



# Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic, castration-resistant prostate cancer (PROSPER): a multicentre, randomised, double-blind, phase 3 trial

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## Summary

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**Background** In the PROSPER trial, enzalutamide significantly improved metastasis-free survival in patients with non-metastatic, castration-resistant prostate cancer. Here, we report the results of patient-reported outcomes of this study.

**Methods** In the randomised, double-blind, placebo-controlled, phase 3 PROSPER trial, done at 254 study sites worldwide, patients aged 18 years or older with non-metastatic, castration-resistant prostate cancer and a prostate-specific antigen doubling time of up to 10 months were randomly assigned (2:1) via an interactive voice web recognition system to receive oral enzalutamide (160 mg per day) or placebo. Randomisation was stratified by prostate-specific antigen doubling time and baseline use of a bone-targeting agent. The primary endpoint was metastasis-free survival, reported elsewhere. Secondary efficacy endpoints, reported here, were pain progression (assessed by the Brief Pain Inventory Short Form [BPI-SF] questionnaire) and health-related quality of life (assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-PR25], the EuroQoL 5-Dimensions 5-Levels health questionnaire visual analogue scale [EQ-5D-FL, EQ-VAS], and the Functional Assessment of Cancer Therapy-Prostate [FACT-P] questionnaires). Patients completed questionnaires at baseline, week 17, and every 16 weeks thereafter until treatment discontinuation. We used predefined questionnaire thresholds to identify clinically meaningful changes. Enrolment for PROSPER is complete and follow-up continues. This trial is registered with ClinicalTrials.gov, number NCT02003924.

**Findings** Between Nov 26, 2013, and June 28, 2017, 1401 patients were enrolled and randomly assigned to receive enzalutamide ( $n=933$ ) or placebo ( $n=468$ ). Median follow-up was 18.5 months (IQR 10.7–29.2) in the enzalutamide group and 15.1 months (7.4–25.9) in the placebo group. Patient-reported outcome scores at baseline were similar between groups. Changes in least squares mean from baseline to week 97 favoured enzalutamide versus placebo for FACT-P social and family wellbeing (0.30 [95% CI –0.25 to 0.85] vs –0.64 [–1.51 to 0.24]; difference 0.94 [95% CI 0.02 to 1.85];  $p=0.045$ ) and disfavoured enzalutamide versus placebo for EORTC QLQ-PR25 hormonal treatment-related symptoms (1.55 [0.26 to 2.83] vs –1.83 [–3.86 to 0.20]; difference 3.38 [1.24 to 5.51];  $p=0.0020$ ); neither of these changes were clinically meaningful. No significant differences were observed between treatments for changes from baseline to week 97 in any other patient-reported outcome score. Time to clinically meaningful pain progression as assessed by BPI-SF pain severity was longer with enzalutamide than with placebo (median 36.83 months, [95% CI 34.69 to not reached [NR] vs NR; hazard ratio [HR] 0.75 [95% CI 0.57 to 0.97];  $p=0.028$ ); there was no significant difference for BPI-SF item 3 or pain interference. Time to clinically meaningful symptom worsening was longer with enzalutamide than with placebo for EORTC QLQ-PR25 urinary symptoms (median 36.86 months [95% CI 33.35 to NR] vs 25.86 [18.53 to 29.47]; HR 0.58 [95% CI 0.46 to 0.72];  $p<0.0001$ ) and bowel symptoms (33.15 [29.50 to NR] vs 25.89 [18.43 to 29.67]; 0.72 [0.59 to 0.89];  $p=0.0018$ ), and clinically meaningful health-related quality of life as assessed by FACT-P total score (22.11 [18.63 to 25.86] vs 18.43 [14.85–19.35]; 0.83 [0.69 to 0.99];  $p=0.037$ ), emotional wellbeing (36.73 [33.12 to 38.21] vs 29.47 [22.18 to 33.15]; 0.69 [0.55 to 0.86];  $p=0.0008$ ), and prostate cancer subscale (18.43 [14.85 to 18.66] vs 14.69 [11.07 to 16.20]; 0.79 [0.67 to 0.93];  $p=0.0042$ ), although there was no significant difference for other FACT-P scores. Time to clinically meaningful deterioration in EORTC QLQ-PR25 hormonal treatment-related symptoms was shorter with enzalutamide than with placebo (median 33.15 months [95% CI 29.60 to NR] vs 36.83 [29.47 to NR]; HR 1.29 [95% CI 1.02 to 1.63];  $p=0.035$ ). Time to deterioration of EQ-VAS was significantly longer for enzalutamide than for placebo (median 22.11 months [95% CI 18.46 to 25.66] vs 14.75 [11.07 to 18.17]; HR 0.75 [95% CI 0.63 to 0.90];  $p=0.0013$ ).

**Interpretation** Patients with non-metastatic, castration-resistant prostate cancer receiving enzalutamide had longer metastasis-free survival than did those who received placebo, while maintaining low pain levels and prostate cancer

symptom burden and high health-related quality of life. Enzalutamide showed a clinical benefit by delaying pain progression, symptom worsening, and decrease in functional status, compared with placebo. These findings suggest that enzalutamide is a treatment option that should be discussed with patients presenting with high-risk, non-metastatic, castration-resistant prostate cancer.

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## Introduction

Prostate cancer is the second most commonly diagnosed cancer worldwide, with more than 300 000 men dying from advanced forms of the disease each year.<sup>1</sup> Castration-resistant prostate cancer refers to the stage when the tumour is no longer responsive to androgen deprivation therapy, despite castration concentrations of testosterone.<sup>2</sup> Approximately a third of patients with prostate-specific antigen recurrence after radical treatment will develop castration-resistant prostate cancer.<sup>3</sup> The exact proportion of patients who progress to castration-resistant prostate cancer before or after metastasis is not known, but it is estimated that more than 50% of patients with non-metastatic castration-resistant prostate cancer will develop metastases within 3 years.<sup>4</sup> Once metastases occur, the disease becomes incurable; survival is estimated to be less than 18 months, although more recent studies indicate it to be approximately 30 months.<sup>5</sup>

Until recently, no treatments with proven efficacy had been approved for non-metastatic, castration-resistant prostate cancer. Clinical guidelines recommended continuation of androgen deprivation therapy and, in some cases, secondary hormonal treatments (first-generation anti-androgens, ketoconazole, and oestrogens).<sup>6–8</sup> However, the evidence of efficacy for these secondary hormonal treatments was restricted to prostate-specific antigen response, mainly in phase 2 trials of castration-resistant prostate cancer.<sup>9</sup> The new-generation androgen receptor signalling inhibitors enzalutamide and apalutamide have shown a clinical benefit in randomised, placebo-controlled, phase 3 trials of patients with non-metastatic, castration-resistant prostate cancer.<sup>10,11</sup> In the PROSPER trial, enzalutamide treatment reduced the risk of metastases or death compared with placebo (hazard ratio [HR] 0·29; 95% CI 0·24–0·35;  $p < 0·0001$ ).<sup>10</sup> Similar results were obtained with apalutamide in the SPARTAN trial (HR 0·28;

## Research in context

### Evidence before this study

There are insufficient clinical trial data about potential treatments for non-metastatic, castration-resistant prostate cancer and how these treatments and the disease affect patients' health-related quality of life (HRQOL). We searched PubMed for papers published up to Feb 1, 2018 (with no prespecified start date), to identify articles in English with the terms "nonmetastatic castration-resistant prostate cancer" OR "non-metastatic castration resistant prostate cancer" AND "quality of life" OR "patient-reported outcomes" OR "pain" OR "symptoms". We identified 71 publications, two of which we deemed relevant. A single-arm phase 2 study (BATMAN) assessed bipolar androgen therapy in patients with non-metastatic castration-resistant prostate cancer. Improvements in quality of life (assessed with the 36-item Short Form Health Survey, the Functional Assessment of Cancer Therapy, and the International Index of Erectile Function) were observed after 6 months of bipolar androgen therapy, complementing a reduction in prostate-specific antigen levels after 18 months of treatment. The double-blind, placebo-controlled phase 3 study (SPARTAN) compared apalutamide to placebo in patients with non-metastatic, castration-resistant prostate cancer. Improvements in health-related quality of life (assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Functional

Assessment of Cancer Therapy-Prostate, and a visual analogue scale) were stable over 29 months of follow-up in patients who received a non-steroidal anti-androgen.

