Juan Camilo Arjona Ferreira, MD
Chief Medical Officer
Myovant Sciences, Inc.
2000 Sierra Point Parkway, 9th Floor, Brisbane, CA 94005
(650) 410-3222
juan.arjona@myovant.com
December 23, 2020

NCCN Guidelines Panel: Prostate Cancer

On behalf of Myovant Sciences, Inc., we respectfully request the NCCN Panel to review the enclosed data for inclusion of relugolix in the guidelines for the treatment of men with prostate cancer.

Specific Request: Taking into account the totality of the demonstrated efficacy and safety of relugolix in the phase 3 HERO trial and benefits of an oral option for ADT, please consider the inclusion of relugolix in the NCCN Prostate Cancer Guidelines as a preferred therapy, including before LHRH agonists based on its safety profile, for the following clinical settings for ADT:

Principles of Androgen Deprivation Therapy (guideline section PROS-G)

1. **PROS-G1 - ADT for clinically localized (N0, M0) disease, bullet 2**: Clinically localized with contraindication to definitive local therapy: Relugolix (category 1 based on phase 3 study)
2. **PROS-G1 - ADT for clinically localized (N0, M0) disease, bullet 3**: Giving ADT before, during, and/or after radiation (neoadjuvant/concurrent/adjuvant): Relugolix (category 1 based on phase 3 study)
3. **PROS-G1 - ADT for regional (N1, M0) disease**: Relugolix (category 1 based on phase 3 study)
4. **PROS-G1 - ADT for pN1 disease**: Relugolix (category 1 based on phase 3 study)
5. **PROS-G2 - ADT for M0 PSA persistence/recurrence after RP/EBRT**: Relugolix (category 1 based on phase 3 study)
6. **PROS-G2 - ADT for metastatic castration-naïve disease**: Relugolix (category 1 based on phase 3 study)
7. **PROS-G3 - Secondary hormone therapy for M0 or M1 CRPC**: Relugolix
8. **PROS-G4 - ADT for patients on observation who require treatment/life expectancy ≤5y**: Relugolix

FDA Clearance: Relugolix (Orgovyx™) is approved by the FDA for the treatment of adult patients with advanced prostate cancer.

Rationale: Please accept this letter of request regarding the FDA approval of relugolix,[1] a new oral GnRH antagonist that demonstrated superior sustained testosterone suppression and rapid testosterone recovery compared with the LHRH agonist, leuprolide, in the pivotal phase 3 HERO trial in men with advanced prostate cancer.[2] Further, relugolix was associated with a lower risk of major adverse cardiovascular events compared with leuprolide. The FDA-approved label for relugolix does not carry the warning and precaution for myocardial infarction, sudden cardiac death and stroke included in the LHRH agonist labels.[3] This is particularly important in light of the high cardiovascular risk in the prostate cancer population,[4] coupled with the cardiovascular toxicity of other prostate cancer treatments such as enzalutamide and abiraterone often used in combination with ADT.[5] In addition, as a direct GnRH antagonist, relugolix does not require flare prevention with co-administration of bicalutamide which carries a risk of hepatotoxicity.[6] Relugolix has also been studied in the phase 2 C27003 study in men with intermediate-risk prostate cancer requiring neoadjuvant/adjuvant androgen deprivation therapy (ADT) with radiotherapy,[7] a clinical setting commonly utilizing ADT, and use in combination with radiotherapy was allowed in the HERO study further supporting the safety of combination with radiotherapy.[8] Additionally, in the setting of rising PSA, use of relugolix concomitantly with enzalutamide or docetaxel was associated with similar efficacy and safety profiles to that observed in patients not receiving concomitant treatments[9] and the continued use of ADT upon development of CRPC is further supported in the dosing recommendation section of the relugolix label.[1] Finally, the oral administration of relugolix provides an important option for prostate cancer patients to eliminate adverse events associated with injectable ADTs and offers patients access to therapy at home during times like the ongoing COVID pandemic.

Clinical Data:

Phase 3 HERO Study: The efficacy and safety of oral relugolix were evaluated in the multinational, randomized, open-label, phase 3 study in patients with androgen-sensitive advanced prostate cancer who required at least one year of continuous ADT.[2] In total, 934 patients were randomized 2:1 to oral relugolix (n=624) or leuprolide acetate (n=310) for 48 weeks. The study included patients with evidence of biochemical or clinical relapse after local primary intervention with curative intent (50%), newly diagnosed hormone-sensitive metastatic disease (23%), and advanced localized disease unlikely to be cured by local primary intervention (27%).

Efficacy: HERO achieved the primary endpoint by demonstrating a 96.7% (95% CI, 94.9 to 97.9) sustained castration rate with relugolix. Compared with 88.8% (95% CI, 84.6 to 91.8) in the leuprolide group, the sustained castration rate with relugolix was non-inferior and superior to leuprolide (between-group difference, 7.9%; 95% CI, 4.1 to 11.8; *P*<0.001). All tested key secondary endpoints showed superiority of relugolix over leuprolide (*P*<0.001). In the testosterone recovery subgroup of 184 patients, the cumulative incidence rate of testosterone recovery to ≥280 ng/dL (lower limit of the normal range) at 90 days after treatment discontinuation was 54% in the relugolix group and 3% in the leuprolide group (nominal *P*=0.002). In the relugolix group, testosterone suppression to castrate levels occurred rapidly (mean testosterone level on Day 4 of 38 ng/dL) and was maintained throughout the treatment period (Fig 1).

