25 February 2021
EMA/202601/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Xtandi

International non-proprietary name: enzalutamide

Procedure No. EMEA/H/C/002639/II/0047/G

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
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# List of abbreviations

| | |
|---|---|
| ACE-27 | Adult Comorbidity Evaluation |
| ADT | androgen deprivation therapy |
| AE | adverse event |
| ANZUP | Australian and New Zealand Urogenital and Prostate |
| AR | androgen receptor |
| BPI-SF | Brief Pain Inventory-Short Form |
| CI | confidence interval |
| CR | complete response |
| CRPC | castration-resistant prostate cancer |
| CSR | Clinical Study Report |
| CYP | cytochrome P450 |
| DRF | dose-range finding |
| ECOG | Eastern Cooperative Oncology Group |
| EQ-5D-5L | EuroQoL Group 5-Dimension 5-Level |
| EU | European Union |
| FACT-P | Functional Assessment of Cancer Therapy - Prostate |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| ICR | independent central review |
| IDSMC | Independent Data and Safety Monitoring Committee |
| ISS | Integrated Summary of Safety |
| ITT | intent-to-treat |
| LHRH | luteinizing-hormone releasing hormone |
| MFS | metastasis-free survival |
| mHSPC | metastatic hormone-sensitive prostate cancer |
| NHMRC CTC | National Health and Medical Research Council Clinical Trials Centre |
| NSAA | nonsteroidal antiandrogen |
| ORR | objective response rate |
| OS | overall survival |
| PCWG2 | Prostate Cancer Clinical Trials Working Group 2 |
| PFS | progression-free survival |
| PR | partial response |

PRES posterior reversible encephalopathy syndrome

PRO patient-reported outcomes

PSA prostate-specific antigen

PSA PFS prostate-specific antigen progression-free survival

QLQ-PR25 Quality of Life Questionnaire-Prostate 25

QoL quality of life

RECIST 1.1 Response Evaluation Criteria in Solid Tumours version 1.1

rPFS radiographic progression-free survival

SAE serious adverse event

SAP statistical analysis plan

SSE symptomatic skeletal event

STOPCAP Systemic Treatment Options for Cancer of the Prostate

TEAE treatment-emergent adverse event

# 1. Background information on the procedure

## *1.1. Type II group of variations*

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 1 July 2019 an application for a group of variations.

The following variations were requested in the group:

| **Variations requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I |
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

C.1.6: Extension of Indication to include the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) for Xtandi in combination with androgen deprivation therapy; as a consequence, sections 4.1, 4.7, 4.8, 5.1, 5.3 and 6.6 of the SmPC are updated. Furthermore, the MAH took the opportunity to make corrections to section 4.7. The Package Leaflet is updated in accordance. The RMP version 13.0 has also been submitted.

C.1.4: Update of section 5.1 of the SmPC based the 5-year Overall Survival (OS) results obtained from the PREVAIL study (MDV310003), a phase 3 study of enzalutamide in chemotherapy naïve patients with metastatic prostate cancer that progressed on ADT.

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Scientific advice*

The MAH received Scientific Advice from the CHMP on 24 September 2015 (EMEA/H/SA/1612/1/FU/5/2015/II). The Scientific Advice pertained to clinical aspects of the dossier.

### *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Concepcion Prieto Yerro

| Timetable | Actual dates |
|---|---|
| Submission date | 1 July 2019 |
| Start of procedure: | 20 July 2019 |
| CHMP Rapporteur Assessment Report | 30 September 2019 |
| PRAC Rapporteur Assessment Report | 24 September 2019 |
| PRAC Outcome | 3 October 2019 |
| CHMP members comments | 7 October 2019 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 14 October 2019 |
| Request for supplementary information (RSI) | 17 October 2019 |
| CHMP Rapporteur Assessment Report | 4 May 2020 |
| CHMP members comments | n/a |
| An Oral explanation took place on: | 26 May 2020 |
| Request for supplementary information (RSI) | 28 May 2020 |
| Summary report of the inspection carried out at the following site(s) Astellas Pharma Global Development, US and Parexel Medical Imaging, Spain between 18 January 2021 and 5 February 2021 was issued on | 19 February 2021 |
| CHMP Rapporteur Assessment Report | 12 Mar 2021 |
| CHMP members comments | 15 Mar 2021 |
| Updated CHMP Rapporteur Assessment Report | 18 Mar 2021 |
| Opinion | 25 Mar 2021 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

