Results from the HERO phase 3 pivotal study of oral androgen deprivation therapy ORGOVYX

Oral Relugolix for Androgen Deprivation Therapy in Advanced Prostate Cancer

Shore ND, Saad F, Cookson MS, et al. *N Engl J Med.* 2020;382(23):2187-2196.

INDICATION

ORGOVYX is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the treatment of adult patients with advanced prostate cancer.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

QT/QTc Interval Prolongation: Androgen deprivation therapy, such as ORGOVYX may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, or frequent electrolyte abnormalities and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

Please see Important Safety Information throughout and full Prescribing Information for ORGOVYX.

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OBJECTIVE[1,2]

To evaluate the efficacy and safety of oral ORGOVYX compared with leuprolide in men with advanced prostate cancer

STUDY DESIGN[1,2]

The HERO study is a multinational, randomized, open-label, phase 3 clinical trial. A total of 934 patients were randomized 2:1 to receive either ORGOVYX (120 mg once daily after a single oral loading dose of 360 mg [n=624]) or leuprolide acetate (22.5 mg [or 11.25 mg in Japan and Taiwan] by injection every 3 months [n=310]) for 48 weeks. Leuprolide acetate 11.25 mg is a dosage regimen that is not recommended for this indication in the United States.

ENROLLMENT CRITERIA[1-3]

Key inclusion criteria:

- Men ≥18 years of age with histologically or cytologically confirmed adenocarcinoma of the prostate
- Requiring at least 1 year of continuous androgen deprivation therapy with 1 of the following clinical disease presentations:
  - — Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent
  - — Newly diagnosed androgen-sensitive metastatic disease
  - — Advanced localized disease unlikely to be cured by local primary intervention with curative intent
- Serum testosterone ≥150 ng/dL
- Serum PSA >2.0 ng/mL*
- ECOG score 0/1

Key exclusion criteria:

- Patients likely to require chemotherapy or surgical therapy for symptomatic disease management within 2 months of initiating androgen deprivation therapy
- Previously received GnRH analog or other form of androgen deprivation therapy for >18 months total duration
  - — If androgen deprivation therapy was received for ≤18 months total duration, then patients must have completed treatment >3 months prior to baseline, or at least as long as the dosing interval of the depot formulation received
- Significant cardiovascular risk conditions:
  - — Myocardial infarction or stroke within 6 months
  - — Arrhythmias
  - — Uncontrolled hypertension

ECOG=Eastern Cooperative Oncology Group; PSA=prostate-specific antigen.

*When applicable, post radical prostatectomy of >0.2 ng/mL, or post radiotherapy, cryotherapy, or high frequency ultrasound >2.0 ng/mL above the postinterventional nadir.

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ENDPOINTS[1,2]

Primary endpoint:

- Sustained testosterone suppression rate (defined as the cumulative probability of testosterone suppression to <50 ng/dL while on study treatment from Day 29 through Week 48)

Key secondary endpoints include:

- Testosterone suppression rates (defined as the cumulative probability of testosterone suppression to <50 ng/dL) on Day 4 and Day 15
- PSA response rate (>50% reduction from baseline) on Day 15, confirmed at Day 29
- Profound testosterone suppression rate (defined as the cumulative probability of testosterone suppression to <20 ng/dL) on Day 15

Testosterone recovery substudy:

- Cumulative probability of testosterone recovery to 280 ng/dL at the 90-day follow-up in 184 patients who completed 48 weeks of treatment and who did not receive subsequent androgen deprivation therapy for at least 90 days after discontinuation*

*This endpoint was analyzed for exploratory purposes without formal testing.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Embryo-Fetal Toxicity: The safety and efficacy of ORGOVYX have not been established in females. Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX

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SELECT BASELINE CHARACTERISTICS[1,2]

