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ORIGINAL RESEARCH

The Hospitalization-Related Costs of Adverse Events for Novel Androgen Receptor Inhibitors in Non-Metastatic Castration-Resistant Prostate Cancer: An Indirect Comparison

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ABSTRACT

Introduction: Three novel androgen receptor inhibitors are approved in the USA for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC): apalutamide, enzalutamide, and darolutamide. All three therapies have demonstrated prolonged metastasis-free survival in their respective phase III trials, with differing safety profiles. The objective of this study was to compare the mean per-patient costs of all-cause adverse events (AEs) requiring hospitalization between darolutamide versus apalutamide and enzalutamide for nmCRPC in the USA.

Methods: All-cause grade ≥ 3 AEs with corresponding any-grade AEs reported among at least 10% of patients in any arm of the ARAMIS (darolutamide), SPARTAN (apalutamide), and PROSPER (enzalutamide) trials were selected for inclusion in the primary analyses. After matching-adjusted indirect comparison, AE costs were calculated by multiplying the AE rates from the trials by their respective unit costs of hospitalization taken from the US Healthcare Cost and Utilization Project (HCUP)

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database. Sensitivity analyses which further included any-grade AEs reported among at least 5% of patients were also performed.
Results: After reweighting and adjusting for the trials' placebo arms, the mean per-patient AE costs were $1021 and $387 lower for darolutamide than for apalutamide and enzalutamide, respectively, over the trials' duration (SPARTAN and PROSPER, 43 months; ARAMIS, 48 months). For darolutamide vs. apalutamide, the largest drivers of the per-patient cost differences were fracture (adjusted difference $416), hypertension ($143), and rash ($219); for darolutamide vs. enzalutamide, they were fatigue not including asthenia ($290) and hypertension including increased blood pressure (i.e., any AE of hypertension or with elevated blood pressure not yet classified as hypertension) ($60). The results of the sensitivity analyses were consistent with the primary results.
Conclusions: Patients with nmCRPC treated with darolutamide in ARAMIS incurred lower AE-related costs (USD), as determined using HCUP costing data, compared with patients treated with either apalutamide (in SPARTAN) or enzalutamide (in PROSPER).

Keywords: Adverse event costs; Apalutamide; Darolutamide; Enzalutamide; Indirect treatment comparison; Non-metastatic castration-resistant prostate cancer

Key Summary Points

Why carry out this study?

Apalutamide, enzalutamide, and darolutamide are novel androgen receptor inhibitors approved in the USA for non-metastatic castration-resistant prostate cancer (nmCRPC) and have each demonstrated prolonged metastasis-free and overall survival in their placebo-controlled phase III trials (SPARTAN, PROSPER, and ARAMIS, respectively).

However, apalutamide, enzalutamide, and darolutamide have differing safety profiles that could impact the cost of treatment, and no studies to date have compared the costs of adverse events (AEs).

This study compared the mean per-patient costs of all-cause grade $\geq$ 3 AEs, assumed to require hospitalization, between darolutamide versus apalutamide and enzalutamide for nmCRPC in the USA.

What was learned from the study?

After reweighting and adjusting for the trials' placebo arms, the mean per-patient AE costs were $1021 and $387 lower for darolutamide than for apalutamide and enzalutamide, respectively, over the trials' duration (SPARTAN and PROSPER, 43 months; ARAMIS, 48 months).

Patients with nmCRPC treated with darolutamide in ARAMIS incurred lower AE-related costs (USD), as determined using Healthcare Cost and Utilization Project costing data, compared with patients treated with either apalutamide (in SPARTAN) or enzalutamide (in PROSPER).

This is an important consideration from a health system perspective and is informative for treatment selection decisions as well.

INTRODUCTION

Approximately 80% of men with prostate cancer do not have detectable metastases at diagnosis, and a subset of these patients experience rising serum prostate-specific antigen (PSA) levels, despite local curative radiation therapy and androgen deprivation therapy (ADT) with medical or surgical castration [1, 2]. These patients with non-metastatic castration-resistant prostate cancer (nmCRPC) are at risk of progression to metastatic disease with worsening clinical outcomes [3]. Thus, delaying disease progression and cancer-related symptoms that may impact daily activities and extending survival are major clinical treatment goals for patients with nmCRPC [4].

Prior to the advent of novel androgen receptor inhibitors (ARIs), there were limited treatment options for patients with nmCRPC experiencing biological recurrence despite ADT [5]. The US Food and Drug Administration (FDA) approval of the novel ARIs apalutamide and enzalutamide in 2018, and darolutamide in 2019, for the treatment of nmCRPC has greatly expanded therapeutic options. The phase III, placebo-controlled trials of enzalutamide (PROSPER) [6], apalutamide (SPARTAN) [7], and darolutamide (ARAMIS) [8] demonstrated that all three treatments significantly prolonged metastasis-free survival (all $p < 0.001$) and delayed further antitumor therapy among patients with nmCRPC, and importantly they improved overall survival [9, 10].

In the absence of head-to-head trials directly comparing the efficacy or safety of the three FDA-approved novel ARIs for nmCRPC, network meta-analyses (NMA) and matching-adjusted indirect comparisons (MAICs) using patient-level data from the pivotal trials have been conducted to compare outcomes [11–15]. Metastasis-free survival has been shown to be comparable between darolutamide, apalutamide, and enzalutamide [13]. However, these patients are asymptomatic from their primary tumor and the need to avoid further morbidity is an important concern. Thus, with the consideration of long-term therapy for patients with nmCRPC and the desire to minimize adverse events (AEs) and, in turn, their impact on daily activities, the differing safety profiles of the novel ARIs often guide the choice of treatment [16]. A recent (2021) MAIC of darolutamide versus apalutamide or enzalutamide by Halabi et al. reported that the safety and tolerability profiles differed across treatments, with darolutamide offering a more favorable tolerability profile after adjusting for cross-trial differences [13]. Specifically, darolutamide was associated with significantly lower rates of fall, fracture, and rash versus apalutamide, and significantly lower rates of fall, dizziness, mental impairment, fatigue, and severe fatigue versus enzalutamide [13].