This application is to extend the indication of Xtandi (enzalutamide) to include the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy. Hormone-sensitive prostate cancer is defined as the absence of evidence of castration resistance, defined as prostate cancer that progresses despite castrate levels of testosterone while on

treatment with a luteinizing-hormone releasing hormone analogue (LHRHa), or following bilateral orchiectomy (J Clin Oncol. 2008;26:1148–59).

## *Epidemiology*

Worldwide, prostate cancer ranks second in cancer incidence and fifth in cancer mortality in men (Bray et al, 2018). In Europe, the estimated number of new prostate cancer cases was approximately 473,344 in 2020 and the number of deaths was approximately 108,088 in 2020 (GLOBOCAN, 2020).

## *Clinical presentation, diagnosis and stage/prognosis*

Prostate cancer may present as localised disease, locally advanced disease or metastatic disease at initial diagnosis. Despite intense use of Prostate-specific antigen (PSA) for screening and early detection of prostate cancer, 2% to 43% of patients initially present with metastatic disease (Cancer Research UK, 2019; Siegel et al, 2019; Schröder et al, 2012; Tombal, 2012).

Staging of Prostate cancer is done using the Clinical Tumour Node Metastasis (TNM) classification, the Gleason Score and/or current International Society of Urological Pathology (ISUP) grading system (N Mottet, 2018 Guidelines for staging of prostate cancer).

The prognosis of men with prostate cancer drops considerably upon the development of metastases (5-year OS rate of 30%) (Noone et al, 2018; James et al, 2016). Moreover, death of patients with metastatic CRPC typically occurs within 24 to 48 months after the onset of metastatic castration resistance and is commonly preceded by a sequence of landmark events associated with deterioration of overall health and worsening symptoms including pain and cachexia (Beer et al, 2017; Devlin et al, 2017; Basch et al, 2013; Logothetis et al, 2012). Prognostic factors that influence survival in metastatic castration-sensitive prostate cancer (mCSPC) include high prostate specific antigen (PSA) concentration at diagnosis, high Gleason score, higher primary tumour stage, worse World Health Organization (WHO) performance status, younger age, and the presence of bone metastases.

## *Management*

Localised disease may be amenable to curative primary intervention such as surgery or radiation therapy, however, a significant proportion of patients have a recurrence of disease and require systemic treatment. Early in the disease, prostate cancer is dependent on androgen for growth and survival. Therefore, depriving prostate cancer cells of androgen is a primary form of therapy. Such prostate cancers are referred to as androgen-dependent or hormone-sensitive and treatments that decrease androgen levels or block androgen activity can inhibit their growth.

Patients with recurrent disease after primary treatment, or those who present with more advanced or metastatic disease, are usually treated with Androgen Deprivation Therapy (ADT). Initially, most patients are sensitive to androgen deprivation (castration), but eventually there is a progression from hormone-sensitive prostate cancer to castration-resistant prostate cancer (CRPC), where CRPC is defined as disease progression in the setting of castrate levels of testosterone (<50 ng/dL).

As metastatic hormone-sensitive prostate cancer is dependent on androgen for growth and survival, depriving prostate cancer cells of androgen is a primary form of therapy for mHSPC patients. ADT has been the basis for the treatment of patients with mHSPC, and results in a median overall survival of 3-4 years. ADT is defined as surgical castration by bilateral orchiectomy or medical castration with

gonadotropin-releasing hormone (GnRH) agonists or antagonists (EAU, ESMO, NCCN 2018, Fizazi 2017). The aim of these approaches is to reduce testosterone concentrations. Although the majority of mHSPC patients have an initial response to treatment with ADT, most men progress to castration-resistant prostate cancer within a median of approximately 1 year.