### Added value of this study

In PROSPER, patients were generally asymptomatic and had low symptom burden and good HRQOL at baseline; these characteristics were similar to those of men of a similar age without prostate cancer. Compared with placebo, enzalutamide increased the time to clinically meaningful pain progression and deterioration in HRQOL, except for hormonal treatment-related symptoms, for which enzalutamide decreased time to deterioration versus placebo.

### Implications of all the available evidence

Because patients with non-metastatic, castration-resistant prostate cancer generally have low levels of pre-treatment pain and favourable HRQOL compared with patients with advanced disease, treatments should aim to improve clinical outcomes while maintaining pain control and HRQOL. The efficacy, tolerability, and HRQOL profile shown in this study suggest that enzalutamide represents a treatment option for patients with non-metastatic, castration-resistant prostate cancer. Further analyses are needed to determine potential associations between pain, HRQOL, and disease progression in non-metastatic, castration-resistant prostate cancer.

95% CI 0·23–0·35;  $p < 0\cdot001$ , vs placebo).<sup>11</sup> On the basis of these results, both enzalutamide and apalutamide were recently approved by the US Food and Drug Administration for non-metastatic, castration-resistant prostate cancer.<sup>12</sup>

Overall survival and disease progression outcomes are used to investigate new treatment approaches, but to be truly valuable to patients, new treatments should not only delay disease progression, but also maintain or, ideally, improve, health-related quality of life (HRQOL) without worsening symptoms.<sup>13</sup> HRQOL can be prognostic of survival in metastatic, castration-resistant prostate cancer,<sup>14,15</sup> a finding that was supported by analysis of data from two phase 3 studies of enzalutamide in patients with metastatic castration-resistant prostate cancer.<sup>16,17</sup> Additionally, HRQOL is central to cost-utility analysis in many countries and is increasingly influencing reimbursement decisions, especially for oncology treatments.<sup>18</sup>

Here, we report the results of the patient-reported outcome measures used in the PROSPER trial to investigate pain progression and the effect of prostate cancer-related symptoms on HRQOL in men with non-metastatic, castration-resistant prostate cancer who were treated with enzalutamide.

## Methods

### Study design and participants

Full details on the study design, patient eligibility criteria, and conduct of the study have been reported elsewhere.<sup>10</sup> Briefly, PROSPER was a multinational, randomised, double-blind, placebo-controlled, phase 3 study done at 254 centres (appendix pp 2–10) that assessed the efficacy and safety of enzalutamide versus placebo in men aged 18 years or older with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell, or small-cell features. Inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, testosterone concentrations of 50 ng/dL ( $\leq 1\cdot73$  nmol/L) at screening or lower, prostate-specific antigen doubling time of 10 months or less, and no previous or present evidence of metastatic disease as assessed by CT or MRI for soft tissue disease and whole-body radionuclide bone scan for bone disease. For patients receiving bisphosphonates or denosumab, doses must have been stable for at least 4 weeks before randomisation. Progressive disease while receiving androgen deprivation therapy at enrolment was defined as a minimum of three increasing prostate-specific antigen values assessed by a local laboratory, with an interval of at least 1 week between each determination. All patients were also required to maintain androgen deprivation therapy during the study, either by use of a gonadotropin-releasing hormone agonist or antagonist, or a previous bilateral orchiectomy.

Patients were excluded if they had received cytotoxic chemotherapy, aminoglutethimide, ketoconazole,

abiraterone acetate, or enzalutamide for the treatment of prostate cancer, or had participated in a clinical trial of an investigational agent that inhibited the androgen receptor or androgen synthesis (unless treatment was placebo). Patients were also excluded if they had received treatment with hormonal therapy or biological therapy for prostate cancer (other than approved bone-targeting agents and gonadotropin-releasing hormone agonist or antagonist therapy) within 4 weeks of randomisation; had used an investigational agent within 4 weeks of randomisation; or had any concurrent disease, infection, or comorbid condition that, in the opinion of the investigator or medical monitor, interfered with the ability of the patient to participate in the trial, placed the patient at undue risk, or complicated the interpretation of data.

Each patient provided written, informed consent, in compliance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice, US Code of Federal Regulations for Protection of Human Subjects, and local regulations. The independent ethics committee or institutional review board for each study site reviewed the ethical, scientific, and medical appropriateness of the study before it was done. A copy of the trial protocol is available online.

### Randomisation and masking

Patients were randomly assigned (2:1) to receive enzalutamide or placebo via an interactive voice web recognition system, which assigned an identification number to each patient and a blinded study drug bottle number according to the randomisation code. Randomisation was stratified by prostate-specific antigen doubling time ( $< 6$  months vs  $\geq 6$  months) and baseline use of a bone-targeting agent (yes vs no). The investigator, study coordinator(s), patients, sponsor, and sponsor's representatives were masked to the identity of the randomised drug assignment. Study drug assignment was to be revealed only for reasons relating to patient safety or when crucial therapeutic decisions were contingent on knowing the assigned study drug. Study drug accountability was done to document compliance with the blinded dosing regimen. Patients were asked to bring all used and unused blinded study drug, including packaging, to study visits. Unreturned capsules were considered to have been taken. Treatment compliance was measured by the number of capsules taken during the study divided by the expected number of capsules, multiplied by 100%.

### Procedures

The daily dose of enzalutamide or placebo was 160 mg per day, given in four capsules (40 mg each) by mouth. Patients self-administered the masked study drug once daily, with or without food, starting on day 1. Radiographic assessments were approximately every 16 weeks; radiographic progression for soft tissue disease was defined by the Response Evaluation Criteria in Solid Tumors, version 1.1. Patients continued study drug until

For the protocol see [http://stellasoncologyprotocols.com/PROSPER\\_final\\_protocol](http://stellasoncologyprotocols.com/PROSPER_final_protocol)

See Online for appendix

the appearance of distant metastasis (metastatic bone lesions, but not soft tissue lesions) were confirmed with a second imaging method. Radiographic metastasis was confirmed by independent central radiology review before stopping radiographic imaging.

Patients completed patient-reported outcome assessments at baseline, week 17, and every 16 weeks thereafter while receiving treatment. For patients who discontinued study treatment, patient-reported outcome data continued to be collected every 16 weeks during long-term follow-up for patients who attended these visits. The patient-reported outcomes were collected at the study sites using self-reported forms and were used to assess the effect of enzalutamide versus placebo on pain, functioning, prostate cancer-related symptoms, HRQOL, and overall health status.

The Brief Pain Inventory Short Form (BPI-SF) is a validated nine-item questionnaire commonly used to assess the severity of and interference from pain.<sup>19</sup> Items 3, 4, 5, and 6 evaluate worst pain (item 3), least pain (item 4), and average pain (item 5) in the previous 24 h, and pain now (item 6), on a scale ranging from 0 (no pain) to 10 (pain as bad as one can imagine). Individual patient scores were used to calculate a composite pain severity score as an average score of these four items. The interference score assesses the degree to which pain interferes with daily activities, from 0 (no interference) to 10 (complete interference), and is the average of seven scores: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-PR25)<sup>20</sup> was developed to assess quality of life in patients with prostate cancer. The questionnaire includes questions to assess the effect of urinary symptoms (eight items), bowel symptoms (four items), and hormonal treatment-related symptoms (six items) over the previous week. Each item in the subscales is scored from 1 to 4 (1=not at all, 2=a little, 3=quite a bit, and 4=very much), in which higher scores reflect a greater effect of symptoms.

The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire (version 4)<sup>21</sup> reports 27 cancer-specific items in four domains (physical wellbeing, social or family wellbeing, emotional wellbeing, and functional wellbeing) and 12 prostate cancer-specific items in the prostate cancer subscale to assess function during the previous 7 days. A summary prostate cancer pain subscale and FACT-P total are also calculated. Each item is rated on a Likert-type scale of 0–4 (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much), for which higher scores indicate better HRQOL.

The European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) health questionnaire visual analogue scale (EQ-VAS)<sup>22</sup> is a standardised questionnaire for measuring generic health status. Patients rate their current health on a vertical scale ranging from 0 (worst imaginable) to 100 (best imaginable).

