Impact of Concomitant Cardiovascular Therapies on Efficacy and Safety of Relugolix vs Leuprolide in Men with Advanced Prostate Cancer: Subgroup Analysis from the Phase 3 HERO Study

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Introduction

- Cardiovascular (CV) events are the leading cause of death in prostate cancer and approximately 30% of men with prostate cancer are reported as having known cardiovascular risk factors[1]
  - Men with prostate cancer are more likely to have CV risk factors, such as obesity, diabetes, hypertension and hyperlipidemia, and use CV-related concomitant medications
  - Men with prostate cancer, depending on the presence of additional cardiovascular risk factors, are estimated to have an increased yearly incidence of major adverse cardiovascular events of approximately 2 to 3%[2-4]
  - Several prior studies have shown the risk of major cardiovascular and cerebrovascular events using GnRH antagonists is significantly lower compared with LHRH agonists,[5-6] although the available data overall is not conclusive
- In the phase 3 HERO study, a 54% lower incidence of major adverse cardiac events was reported in men treated with the oral GnRH receptor antagonist relugolix vs leuprolide[7]
  - Key baseline factors including age, metastatic disease, prior history of major adverse cardiovascular events and other cardiovascular risk factors were similar across the two treatment groups
- Men with cardiovascular risk factors are often on multiple medications to manage their CV disease and due to the frequency of these medications, it is important to investigate their impact on efficacy/safety of relugolix
- Herein, we characterize the impact of concomitant CV therapies on efficacy and safety in the HERO study

Methods

- In the phase 3 HERO study, 934 men were randomized 2:1 to receive relugolix 120 mg orally once daily after a single loading dose of 360 mg or leuprolide injections every 12 weeks for 48 weeks[7]
- Patients with major adverse cardiovascular events within 6 months before trial initiation were excluded
- Subgroups analyzed included men who received antihypertensives, antithrombotics, or lipid-modifying therapies, as well as the most common drug classes (>10%) within these categories (angiotensin receptor blockers, calcium channel blockers, beta blockers, COX inhibitors, ADP receptor inhibitors, and statins), and single most common agent within each class (losartan, amlodipine, metoprolol, acetylsalicylic acid, clopidogrel, and simvastatin)
- Assessments included sustained testosterone suppression to castrate levels (<50 ng/dL) through 48 weeks, which was the primary efficacy endpoint in HERO, and safety parameters (adverse events)

Results

Baseline Characteristics

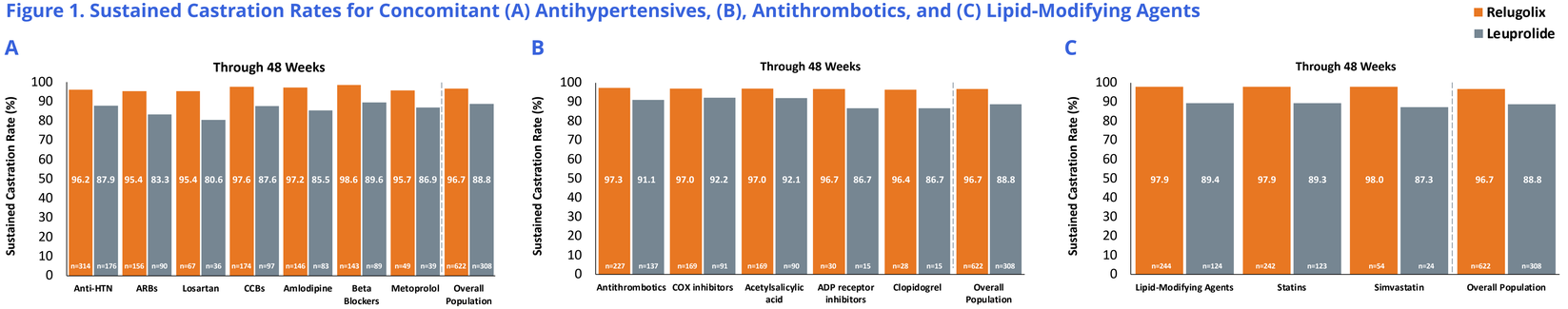
- Antihypertensives, antithrombotics, and lipid modifying agents were utilized by 52.7%, 39.1%, and 39.6% of men in the HERO trial, respectively

