Oral Relugolix for Androgen Deprivation Therapy in Advanced Prostate Cancer: Detailed Safety Analysis from the Randomized Phase 3 HERO Study

Bryan Mehlhaff;[1] Neal D. Shore;[2] Daniel J. George;[3] Michael S. Cookson;[4] Daniel R. Saltzstein;[5] Ronald Tutrone;[6] James L. Bailen;[7] Bruce Brown;[8] Andria G. M. Langenberg;[8] Mark Fallick;[8] Sophia Lu;[8] Sarah Hanson;[9] Bertrand Tombal;[10] Fred Saad[11]

[1]Oregon Urology Institute, Springfield, OR. [2]Carolina Urologic Research Center, Myrtle Beach, SC. [3]Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC. [4]Department of Urology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK. [5]Urology San Antonio, San Antonio, TX. [6]Chesapeake Urology, Towson, MD. [7]First Urology, Jeffersonville, IN. [8]Myovant Sciences, Inc., Brisbane, CA. [9]Pfizer Inc. New York, NY. [10]Institut de Recherche Clinique, Université Catholique de Louvain, Brussels, Belgium. [11]University of Montreal Hospital Centre, Montreal, QC, Canada.

For questions or comments on this poster, please contact Dr. Mehlhaff at bmehlhaff@comcast.net

Introduction

- Relugolix is an FDA-approved, first-in-class oral, highly selective, nonpeptide GnRH receptor antagonist that is given once daily[1]
- Relugolix lowered testosterone by rapidly inhibiting pituitary release of LH and FSH in multiple clinical studies[2-6]
- In the phase 3 HERO study in men with advanced prostate cancer, relugolix was well tolerated[6]
- Herein, we provide a review of the safety results from the HERO study, including reviewing adverse event (AE) onset and duration data

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
- Men were eligible if they were 18 years of age or older and had histologically or cytologically confirmed adenocarcinoma of the prostate that required at least one year of continuous androgen deprivation therapy
  - Eligible men could have one of three clinical disease presentations: evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent, newly diagnosed hormone-sensitive metastatic disease, or advanced localized disease unlikely to be cured by local primary intervention with curative intent
  - Men with major adverse cardiovascular events within 6 months of study initiation were excluded
- Safety assessments included AEs (assessed according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.03), major adverse cardiovascular events (MACE; defined as nonfatal myocardial infarction, nonfatal 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

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Results

- The safety population included 622 men who received relugolix and 308 men who received leuprolide
- 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 1**)
  - The most common AEs reported in both the relugolix and leuprolide groups were hot flash and fatigue
- Grade ≥3 AEs were reported in 18.0% of men in the relugolix group and 20.5% of men in the leuprolide group
- The most frequently reported (≥1%) grade ≥ 3 AEs in any treatment group included hypertension, diabetes, and syncope. All other grade ≥ 3 AEs were reported with similar incidence in both treatment groups

Table 1. 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)
AEs in > 10% of men						
Hot flash	338 (54.3)	19 (1, 343)	342 (15, 477)	159 (51.6)	33 (1, 200)	331 (1, 428)
Fatigue	134 (21.5)	46 (1, 342)	289 (2, 429)	57 (18.5)	41 (1, 326)	274 (3, 426)
Constipation	76 (12.2)	128 (1, 359)	67 (2, 409)	30 (9.7)	61 (1, 273)	92 (3, 410)
Diarrhea[d]	76 (12.2)	76 (1, 338)	9 (1, 370)	21 (6.8)	133 (2, 313)	3 (1, 224)
Arthralgia	75 (12.1)	142 (1, 355)	160 (1, 495)	28 (9.1)	189 (1, 370)	130 (2, 589)
Grade ≥ 3 AEs in ≥ 1% men						
Hypertension[e]	10 (1.6)	206 (15, 334)	15 (1, 328)	2 (0.6)	55 (21, 89)	27 (2, 51)
Diabetes	6 (1.0)	203 (85, 338)	118 (1, 204)	2 (0.6)	32 (29, 34)	192 (53, 330)
Syncope	6 (1.0)	163 (79, 315)	N/A	3 (1.0)	83 (45, 214)	N/A
MACE[c]	18 (2.9)	177 (38, 343)	N/A	19 (6.2)	132 (8, 352)	N/A

Abbreviations: AEs, adverse events; 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 subjects withdrew due to diarrhea.
[e]Grade ≥ 3 hypertension were reported in a higher proportion of men 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.