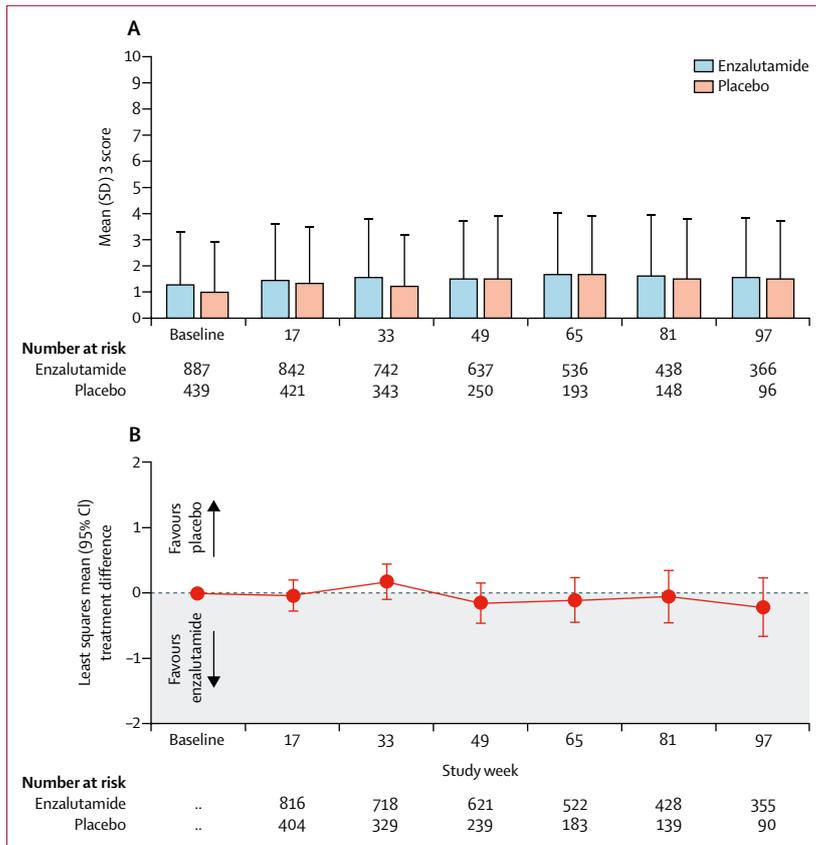
	Enzalutamide group (n=933)	Placebo group (n=468)
Age, years (median [range])	74 (50–95)	73 (53–92)
<75 years	489 (52%)	267 (57%)
≥75 years	444 (48%)	201 (43%)
Geographical region		
Europe	458 (49%)	232 (50%)
North America	141 (15%)	63 (13%)
Other	334 (36%)	173 (37%)
Disease status*		
Non-metastatic	910 (98%)	454 (97%)
Metastatic	23 (2%)	14 (3%)
ECOG performance status		
0	747/932 (80%)	382/467 (82%)
1	185/932 (20%)	85/467 (18%)
Prostate-specific antigen doubling time†		
<6 months	719 (77%)	361 (77%)
≥6 months	214 (23%)	107 (23%)
Previous or current use of bone-targeting agents†		
Yes	96 (10%)	49 (10%)
No	837 (90%)	419 (90%)
Pain at its worst, at baseline (BPI-SF item 3)		
Asymptomatic (score 0)	580/887 (65%)	303/439 (69%)
Mildly symptomatic (score 1–4)	206/887 (23%)	101/439 (23%)
Moderately symptomatic (score 5–6)	72/887 (8%)	20/439 (5%)
Severely symptomatic (score 7–10)	29/887 (3%)	15/439 (3%)
Mean BPI-SF scores at baseline		
Item 3: pain at its worst	n=887; 1.24 (2.09)	n=439; 1.01 (1.94)
Pain severity	n=887; 0.93 (1.50)	n=439; 0.71 (1.35)
Pain interference	n=887; 0.75 (1.47)	n=439; 0.59 (1.43)
Mean EORTC QLQ-PR25 at baseline		
Bowel symptoms and function	n=884; 5.14 (8.39)	n=439; 4.65 (7.70)
Hormonal treatment-related symptoms	n=884; 14.92 (12.50)	n=439; 15.79 (13.30)
Urinary symptoms and problems	n=884; 20.69 (17.55)	n=439; 20.02 (17.68)
Mean FACT-P at baseline		
Physical wellbeing	n=887; 25.02 (3.32)	n=439; 25.28 (3.23)
Functional wellbeing	n=887; 19.99 (5.17)	n=439; 20.14 (5.15)
Emotional wellbeing	n=887; 19.18 (3.54)	n=439; 19.16 (3.64)
Social and family wellbeing	n=887; 20.69 (5.57)	n=439; 20.73 (5.12)
Prostate cancer subscale	n=887; 34.67 (6.13)	n=439; 35.47 (5.73)
Prostate cancer pain subscale	n=887; 13.16 (3.44)	n=439; 13.56 (3.15)
FACT-P total score	n=887; 119.54 (17.75)	n=439; 120.79 (16.73)
Mean EQ-5D-5L at baseline		
EQ-VAS	n=884; 76.17 (16.92)	n=439; 77.53 (15.97)

Data are n (%), n/N (%), median (range), or n; mean (SD). ECOG=Eastern Cooperative Oncology Group. BPI-SF=Brief Pain Inventory Short Form. EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire. FACT-P=Functional Assessment of Cancer Therapy-Prostate. EQ-5D-5L=European Quality of Life 5-Dimensions 5-Levels health questionnaire. EQ-VAS=EuroQoL 5-Dimensions 5-Levels health questionnaire visual analogue scale. \*Patients may have been determined by the blinded independent central review to be metastatic after entry into the study. †Data were collected from interactive voice web recognition system; previously published data<sup>19</sup> were collected from case report forms. ‡Percentages are calculated based on the number of patients with non-missing data.

**Table 1: Baseline characteristics**

## Outcomes

The primary endpoint was metastasis-free survival, as reported elsewhere. Secondary endpoints, also previously



**Figure 1: Changes in BPI-SF item 3 (pain at its worst)**  
 (A) Scores by study visit. (B) Least squares mean treatment difference in change from baseline. BPI-SF=Brief Pain Inventory Short Form.

reported,<sup>10</sup> included time to prostate-specific antigen progression; prostate-specific antigen response; time to the first use of subsequent antineoplastic therapy; time to first use of cytotoxic chemotherapy; overall survival; chemotherapy-free, disease-specific survival; quality of life assessments (time to deterioration of FACT-P score); and safety. Here we report time to pain progression (assessed with the BPI-SF questionnaire) and HRQOL (assessed with the EORTC QLQ-PR25, EQ-5D-5L, and FACT-P questionnaires) from baseline to week 97.

**Statistical analysis**

The trial size was calculated on the basis of estimates related to the primary endpoint of metastasis-free survival, reported previously,<sup>10</sup> and was not specifically powered for the secondary patient-reported outcome endpoints reported here. 440 metastasis-free survival events provided 90% power to detect a target HR of 0.72, on the basis of a two-sided log-rank test and an overall significance level of 0.05, and non-uniform accrual of 0.25 patients per month, per site. The trial was stopped after these thresholds were reached. A sample size of approximately 1440 patients was targeted to be randomised. We used data from the cutoff date of

June 28, 2017, for our analyses of patient-reported outcome endpoints.

Analyses were done in the intention-to-treat population (ie, all patients randomly assigned to study treatment). We calculated completion of each planned assessment timepoint for all questionnaires as the number of patients returning evaluable forms divided by the total number of patients expected to complete the patient-reported outcome assessment at the study visit. A form was defined as evaluable if it contained answers to at least the number of items required to calculate the corresponding scale (FACT-P ≥80% of items completed; EORTC QLQ-PR25 and BPI-SF ≥50% items completed; and 100% of EQ-5D-5L or EQ-VAS items completed).<sup>19,20,22</sup>

To estimate longitudinal changes from baseline in patient-reported outcome scores, we used a mixed-effects model for repeated measures, controlling for the baseline covariates prostate-specific antigen doubling time, baseline use of a bone-targeting agent, age, ECOG performance status, number of previous hormonal therapies, time from initial diagnosis to randomisation, and baseline patient-reported outcome score. Time was included in the model as a categorical variable and we used an unstructured variance-covariance matrix to model the covariance structure among each patient's repeated measures. Mixed-model repeated measures analyses use all available data and assume that missing observations are missing at random. To address the possibility that missing data were not missing at random, we also did sensitivity analyses using a pattern mixture model.

The primary hypothesis tested the difference between least squares mean change from baseline to week 97. The timepoint of week 97 was prespecified and based on the assumed median metastasis-free survival for the placebo group to reduce the effect of missing data due to treatment discontinuation. The median metastasis-free survival for the placebo group was informed by historical data for similar patient populations.<sup>23,24</sup>

When assessing study questionnaires, a negative value for the least squares mean difference would favour enzalutamide over placebo for BPI-SF scores and bowel symptoms and function, hormonal treatment-related symptoms, and urinary symptoms and problems, whereas a positive number would favour enzalutamide over placebo for FACT-P scores and EQ-VAS.