Efficacy

- In each subgroup analyzed, point estimates for sustained castration rates were consistent with the overall estimates of relugolix and leuprolide observed in the overall population (**Figure 1**)

Results

Figure 1. Sustained Castration Rates for Concomitant (A) Antihypertensives, (B), Antithrombotics, and (C) Lipid-Modifying Agents



Abbreviations: Anti-HTN = antihypertensives; ARBs = angiotensin receptor blockers; CCBs = calcium channel blockers; ADP = adenosine-diphosphate.

Safety

- Incidence and types of adverse events were generally similar among men who received antihypertensives, antithrombotics, and lipid modifying agents (**Table 1**)
- Men on concomitant antithrombotics had a higher incidence of serious adverse events vs the overall population (13.2%), with 23.3% and 24.8% in the relugolix and leuprolide groups, respectively

Table 1. Adverse Events

	Relugolix								Leuprolide							
	Overall Population (N = 622)		Antihypertensives (N = 314)		Antithrombotics (N = 227)		Lipid Modifying Agents (N = 244)		Overall Population (N = 308)		Antihypertensives (N = 176)		Antithrombotics (N = 137)		Lipid Modifying Agents (N = 124)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Any AE	578 (92.9)	112 (18.0)	292 (93.0)	69 (22.0)	218 (96.0)	65 (28.6)	234 (95.9)	52 (21.3)	288 (93.5)	63 (20.5)	163 (92.6)	36 (20.5)	131 (95.6)	40 (29.2)	119 (96.0)	32 (25.8)
Serious AE	76 (12.2)	—	47 (15.0)	—	53 (23.3)	—	37 (15.2)	—	47 (15.3)	—	25 (14.2)	—	34 (24.8)	—	22 (17.7)	—
Fatal AE	7 (1.1)	—	5 (1.6)	—	6 (2.6)	—	4 (1.6)	—	9 (2.9)	—	5 (2.8)	—	8 (5.8)	—	6 (4.8)	—
AEs that occurred in > 10% of patients in either group in the overall safety population																
Hot flash	338 (54.3)	4 (0.6)	182 (58.0)	3 (1.0)	130 (57.3)	2 (0.9)	141 (57.8)	0	159 (51.6)	0	87 (49.4)	0	71 (51.8)	0	73 (58.9)	0
Fatigue	134 (21.5)	2 (0.3)	71 (22.6)	2 (0.6)	62 (27.3)	2 (0.9)	68 (27.9)	1 (0.4)	57 (18.5)	0	31 (17.6)	0	36 (26.3)	0	26 (21.0)	0
Constipation	76 (12.2)	0	40 (12.7)	0	40 (17.6)	0	30 (12.3)	0	30 (9.7)	0	20 (11.4)	0	17 (12.4)	0	12 (9.7)	0
Diarrhea	76 (12.2)	0	51 (16.2)	0	40 (17.6)	0	38 (15.6)	0	21 (6.8)	0	11 (6.3)	0	11 (8.0)	0	10 (8.1)	0
Arthralgia	75 (12.1)	2 (0.3)	39 (12.4)	1 (0.3)	27 (11.9)	1 (0.4)	31 (12.7)	0	28 (9.1)	0	14 (8.0)	0	16 (11.7)	0	9 (7.3)	0
Hypertension	49 (7.9)	10 (1.6)	29 (9.2)	10 (3.2)	20 (8.8)	5 (2.2)	17 (7.0)	7 (2.9)	36 (11.7)	2 (0.6)	25 (14.2)	2 (1.1)	15 (10.9)	1 (0.7)	14 (11.3)	2 (1.6)

Abbreviation: AE = adverse event. Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. MedDRA Version 22.0.

CONCLUSION

- In the HERO trial, relugolix suppressed testosterone and was generally effective and well tolerated when given with concomitant cardiovascular agents, with results consistent with those of the overall population

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