Given the high economic burden for health systems attributed to prostate cancer in the USA [17], understanding the cost impact of AEs associated with the different novel ARIs available for nmCRPC can help inform management strategies to reduce the overall direct medical cost burden of nmCRPC. No studies to date have compared AE costs among these three novel ARIs. To address this knowledge gap, this study quantified the mean per-patient costs of all-cause grade ≥ 3 AEs, assumed to require hospitalization, over the trials' duration (SPARTAN and PROSPER, 43 months; ARAMIS, 48 months), of darolutamide versus apalutamide, and darolutamide versus enzalutamide.

METHODS

Data Sources

All-grade and grade ≥ 3 AE rates associated with darolutamide, apalutamide, and enzalutamide were obtained from their corresponding pivotal trials, which were randomized, double-blind, placebo-controlled phase III trials conducted in adult men (at least 18 years of age) with nmCRPC, comparing the active agent plus ADT vs. ADT alone. AE rates associated with darolutamide were obtained from individual patient-level data (IPD) from ARAMIS (ClinicalTrials.gov Identifier NCT02200614; data on file, Bayer; database cutoff September 3, 2018) [8]. AE rates associated with apalutamide and enzalutamide were from the publications of SPARTAN

(NCT01946204) [6] and PROSPER (NCT02003924) [7], respectively. Rates of grade 3/4 AEs were reported in SPARTAN [6], whereas rates of grade 3/4/5 AEs were reported in PROSPER [7].

In addition, mean hospitalization costs per discharge for male patients were obtained for each all-cause grade $\geq$ 3 AE using the 2016 US Healthcare Cost and Utilization Project (HCUP) database [18] and inflated to 2019 US dollars using the Consumer Price Index for all urban consumers in medical care service [19]. Table S1 in the supplementary material lists the International Classification of Diseases, 10th edition, Clinical Modification codes used to identify hospitalization costs for each AE in the HCUP database. All three trials used the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) to grade AEs [20], which explicitly indicate hospitalization or urgent intervention for grade $\geq$ 3 AEs. Namely, the CTCAE guidance provides unique clinical descriptions of severity for each AE whereby grade 1 AEs are mild (intervention not indicated), grade 2 AEs are moderate (local or noninvasive intervention indicated), grade 3 AEs are severe (hospitalization or prolongation of hospitalization indicated), and grade 4 AEs are life-threatening (urgent intervention [including hospitalization] indicated). Per these criteria, it was assumed that grade $\geq$ 3 AEs would require hospitalization while grade 1 and 2 AEs would not incur hospitalization costs [20]. In order to assess the impact of this assumption, a sensitivity analysis was conducted assuming that different proportions of grade $\geq$ 3 AEs would require hospitalization. For that analysis, outpatient visit costs were obtained from the Centers for Medicare & Medicaid Services Physician Fee Schedule as the 2019 costs for the facility price for Healthcare Common Procedure Coding System code 99214 (office/outpatient visit; unit costs for outpatient visit $80.01).

As this post hoc analysis was based on previously collected data, no institutional board review was required. The research was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Deidentified data for darolutamide were provided by Bayer to the authors for use in this study and comparator data were sourced from publicly available literature.

Outcomes

AE Costs

The main outcomes in this study were mean per-patient costs of all-cause AEs requiring hospitalization. It was assumed that grade $\geq$ 3 AEs would require hospitalization and that the trials' grade $\geq$ 3 AEs resulted in one hospitalization per patient [21].

AEs Included in the Primary Analyses

All-cause grade $\geq$ 3 AEs with corresponding any-grade AEs reported among at least 10% of patients, in any arm for any of the three trials of interest, were selected for inclusion in the primary analyses in order to include all AEs that occurred frequently in patients with nmCRPC and due to data availability for the comparators. For each of the two treatment comparisons (darolutamide versus apalutamide and darolutamide versus enzalutamide), only AEs that were reported in the two relevant trials were included in the comparison. For darolutamide versus apalutamide, AEs included hypertension, fracture, falls, fatigue including asthenia (any AE of fatigue or asthenia), arthralgia, nausea, dizziness, rash, diarrhea, and weight loss. For darolutamide versus enzalutamide, AEs included hypertension including increased blood pressure (any AE of hypertension or inclusive of the term "increased blood pressure"), falls, fatigue, arthralgia, nausea, dizziness, diarrhea, and weight loss.

AEs Included in the Sensitivity Analyses

All-cause grade $\geq$ 3 AEs with corresponding any-grade AE reported in at least 5% of patients, in any arm for any of the three trials of interest, were selected for inclusion in the sensitivity analyses. Similar to the primary analyses, only the AEs that were reported in the two relevant trials being compared in each pairwise comparison were included. For darolutamide versus apalutamide, mental-impairment disorder and hypothyroidism were included in addition to the AEs in the primary analysis. For

darolutamide versus enzalutamide, back pain, constipation, urinary tract infection, headache, asthenia, urinary retention, and mental-impairment disorder were included in addition to those in the primary analysis.

Statistical Methods

For consistency with the inclusion and exclusion criteria of SPARTAN [6] and PROSPER [7], and to ensure fair comparisons, patients in ARAMIS with a history of seizure were excluded from the analyses.

