile compared to leuprolide (and degarelix in a phase II trial), evidence gaps remain such as absence of a direct comparison with other ADTs besides leuprolide; limited evidence regarding the safety and effectiveness of relugolix when used in combination with other systemic anticancer therapies and/or radiation, and the use of outcomes with no proven reliability (depth of testosterone suppression) as surrogates for duration of clinical response, progression-free survival, or overall survival.
- pERC deliberated using relugolix as an adjuvant/neoadjuvant with or without radiation in locally advanced settings where the treatment may be stopped after 18 months and noted a lack of evidence for sustained efficacy of oral relugolix compared to parenteral ADTs. In particular, the committee noted that, unlike the parenteral ADTs, which may confer many months of testosterone suppression after treatment, relugolix has a rapid testosterone recovery, which could reverse the efficacy gains due to testosterone suppression.
- pERC discussed the need to highlight patient adherence with relugolix since the faster suppression and recovery profile of the drug suggest that patients could have a significant impact on their testosterone levels and treatment effects if they do not take the drug as prescribed.
- pERC discussed that patients in Ontario and the Eastern provinces may have additional costs, which may make oral relugolix less accessible through publicly funded programs, and they may require private coverage.
- The pricing condition is based on the assumption of equal effectiveness and safety between relugolix and other ADTs. There is insufficient evidence to base conclusions around the long-term comparative effectiveness and safety of relugolix versus other ADTs and further price reductions may be warranted.

Background

Prostate cancer (PC) is a malignancy where prostate cells grow uncontrollably, often driven by testosterone-producing pathways. In its early stages, PC may be asymptomatic or present with non-specific symptoms like altered urination patterns, blood in urine or semen, painful urination/ejaculation, pelvic area pain, and erectile dysfunction. As the tumor grows or metastasizes, typically to bones in 90% of cases, symptoms like bone pain or mobility issues can severely affect quality of life.

PC spans various stages, from non-metastatic, localized disease to castration-resistant metastatic PC. Advanced PC (aPC) is a severe subset of PC with a high risk of progression or death, requiring androgen deprivation therapy (ADT). It represents a broad range of incurable disease states with diverse clinical options and survival times. Survival rates vary significantly, from nearly 100% over five years for localized and locally advanced PC to 34% for metastatic PC.

In Canada, PC is the most common cancer among men, with about 24,600 diagnoses in 2022. It's estimated that 1 in 8 Canadian men will develop PC in their lifetime. The prevalence was 0.66% in 2018, calculated using prevalent cases and the adult male population at the time, and this rate is assumed to remain stable into 2024, balancing out incidence and mortality rates.

Relugolix (Orgovyx) has been approved by Health Canada for advanced prostate cancer in adult patients. Relugolix (Orgovyx) is an androgen deprivation therapy. It is available as a 120 mg oral tablet and the dosage recommended in the product monograph is a loading dose of 360 mg on the first day followed by 120 mg orally once daily.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 Phase 3, randomized, multi-centre, open-label, parallel group clinical study in adult patients with advanced prostate cancer.
- patients' perspectives gathered by patient groups, The Androgen Deprivation Therapy (ADT) Education Program, The Canadian Cancer Society, and PROCURE.
- input from public drug plans and cancer agencies that participate in the CADTH review process.
- Opinions from two clinical specialists with expertise diagnosing and treating patients with advanced prostate cancer.
- input from 2 clinician groups, including The ADT Education Program and the British Columbia Genitourinary Group with the Vancouver Prostate Centre.
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

A total of 3 patient groups submitted 3 inputs. The Androgen Deprivation Therapy (ADT) Education Program supports patients living with prostate cancer undergoing hormone therapies (formally referred to as androgen deprivation therapy or ADT). The Canadian Cancer Society (CCS) is the only national charity that supports patients living with all types of cancer across the country with research, compassionate support system, and by engaging in establishing health policies. These patient groups were represented by 1 patient each in their submissions. The third patient group, PROCURE, is a charitable organization that educates, supports, and informs people affected by prostate cancer and promotes and contributes to financing research. PROCURE collected information from an online survey conducted in May 2022, in which 263 patients participated.