We used predefined thresholds indicating the minimal clinically important differences for patients to interpret group differences between the two treatment groups in the longitudinal analyses and to define pain progression, symptom worsening, and HRQOL deterioration (appendix p 12). Because there are no established cutoff points for clinically meaningful change for the EORTC QLQ-PR25, we used a distribution-based approach using a threshold of 0.5 SDs. We defined time to confirmed pain progression, symptom worsening, and HRQOL

	Least squares mean difference from baseline (95% CI)		Least squares mean difference from baseline (95% CI)	p value
	Enzalutamide group	Placebo group		
<b>BPI-SF</b>				
Item 3: pain at its worst	0.52 (0.27 to 0.77)	0.73 (0.31 to 1.16)	-0.21 (-0.66 to 0.24)	0.353
Pain severity	0.49 (0.30 to 0.69)	0.55 (0.23 to 0.87)	-0.06 (-0.40 to 0.29)	0.746
Pain interference	0.65 (0.45 to 0.84)	0.85 (0.53 to 1.16)	-0.20 (-0.53 to 0.13)	0.237
<b>EORTC QLQ-PR25</b>				
Bowel symptoms and function	2.28 (1.34 to 3.23)	1.42 (-0.14 to 2.99)	0.86 (-0.80 to 2.52)	0.309
Hormonal treatment-related symptoms	1.55 (0.26 to 2.83)	-1.83 (-3.86 to 0.20)	3.38 (1.24 to 5.51)	0.0020
Urinary symptoms and problems	3.07 (1.31 to 4.83)	3.93 (1.08 to 6.77)	-0.86 (-3.89 to 2.18)	0.579
<b>FACT-P</b>				
Physical wellbeing	-2.26 (-2.71 to -1.81)	-2.00 (-2.71 to -1.29)	-0.26 (-1.00 to 0.49)	0.499
Social and family wellbeing	0.30 (-0.25 to 0.85)	-0.64 (-1.51 to 0.24)	0.94 (0.02 to 1.85)	0.045
Emotional wellbeing	-0.24 (-0.63 to 0.14)	-0.58 (-1.19 to 0.03)	0.34 (-0.30 to 0.98)	0.303
Functional wellbeing	-2.44 (-2.98 to -1.90)	-2.57 (-3.44 to -1.70)	0.13 (-0.78 to 1.05)	0.774
Prostate cancer subscale	-2.61 (-3.24 to -1.99)	-3.32 (-4.31 to -2.32)	0.70 (-0.35 to 1.75)	0.189
Prostate cancer pain subscale	-0.93 (-1.28 to -0.59)	-1.06 (-1.62 to -0.51)	0.13 (-0.46 to 0.71)	0.668
FACT-P total	-7.17 (-8.98 to -5.35)	-9.20 (-12.05 to -6.36)	2.04 (-0.97 to 5.04)	0.184
<b>EQ-5D-5L</b>				
EQ-VAS	-4.57 (-6.36 to -2.77)	-5.29 (-8.17 to -2.41)	0.72 (-2.30 to 3.75)	0.639

A negative number for the least squares mean difference favours enzalutamide over placebo for BPI-SF scores and bowel symptoms and function, hormonal treatment-related symptoms, and urinary symptoms and problems, whereas a positive number favours enzalutamide over placebo for FACT-P scores, and EQ-VAS. p values are from the mixed-model repeated measures analyses. BPI-SF=Brief Pain Inventory Short Form. EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire. FACT-P=Functional Assessment of Cancer Therapy-Prostate. EQ-5D-5L=European Quality of Life 5-Dimensions 5-Levels health questionnaire. EQ-VAS=European Quality of Life 5-Dimensions 5-Levels health questionnaire visual analogue scale.

**Table 2: Least squares mean change in patient-reported outcome scores at week 97**

deterioration as time from the date of randomisation to date of the first clinically meaningful deterioration in patient-reported outcome scores of at least one threshold unit, compared with the baseline score and confirmed at the next consecutive visit (appendix p 12). Patients who did not have a confirmed deterioration were censored at the date of the last questionnaire completion (ie, date of the last non-missing value). Death was not included in the definition of confirmed deterioration; therefore, patients who died and did not have confirmed deterioration before death were censored at the last completed assessment. Patients with no baseline assessment were censored at the date of randomisation. We also did sensitivity analyses using unconfirmed deterioration or progression (ie, reported at one visit).

We estimated time-to-event analyses using the Kaplan-Meier product limit method. We assessed inferences for time-to-event endpoints using a log-rank test that employed stratification factors used at randomisation. We determined HRs and associated 95% CIs using a stratified Cox proportional hazards model. We analysed data using SAS (version 9.3 or higher). p values of less than 0.05 were judged to be significant; because of the exploratory nature of the analyses, adjustments were not made for multiple comparisons.

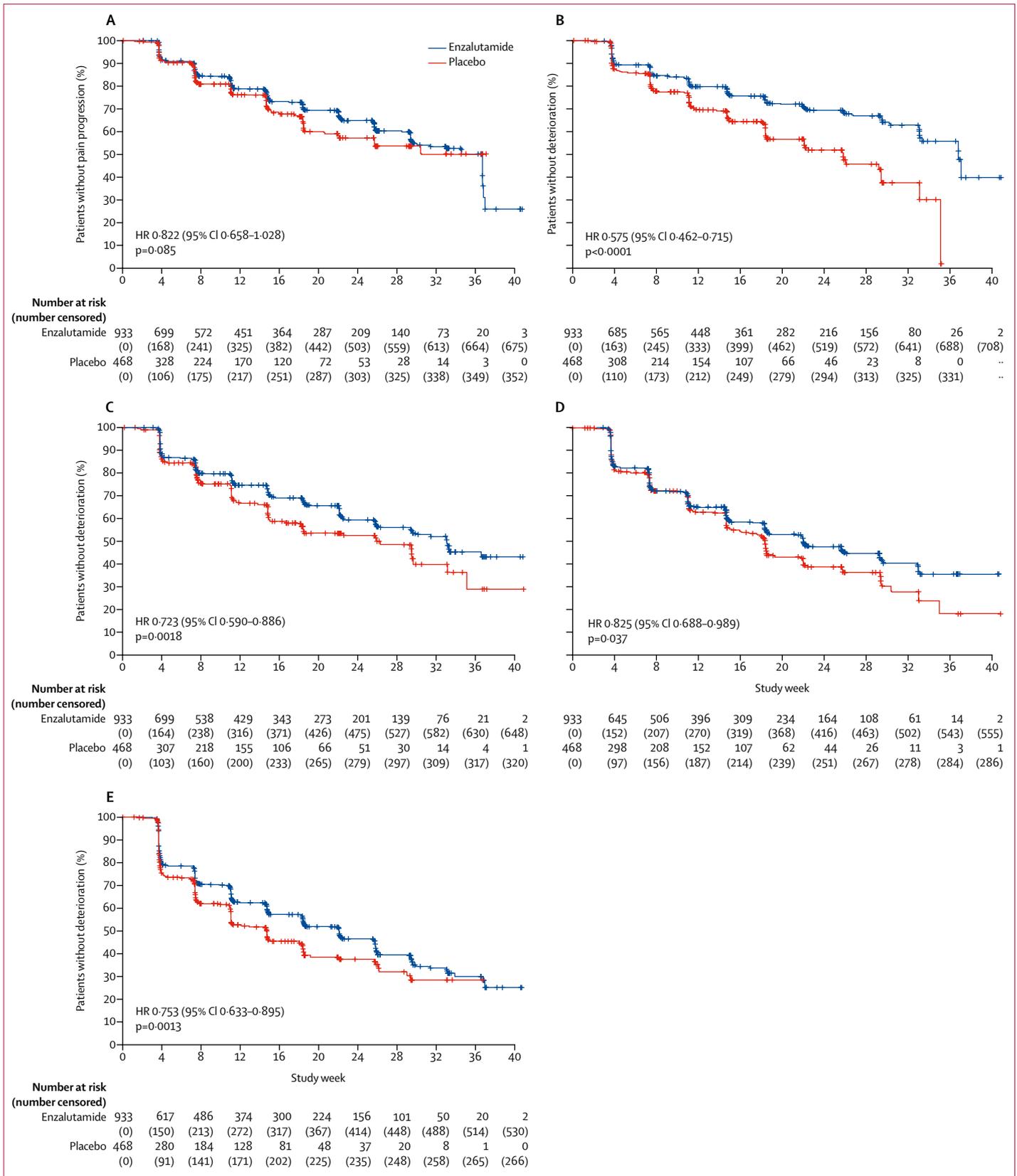
PROSPER is registered with ClinicalTrials.gov, number NCT02003924.