To minimize inter-trial differences, MAICs [22] were separately conducted to compare selected AE costs for darolutamide versus apalutamide and darolutamide versus enzalutamide. Patients in the darolutamide and placebo arms of ARAMIS were reweighted such that the mean baseline characteristics of the arms exactly matched the respective active treatment and placebo arms reported in the comparator trials. Weights meeting these conditions were obtained via a logistic regression model for the propensity of enrollment in ARAMIS versus the comparator trial, with all matched-on baseline characteristics included as predictors in the model. For the darolutamide versus apalutamide comparisons, matching variables included age, serum PSA level, PSA doubling time, Eastern Cooperative Oncology Group (ECOG) performance status, Gleason score, previous surgical prostate cancer procedures, and use of bone-sparing agents. For the darolutamide versus enzalutamide comparisons, matching variables included age, region, serum PSA level, PSA doubling time, ECOG performance status, Gleason score, use of bone-sparing agents, and metastatic disease status.

Mean per-patient costs for AEs associated with each treatment were calculated by multiplying the AE rates (after weighting) by the corresponding AE unit costs (from HCUP data). For AEs with multiple codes (e.g., fracture), a weighted average of the mean hospitalization costs across the codes was calculated, weighted by the number of hospitalizations for each code. For the sensitivity analysis about the proportion of grade ≥ 3 AEs requiring hospitalization, mean per-patient costs were calculated as a weighted average of the AE unit costs for hospitalization and the cost of an outpatient visit, using assumptions of different proportions (i.e., 10%, 25%, 50%, 75%, and 90%) of grade ≥ 3 AEs requiring hospitalizations. Differences in mean per-patient AE costs were assessed for darolutamide versus apalutamide and darolutamide versus enzalutamide and adjusted for their respective placebo arms.

RESULTS

Darolutamide (ARAMIS) Versus Apalutamide (SPARTAN)

Sample Selection

In total, 1496 patients from ARAMIS (placebo, $n = 553$; darolutamide, $n = 943$) were included in the MAIC and considered for weighting after excluding patients with seizure history (placebo, $n = 1$; darolutamide, $n = 12$). SPARTAN included 401 and 806 patients in its placebo and apalutamide arms, respectively.

Baseline Characteristics

Prior to weighting, several baseline characteristics differed between the patient cohorts of ARAMIS and SPARTAN (Table 1). After weighting, the seven matched-on baseline characteristics were balanced between ARAMIS and SPARTAN; the effective sample sizes (ESS) of darolutamide and its placebo arm were 604 and 391, respectively. Differences remained between the trials post-weighting for race, geographic region, classification of nodal disease, serum testosterone level and, for the active treatment-arm patients, tumor stage at diagnosis. Variables that were considered to be effect modifiers or prognostic of the outcomes and could potentially impact the results were included in the weighting.

Primary Analysis

The rates and unit costs of selected grade 3 and 4 AEs for the primary analysis of ARAMIS and SPARTAN, including the extracted AE rates from SPARTAN and those before and after weighting

Table 1 Observed patient baseline characteristics in ARAMIS and SPARTAN, before and after weighting

	Before weighting				After weighting			
	ARAMIS		SPARTAN		ARAMIS		SPARTAN	
	DARO $N = 943$ (%)	Placebo $N = 553$ (%)	APA $N = 806$ (%)	Placebo $N = 401$ (%)	DARO ESS = 604 (%)	Placebo ESS = 391 (%)	APA $N = 806$ (%)	Placebo $N = 401$ (%)
Age in years > SPARTAN median	49.1	45.8	50.0	50.0	50.0	50.0	50.0	50.0
Race								
White	79.5	78.3	65.0	68.8	79.9	77.3	65.0	68.8
Black	3.0	4.3	6.0	5.0	2.8	4.5	6.0	5.0
Asian	12.8	12.8	11.5	11.7	12.4	13.9	11.5	11.7
Region								
Asia–Pacific	12.5	12.1	15.6	15.7	12.0	13.1	15.6	15.7
North America	11.2	13.6	35.4	33.4	17.4	16.9	35.4	33.4
Europe	65.2	62.6	49.0	50.9	60.4	57.9	49.0	50.9
Years from initial diagnosis > SPARTAN median	44.2	43.2	50.0	50.0	47.7	45.7	50.0	50.0
Serum PSA level (ng/mL) > SPARTAN median	54.8	57.7	50.0	50.0	50.0	50.0	50.0	50.0
Classification of local or regional nodal disease								
N0	54.8	51.7	83.5	83.8	58.0	54.5	83.5	83.8
N1	9.1	11.0	16.5	16.2	9.6	13.0	16.5	16.2
PSA doubling time								
> SPARTAN median	49.6	51.5	50.0	50.0	50.0	50.0	50.0	50.0
≤ 6 months	69.8	66.9	71.5	70.8	71.5	70.8	71.5	70.8
> 6 months	30.2	33.1	28.5	29.2	28.5	29.2	28.5	29.2
Serum testosterone level (nmol/L) > SPARTAN median	16.4	16.6	50.0	50.0	14.1	15.7	50.0	50.0