CHARACTERISTIC	ORGOVYX (n=622)	Leuprolide (n=308)	Total (N=930*)
Age			
Median age (range) — yr	72 (48–91)	71 (47–97)	71 (47–97)
≤75 yr — no. (%)	444 (71.4)	220 (71.4)	664 (71.4)
>75 yr — no. (%)	178 (28.6)	88 (28.6)	266 (28.6)
Geographic region — no. (%)			
North and South America	216 (34.7)	106 (34.4)	322 (34.6)
North America	182 (29.3)	87 (28.2)	269 (28.9)
Europe	247 (39.7)	122 (39.6)	369 (39.7)
Asia–Pacific region	159 (25.6)	80 (26.0)	239 (25.7)
Clinical disease presentation — no. (%)			
Evidence of biochemical or clinical relapse after local primary intervention with curative intent†	309 (49.7)	158 (51.3)	467 (50.2)
Newly diagnosed androgen-sensitive metastatic disease	141 (22.7)	70 (22.7)	211 (22.7)
Advanced localized disease not suitable for primary surgical intervention with curative intent	172 (27.7)	80 (26.0)	252 (27.1)
ECOG performance status — no. (%)‡			
0	548 (88.1)	271 (88.0)	819 (88.1)
1	74 (11.9)	36 (11.7)	110 (11.8)
3§	0	1 (0.3)	1 (0.1)
Previous androgen deprivation therapy — no. (%)	81 (13.0)	30 (9.7)	111 (11.9)
PSA level — ng/mL			
Mean ± SD	104.2±416.0	68.6±244.0	92.4±368.3
Median	11.7	9.4	10.8
Mean testosterone level ± SD, ng/dL	436.1±159.0	410.0±149.1	427.5±156.2
Cardiovascular risk factors — no. (%)‖	570 (91.6)	290 (94.2)	860 (92.5)
Lifestyle risk factors¶	422 (67.8)	202 (65.6)	624 (67.1)
Cardiovascular or cerebrovascular risk factors#	488 (78.5)	254 (82.5)	742 (79.8)
History of major adverse cardiovascular events**	84 (13.5)	45 (14.6)	129 (13.9)

*Two patients in each arm did not receive the study treatment and were not included.

†Biochemical relapse was defined by a rising PSA level.

‡ECOG performance status ranges from 0 to 5, with higher scores reflecting greater disability.

§One patient in the leuprolide group had a surgical vascular procedure on his leg and was given an ECOG score of 3 at screening because of the use of crutches. By the baseline day 1 visit, the patient no longer used crutches, and his ECOG score had improved to 0.

‖Patients with multiple risk factors were counted only once.

¶Included tobacco smoking (current or past), heavy alcohol use, and a body-mass index of >30 kg/m^2.

#Included prespecified event terms in the major cardiovascular adverse event query and a manual search of known risk factors, including hypertension; dyslipidemia; diabetes; a history of myocardial infarction or cardiovascular disease; a history of stroke, transient ischemic attack, or cerebral hemorrhage; peripheral arterial disease; atrial fibrillation and other arrhythmias; heart-valve disease; chronic obstructive pulmonary disease; chronic kidney disease; chronic liver disease; carotid-artery stenosis or occlusion; venous thromboembolic events; and heart failure.

**Search criteria included "myocardial infarction" (broad standardized MedDRA query) and "central nervous system hemorrhages and cerebrovascular conditions" (broad standardized MedDRA query).

MedDRA=Medical Dictionary for Regulatory Activities; SD=standard deviation.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Laboratory Testing: Therapy with ORGOVYX results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after ORGOVYX may be affected. The therapeutic effect of ORGOVYX should be monitored by measuring serum concentrations of prostate-specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.