In ADT Education Program input, a patient living with advanced prostate cancer said he has been on ADT almost continuously for over 20 years and experienced many side effects. The patient on behalf of other patients stated that the most disturbing are hot

flashes, fatigue, and loss of sexual interest. Besides, he said they also regularly experience loss of muscle mass, yet weight gain as fat, making simple tasks like walking upstairs difficult. Also, based on input, ADT affects memory, can lead to depression and insomnia, and makes patients feel weak, old, flabby, and demoralized. Lastly, he stated that depot injection form of ADT agents may cause inflammation at the injection site making him feel uncomfortable for days after injection. According to the input just to avoid injections, some patients may delay getting repeated injections or take risky drug holidays that can cause their cancer to fulminate. PROCURE said some patients decided to opt for orchiectomy to avoid regular injections. Similarly, another patient from CCS stated that he experienced side effects such as weight gain, impact on kidneys and liver, as well as reduced sexual desire, which was noted as a key side effect by the patient. In both inputs, patients said taking ADT can cause side effects that may require other medications such as antidepressants or kidney protective agent. The patient from CCS said he felt weak and tired, which reduced his motivation to exercise. The patient's wife said she didn't feel a significant impact on her life, besides the limited sexual desire the patient felt as the side effect of treatment. According to PROCURE input, patient and partners often mourn the loss of a satisfying sexual relationship and advanced cancer creates anxiety within the couple. Also, PROCURE stated that children and family may experience anxiety as their father passes away from the cancer, or they may be at risk of getting prostate, breast, and ovarian cancers if their father living with prostate cancer is a carrier of a BRCA mutation. PROCURE said that frequent travel to clinics or hospital for medical follow up exams can be costly with injection hormone therapy and it takes too long, i.e., from months to years, to see their testosterone levels return to normal after end of their long-term ADT.

Based on inputs, one of the key outcomes important to patients was safety of medication and minimizing side effects. Other key outcomes cited by patients to be important include maintaining long-term survival (with ADT) and a good quality of life. PROCURE also stated that patients want improved outcomes in treatment such as slowing down the progression of cancer, extension of life expectancy, and decreased PSA levels. All inputs indicated that patients living with prostate cancer would appreciate new treatment that is not a difficult, invasive, patient-friendly alternative form of ADT.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Despite advancements in prostate cancer treatment leading to longer overall survival, resistance to therapies is inevitable, and most men will eventually succumb to the disease. All current ADT options effectively induce profound medical castration (testosterone suppression).

One gap in current ADT options is the lack of oral administration; the available injectable forms may not suit all patients, although, according to the clinical expert, there's no published evidence that have influenced the Canadian clinical practice regarding a preference for oral options or that injectables negatively impact compliance. Given that patients with advanced prostate cancer typically see their physicians semi-annually, the current treatment regimen does not greatly burden the healthcare system. However, for patients in remote areas of Canada who find travel challenging, an oral ADT option could address this unmet need. Relugolix is positioned as a foundational ADT. It may be particularly beneficial for patients in remote locations, those who prefer oral medication, or those needing intermittent rather than continuous ADT (for example, where intermittent ADT is attempted to minimize the adverse effects of medical castration by withdrawing treatment in patients who have responded to continuous ADT), due to its rapid testosterone and quality of life recovery.

The Canadian consensus recommends a castrate level threshold of $\leq$0.7nmol/L for patients with metastatic androgen-sensitive prostate cancer (MCSPC), along with ARAT therapy intensification. Response measures include prolonging overall survival, progression-free survival, time to skeletal events, symptomatic deterioration, and castration resistance. For patients with clinical/biochemical relapse after curative local therapy, goals include achieving castrate levels of testosterone, extending overall and metastasis-free survival, and delaying castration resistance.

Discontinuation of ADT in the MCSPC setting is rare, except in cases of intolerable toxicities. In the high-risk curative setting, ADT might be stopped more frequently due to toxicities, and decisions are based on a risk-benefit analysis at that time. Most ADT toxicities are manageable. Relugolix is prescribed by specialist oncologists and self-administered orally by the patient.

Clinician Group Input

Two clinician groups, the Androgen Deprivation Therapy (ADT) Education Program and the British Columbia Genitourinary Group with the Vancouver Prostate Centre, contributed their insights on prostate cancer treatment, specifically focusing on the need for better-tolerated and more convenient treatment options that enhance compliance. These groups support the development of an oral formulation of LHRH antagonist to overcome the disadvantages of injectable forms, such as injection site reactions, discomfort due to high dosage volume, and the need for travel to clinics.