- Graphs depicting the most common AEs and MACE by week are shown in **Figure 1**
- MACE occurred in 2.9% and 6.2% of men on relugolix and leuprolide, respectively
  - Kaplan-Meier estimates of incidence rate indicated a 54% risk reduction (hazard ratio of 0.46, 95% CI, 0.24 to 0.88) in the relugolix group vs the leuprolide group
  - The major adverse cardiovascular event rate on study drug treatment was 3.6% in the relugolix group compared with 17.8% in the leuprolide group in a subgroup of men with a reported medical history of cardiovascular events (5.8-fold higher odds with leuprolide compared with relugolix)
- For AEs occurring in > 10% of men, 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 1**)
  - Diarrhea had a relatively short median duration (relugolix: 9 days; leuprolide: 3 days) vs other AEs
  - Fatigue (relugolix: 289 days; leuprolide: 274 days) and hot flash (relugolix: 342 days; leuprolide: 331 days) were most persistent in duration

References / Acknowledgements

1. Myovant Sciences. Relugolix. Full prescribing information. (2020). 2. Suzuki H, et al. Cancer Med 2019;8:5891-902. 3. MacLean DB, Shi H, Faessel HM, Saad F. J Clin Endocrinol Metab 2015;100:4579-87. 4. Dearnaley DP, et al. Eur Urol. 2020 Aug;78:184-192. 5. Saad F, et al. J Clin Oncol 2016;34(no. 2_suppl):200-200. 6. Shore N, et al. N Engl J Med. 2020 Jun 4;382:2187-2196.

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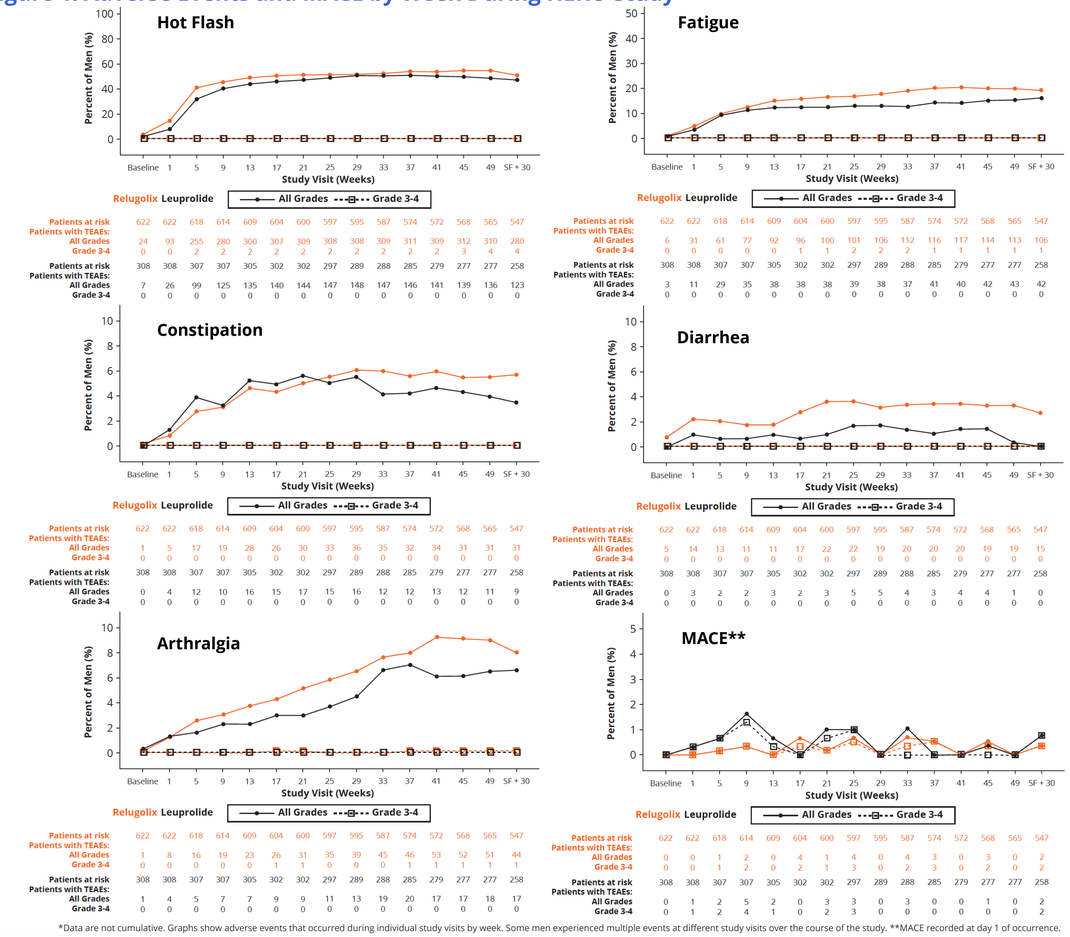
Figure 1. Adverse Events and MACE by Week During HERO Study*



*Data are not cumulative. Graphs show adverse events that occurred during individual study visits by week. Some men experienced multiple events at different study visits over the course of the study. **MACE recorded at day 1 of occurrence.

Conclusions

- Relugolix, an oral nonpeptide GnRH receptor antagonist, was generally well tolerated in the phase 3 HERO study
- AEs occur with varying time of onset and duration depending on the type of event
- MACE appeared to occur earlier and with a higher percentage in leuprolide vs relugolix groups, possibly supporting a different risk/mechanism between GnRH agonists and antagonists