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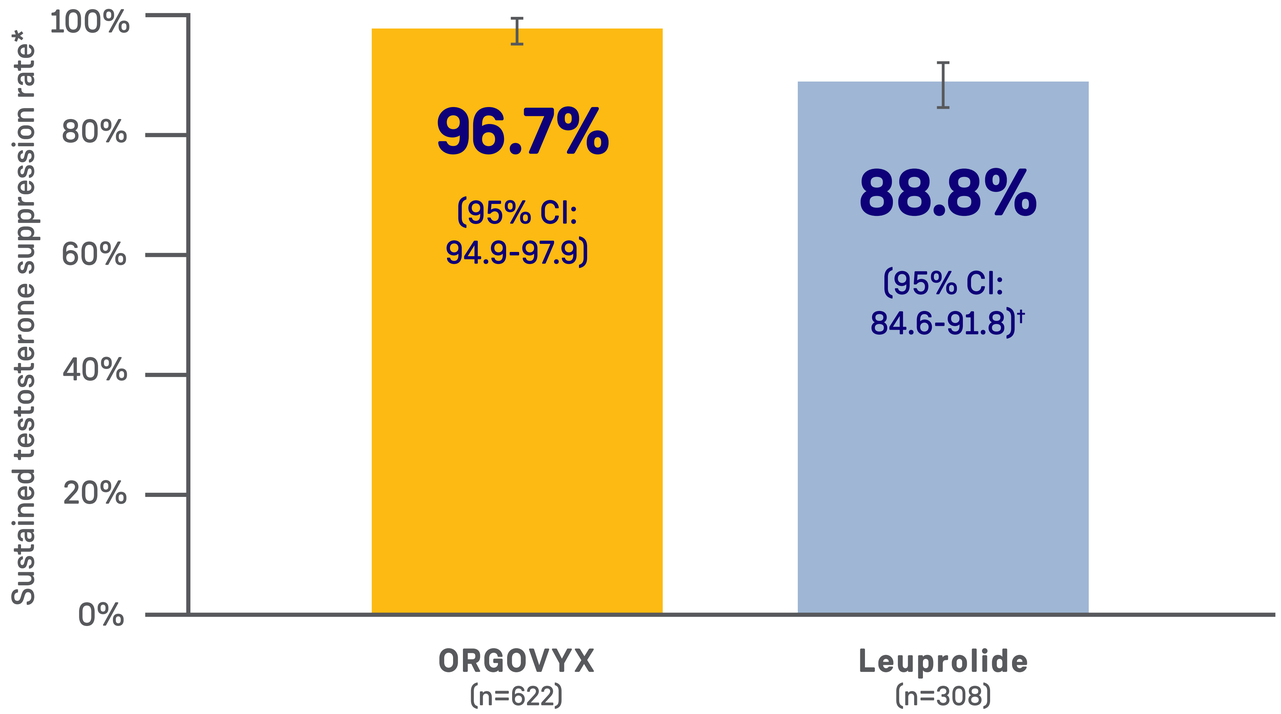
97% OF MEN RECEIVING ORGOVYX ACHIEVED SUSTAINED TESTOSTERONE SUPPRESSION[1,2]

MAJOR EFFICACY OUTCOME MEASURE: SUSTAINED TESTOSTERONE SUPPRESSION RATE (TESTOSTERONE LEVELS <50 ng/dL FROM DAY 29 THROUGH WEEK 48)[2]



*Kaplan-Meier estimates within each group.
†The testosterone suppression rate of the subgroup of patients receiving leuprolide 22.5 mg (n=264) was 88.0% (95% CI: 83.4-91.4).

- Results from the major efficacy outcome measure: sustained testosterone suppression rate (testosterone suppression to <50 ng/dL) from Day 29 through Week 48
- The criterion for success with respect to the primary endpoint was a lower boundary of the 95% confidence interval in the ORGOVYX group of 90% or higher

IMPORTANT SAFETY INFORMATION (cont'd)

Adverse Reactions

Serious adverse reactions occurred in 12% of patients receiving ORGOVYX. Serious adverse reactions in ≥0.5% of patients included myocardial infarction (0.8%), acute kidney injury (0.6%), arrhythmia (0.6%), hemorrhage (0.6%), and urinary tract infection (0.5%). Fatal adverse reactions occurred in 0.8% of patients receiving ORGOVYX including metastatic lung cancer (0.3%), myocardial infarction (0.3%), and acute kidney injury (0.2%). Fatal and non-fatal myocardial infarction and stroke were reported in 2.7% of patients receiving ORGOVYX.