The clinician groups highlight the current unmet need in prostate cancer treatment: resistance to therapies due to androgen-independent mechanisms. They believe that an oral form of ADT would be particularly beneficial for patients living far from cancer centers. However, they caution that long-term ADT might lead to compliance issues or increased pill burden, especially when combined with other therapies. The goal for ideal prostate cancer treatment is cure, but for advanced stages that have spread beyond the gland, the objectives shift to suppressing androgen with fewer side effects or less invasive administration, prolonging survival, and improving quality of life. Other important therapy goals include prolonging time to skeletal related events, symptomatic deterioration, and castration resistance.

Patients best suited for relugolix include those with hormone-sensitive disease, newly diagnosed or substantial metastatic disease requiring prompt androgen suppression, patients needing short-term ADT, and those having difficulty accessing injection clinics. Additionally, it's beneficial for those preferring oral medication or needing intermittent ADT.

Response to relugolix is measured via serum PSA or imaging, similar to current ADT agents. For relugolix monotherapy, a “profound castration” level of testosterone (≤ 0.7 nm/L) is indicative of a pharmacologic effect. Generally, ADT is continuous and indefinite for patients with metastatic, locally advanced, or castrate-resistant prostate cancer, unless contraindications or intolerable side effects arise. Relugolix can also be administered intermittently based on serum PSA levels or for a fixed duration in patients receiving ADT with curative-intent radiation.

Urologists, medical- or uro-oncologists, and radiation oncologists experienced in managing advanced prostate cancer should prescribe and monitor relugolix treatment. The medication can be dispensed in an outpatient setting, and patients take relugolix orally at home.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for Orgovyx:

- considerations regarding relevant comparators
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- potential need for a provisional funding algorithm

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Additional Implementation Questions from the Drug Programs	
Implementation Issues	**Advice from CADTH**
Relevant Comparators	
Relevant comparators funded in most jurisdictions include leuprolide (comparator in the HERO trial),	This was a comment from the drug programs to inform pERC deliberations.

Additional Implementation Questions from the Drug Programs	
degarelix, buserelin, and goserelin, all of which are injectables.	
The primary efficacy outcome measure was medical castration rate, defined as achieving and maintaining serum testosterone suppression to castrate levels (< 50 ng/dL) by day 29 through 48 weeks of treatment. Other key secondary endpoints included castration rates on day 4 and 15, castration rates with testosterone < 20 ng/dL at day 15, and PSA response rate at day 15, and FSH level at day 176 (Week 25 Day 1). In clinical practice what is the most appropriate frequency to determine treatment response?	Clinical experts consulted by CADTH reported that, currently, most patients with advanced prostate cancer would visit their physicians at least twice a year for review of disease control/symptoms/toxicity management. In the management of MCSPC, the Canadian consensus statement recommends maintaining testosterone levels at or below 0.7 nmol/L, aligning with the "profound" castration level proposed by the drug sponsor. Additionally, patient treatment in this context should be intensified with ARAT therapy. According to the clinical experts, PSA levels and clinical endpoints are primarily used to assess clinical response. pERC agreed with the clinical expert regarding the relevant endpoints and the frequency of clinical assessment.
Patients in the HERO trial with disease progression during the treatment period were encouraged to remain on study and if indicated, may have received radiotherapy as prescribed by the investigator. If patients had PSA progression (i.e. CRPC), they were allowed to receive enzalutamide or docetaxel during the study. What are the discontinuation criteria for Relugolix?	The clinical experts noted that ADT is rarely ceased in the MCSPC and CRPC setting unless toxicities are truly intolerable. They also reported that, in the high-risk curative setting, ADT may be ceased due to toxicities more often, however it is a balanced discussion based on risks and benefits at that time point. According to the clinical experts, most of the toxicities from ADTs are manageable. pERC agreed with the clinical experts that the attending physician should use clinical judgement regarding the discontinuation of therapy.
Considerations for prescribing of therapy	
Relugolix should be initiated with a loading dose of 360mg (three tablets) on the first day and continued with a 120mg tablet taken once daily at approximately the same time each day.	This was a comment from the drug programs to inform pERC deliberations.
Generalizability	
Can the trial results be generalized to patients with ECOG >1?	The clinical experts agree that the results are generalizable to patients with ECOG >1. pERC agreed with the clinical experts, noting that patients with an ECOG performance status of greater than 1 may be eligible for the treatment with relugolix, at the discretion of the treating clinician.
Funding algorithm (oncology only)	
Under what clinical circumstances would relugolix be used over existing agents?	The clinical experts noted that patient preference for oral treatment or preference for rapid return of testosterone to normal levels upon cessation of drug may be factors where relugolix is used over existing agents. pERC agreed with the clinical experts that choice of relugolix over other treatments can be made in case of patient preference for oral treatment or preference for rapid return of testosterone to normal levels upon drug cessation.,
Care provision issues	
Relugolix has the potential for drug-drug and drug-laboratory interactions, requiring assessment and/or	The study did not include Abiraterone and Apalutamide, which are significant intensification options in this therapeutic area.