### Role of the funding source

The study sponsors developed the study design in consultation with MH and CNS, and contributed to collection, analysis, and interpretation of data, and writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

### Results

Between Nov 26, 2013, and June 28, 2017, 1401 patients were enrolled and randomly assigned enzalutamide (n=933) or placebo (n=468). Adjudication by masked independent central review was not required to enter the study. Thus, some patients were randomly assigned, but later confirmed by masked independent central review to be ineligible (n=37 [3% of the intention-to-treat population]). Of these, 21 (2.3% of the enzalutamide intention-to-treat arm) were in the enzalutamide group and 16 (3.4% of the placebo intention-to-treat arm) were in the placebo group. The most common reasons were patients were found to have metastatic disease (n=10 [1%], five in each group); progressive disease on androgen deprivation therapy at enrolment, defined as a minimum of three increasing prostate-specific antigen values (n=9 [1%]; five [1%] in the enzalutamide group and four [1%] in the placebo group); and prostate-specific antigen doubling time values greater than 10 months that were



not reported on the initial case report forms ( $n=7$  [ $<1\%$ ]; four [ $<1\%$ ] in the enzalutamide group and three [ $1\%$ ] in the placebo group). These patients are included in the intention-to-treat population and patient-reported outcome analyses. Evaluable baseline BPI-SF, EORTC QLQ-PR25, FACT-P, and EQ-5D-5L forms were completed by 887 (95%) of 933 patients in the enzalutamide group and 439 (94%) of 468 patients in the placebo group. More than 85% of patients completed all patient-reported outcome questionnaires in both treatment groups throughout all visits. At week 97, evaluable BPI-SF and EORTC QLQ-PR25 forms were completed by 366 (94%) of 389 patients expected to fill in a patient-reported outcome assessment in the enzalutamide group and by 96 (93%) of 103 patients in the placebo group. Similar numbers were observed for the FACT-P and EQ-5D-5L questionnaires: 365 (94%) patients in the enzalutamide group completed both evaluable forms at week 97, and 96 (93%) and 95 (92%) patients in the placebo group completed evaluable forms, respectively.

Median follow-up, based on reverse Kaplan-Meier estimation, was 18.5 months (IQR 10.7–29.2) in the enzalutamide group and 15.1 months (7.4–25.9) in the placebo group. Median treatment duration was longer in the enzalutamide group than in the placebo group (18.4 months [IQR 9.7–27.2] vs 11.1 [6.4–18.7]). Additionally, a greater proportion of patients in the enzalutamide group received at least 24 months of treatment (321 [34%] vs 60 [13%]). The primary reason for treatment discontinuation was disease progression, as reported elsewhere.<sup>10</sup> Of 1401 patients, 249 (18%) had at least one patient-reported outcome assessment post-study drug discontinuation, and patient-reported outcome data were collected from 194 (14%) patients after starting a new antineoplastic treatment (most commonly abiraterone, docetaxel, or bicalutamide).

Demographic characteristics of patients and baseline pain, prostate cancer symptoms, and functional status scores were well balanced and patient-reported outcome scores were comparable between treatment groups at baseline (table 1). Many patients in the enzalutamide and placebo groups were asymptomatic for pain at baseline; mean baseline BPI-SF scores denoted minimal pain. EORTC QLQ-PR25 scores suggested low symptom burden. FACT-P subscores, FACT-P total score, and EQ-VAS at baseline indicated relatively high functioning and good HRQOL.

#### Figure 2: Time to confirmed pain progression and HRQOL deterioration

Outcomes estimated with the Kaplan-Meier product limit method; time-to-event endpoint inferences were assessed by a log-rank test. (A) Brief Pain Inventory Short Form item 3. (B) European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-PR25 urinary symptoms. (C) EORTC QLQ-PR25 bowel symptoms. (D) Functional Assessment of Cancer Therapy-Prostate total score. (E) European Quality of Life 5-Dimensions 5-Levels health questionnaire visual analogue scale. HRQOL=health-related quality of life. HR=hazard ratio.

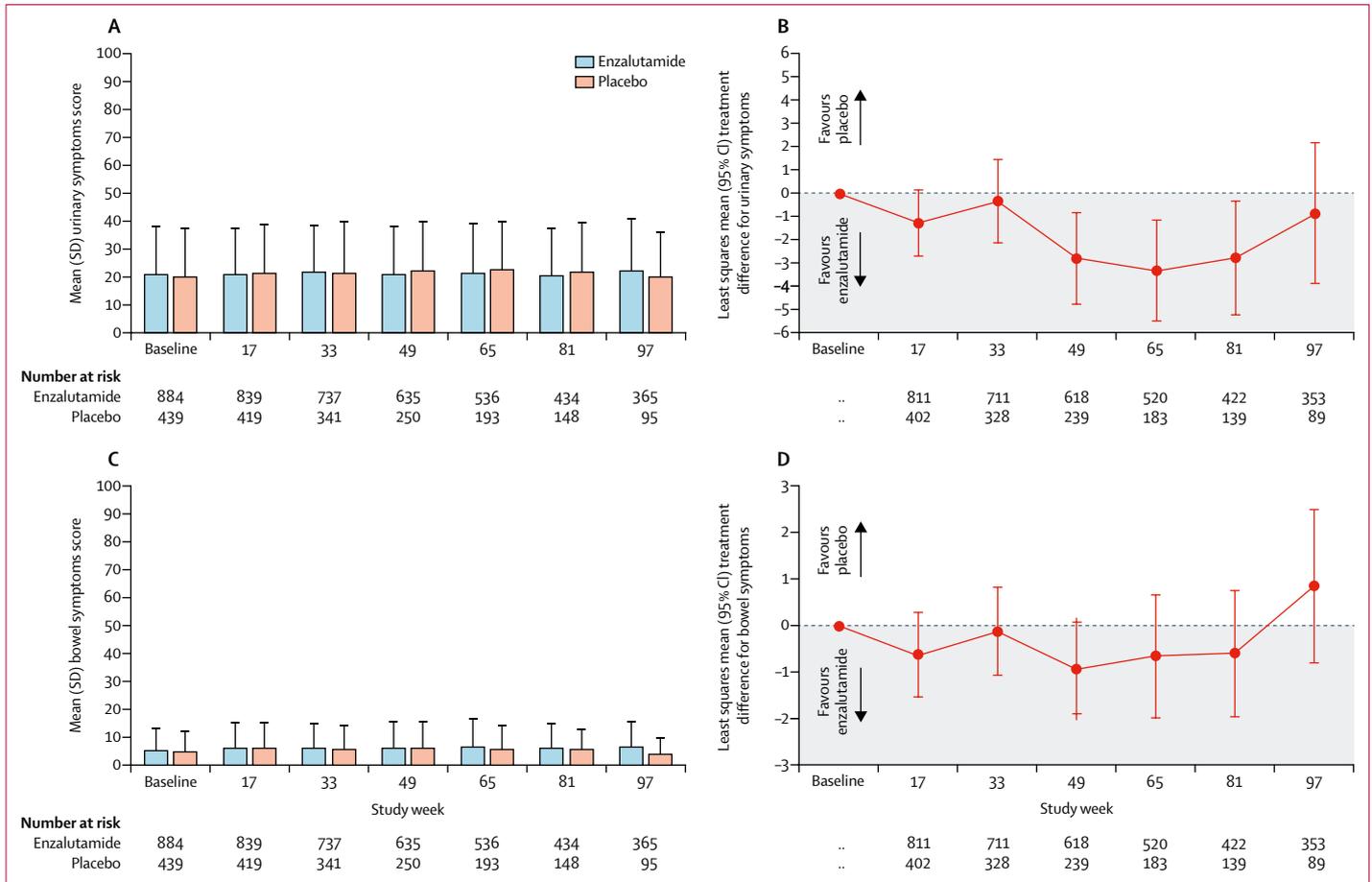
	Median time, months (95% CI)		Hazard ratio (95% CI)	p value
	Enzalutamide group	Placebo group		
<b>BPI-SF</b>				
Item 3	34.69 (29.73–36.86)	30.52 (22.11–NR)	0.82 (0.66–1.03)	0.085
Pain severity	36.83 (34.69–NR)	NR	0.75 (0.57–0.97)	0.028
Pain interference	33.15 (29.54–NR)	30.52 (22.11–NR)	0.94 (0.76–1.18)	0.602
<b>EORTC QLQ-PR25</b>				
Bowel symptoms and function	33.15 (29.50–NR)	25.89 (18.43–29.67)	0.72 (0.59–0.89)	0.0018
Hormonal treatment-related symptoms	33.15 (29.60–NR)	36.83 (29.47–NR)	1.29 (1.02–1.63)	0.035
Urinary symptoms and problems	36.86 (33.35–NR)	25.86 (18.53–29.47)	0.58 (0.46–0.72)	<0.0001
<b>FACT-P</b>				
Physical wellbeing	18.56 (16.82–22.18)	19.35 (18.33–25.79)	1.15 (0.96–1.38)	0.135
Social and family wellbeing	34.04 (29.60–NR)	29.50 (25.79–NR)	0.87 (0.71–1.08)	0.219
Emotional wellbeing	36.73 (33.12–38.21)	29.47 (22.18–33.15)	0.69 (0.55–0.86)	0.0008
Functional wellbeing	18.60 (18.20–22.14)	18.37 (14.78–18.66)	0.94 (0.79–1.13)	0.524
Prostate cancer subscale	18.43 (14.85–18.66)	14.69 (11.07–16.20)	0.79 (0.67–0.93)	0.0042
Prostate cancer pain subscale	25.76 (22.11–29.47)	22.11 (18.40–30.52)	0.94 (0.78–1.14)	0.521
FACT-P total	22.11 (18.63–25.86)	18.43 (14.85–19.35)	0.83 (0.69–0.99)	0.037
<b>EQ-5D-5L</b>				
EQ-VAS	22.11 (18.46–25.66)	14.75 (11.07–18.17)	0.75 (0.63–0.90)	0.0013