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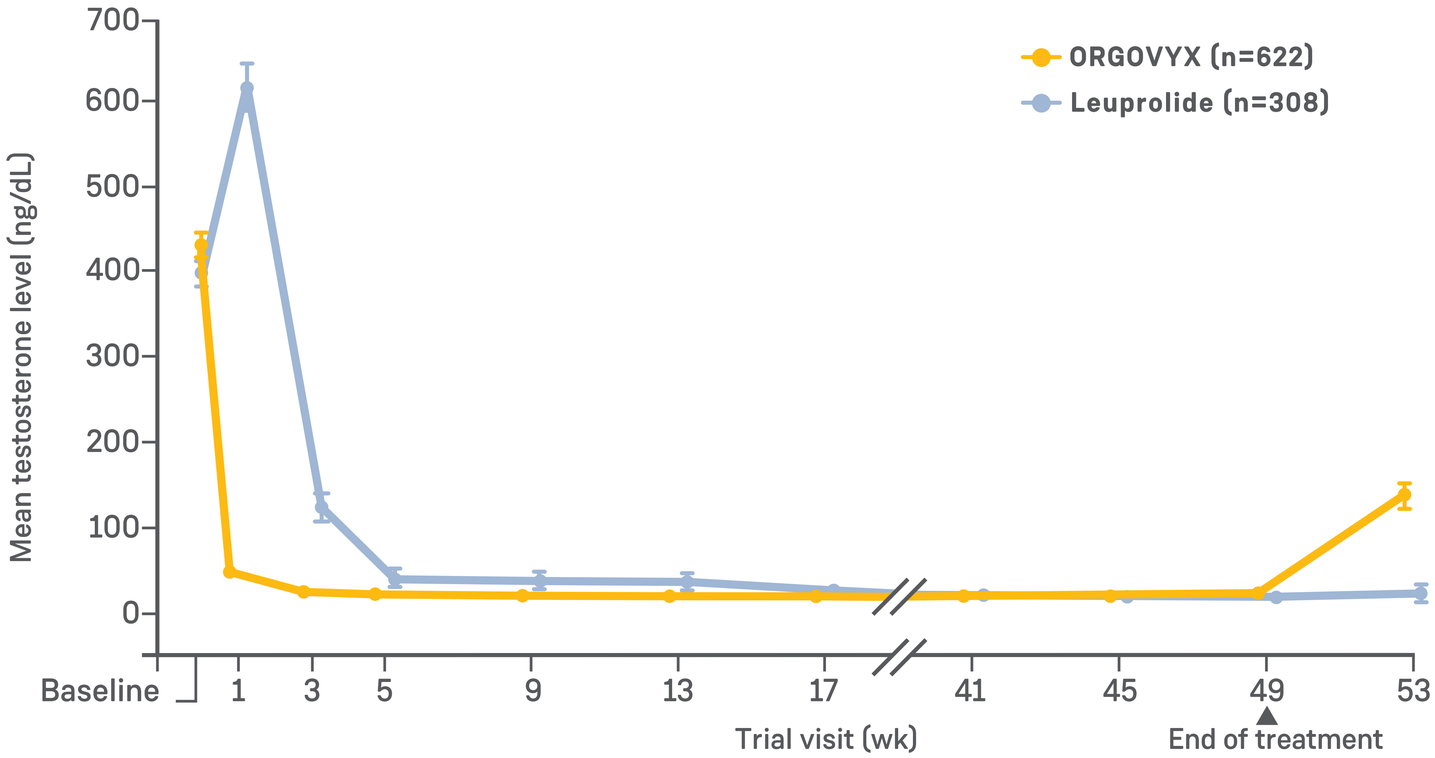
ORGOVYX DEMONSTRATED RAPID TESTOSTERONE SUPPRESSION WITH NO SURGE, AND PROFOUND TESTOSTERONE SUPPRESSION[1,2]

- Rapid mean testosterone suppression to 38 ng/dL on Day 4 for the ORGOVYX group
  - — Testosterone levels were 625 ng/dL in the leuprolide group on Day 4
- Profound testosterone suppression to <20 ng/dL was attained in 78.4% of patients in the ORGOVYX group on Day 15*
  - — Profound testosterone suppression to <20 ng/dL was attained in 1.0% of patients in the leuprolide group on Day 15

MEAN TESTOSTERONE LEVEL AMONG ALL PATIENTS[1]



*Kaplan-Meier estimates within each group.
†This endpoint was analyzed for exploratory purposes without formal testing. The data from the leuprolide arm were not included in the US Prescribing Information for ORGOVYX.

Adapted with permission from the *New England Journal of Medicine.*

ORGOVYX TESTOSTERONE RECOVERY 90 DAYS AFTER DISCONTINUATION[1,2,4]

- In a substudy of 184 patients who completed 48 weeks of treatment, 55% of men treated with ORGOVYX (n=137) had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values at 90 days after treatment discontinuation*†
  - — 3% of 47 men treated with leuprolide had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after discontinuation

IMPORTANT SAFETY INFORMATION (cont'd)

Adverse Reactions (cont'd)

Most common adverse reactions (≥10%) and laboratory abnormalities (≥15%) in patients receiving ORGOVYX were hot flush (54%), glucose increased (44%), triglycerides increased (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), alanine aminotransferase increased (27%), fatigue (26%), aspartate aminotransferase increased (18%), constipation (12%), and diarrhea (12%).