Additional Implementation Questions from the Drug Programs	
intervention. Would this limit its use in combination regimens (i.e., apalutamide is a strong CYP3A4/P-gp inducer, and abiraterone was a prohibited medication in the trial)?	The sponsor has proposed a comprehensive listing for the use of relugolix in combination with all ARATs. However, it may be appropriate to consider restricting combination partners to those explicitly included in the study, such as the use of enzalutamide specifically in the context of metastatic castration-resistant prostate cancer, as suggested by the clinical experts. pERC agreed with the clinical experts and noted limited evidence on efficacy of relugolix as part of an intensification therapy or in combination with radiation therapy for advanced prostate cancer.

ADT = Androgen Deprivation Therapy; ARAT = Androgen Receptor Axis-Targeted therapy; CRPC = Castration-Resistant Prostate Cancer; CYP3A4/P-gp = Cytochrome P450 3A4 and P-glycoprotein; ECOG = Eastern Cooperative Oncology Group performance status; FSH = Follicle Stimulating Hormone; MCSPC = Metastatic Castration-Sensitive Prostate Cancer; pERC = Pan-Canadian Oncology Drug Review Expert Review Committee; PSA = Prostate-Specific Antigen.

Clinical Evidence

Systematic Review

Description of Studies

The HERO trial was a Phase 3, randomized, multicenter, open-label, parallel-group study conducted across 160 sites in 22 countries. The trial enrolled patients from April 2017 to October 2019 for the primary analysis and until August 2020 for the final analysis. A total of 934 patients were included in the primary analysis, with this number increasing to 1078 in the final analysis. Patients were divided into two groups: 624 received relugolix and 310 received leuprolide in the primary analysis. Eligible participants were adult males with histologically or cytologically confirmed prostate cancer, candidates for at least one year of continuous ADT, and meeting specific criteria such as evidence of biochemical or clinical relapse, newly diagnosed androgen-sensitive metastatic disease, or advanced localized disease. Exclusions included likely need for chemotherapy or surgical therapy soon after ADT initiation, prior extensive ADT or systemic cytotoxic treatment, brain metastases, recent significant cardiac events, conduction system abnormalities, and uncontrolled hypertension.

The intervention consisted of administering relugolix as a 120 mg tablet daily following a 360 mg oral loading dose on Day 1, compared to leuprolide given as 22.5 mg 3-month depot injections every 12 weeks, both for a duration of 48 weeks. The study was structured into a 28-day screening phase, a 48-week treatment phase, and a follow-up phase of 30 days for safety and up to 90 days for assessing testosterone recovery. The primary endpoint was the sustained castration rate from Week 5 to Week 49. Secondary efficacy endpoints included sustained castration rate, profound castration rate, PSA response rate, FSH level, castration recurrence-free survival (CRFS) for patients with or without metastatic cancer (final analysis), and testosterone recovery rate. Other endpoints assessed changes in quality of life, serum concentrations of various hormones, and safety endpoints like treatment-emergent adverse events (TEAEs), major adverse cardiac events (MACE), clinical laboratory tests, vital signs, and ECGs. Exploratory endpoints included overall survival (OS) and the presence of polymorphisms in germline genes.