Time-to-event endpoints were analysed with a stratified log-rank test; HRs and 95% CIs were evaluated with a Cox proportional hazards model. BPI-SF=Brief Pain Inventory Short Form. NR=not reached. EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire. FACT-P=Functional Assessment of Cancer Therapy-Prostate. EQ-5D-5L=European Quality of Life 5-Dimensions 5-Levels health questionnaire. EQ-VAS=EuroQoL 5-Dimensions 5-Levels health questionnaire visual analogue scale.

Table 3: Time to first confirmed pain progression and deterioration in health-related quality of life

Mean BPI-SF scores remained stable, at values less than 2 points, up to week 97, in both treatment groups (figure 1A; appendix p 14). The difference between groups in least squares mean change from baseline in all BPI-SF scores was not significant at any timepoint, on the basis of p values obtained from the mixed-measures repeated models analysis (figure 1B; appendix p 14). At week 97, both treatment groups had increased pain scores from baseline ( $\leq 0.85$  points in each group); there were no significant differences between the groups (table 2). Similar results were observed in the pattern mixture model analysis (data not shown). Time to first confirmed pain progression was not significantly different between groups for the BPI-SF item 3 or pain interference scores, but was significantly longer for patients receiving enzalutamide than for patients receiving placebo for the pain severity composite score (figure 2; table 3; appendix p 15). Similar results were observed in the sensitivity analysis (appendix p 13).

Mean EORTC QLQ-PR25 symptom scores remained stable during the study in both treatment groups



**Figure 3: Changes in EORTC QLQ-PR25 scores**

Scores are for study visit and treatment difference in least squares mean change from baseline for urinary symptoms (A, B) and bowel symptoms (C, D). EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire.

(figures 3A, 3C; appendix p 18). At 97 weeks, the least squares mean difference from baseline between treatment groups in urinary and bowel symptoms was not statistically significant ( $p=0.579$  and  $p=0.309$ , respectively; figure 3B, 3D). At 65 and 81 weeks, the least squares mean between treatment groups for the urinary symptom score was statistically significant in favour of enzalutamide ( $p=0.028$  and  $p=0.0251$ , respectively; figure 3B, 3D). At week 97, there was no significant difference between groups for urinary or bowel symptoms, but there was a significant difference between groups in hormonal treatment-related symptoms that favoured placebo; this difference was not clinically meaningful (table 2; appendix p 18). Similar results were observed in the pattern mixture model analysis (data not shown). The least squares mean difference from baseline between treatment groups for the treatment-related symptom score was statistically significant (favouring placebo) for all weeks ( $p=0.0004$  to  $p=0.0257$ ; data not shown). Compared with placebo, the time to first confirmed worsening of urinary symptoms and bowel symptoms was significantly longer with enzalutamide

compared with placebo (table 3; figure 3B and 3C). By contrast, time to first confirmed worsening in hormonal treatment-related symptoms was significantly shorter with enzalutamide than with placebo (table 3; appendix p 15). Similar results were observed in the unconfirmed sensitivity analysis (appendix p 13).

Results for mean FACT-P scores indicated that patients in both groups maintained stable HRQOL over time (figure 4A; appendix pp 19–21). At 97 weeks, the least squares mean difference between treatment groups for FACT-P total score was not significant ( $p=0.184$ ; figure 4B), although statistical (but not clinical) significance in favour of enzalutamide was observed at week 81 ( $p=0.018$ ). Social and family wellbeing increased from baseline to week 97 in both groups; the difference at week 97 was significant, but not clinically meaningful (table 2; appendix p 19). There was no significant difference between treatment groups at any timepoint for any other FACT-P scores (figure 4B; appendix pp 19–21). Results were similar in the pattern mixture model analysis (data not shown). Time to first confirmed deterioration in FACT-P scores was significantly longer

for enzalutamide than for placebo for the emotional wellbeing, prostate cancer subscale, and FACT-P total score (table 3; figure 2; appendix pp 16, 17), but did not differ for any other FACT-P scores. A similar result was observed in the unconfirmed sensitivity analysis (appendix p 13).

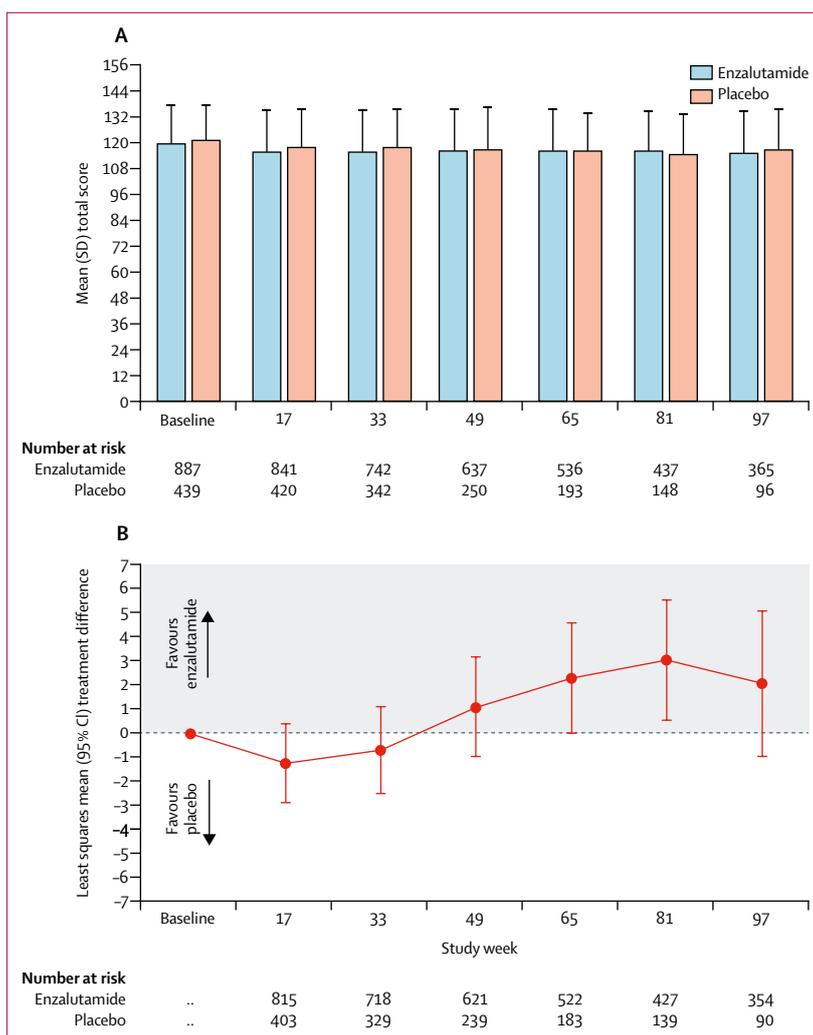
Mean EQ-VAS results indicated that patients in both treatment groups maintained their health status over time (figure 5A). At week 97, patients receiving enzalutamide reported a smaller decrease from baseline than patients receiving placebo; this difference was not significant (table 2; figure 5B). At 65 and 81 weeks, the least squares mean between treatment groups for the EQ-VAS was statistically significant in favour of enzalutamide ( $p=0.024$  and  $p=0.022$ , respectively; figure 5B). Similar results were observed in the pattern mixture model analysis (data not shown). Compared with placebo, enzalutamide significantly increased time to confirmed and unconfirmed deterioration in EQ-VAS (table 3; figure 2E; appendix p 13).