Table 1 continued

	Before weighting				After weighting			
	ARAMIS		SPARTAN		ARAMIS		SPARTAN	
	DARO *N* = 943 (%)	Placebo *N* = 553 (%)	APA *N* = 806 (%)	Placebo *N* = 401 (%)	DARO ESS = 604 (%)	Placebo ESS = 391 (%)	APA *N* = 806 (%)	Placebo *N* = 401 (%)
ECOG performance status								
0	68.2	70.7	77.3	77.8	77.3	77.7	77.3	77.8
1	31.8	29.3	22.7	22.3	22.7	22.3	22.7	22.3
Gleason score								
< 7	22.8	25.7	18.9	18.0	18.9	18.0	18.9	18.0
≥ 7	74.4	71.2	78.4	78.6	78.4	78.6	78.4	78.6
Missing	2.8	3.1	2.7	3.5	2.7	3.4	2.7	3.5
Previous surgical prostate cancer procedures	32.7	31.8	57.1	55.4	57.1	55.4	57.1	55.4
Use of bone-sparing agent	3.2	5.8	10.2	9.7	10.2	9.7	10.2	9.7
Tumor stage at diagnosis								
T1	13.9	12.1	17.5	15.7	13.6	12.0	17.5	15.7
T2	31.2	35.3	32.9	30.7	31.0	35.8	32.9	30.7
T3	43.3	38.9	36.7	40.6	44.2	39.3	36.7	40.6
T4	4.2	4.7	4.0	4.0	3.8	3.8	4.0	4.0
TX	4.7	6.3	7.4	7.2	4.2	6.5	7.4	7.2
Missing	2.8	2.7	1.5	1.7	3.2	2.6	1.5	1.7

APA apalutamide, *DARO* darolutamide, *ECOG* Eastern Cooperative Oncology Group, *ESS* effective sample size, *PSA* prostate-specific antigen

Table 2 Rates and unit costs of selected grade 3 and 4 AEs in ARAMIS and SPARTAN

	AE unit costs	AE rate (%)					
		SPARTAN		ARAMIS			
				Before weighting		After weighting	
		APA	SPARTAN placebo	DARO	ARAMIS placebo	DARO	ARAMIS placebo
Hypertension	$10,926	14.32	11.81	3.18	2.17	3.57	2.36
Fracture	$20,589	2.74	0.75	0.95	0.90	0.88	0.91
Falls	$6707	1.74	0.75	0.85	0.54	0.83	0.68
Fatigue (including asthenia)	$11,501	0.87	0.25	0.64	1.08	0.66	0.76
Arthralgia	$7954	0.00	0.00	0.32	0.36	0.32	0.44
Nausea	$7081	0.00	0.00	0.21	0.00	0.47	0.00
Dizziness	$6513	0.62	0.00	0.21	0.18	0.36	0.11
Rash	$4467	5.23	0.25	0.11	0.00	0.07	0.00
Diarrhea	$7744	1.00	0.50	0.00	0.18	0.00	0.12
Weight loss	$6446	1.12	0.25	0.00	0.00	0.00	0.00

All-cause grade 3 and 4 AEs with corresponding any-grade AE reported in at least 10% of patients
Costs in 2019 US dollars
AE adverse event, *APA* apalutamide, *DARO* darolutamide

in ARAMIS, are listed in Table 2. The three costliest AEs occurring in at least 10% of patients were fracture ($20,589), fatigue including asthenia ($11,501), and hypertension ($10,926). The most common AE across arms was hypertension, with higher rates in SPARTAN (apalutamide, 14.32%; placebo, 11.81%) compared with ARAMIS both before (darolutamide, 3.18%; placebo, 2.17%) and after weighting (3.57% and 2.36%, respectively).

Figure 1 displays the mean per-patient costs for the selected AEs in SPARTAN and ARAMIS, obtained by multiplying the AE rates after weighting by the corresponding unit costs. The mean AE cost difference per patient was $1179 between apalutamide and the SPARTAN placebo arm (SPARTAN trial duration 43 months [7]) and $158 between darolutamide and the ARAMIS placebo arm (ARAMIS trial duration 48 months [8]). Thus, after weighting and adjusting for the trials' placebo arms, the mean total AE costs were $1021 higher for patients treated with apalutamide compared with darolutamide. The largest drivers of the per-patient cost differences were fracture (adjusted difference between apalutamide and darolutamide $416), hypertension ($143), and rash ($219). After excluding hypertension, which was associated with high treatment costs and large differences in the observed incidence between ARAMIS and SPARTAN, the results remained consistent with the primary findings. Specifically, the mean total AE costs per patient after weighting were $879 higher for patients treated with apalutamide versus darolutamide after excluding hypertension (apalutamide vs. SPARTAN placebo arm, $905; darolutamide vs. ARAMIS placebo, $26).

Sensitivity Analyses

In the sensitivity analysis of AEs in ARAMIS and SPARTAN, two additional AEs were included:

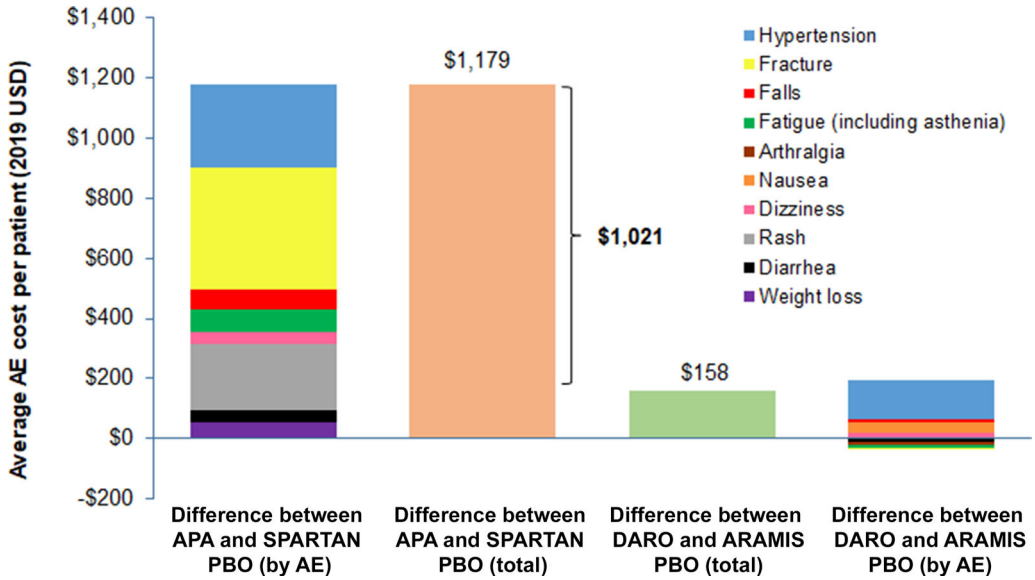

Fig. 1 Mean AE costs per patient for apalutamide and darolutamide adjusted for their trials' placebo arms. The bolded number (i.e., $1021) corresponds to the mean total AE cost difference for apalutamide compared to darolutamide, after weighting and adjusting for trials' placebo arms. *AE* adverse event, *APA* apalutamide, *DARO* darolutamide, *PBO* placebo, *USD* US dollars