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HERO STUDY ADVERSE EVENTS[1,2]

ADVERSE EVENTS*	ORGOVYX (n=622)		Leuprolide (n=308)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Any adverse event — no. (%)	578 (92.9)	112 (18.0)	288 (93.5)	63 (20.5)
Serious adverse event — no. (%)	76 (12.2)	61 (9.8)	47 (15.3)	35 (11.4)
Fatal adverse event — no. (%)	7 (1.1)	–	9 (2.9)	–
Major adverse cardiovascular event — no. (%)†	18 (2.9)	8 (1.3)	19 (6.2)	4 (1.3)

*Shown are the numbers of patients with an event, rather than the number of events. Adverse events were evaluated with the use of MedDRA, version 22.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

†Search criteria included "myocardial infarction" (broad standardized MedDRA query), "central nervous system hemorrhages and cerebrovascular conditions" (broad standardized MedDRA query), and deaths from any cause.

‡Reported in 2.3% of patients treated with leuprolide.[4]

- In a prespecified analysis, major adverse cardiovascular events were defined as nonfatal myocardial infarction, nonfatal stroke, and all-cause death
- In a separate analysis reported in the US Prescribing Information, fatal and nonfatal myocardial infarction and stroke were reported in 2.7% of patients receiving ORGOVYX. Fatal adverse events, excluding prostate cancer-related deaths, were reported in 0.8% of patients receiving ORGOVYX‡

ADVERSE EVENTS THAT OCCURRED IN >10% OF PATIENTS IN EITHER GROUP — NO. (%)*	ORGOVYX (n=622)		Leuprolide (n=308)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Hot flush	338 (54.3)	4 (0.6)	159 (51.6)	0
Fatigue	134 (21.5)	2 (0.3)	57 (18.5)	0
Constipation	76 (12.2)	0	30 (9.7)	0
Diarrhea	76 (12.2)	0	21 (6.8)	0
Arthralgia	75 (12.1)	2 (0.3)	28 (9.1)	0
Hypertension	49 (7.9)	10 (1.6)	36 (11.7)	2 (0.6)

- Most common laboratory abnormalities (≥15%, all grades) in patients receiving ORGOVYX vs leuprolide were glucose increased (44% vs 54%), triglycerides increased (35% vs 36%), hemoglobin decreased (28% vs 29%), alanine aminotransferase increased (27% vs 28%), and aspartate aminotransferase increased (18% vs 19%)
- Permanent discontinuation of ORGOVYX due to an adverse reaction occurred in 3.5% of patients

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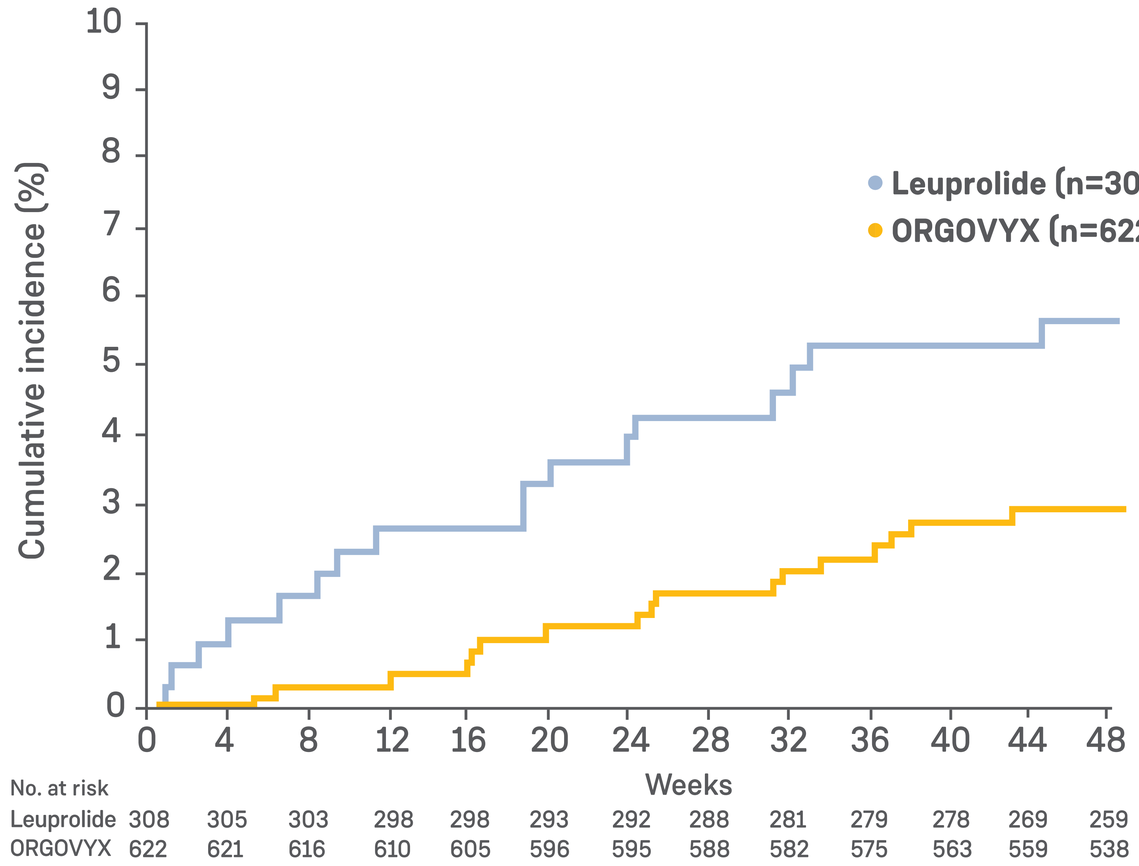
CUMULATIVE INCIDENCE OF MAJOR ADVERSE CARDIOVASCULAR EVENTS THROUGH WEEK 48 IN A POST-HOC ANALYSIS[1,4]