## Discussion

The findings from the PROSPER study showed that enzalutamide treatment maintains low baseline pain and high HRQOL and health status scores in patients with non-metastatic, castration-resistant prostate cancer. When assessing overall differences between enzalutamide and placebo throughout the study, there were no clinically meaningful differences. However, when assessing the time to clinically meaningful pain progression (BPI-SF pain severity) and the time to confirmed deterioration in HRQOL, significant differences in favour of enzalutamide were observed in several FACT-P and EORTC QLQ-PR25 scores (except for hormonal treatment-related symptoms) and EQ-VAS. These results, combined with the primary efficacy findings, suggest that in addition to reducing the risk of metastasis (HR 0.29; 95% CI 0.24–0.35),<sup>10</sup> enzalutamide also increases time to pain progression, symptom worsening, and HRQOL deterioration when compared with placebo.

Patients enrolled in the PROSPER study were generally asymptomatic for pain or had low symptom burden and reported good HRQOL at baseline. For patients with prostate cancer who do not initially have substantial cancer-related or disease-related symptom burden, controlling and delaying the time to symptomatic manifestations of disease are important therapeutic objectives.<sup>13</sup> In this regard, the PROSPER study offered an opportunity to examine the effect of an active antineoplastic therapy on HRQOL in patients not yet burdened by substantial disease-related symptoms.

Median time to first clinically meaningful pain progression (BPI-SF item 3 [worst pain], pain severity, and pain interference) was longer with enzalutamide than with placebo, although the difference was significant only for pain severity. In patients with metastatic, castration-resistant prostate cancer, pain is generally

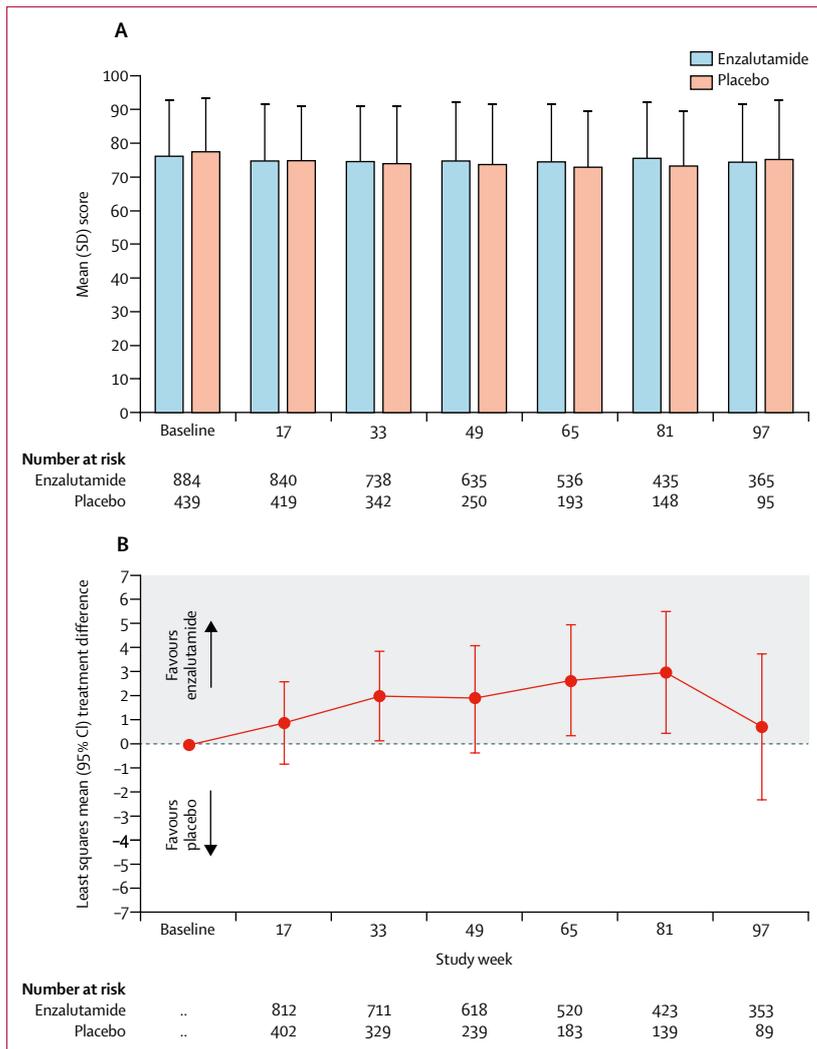


**Figure 4: Patient-reported changes in FACT-P total score**

Scores are for study visit (A) and treatment difference in least squares mean change from baseline (B). FACT-P=Functional Assessment of Cancer Therapy-Prostate.

reported with poor HRQOL and has been shown to be prognostic of overall and progression-free survival.<sup>14,17</sup> Although pain is not a salient symptom in patients with non-metastatic, castration-resistant prostate cancer,<sup>25</sup> pain progression might be associated with disease progression in this population.

There were significant, but not clinically meaningful differences between enzalutamide and placebo in the EORTC QLQ-PR25 scales. The reported time to confirmed worsening of EORTC QLQ-PR25 urinary and bowel symptoms was significantly longer with enzalutamide treatment than with placebo. However, the frequency of reported adverse events for urinary and bowel complications (eg, urinary tract infection, urinary retention, diarrhoea, and constipation) reported with enzalutamide treatment was similar to that with placebo, as previously reported.<sup>10</sup> Patients with prostate cancer have a strong preference to avoid urinary incontinence when choosing



**Figure 5: Patient-reported changes in EQ-VAS**  
 Scores are for study visit (A) and treatment difference in least squares mean change from baseline (B).  
 EQ-VAS=European Quality of Life 5-Dimensions 5-Levels health questionnaire visual analogue scale.

treatment,<sup>26</sup> and a discrete choice experiment found that men with prostate cancer were willing to give up nearly 2 months of life expectancy in order to lessen the severity of treatment-related diarrhoea.<sup>27</sup> In patients with non-metastatic, castration-resistant prostate cancer, urinary and bowel symptoms are common and negatively affect HRQOL.<sup>25</sup> One plausible explanation for this is that disease can progress locally, aggravating local symptoms before remission or progression. Intervening early with an active treatment might delay local progression and provide an important benefit. EORTC QLQ-PR25 hormonal treatment-related symptoms disfavoured enzalutamide with a significant, but not clinically meaningful, treatment difference from baseline to week 97, and a longer time to confirmed worsening of symptoms. The score comprises six items: hot flushes, sore or enlarged nipples or breasts, swelling in legs or

ankles, weight loss, weight gain, and feeling less masculine. As previously reported,<sup>10</sup> the proportion of patients with these symptoms as adverse events in the PROSPER study was less than 5% in both treatment groups, except for hot flushes (13.0% vs 7.7%) and weight loss (5.9% vs 1.5%), which were reported by more patients in the enzalutamide group and could account for the observed EORTC QLQ-PR25 questionnaire results.

We previously reported a similar time to deterioration in FACT-P total score for enzalutamide and placebo in the unconfirmed analysis.<sup>10</sup> In our analysis of confirmed time to deterioration, enzalutamide significantly increased the time to deterioration in FACT-P total score compared with placebo. Reported differences in time to deterioration in FACT-P prostate cancer subscale and emotional wellbeing were also significantly in favour of enzalutamide. By contrast, there were no significant or clinically meaningful differences between groups at any timepoint for the other FACT-P scores, except for social and family wellbeing. Patients with non-metastatic, castration-resistant prostate cancer commonly experience an array of emotional effects, including frustration, anxiety, depression, and stress.<sup>25</sup> Delayed symptom worsening might allow patients to be better equipped to manage treatment-related and disease-related symptoms.