The age distribution was similar between the two groups, with approximately 71% of patients in both groups being 75 years or younger. The mean age was around 71 years, with a slightly higher median age in the relugolix group (72 years) compared to the leuprolide group (71 years). Ethnicity and race distributions were broadly comparable across both groups, with the majority being non-Hispanic or Latino and white. The study included participants from various geographic regions, with the largest proportion from Europe (around 40% in both groups), followed by North America, Asia, and other regions.

Clinically, around half of the participants in both groups presented with evidence of biochemical or clinical relapse following local primary intervention with curative intent. Newly diagnosed androgen-sensitive metastatic disease and advanced localized disease not suitable for primary surgical intervention were other major disease presentations. The distribution of disease stages at study entry was similar across both groups, with approximately 32% having metastatic, 30% locally advanced, and around 29% localized

disease. Gleason scores were also similar, with the most common being 7 and 8-10. The majority of participants had an ECOG status of 0. Prior ADT and radiation therapy (RT) histories were noted in both groups, with a slightly higher numerical percentage of prior ADT in the relugolix group. Cardiovascular risk factors were prevalent in over 90% of participants in both groups, with a notable proportion also having lifestyle risk factors and a history of MACE.

Efficacy Results

The proportion of patients who achieved sustained testosterone suppression was 96.7% (95% CI, 94.9 to 97.9) in the relugolix treatment group compared with 88.8% (95% CI, 84.6 to 91.8) in the leuprolide group, with a mean difference between the relugolix and leuprolide treatment groups being 7.9% (95% CI: 4.1% to 11.8%). These results demonstrated noninferiority of relugolix to leuprolide (the lower bound of the 95% CI for the difference between groups was greater than the pre-specified noninferiority margin of −10%), with $p < 0.0001$), and also statistical superiority of relugolix compared with leuprolide (lower bound of the 95% CI > 0, with $p < 0.0001$).

Patients in the relugolix group had a shorter time to achieve castration compared to leuprolide group at profound castration levels of testosterone (< 20 ng/dL). The median time to profound castration was 15 days in the relugolix group compared with 29 days in the leuprolide group. At Day 15, the difference in the proportion of patients achieving profound castration was more pronounced in the relugolix group compared with leuprolide group (78.38% vs 0.98%), with a statistically significant difference of 77.41% (95% CI: 73.98%, 80.83%; $p < 0.0001$).

Treatment with relugolix resulted in a higher proportion of patients achieving and maintaining profound castration (81.6%; 95% CI: 78.1%, 84.5%) compared with the leuprolide group (68.6%; 95% CI: 63.0%, 73.5%) from day 29 through 48 weeks, with a difference between groups of 13.0%.

Harms Results

Overall, the safety profile of relugolix suggests a profile that is consistent with the safety profile of the ADT therapeutic class. In the HERO trial, adverse events (AEs) were reported by a similar proportion of patients in both the relugolix (92.9%) and leuprolide (93.5%) groups. The most common AE for both groups was hot flush, occurring in over half of the patients. Gastrointestinal issues like constipation and diarrhea were more frequently reported in the relugolix group. All cases of constipation and diarrhea were mild to moderate, with only one patient withdrawing from the study due to these AEs. Serious adverse events (SAEs) were slightly numerically less common in the relugolix group (12.2%) compared to the leuprolide group (15.3%). The SAEs in the relugolix group included myocardial infarction (0.8%), acute kidney injury (0.6%), and urinary tract infections (0.5%). Within the leuprolide group, SAEs included anemia (1.0%), cardio-respiratory arrest (1.0%), and urinary tract infection (0.6%), Grade 3 or 4 SAEs were slightly more common, numerically, in the leuprolide group.

Treatment discontinuation due to AEs was higher in the relugolix group (3.5%) compared to the leuprolide group (0.3%). The deaths reported were slightly, numerically, higher in the leuprolide group (2.9%) than in the relugolix group (1.1%), with cardiovascular-related deaths being more common in the leuprolide group. Vasomotor symptoms like hot flushes and fatigue were common in both groups (56.1% in relugolix, 54.9% in leuprolide), but hepatic transaminase elevations were numerically higher in the relugolix group (7.6%) contrasted with the leuprolide group (5.5%). The incidence of major adverse cardiac events (MACE) was numerically higher in the leuprolide group. Loss of bone mineral density was reported in similar proportions in both groups, and there were no significant liver-related toxicities meeting Hy's law criteria in either group.