hypothyroidism and mental-impairment disorder. However, these additions did not affect the cost difference for darolutamide versus apalutamide because the corresponding grade 3 and 4 AE rates that were used for the calculations were zero for all four treatment arms for both hypothyroidism and mental-impairment disorder.

The results of the sensitivity analysis varying the proportion (10% to 90%) of grade ≥ 3 AEs in ARAMIS and SPARTAN that would require hospitalization are presented in Table S2 in the supplementary material. The differences in costs between apalutamide and darolutamide assuming that only 75% or 50% of AEs required hospitalization were $769 and $516, respectively.

Darolutamide (ARAMIS) Versus Enzalutamide (PROSPER)

Sample Selection

In the MAIC, 553 patients in the placebo arm and 943 in the darolutamide arm were included from ARAMIS and considered for weighting. PROSPER included 468 and 933 patients in its placebo and enzalutamide arms, respectively.

Baseline Characteristics

Before weighting, several baseline characteristics differed between ARAMIS and PROSPER. After weighting, all baseline characteristics were balanced between the trial populations, and no differences remained between the trials post-weighting. The ESS for the ARAMIS placebo and darolutamide arms were $n = 395$ and $n = 580$, respectively (Table 3).

Primary Analysis

The rates and unit costs of selected grade ≥ 3 AEs for the primary analysis of ARAMIS and PROSPER, including the extracted AE rates from PROSPER and those before and after weighting in ARAMIS, are listed in Table 4. The three costliest AEs occurring in at least 10% of patients were fatigue not including asthenia ($13,284), hypertension including increased blood pressure ($10,926), and arthralgia ($7954). The most common AE across arms was hypertension including increased blood pressure, with higher rates in PROSPER

Table 3 Observed baseline characteristics in ARAMIS and PROSPER, before and after weighting

	Before weighting				After weighting			
	ARAMIS		PROSPER		ARAMIS		PROSPER	
	DARO *N* = 943 (%)	Placebo *N* = 553 (%)	ENZA *N* = 933 (%)	Placebo *N* = 468 (%)	DARO ESS = 580 (%)	Placebo ESS = 395 (%)	ENZA *N* = 933 (%)	Placebo *N* = 468 (%)
Age in years > PROSPER median	49.1	51.2	50.0	50.0	50.0	50.0	50.0	50.0
Region								
North America	11.2	13.6	15.1	13.5	15.1	13.5	15.1	13.5
Europe	65.2	62.6	49.1	49.6	49.1	49.6	49.1	49.6
Serum PSA level (ng/mL) > PROSPER median	43.6	48.1	50.0	50.0	50.0	50.0	50.0	50.0
PSA doubling time								
> PROSPER median	60.1	66.0	50.0	50.0	50.0	50.0	50.0	50.0
≤ 6 months	69.8	66.9	76.7	77.1	76.7	77.1	76.7	77.1
> 6 months	30.2	33.1	23.3	22.9	23.3	22.9	23.3	22.9
ECOG performance status								
0	68.2	70.7	80.2	81.8	80.2	81.8	80.2	81.8
1	31.8	29.3	19.8	18.2	19.8	18.2	19.8	18.2
Gleason score								
Low (2–4)	3.8	4.2	2.3	2.6	2.3	2.6	2.3	2.6
Medium (5–7)	54.3	52.3	52.6	49.1	52.6	49.1	52.6	49.1
High (8–10)	38.9	40.1	40.8	44.2	40.8	44.2	40.8	44.2
Use of bone-sparing agent	3.2	5.8	11.3	10.3	11.3	10.3	11.3	10.3
Disease status								
Metastatic	5.3	7.1	2.5	3.0	2.5	3.0	2.5	3.0
Non-metastatic	94.7	92.9	97.5	97.0	97.5	97.0	97.5	97.0

DARO darolutamide, *ECOG* Eastern Cooperative Oncology Group, *ENZA* enzalutamide, *ESS* effective sample size, *PSA* prostate-specific antigen

Table 4 Rates and unit costs of selected grade ≥ 3 AEs for ARAMIS and PROSPER (primary analysis)

	AE unit costs	AE rate (%)					
		PROSPER		ARAMIS			
				Before weighting		After weighting	
		ENZA	PROSPER placebo	DARO	ARAMIS placebo	DARO	ARAMIS placebo
Hypertension (including increased blood pressure)	$10,926	4.62	2.37	3.29	2.35	3.54	1.83
Fall	$6707	1.29	0.65	0.85	0.54	0.76	0.21
Fatigue (not including asthenia)	$13,284	2.90	0.65	0.42	0.90	0.86	0.78
Arthralgia	$7954	0.11	0.22	0.32	0.36	0.35	0.37
Nausea	$7081	0.32	0.00	0.21	0.00	0.28	0.00
Dizziness	$6513	0.43	0.00	0.21	0.18	0.18	0.10
Diarrhea	$7744	0.32	0.43	0.11	0.18	0.10	0.23
Weight loss	$6446	0.22	0.00	0.00	0.00	0.00	0.00