Treatment options for men with mHSPC have expanded beyond ADT alone. Two studies (STAMPEDE ARM C and CHAARTED) provide evidence that combining a short course of docetaxel chemotherapy with ADT in mCSPC resulted in prolonged survival compared with treatment with ADT alone. Docetaxel is currently approved in combination with ADT, with or without prednisone or prednisolone, for the treatment of patients with metastatic hormone-sensitive prostate cancer (see EPAR docetaxel). Additionally, the STAMPEDE ARM G and LATITUDE studies showed that abiraterone acetate plus low-dose prednisone (AAP) added to ADT was effective in prolonging overall survival (OS) compared with ADT alone. Abiraterone acetate is indicated with prednisone or prednisolone for the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see EPAR Zytiga). Both ADT plus docetaxel and ADT plus abiraterone/prednisone are recommended by ESMO guideline as first-line treatment of metastatic, hormone-naïve disease (ESMO 2015; ESMO eUpdate 2019).

Furthermore, apalutamide has also recently been approved in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) (see EPAR Erleada).

### 2.1.2. About the product

Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently; inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. In preclinical studies enzalutamide lacks androgen receptor agonist activity (see SmPC section 5.1).

Enzalutamide was approved in the EU in June 2013. Enzalutamide is currently approved for the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated and for those whose disease has progressed on or after docetaxel therapy. Enzalutamide is also authorised for the treatment of adult men with high-risk non-metastatic CRPC (see SmPC 4.1).

The MAH applied for an extension of indication for Xtandi as follows: "Xtandi is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (see section 5.1)."

The recommended dose is 160 mg enzalutamide (four 40 mg soft capsules) as a single oral daily dose.

Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

Additionally, the MAH provided the updated 5-year overall survival results obtained from the PREVAIL study (MDV3100-03) in chemo-naïve mCRPC for inclusion in the SmPC.

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific Advice was sought from CHMP on the adequacy of the design and statistical analysis of a phase 3 study to support the proposed indication. The proposed study (Study 9785-CL-0335) was a multinational, phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of enzalutamide plus ADT versus placebo plus ADT in patients with mHSPC.

### 2.1.4. General comments on compliance with GCP

A request for GCP inspection was adopted for the following study: Study 9785-CL-0335 (ARCHES). The outcome of this inspection was satisfactory and no critical findings that could have compromised the integrity of the trial were found.

## *2.2. Non-clinical aspects*

### 2.2.1. Pharmacology

No additional nonclinical pharmacology studies were submitted to support the current application (see non-clinical discussion).

### 2.2.2. Pharmacokinetics

No additional nonclinical pharmacokinetics studies were submitted to support the current application (see non-clinical discussion).

### 2.2.3. Toxicology

#### *Carcinogenicity*

The MAH had previously submitted the report for the 26-week definitive carcinogenicity study in the Tg rasH2 mouse (EMEA/H/C/002639/II/0039/G). The current submission completes the carcinogenicity evaluation of enzalutamide by providing data in both sexes from a preliminary 13-week dose-range finding (DRF) study in Wistar Hannover (WH)rats and a definitive 104-week carcinogenicity study in WH rats.

***13-week DRF Study [9785-TX-0016]:***

Wistar Hannover rats (12/gender/group, 6 weeks of age at the start of treatment) were treated with enzalutamide for 13 weeks (once a day), at dose levels of 0 (Water for injection), 0 (vehicle, Labrasol), 50, 100 and 200 mg/kg/day. Clinical observation, body weight, food consumption, ophthalmology, urinalysis, haematology, clinical chemistry, organ weight, necropsy and histopathological examination were conducted. In addition, systemic exposure was evaluated by determining plasma concentrations of enzalutamide and its metabolites on Day 1 (first administration), in Week 4 and in Week 13 of administration in the satellite animals.