Critical Appraisal

The HERO study, a phase 3 trial comparing relugolix with leuprolide in men with advanced prostate cancer, demonstrated a robust methodology in terms of randomization, stratification, and sample size. Its open-label design, while potentially introducing bias, is mitigated by the objective nature of the primary outcome. The sensitivity analyses for the primary outcome and the approach to handling missing data enhance the study's robustness.

HERO's applicability to typical Canadian practice may be limited due to several factors, including its lack of clear definition on what constitutes locally advanced disease in the inclusion criteria and patient population. The study's focus on biomarkers like testosterone and PSA, while relevant for advanced prostate cancer, doesn't fully capture the clinical outcomes of the disease. The

study also doesn't address the combination of ADT with other systemic therapies, nor does it inform on relugolix's use in patients undergoing radiation therapy. In addition, several additional standard of care medicines (available and re-imbursed) in Canada that would ordinarily be combined with relugolix if it was approved in the MCSPC setting: abiraterone, enzalutamide and apalutamide were not permitted to be given concurrently in the HERO study. This raises concerns given the potential use of relugolix in the MCSPC setting.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Sustained castration rate
- Profound castration rate
- MACE
- Loss of bone mineral density

Table 3: Summary of Findings for Relugolix versus Leuprolide for Patients with Advanced Prostate Cancer

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Leuprolide (N = 308)	Relugolix (N = 622)	Difference		
Sustained Castration Rate							
Sustained Castration Rate (< 50 ng/dL) Follow-up: From Day 29 to Day 337	930 (1 RCT)	HR = 0.2621 (0.1489 to 0.4613)	88.8 per 100 persons	96.7 per 100 (94.9, 97.9)	7.9 more persons per 100 (95%CI 4.1, 11.8)	High[a]	Relugolix likely results in an increase in the number of patients with sustained castration compared to leuprolide.
Profound Castration Rate							
Profound castration rate (< 20 ng/dL) Follow-up: Day 15	930 (1 RCT)	NR	0.98 per 100 persons	78.38 per 100 persons (75.06, 81.53)	77.41 more persons per 100 (95%CI 73.98, 80.83)	High[b]	Relugolix results in an increase in the number of patients with profound castration at Day 15 compared to leuprolide.
Cumulative Probability of Profound Castration Rate (< 20 ng/dL) Follow-up: Day 29 to Day 337	930 (1 RCT)	NR	68.6 per 100 persons	81.6 per 100 persons (78.1, 84.5)	13.0 more persons per 100 (95%CI 6.9, 19.1)	High[b]	Relugolix results in an increase in the number of patients with profound castration compared to leuprolide.
Harms							
MACE Follow-up: Day 337	930 (1 RCT)	NR	6.2 per 100 persons	2.9 per 100 persons (NR)	NR	Very Low[c]	The evidence is very uncertain about the effects of relugolix compared to leuprolide on MACE.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Leuprolide (N = 308)	Relugolix (N = 622)	Difference		
Loss of bone mineral density Follow-up: Day 337	930 (1 RCT)	NR	3.9 per 100 persons	3.2 per 100 persons (NR)	NR	Very Low[c]	The evidence is very uncertain about the effects of relugolix compared to leuprolide on loss of bone mineral density.

CI = Confidence Interval; RCT = Randomized Controlled Trial; HR = Hazard Ratio; NR = Not Reported; MACE = Major Adverse Cardiac Events

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects, therefore the null was used. Did not rate down for imprecision; a between-group difference of larger than the null and a confidence interval that excludes the null suggest benefit compared to leuprolide as judged by the CADTH review team.

[b] No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects, therefore the null was used. Did not rate down for imprecision; a between-group difference of larger than the null and a confidence interval that excludes the null suggest benefit compared to leuprolide as judged by the CADTH review team.

[c] Rated down 2 levels for very serious concerns about imprecision due to very small number of events. Rated down 1 level for serious indirectness due to insufficient duration of follow-up for the outcome according to clinical expert input.

Source: Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

None submitted.

