P081 Oral relugolix for androgen deprivation therapy in advanced prostate cancer: Detailed safety analysis from the randomized phase 3 HERO study

Eur Urol Open Sci 2022;45(Suppl 2):S156

Tombal B.[1], Mehlhaff B.[2], Shore N.D.[3], George D.J.[4], Cookson M.S.[5], Saltzstein D.R. [6], Tutrone R.F.[7], Bailen J.L[8], Brown B.[9], Langenberg A.G.M.[9], Lu S.[9], Fallick M.[9], Hanson S.[10], Saad F.[11]

[1]Institut de Recherche Clinique, Université Catholique de Louvain, Dept. of Urology, Brussels, Belgium, [2]Oregon Urology Institute, Dept. of Urology, Springfield, United States of America, [3]Carolina Urologic Research Center, Dept. of Surgery and Oncology, Myrtle Beach, United States of America, [4]Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, United States of America, [5]The University of Oklahoma Health Sciences Center, Dept. of Urology, Oklahoma City, United States of America, [6]Urology San Antonio, Dept. of Urology, San Antonio, United States of America, [7]Chesapeake Urology, Dept. of Urology, Towson, United States of America, [8]First Urology, Dept. of Urology, Jeffersonville, United States of America, [9]Myovant Sciences, Inc, Brisbane, United States of America, [10]Pfizer, Inc, New York, United States of America, [11]University of Montreal Hospital Centre, Dept. of Surgery, Montreal, Canada

Introduction & Objectives: In the HERO study in men with advanced prostate cancer, relugolix, a highly selective nonpeptide oral GnRH antagonist, was well tolerated, with hot flash and fatigue as the most frequently reported adverse events (AE) for men in both relugolix and leuprolide groups. A 54% lower risk of major adverse cardiovascular events (MACE) was observed for men on relugolix vs leuprolide. Herein, we provide a detailed analysis of the safety results from the HERO study, including reviewing AE onset and duration data.

Materials & Methods: The phase 3 HERO study evaluated 930 men with advanced prostate cancer who were randomized 2:1 and treated with relugolix 120 mg orally once daily (after a 360 mg day 1 loading dose) or leuprolide injections every 12 weeks for 48 weeks. Safety assessments included AEs (assessed according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.03), MACE (defined as nonfatal myocardial infarction, non-fatal stroke, and death from any cause), as well as onset (median days from the date of first dose to the initial event) and duration (median days from start to end date of the event) of the most common events.

Results: AEs were reported in 92.9% of men in relugolix group and 93.5% in the leuprolide group, with hot flash, fatigue, constipation, diarrhea, and arthralgia occurring most frequently (table). Grade ≥3 AEs were reported in 18.0% in the relugolix group and 20.5% men in the leuprolide group. The most frequently reported (≥1%) grade ≥ 3 AEs in any treatment group included hypertension, diabetes mellitus, and syncope. All other grade ≥ 3 AEs were reported with similar incidence in both treatment groups. MACE occurred in 2.9% and 6.2% of patients on relugolix and leuprolide, respectively. For AEs occurring in ≥ 10% patients, median time to onset was 19.0-142.0 days in the relugolix group and 41.0-188.5 days in the leuprolide group. Duration varied among the AEs (table).

Table. Onset and Duration of Adverse Events

	Relugolix (N = 622)			Leuprolide (N = 308)		
	AE n (%)	Onset (Days)[a] Median (min, max)	Duration (Days)[b] Median (min, max)	AE n (%)	Onset (Days)[a] Median (min, max)	Duration (Days)[b] Median (min, max)
MACE[c]	18 (2.9)	176.5 (38, 343)	N/A	19 (6.2)	132.0 (8, 352)	N/A
AEs occurring in ≥ 10% of patients						
Hot flash	338 (54.3)	19.0 (1, 343)	342.0 (15, 477)	159 (51.6)	33.0 (1, 200)	331.0 (1, 428)
Fatigue	134 (21.5)	45.5 (1, 342)	289.0 (2, 429)	57 (18.5)	41.0 (1, 326)	274.0 (3, 426)
Constipation	76 (12.2)	128.0 (1, 359)	66.5 (2, 409)	30 (9.7)	61.0 (1, 273)	92.5 (3, 410)
Diarrhea[d]	76 (12.2)	75.5 (1, 338)	9.0 (1, 370)	21 (6.8)	133.0 (2, 313)	3.0 (1, 224)
Arthralgia	75 (12.1)	142.0 (1, 355)	160.0 (1, 495)	28 (9.1)	188.5 (1, 370)	129.5 (2, 589)
Grade ≥ 3 AEs in ≥ 1% patients						
Hypertension[e]	10 (1.6)	206.0 (15, 334)	14.5 (1, 328)	2 (0.6)	55.0 (21, 89)	26.5 (2, 51)
Diabetes	6 (1.0)	202.5 (85, 338)	117.5 (1, 204)	2 (0.6)	31.5 (29, 34)	191.5 (53, 330)
Syncope	6 (1.0)	163.0 (79, 315)	N/A	3 (1.0)	83.0 (45, 214)	N/A

Abbreviations: AE, adverse event; MACE, major adverse cardiovascular event; N/A, not applicable.
[a]Time to event is defined as the time from the date of first dose to the initial event (median days).
[b]Duration of AE defined as end date of the event – start date of the event + 1 (median days). Duration is not applicable to point in time events (ie, MACE and syncope).
[c]Search criteria included Myocardial Infarction SMQ (broad), Central Nervous System Hemorrhages and Cerebrovascular Conditions SMQ (broad), and deaths due to all causes.
[d]All diarrhea events were mild or moderate (grade 1 or grade 2) and no patient was withdrawn due to diarrhea.
[e]Grade ≥ 3 hypertension were reported in a higher proportion of patients in the relugolix group (1.6%) than the leuprolide group (0.6%); however, no meaningful differences were observed between groups in the mean changes from baseline over time in systolic or diastolic blood pressure
Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. MedDRA Version 22.0.

Conclusions: Relugolix, an oral nonpeptide GnRH receptor antagonist, was generally well tolerated in the phase 3 HERO study. Results for AE onset and duration suggest AEs occur early during treatment with varying duration depending on the type of event.

Clinical Trial ID: NCT03085095

This abstract was accepted and previously presented at the 2022 American Urological Association Annual Meeting.