All-cause grade ≥ 3 AEs with corresponding any-grade AE reported in at least 10% of patients
Costs in 2019 US dollars
AE adverse event, *DARO* darolutamide, *ENZA* enzalutamide

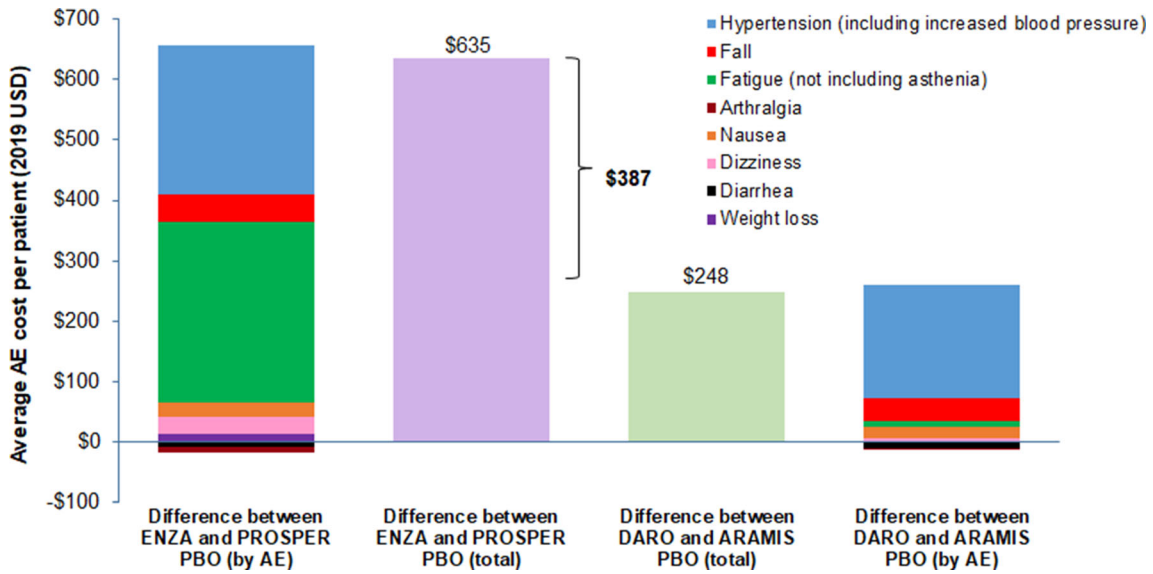

Fig. 2 Mean AE costs per patient for enzalutamide and darolutamide adjusted for their trials' placebo arms (primary analysis). The bolded number (i.e., $387) corresponds to the mean total AE cost difference for enzalutamide compared to darolutamide, after weighting and adjusting for trials' placebo arms. *AE* adverse event, *DARO* darolutamide, *ENZA* enzalutamide, *PBO* placebo, *USD* US dollars

Table 5 Rates and unit costs of selected grade ≥ 3 AEs for ARAMIS and PROSPER (sensitivity analysis)

	AE unit cost	AE rate (%)					
		PROSPER		ARAMIS			
				Before weighting		After weighting	
		ENZA	PROSPER placebo	DARO	ARAMIS placebo	DARO	ARAMIS placebo
Hypertension (including increased blood pressure)	$10,926	4.62	2.37	3.29	2.35	3.54	1.83
Fall	$6707	1.29	0.65	0.85	0.54	0.76	0.21
Fatigue (not including asthenia)	$13,284	2.90	0.65	0.42	0.90	0.86	0.78
Arthralgia	$7954	0.11	0.22	0.32	0.36	0.35	0.37
Nausea	$7081	0.32	0.00	0.21	0.00	0.28	0.00
Dizziness	$6513	0.43	0.00	0.21	0.18	0.18	0.10
Diarrhea	$7744	0.32	0.43	0.11	0.18	0.10	0.23
Weight loss	$6446	0.22	0.00	0.00	0.00	0.00	0.00
Urinary retention	$7578	0.43	1.08	1.59	1.99	1.60	1.55
Urinary tract infection	$7959	0.75	0.65	0.64	0.54	0.51	0.34
Back pain	$11,784	0.22	0.22	0.42	0.00	0.37	0.00
Asthenia	$10,513	1.18	0.22	0.21	0.36	0.09	0.26
Mental-impairment disorder	$11,977	0.11	0.00	0.21	0.00	0.09	0.00
Constipation	$6688	0.22	0.43	0.00	0.00	0.00	0.00
Headache	$7676	0.22	0.00	0.00	0.18	0.00	0.07

All-cause grade ≥ 3 AEs with corresponding any-grade AE reported in at least 5% of patients
Costs in 2019 US dollars
AE adverse event, *DARO* darolutamide, *ENZA* enzalutamide

(enzalutamide, 4.62%; placebo, 2.37%) compared with ARAMIS both before (darolutamide, 3.29%; placebo, 2.35%) and after weighting (3.54% and 1.83%, respectively).

Figure 2 shows that the mean AE cost difference per patient was $635 between enzalutamide and PROSPER placebo (PROSPER trial duration, 43 months [6]) and was $248 between darolutamide and ARAMIS placebo (ARAMIS trial duration, 48 months [8]). Thus, the mean total AE costs were $387 higher for enzalutamide compared with darolutamide after weighting and adjusting for the trials' placebo arms. The largest drivers of the cost difference were fatigue not including asthenia (adjusted difference between enzalutamide and darolutamide, $290) and hypertension including increased blood pressure ($60).