Indirect Comparisons

Description of Studies

The sponsor submitted an Indirect Treatment Comparison (ITC), designed to assess the efficacy and safety of relugolix compared to other medical ADTs available in Canada for adult male patients with advanced prostate cancer. The analysis included a network meta-analysis (NMA) of RCTs identified from a systematic literature search that reported on testosterone suppression to castration levels and MACE outcomes at a 12-month (+/- 3 months) timepoint. The quality assessment of these RCTs utilized the Cochrane Risk of Bias tool. The NMA used a Bayesian framework, employing various models to estimate treatment effects for each outcome. Model fit assessment relied on the deviance information criterion (DIC), resulting in the selection of the random effects with informed prior (REIP) model for testosterone castration and random effects model with vague priors (REV) model for MACE, as the primary analysis. Additional hierarchical approach was adopted, accounting for treatment class exchangeability and assuming normal distribution around class-specific means. Statistical heterogeneity was evaluated using the I^2 statistic. Sensitivity analyses were conducted using different models and priors.

Efficacy Results

The NMA included seven studies for testosterone suppression, defined as sustained chemical castration with testosterone levels lower than 50 ng/dL at 12 ± 3 months. [redacted]

Harms Results

The NMA included four studies for MACE, primarily comparing relugolix to degarelix and leuprolide. [redacted]

Critical Appraisal

Various limitations of the ITC were noted, including the heterogeneity in study characteristics and patient populations. The exploration of between study differences and potential biases was further limited by incomplete data in the published trials included in the networks. Clinical experts consulted for this CADTH review noted imbalances in certain prognostic factors and effect modifiers (baseline testosterone concentrations, metastatic status of participants, previous hormonal treatment), which raises concerns for bias in the comparisons in the NMA. The clinical experts noted that in the Canadian clinical practice MACE assessment occurs later than 12 ± 3 months and that profound castration levels (<20ng/dl) would have been a more appropriate outcome measure, thus presenting notable generalizability issues. Considering these limitations, there is a high risk of bias in the comparison in this NMA, and the direction of that bias is unclear; hence, the findings of the sponsor submitted ITC remain highly uncertain.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

The clinical evaluation of relugolix in advanced prostate cancer treatment encompassed three key studies. The C27300 Study, a Phase II, open-label trial, focused on comparing relugolix with degarelix in patients with intermediate-risk localized prostate cancer, specifically assessing its role in neoadjuvant/adjuvant therapy alongside external beam radiation therapy. The MVT-601-049 Study, a Phase I, open-label trial, investigated the combination of relugolix with abiraterone or apalutamide in men diagnosed with either metastatic castration-sensitive or castration-resistant prostate cancer. Lastly, the Apa-RP Study, a Phase II, open-label trial, evaluated the efficacy of ADT in combination with apalutamide in treatment-naïve men post radical prostatectomy, particularly those at high risk of metastases.

Efficacy Results

The C27300 Study enrolled 103 patients, with 65 receiving relugolix and 38 on degarelix. The study highlighted that relugolix achieved sustained castration rate of 95% and profound castration rate of 82% by 24 weeks. In comparison, degarelix showed sustained castration rate of 89% and profound castration rate of 68% by 24 weeks. The MVT-601-049 Study involved 25 patients and demonstrated consistent testosterone suppression in combinations of relugolix either with abiraterone or apalutamide for 12 weeks. The Apa-RP Study, with 108 patients in the main study and 12 in the sub-study, revealed a 100% sustained castration rate in both the sub-study for 28 days and main study after one year.

Harms Results

In the C27300 Study, the most common adverse events were hot flushes (57%), fatigue (26%), and diarrhea (18%) in relugolix cohort. Deterioration in quality of life during treatment followed by improving HRQoL post-treatment was noted when assessed with EORTC QLQ-C30 and QLQ-PR25. The MVT-601-049 Study Part 1 reported common adverse events including pain in extremity (20%), increased ALT (13.3%), and anemia (13.3%), with 1 incident (6.7%) of serious adverse event reported for a left femur fracture in relugolix + abiraterone cohort (n = 15). The Apa-RP Study identified hot flushes (50%) as the most common adverse event in relugolix cohort (n = 12), with no significant serious adverse events or treatment discontinuations due to adverse events reported.