Safety: The overall incidence of adverse events in the relugolix and leuprolide groups was consistent (92.9% vs. 93.5%, respectively). In a prespecified safety analysis, the incidence of major adverse cardiovascular events was 2.9% in the relugolix group and 6.2% in the leuprolide group, consistent with a 54% lower risk of an event for relugolix treated patients compared to those receiving leuprolide (hazard ratio, 0.46; 95% CI, 0.24 to 0.88) (Fig 2).

Figure 1. Mean testosterone level among all patients

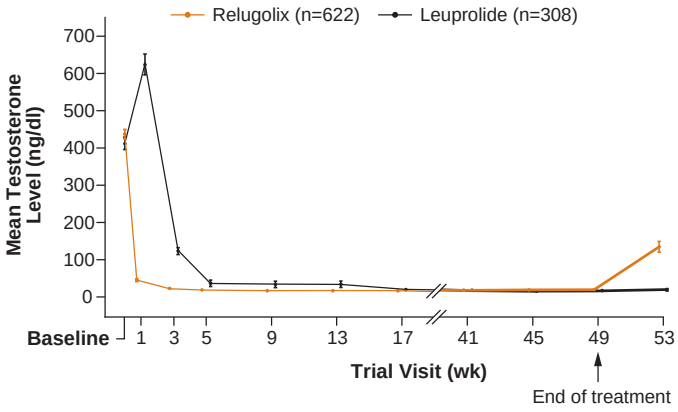
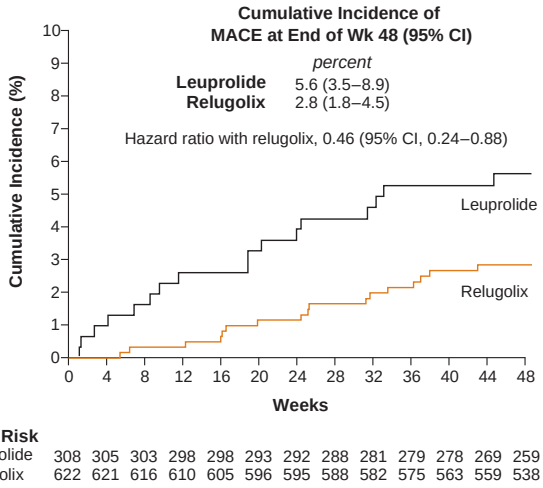


Figure 2. Cumulative incidence of major adverse cardiovascular events



№ at Risk

Leuprolide	308	305	303	298	298	293	292	288	281	279	278	269	259
Relugolix	622	621	616	610	605	596	595	588	582	575	563	559	538

Phase 2 C27003 Study: In this phase 2 study, 103 patients with intermediate-risk prostate cancer patients undergoing primary radiation therapy were randomized to neoadjuvant/adjuvant oral relugolix (n=65) or degarelix (n=38).[7] Relugolix achieved a 95% castration rate (testosterone suppression to <50 ng/dL) over 24 weeks compared to 89% with degarelix. Three months after treatment discontinuation, the testosterone recovery rate (return of testosterone to baseline or to >280 ng/dL) was 52% with relugolix and 16% with degarelix. The safety of relugolix was consistent with that observed in HERO.[2]

Thank you for considering the evidence supporting oral relugolix for inclusion in the guidelines.

Yours Sincerely,

Juan Camilo Arjona Ferreira, MD
Chief Medical Officer

References:

1. Myovant Sciences. Orgovyx™ (relugolix) Prescribing Information. December 2020. www.orgovyxhcp.com
2. Shore ND, Saad F, Cookson MS, et al. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. *N Engl J Med.* Jun 4 2020;382(23):2187-2196. https://www.ncbi.nlm.nih.gov/pubmed/32469183
3. US Food and Drug Administration. FDA Drug Safety Communication: Update to Ongoing Safety Review of GnRH Agonists and Notification to Manufacturers of GnRH Agonists to Add New Safety Information to Labeling Regarding Increased Risk of Diabetes and Certain Cardiovascular Diseases. October 20, 2010. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-update-ongoing-safety-review-gnrh-agonists-and-notification
4. Leong DP, Fradet V, Shayegan B, et al. Cardiovascular Risk in Men with Prostate Cancer: Insights from the RADICAL PC Study. *J Urol.* Jun 2020;203(6):1109-1116. https://www.ncbi.nlm.nih.gov/pubmed/31899651
5. Iacovelli R, Ciccarese C, Bria E, et al. The Cardiovascular Toxicity of Abiraterone and Enzalutamide in Prostate Cancer. *Clin Genitourin Cancer.* Jun 2018;16(3):e645-e653. https://www.ncbi.nlm.nih.gov/pubmed/29339044
6. Bicalutamide. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* 2012-. [Updated 2017 Jul 5]; https://www.ncbi.nlm.nih.gov/pubmed/31643176
7. Dearnaley DP, Saltzstein DR, Sylvester JE, et al. 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. *Eur Urol.* Aug 2020;78(2):184-192. https://www.ncbi.nlm.nih.gov/pubmed/32273183
8. Spratt DE, Shore N, Bossi A, et al. Relugolix, A Novel Oral GnRH Receptor Antagonist, versus Leuprolide Depot for Prostate Cancer: The HERO Phase 3 Trial. Abstract 35. Oral presentation at the American Society for Radiation Oncology (ASTRO) Virtual Annual Meeting, October 25−28, 2020. https://www.redjournal.org/article/S0360-3016(20)33521-5/fulltext
9. Myovant Sciences. Data on file.