Sensitivity Analyses

In the sensitivity analysis of AEs in ARAMIS and PROSPER, seven additional AEs were included: back pain, constipation, urinary tract infection, headache, asthenia, urinary retention, and mental-impairment disorder (Table 5). The mean grade ≥ 3 AE cost difference per patient was $711 between enzalutamide and PROSPER placebo (PROSPER trial duration 43 months [6])

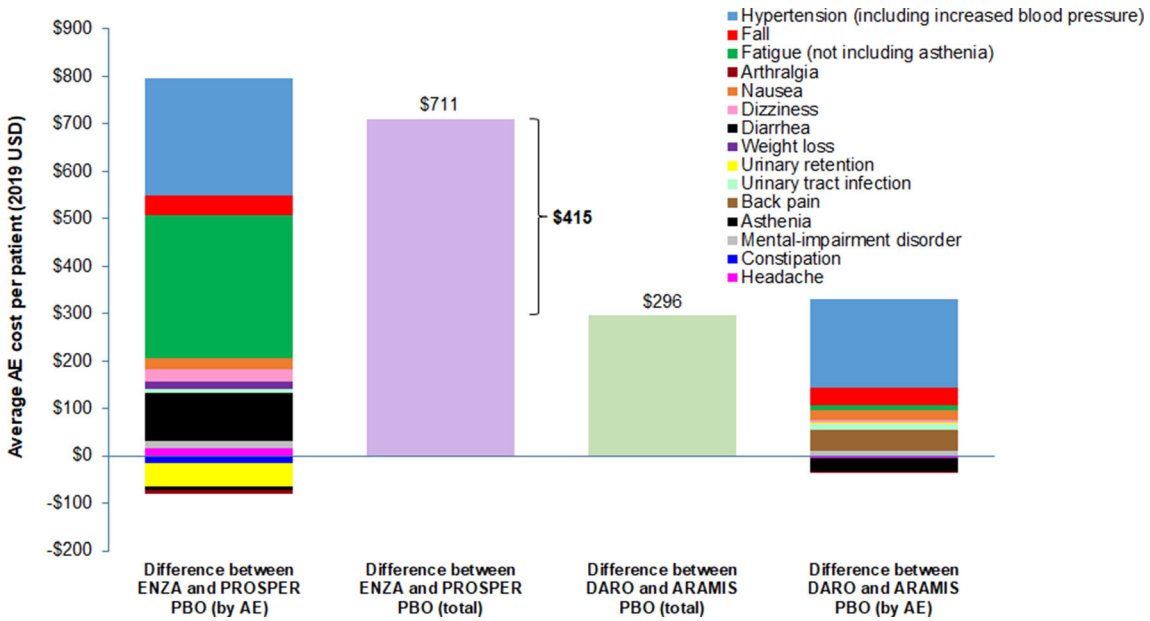

Fig. 3 Mean AE costs per patient for enzalutamide and darolutamide adjusted for their trials' placebo arms (sensitivity analysis). The bolded number (i.e., $415) corresponds to the mean total AE cost difference for enzalutamide compared to darolutamide, after weighting and adjusting for trials' placebo arms. *AE* adverse event, *DARO* darolutamide, *ENZA* enzalutamide, *PBO* placebo, *USD* US dollars

and $296 between darolutamide and ARAMIS placebo (ARAMIS trial duration 48 months [8]) (Fig. 3). Thus, the mean total AE costs were $415 higher for enzalutamide compared with darolutamide after weighting and adjusting for the trials' placebo arms. In the sensitivity analysis, the largest drivers of the cost difference were fatigue not including asthenia ($290), asthenia ($120), and hypertension including increased blood pressure ($60).

The results of the sensitivity analysis varying the proportions (10% to 90%) of grade ≥ 3 AEs in ARAMIS and PROSPER that would require hospitalization are presented in Table S3 (main analysis) and Table S4 in the supplementary material (sensitivity analysis of grade ≥ 3 AEs with corresponding any-grade AE reported in at least 5% of patients). The differences in costs between enzalutamide and darolutamide assuming that only 75% or 50% of AEs required hospitalization were $293 and $196, respectively, in the main analysis, and $314 and $211 in the sensitivity analysis.

DISCUSSION

This study utilized established MAIC methodology to adjust for cross-trial differences between the ARAMIS, SPARTAN, and PROSPER trials [13] and compare the costs of grade ≥ 3 AEs associated with darolutamide versus apalutamide and enzalutamide for the treatment of patients with nmCRPC. Using patient-level data from the pivotal ARAMIS trial of darolutamide, and published data from the pivotal trials of apalutamide and enzalutamide (SPARTAN and PROSPER, respectively), we assessed patient baseline characteristics and adjusted AE rates prior to AE cost calculations. The results indicated that, after weighting, estimated mean costs for grade ≥ 3 AEs, assumed to require hospitalization, were lower for patients with nmCRPC treated with darolutamide than for patients treated with apalutamide (by $1021) or enzalutamide (by $387 to $415). The largest contributors to the AE cost differences compared to darolutamide were fracture, hypertension, and rash for apalutamide, and fatigue, not

including asthenia, and hypertension for enzalutamide.

The results of this analysis provide additional insights into the potential safety and tolerability profile advantages of darolutamide over apalutamide and enzalutamide and are consistent with prior comparisons of these therapies, noting the favorable safety profile of darolutamide in nmCRPC [13]. The benefits of darolutamide are also sustained over the trial period and apply to sicker patients at baseline, as shown in an NMA of ARAMIS (darolutamide), SPARTAN (apalutamide), and PROSPER (enzalutamide) by Maggi et al. [11]. That study reported that the rates of grade 3–4 AEs remained stable in ARAMIS but increased over time in PROSPER and SPARTAN, despite worse baseline prognostic scores among ARAMIS patients [11]. In addition, the 2021 MAIC by Halabi et al. comparing any-grade AEs of darolutamide versus apalutamide or enzalutamide found that, after adjusting for cross-trial differences, darolutamide was associated with a more favorable tolerability profile than the comparators [13]. After additional adjustments for differences in the trials' AE assessment schedules (i.e., SPARTAN's more frequent assessments), Halabi et al. noted insubstantial increases in AEs as a result.