Critical Appraisal

The internal validity of these studies is limited due to their open-label nature and the absence of true comparators. This design potentially biases the reporting of adverse events, which are typically reported by patients whose responses may be subjective. Furthermore, the objective of phase I and phase II clinical trials are limited in terms of establishing causal inference. Additionally, the study durations may not be long enough to assess long-term outcomes, particularly major adverse cardiac events, which are identified by clinical experts to be notable adverse events in patients with advanced prostate cancer. Externally, the studies' applicability to the Canadian context is questionable, as none of the study sites was located in Canada, and patients with cardiovascular diseases, a common comorbidity in the aPC patient population, were excluded.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adult patients with advanced prostate cancer
Treatment	Relugolix
Dose regimen	360 mg once (loading dose) then 120 mg once daily (maintenance dose)
Submitted price	Relugolix: $9.00 per 120 mg oral tablet
Treatment cost	$3,303 in Year 1; $3,285 in subsequent years
Comparators	Androgen deprivation therapies (ADTs) include: • buserelin, • degarelix • goserelin acetate • leuprolide acetate, and • triptorelin
Perspective	Canadian publicly funded health care payer
Time horizon	Undefined (year 1 and subsequent year)
Key data sources	Key assumption of equal treatment efficacy and safety of relugolix based on: • Phase III non-inferiority HERO trial comparing relugolix to leuprolide acetate • Sponsor-commissioned indirect treatment comparison (ITC) comparing relugolix to selected ADTs (degarelix, leuprolide acetate, triptorelin, and goserelin acetate).
Costs considered	Drug acquisition costs
Key limitations	• The assumption of clinical similarity between relugolix and other ADTs is uncertain due to limitations with the sponsored ITC and the limited duration of the pivotal non-inferiority trial. • Cost savings associated with relugolix are highly variable depending on the ADT received, as well as the choice of dosing form. The largest estimated cost savings are relative to buserelin, which is not commonly used in clinical practice (0.03%) which was confirmed by clinical expert feedback consulted by CADTH. The cost savings of relugolix relative to the most commonly used ADT forms (leuprolide acetate [Eligard], 45 mg and 22.5 mg) are highly uncertain. • Confidential pricing agreements for comparators (ADTs) are unknown.
CADTH reanalysis results	• CADTH did not conduct reanalyses for the base case. Uncertainty in the comparative clinical effects and whether relugolix is similar to other ADTs could not be addressed. • CADTH conducted additional scenario analyses where the drug costs of relugolix were compared to the most commonly used ADT in clinical practice and its most frequently used drug formulations (leuprolide acetate [Eligard], 45 mg and 22.5 mg). Across these scenarios, the cost differences ranged from added costs of $13 per patient in Year 1 to cost savings of $279 per patient in subsequent years of treatment. • The extent of (and whether there is) cost savings associated with relugolix compared to other ADTs is highly dependent on the specific comparator(s) and the dosing form(s) used in each jurisdiction, as well as their specific confidential negotiated prices.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: (1) the sponsor's prevalence-based approach to estimate the target population was uncertain. Clinical experts indicated that an incidence-based approach is more clinically relevant (i.e., only incident patients would likely be considered for treatment with relugolix) and that the sponsor's derivation of patients with localized PC eligible for treatment did not meet face validity; (2) the market shares of relugolix may be overestimated based on its anticipated use in clinical practice, shorter duration of testosterone suppression compared to currently used ADTs, and patient preference for less frequent administrations. The market uptake of relugolix would likely not surpass those of degarelix according to clinical experts consulted by CADTH; (3) the price of drugs paid by public plans is uncertain as confidential pricing is likely in place.

The CADTH reanalysis estimated that the budget impact of reimbursing relugolix for the treatment of adult patients with advanced prostate cancer would result in cost savings to the drug plans of $864,382 across three years. CADTH conducted scenario analyses to address remaining uncertainty. Based on these results, CADTH found that the drug expenditure of relugolix is highly sensitive to the size of the eligible population and predicted market uptake. Estimated from these scenario analyses ranged from cost savings of $220,627 to $6,548,612 based on public list prices.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: April 10, 2024

Regrets:

Three of expert committee member(s) did not attend.

Conflicts of interest:

None.