- In a prespecified analysis, major adverse cardiovascular events were defined as nonfatal myocardial infarction, nonfatal stroke, and all-cause death

CUMULATIVE INCIDENCE OF MAJOR ADVERSE CARDIOVASCULAR EVENTS[1]



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The incidence of major adverse cardiovascular events was a prespecified safety analysis. This was not a prospective efficacy endpoint in the study, the events were not adjudicated, and only descriptive analyses were performed. For these reasons, the FDA did not include the incidence of major adverse cardiovascular events for leuprolide in the label. The major adverse cardiovascular event data for ORGOVYX compared with leuprolide should be interpreted with caution and in this context. The study excluded patients with myocardial infarction or thromboembolic events within 6 months, arrhythmias, and uncontrolled hypertension.

This reprint contains information that is not included in the FDA-approved full Prescribing Information for ORGOVYX™ (relugolix).

Please see accompanying full Prescribing Information for ORGOVYX™ (relugolix).

Author(s) of this article have received remuneration from Myovant Sciences.

VIEW HERO TRIAL RESULTS

Learn more about ORGOVYX, the only oral androgen deprivation therapy for men with advanced prostate cancer,[1,2] at orgovyxhcp.com

IMPORTANT SAFETY INFORMATION (cont'd)

Drug Interactions

Co-administration of ORGOVYX with a P-gp inhibitor increases the area under the curve (AUC) and maximum concentration (C_{max}) of ORGOVYX, which may increase the risk of adverse reactions associated with ORGOVYX. Avoid co-administration of ORGOVYX with oral P-gp inhibitors. If co-administration is unavoidable, take ORGOVYX first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions. Treatment with ORGOVYX may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors. If treatment with ORGOVYX is interrupted for more than 7 days, resume administration of ORGOVYX with a 360 mg loading dose on the first day, followed by 120 mg once daily.

Co-administration of ORGOVYX with a combined P-gp and strong CYP3A inducer decreases the AUC and C_{max} of ORGOVYX, which may reduce the effects of ORGOVYX. Avoid co-administration of ORGOVYX with combined P-gp and strong CYP3A inducers. If co-administration is unavoidable, increase the ORGOVYX dose to 240 mg once daily. After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended ORGOVYX dose of 120 mg once daily.

Please see Important Safety Information throughout and full Prescribing Information for ORGOVYX.

References: 1. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med*. 2020;382(23):2187-2196 and supplementary material, available online. **2.** ORGOVYX [prescribing information]. Brisbane, CA: Myovant Sciences, Inc.; 2020. **3.** Shore ND, Saad F, Cookson MS, et al. HERO phase 3 trial: results comparing relugolix, an oral GnRH receptor antagonist, versus leuprolide acetate for advanced prostate cancer. Presented at: American Society of Clinical Oncology Virtual Scientific Program; May 29-June 2, 2020; virtual. Abstract 5602. **4.** Data on file. Myovant Sciences, Inc.

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