Safety and tolerability are important considerations for therapy selection in nmCRPC for patients, caregivers, and healthcare providers alike [23, 24], with reductions in the risk of fracture, fatigue, and cognitive problems listed as the top concerns in a recent survey of treating physicians [23]. In this study, darolutamide was associated with a lower direct medical cost burden related to AEs in nmCRPC compared with apalutamide or enzalutamide, resulting from lower incidence of the costliest AEs with darolutamide. The AEs that were the primary cost drivers in the present analyses (i.e., fracture, rash, fatigue) align with those that physicians, patients, and caregivers desired to avoid [23, 24].

As a result of the recent FDA approval of darolutamide, real-world studies of AE incidence or the economic burden of AEs associated with novel ARIs for nmCRPC are currently limited to enzalutamide and/or apalutamide [25–29]. However, preliminary research has noted that rates of treatment discontinuation of enzalutamide and apalutamide due to AEs are higher in the real world compared to those in their respective trials [28], namely, 32% higher for apalutamide and 49% higher for enzalutamide (median follow-up 18.7 and 12.1 months, respectively). Thus, the economic burden of AE associated with these two therapies may be even greater than that indicated by the present findings based on AE incidence in their pivotal trials.

The current study has several strengths. First, the MAICs permitted a fair comparison of darolutamide vs. apalutamide and enzalutamide via the adjustment of observed cross-trial differences between ARAMIS and the SPARTAN and PROSPER trials, respectively. MAICs use IPD from trials of one treatment to match baseline summary statistics reported from trials of comparator treatments, using an approach similar to propensity score weighting. After weighting, outcomes can then be compared across balanced trial populations. Second, the use of ARAMIS IPD enabled granularity in data handling for greater comparability with SPARTAN and PROSPER (e.g., excluding patients with history of seizure). Third, unit costs were procured from reliable public sources in the USA (i.e., HCUP) to provide an accurate estimation of AE-related costs. Finally, the findings contribute to the understanding of the comparative AE costs associated with darolutamide, apalutamide, and enzalutamide, which can help inform ideal treatment selection for patients with nmCRPC.

This study also has limitations, some of which are inherent to indirect treatment comparisons. First, AEs in SPARTAN (other than AEs of special interest) were only reported if they occurred in at least 15% of patients in either the apalutamide or placebo group (or if they were AEs of special interest); as a result, it is possible that additional AEs occurring in at least 10% but less than 15% of patients in an arm in SPARTAN were not included because of lack of data availability. Second, only known baseline factors that were consistently reported across trials were included as matching covariates in the MAICs; results may be impacted if factors that

are treatment effect modifiers or prognostic of the outcomes could not be included as matching variables. Third, this analysis focused only on costs associated with all-cause grade ≥ 3 AEs because HCUP data are available for hospitalizations only and grade ≥ 3 AEs were assumed to require hospitalization, while grade 1 and 2 AEs would not incur hospitalization costs. As a result, this analysis may underestimate the total treatment-related AE costs because of the exclusion of grade 1 and 2 AEs. However, using grade ≥ 3 AEs to model costs in cancer by assuming that these AEs would require hospitalization is a common technique in the literature [30–32]. Fourth, the difference in inpatient costs is likely to be sensitive to the proportion of grade ≥ 3 AEs that required hospitalization, as explored in the sensitivity analyses assuming that different proportions of grade ≥ 3 AEs would require hospitalization. Fifth, only the proportions of patients with each AE were reported in the trials, which may also lead to underestimation of the total treatment-related AE costs (i.e., it was assumed that for patients with a selected AE, only one instance occurred, although multiple instances of the same AE and/or hospitalizations may have occurred during the trial). Furthermore, confidence intervals for the total cost estimates are not provided as a result of data limitations that make assessment of correlations between AEs infeasible. Sixth, costs were obtained from HCUP data describing male patients who had diagnoses for the selected AEs in inpatient settings. The estimated costs may differ for the general population of patients with nmCRPC if they experience these selected AEs differently from the HCUP population. Seventh, the results of the study may not be generalizable beyond the study sample. Finally, IPD were not available for the trials of apalutamide or enzalutamide; therefore the rates of AEs were obtained from their primary publications.

CONCLUSIONS

After adjusting for cross-trial differences with MAIC, patients with nmCRPC treated with darolutamide incurred lower mean costs related to AEs requiring hospitalization than patients treated with apalutamide in SPARTAN (by $1021) or enzalutamide in PROSPER (by $387), as determined using HCUP costing data. The comparatively lower AE costs of darolutamide reflect the lower incidence of costly grade ≥ 3 AEs such as a skeletal fracture. Minimizing the AE-related direct medical costs of novel ARI treatment is an important component of optimizing the economic efficiency of treating nmCRPC. The present results provide valuable insight into an important class of AEs, albeit within the confines of an indirect treatment comparison across the three trials. Further research is needed to investigate the full spectrum of potential downstream clinical and economic consequences associated with all grades of AEs related to treatments for nmCRPC.

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Prior Presentation. Portions of this research have been presented in poster form at the AMCP Annual Meeting on April 12–16, 2021 (virtual).

Compliance with Ethics Guidelines. As this post hoc analysis was based on previously collected data, no institutional board review was required. The research was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Deidentified data for darolutamide were provided by Bayer to the authors for use in this study and comparator data were sourced from publicly available literature.

Data Availability. Data are not available to other researchers as the data from the ARAMIS trial were collected in a proprietary database; summary data from the SPARTAN and PROSPER trials are publicly available.

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