Generally, data for non-metastatic, castration-resistant prostate cancer are scarce, as very few clinical trials have focused on this patient subgroup. SPARTAN,<sup>11</sup> the only other randomised, double-blind trial in this patient population with published results to date, assessed the efficacy and safety of apalutamide compared with placebo.<sup>11</sup> Results of the SPARTAN study are consistent with our findings: FACT-P and EQ-5D-5L data indicated that patients who received apalutamide in addition to androgen deprivation therapy maintained stable overall HRQOL over time (up to 29 months).<sup>11</sup> Taken together, these data suggest that a second-generation androgen receptor inhibitor might provide a valuable therapeutic method for non-metastatic, castration-resistant prostate cancer. Further analyses to identify potential correlations between objective clinical responses and surrogate markers of efficacy and specific patient-reported outcomes in this population could enhance understanding of progression in castration-resistant prostate cancer, guide treatment decisions, and improve patient outcomes.

Both the PROSPER and SPARTAN trials were done with technetium-99m bone scanning and CT scanning to detect metastases. These technologies have limited diagnostic accuracy and detect metastatic deposits quite late,<sup>28</sup> which might change rapidly with the widespread use of new imaging technologies such as PET-CT with prostate-specific tracers, including <sup>18</sup>F-choline, <sup>68</sup>Ga-prostate-specific membrane antigen, or fluciclovine (<sup>18</sup>F), and whole-body MRI. Incorporating these technologies in the clinic will probably lead to the earlier diagnosis of metastases and reduced overall burden.

Indeed, up to a third of patients diagnosed by new imaging technologies will show at least three metastases; this offers the opportunity for metastases-targeted treatment in place of, or in conjunction with, modern systemic therapy.<sup>29</sup> The implication of these new imaging technologies on the treatment landscape and clinical trial development was recently reviewed by the EORTC Imaging Group.<sup>30</sup>

Several previous studies show that HRQOL scores can be prognostic for survival in prostate cancer.<sup>16,31–33</sup> The prognostic value of HRQOL could reflect patient experience beyond conventional clinical characteristics. In this study, evaluable overall survival data at the time of data cutoff were not yet mature, with only 596 (28%) expected deaths. Further analyses exploring the association between overall survival and HRQOL changes will be done at a later date. Ultimately, the identification of prognostic HRQOL factors for survival could contribute to the modification of treatment regimens and help identify patient groups for interventions.

A key strength of our analysis was the prespecified assessment of the effects of enzalutamide treatment, in addition to standard of care (androgen deprivation therapy), on HRQOL in a large, randomised, double-blind, placebo-controlled clinical trial. Additionally, both generic (BPI-SF and EQ-5D-5L) and prostate-cancer-specific (FACT-P and EORTC QLQ-PR25) questionnaires were used.

Our analysis had some limitations that should be considered when interpreting the results. Although we enrolled patients who were more likely to develop overt disease rapidly (prostate-specific antigen doubling time of  $\leq 10$  months), further study is needed to identify whether patients with even more aggressive tumours at baseline (prostate-specific antigen doubling time of  $< 3$  months *vs* 3–10 months) would benefit from enzalutamide with respect to HRQOL. Because of the abnormal distribution of patients with prostate-specific antigen doubling time of 10 months or less in the PROSPER population, the sample sizes would not be large enough to draw meaningful conclusions.

Patients were enrolled in the study on the basis of documentation submitted by sites at the time of enrolment. However, after these eligible patients were enrolled, masked independent central review identified 37 (3%) of the 1401 randomly assigned patients that were ineligible. These patients were included in the analyses.

Since several patient-reported outcome measures were collected at different timepoints, multiplicity could be an issue; we used repeated-measures analyses to adjust for this over time. Patient numbers were low (ie,  $< 10$ ) for some assessments, particularly after week 97. Overall, a higher proportion of patients receiving enzalutamide completed self-rating questionnaires than did patients receiving placebo; this difference was mainly due to

disease progression occurring earlier in patients given placebo, at which time the study drug was discontinued and patient-reported outcome data collection continued only for patients attending clinic visits. Moreover, because some patients who continued attending clinic visits after treatment discontinuation also initiated secondary treatments, it is possible that secondary treatments benefited placebo in the comparison against enzalutamide. However, many different secondary treatments were used, making it difficult to clearly assess their effect on HRQOL.

The absence of HRQOL data after treatment discontinuation is a well-established drawback of clinical studies incorporating patient-reported outcomes as secondary or exploratory endpoints. This pattern of attrition makes data interpretation difficult and can lead to overestimation of HRQOL at later timepoints. To address this imbalance, the mixed-effects model for repeated measures analysis of longitudinal data was limited to 97 weeks; it has been shown that this approach works well when there is unbalanced withdrawal.<sup>34,35</sup> Lastly, because there are no established cutoff points for clinically meaningful change for the EORTC QLQ-PR25, we used a distribution-based approach using a threshold of 0.5 SDs. Although this approach is sample-dependent, it has shown consistency with other methods.<sup>36</sup>

In conclusion, the PROSPER study showed that, in addition to significantly increased metastasis-free survival,<sup>10</sup> enzalutamide treatment maintained HRQOL and increased time to clinically meaningful pain progression and symptom worsening compared with placebo.

#### Contributors

BT contributed to the literature search, study design, data analysis, data interpretation, and writing of the manuscript. FS contributed to the study design, data collection, data interpretation, and writing of the manuscript. MH contributed to the study design, data collection, data analysis, data interpretation, and writing of the manuscript. CNS contributed to the literature search, figures, study design, data collection, data analysis, data interpretation, and writing of the manuscript. DP contributed to data interpretation. RM and KR contributed to data analysis, data interpretation, and writing of the manuscript. CI contributed to data analysis and data interpretation. GA contributed to provision of study patients, figures, data analysis, data interpretation, and writing of the manuscript. All authors critically reviewed and approved the manuscript.

#### Declaration of interests

BT reports personal fees from Astellas during the conduct of the study; grants and personal fees from Bayer, Janssen, and Sanofi outside the submitted work; grants, personal fees, and non-financial support from Ferring, and personal fees from Amgen outside the submitted work. FS reports grants and personal fees from Astellas, and Janssen during the conduct of the study; and grants and personal fees from Sanofi, and Bayer, outside the submitted work. DP reports grants and personal fees from Astellas and Medivation during the conduct of the study; and grants and personal fees from Dendreon outside the submitted work. MH reports a consultant or advisory role; travel, accommodation, and expenses; and research funding from Genentech/Roche; a consultant or advisory role; travel, accommodation, and expenses from AbbVie and Bayer, honoraria from Onclive, and research funding from Pfizer, Prostate Cancer Clinical Trials Consortium, and AstraZeneca, outside the submitted work. In addition, MH holds the following planned, pending, or issued patents: SYSTEMS AND METHODS FOR TISSUE IMAGING, 3676: serial number UM-14437/US-1/PRO

60/923,385 UM-14437/US-2/ORD 12/101,753; METHOD OF TREATING CANCER : serial number 224990/10-016P2/311733 61/481/671; and dual Inhibition of MET and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases, Applicant/Proprietor Exelixis; application number 11764665.4-1464. CNS reports personal fees from Janssen, Astellas, Clovis Oncology, AstraZeneca, Sanofi, Bayer, and Pfizer outside the submitted work. RM reports personal fees from Astellas during the conduct of the study, and personal fees from Abbot Medical Optics, Ironwood, and Genentech, outside the submitted work. KR is an employee of Pfizer during the conduct of the study and owns stock in Johnson & Johnson, outside the submitted work. CI is an employee of IQVIA, which received funding from Astellas to conduct the statistical analyses for this work under consultancy contract. GA reports personal fees and non-financial support from Astellas and Medivation/Pfizer, during the conduct of the study; grants, personal fees, and non-financial support from Janssen; personal fees from Veridex, Novartis, Millenium Pharmaceuticals, Takeda, and Sanofi-Aventis; personal fees and non-financial support from Roche/Ventana, Abbott Laboratories, Essa Pharmaceuticals, Bayer Healthcare Pharmaceuticals; grants from AstraZeneca, Arno Therapeutics, and Innocrin Pharma; and is on The Institute of Cancer Research (ICR) rewards to inventors scheme for abiraterone acetate, outside the submitted work.

#### Data sharing

Upon request, and subject to certain criteria, conditions, and exceptions, Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the USA, the EU, or both or (2) in programmes that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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