Enzalutamide was well tolerated in rats for 13 weeks at dose levels up to 200 mg/kg/day. Enzalutamide-related findings in males included increases in absolute and relative weights of the testes, and decreases

in absolute and relative weights of the prostate, epididymides and seminal vesicles; associated decreases in the sizes of the prostate and seminal vesicles, as well as microscopic findings of diffuse Leydig cell hyperplasia in the testes and minimal atrophy of the prostate and seminal vesicles (≥ 50 mg/kg/day). Necropsy revealed calculi in the urinary bladder in males. In the kidney, enzalutamide-related findings included increases in kidney weight (≥ 100 mg/kg/day, males; ≥50 mg/kg/day, females) and microscopic findings of pelvic crystals (200 mg/kg/day, male), dilatation of the distal tubules and collecting ducts (≥ 50 mg/kg/day, males), regeneration of collecting duct in papilla (≥ 100 mg/kg/day, both sexes), and urothelial hyperplasia (≥ 100 mg/kg/day, both sexes).

These findings were associated with increases in plasma creatinine (≥ 50 mg/kg/day, males) and blood urea nitrogen (≥ 100 mg/kg/day, males). In the urinary bladder, there were crystals (≥ 100 mg/kg/day, males) and urothelial hyperplasia (≥ 50 mg/kg/day, males). Urinalysis indicated unidentified needle-like crystals in the urinary sediments (≥ 50 mg/kg/day, both sexes).

Based on the saturation of absorption, lack of exposure increase and generally similar findings between 100 and 200 mg/kg/day in the 13-week dose range finding study, 100 mg/kg/day was selected as the highest dose for the 2-year carcinogenicity study. The low (10 mg/kg/day) and mid (30 mg/kg/day) doses were selected to cover a wide range of clinical exposure margins and study dose responses.

***104-week (104-week) Carcinogenicity Study [9785-TX-0017]:***

A 2-year carcinogenicity study in rats was conducted with Wistar Han (both sexes). In this study dose levels: 0, 10, 30 and 100 mg/kg were given per day. Survival rates in the Control II (Labrasol vehicle) group were 51.4% in males and 55.7% in females. Survival rates in the 100 mg/kg/day (high dose) dose group were slightly lower in males (38.6%) compared to concurrent male controls and to the female high dose group (40.0%). The mortality in males at 100 mg/kg/day was largely attributed to urinary bladder tumours, which were occasionally accompanied by reddish urine and additional non-neoplastic renal and urogenital tract findings, without palpable masses.

Daily dosing of rats for two years with enzalutamide at 10–100 mg/kg/day produced an increased incidence of neoplastic findings (compared to control).

Enzalutamide-related neoplastic findings can be divided into 1) tumours that were potentially related to the primary pharmacology and 2) tumours in males that were likely secondary to the continuous irritation caused by the urinary crystals and calculi in the rat kidney and urinary bladder. The tumours related to the primary pharmacology included benign thymoma of the thymus, fibroadenoma of the mammary glands, and benign Leydig cell tumours of the testes in males; benign granulosa cell tumours of the ovaries in females; and adenoma of the pituitary pars distalis in both sexes. The tumours that were considered secondary to irritation caused by crystals/calculi included urothelial papilloma/carcinoma of the urinary bladder in males. The dose-specific animal to human exposure margins for each sex in the carcinogenicity study are summarized in

Table 1.

*Table 1:* ***Summary of Animal to Human Exposure Multiples for Enzalutamide and Its Metabolites in Rats***

| Analytes | Human AUC† (µg·h/mL) | Exposure Multiples (Day 178) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 10 mg/kg/day | | 30 mg/kg/day | | 100 mg/kg/day | |
| | | Male | Female | Male | Female | Male | Female |
| Enzalutamide | 322 | 0.28× | 0.34× | 0.76× | 0.89× | 1.42× | 1.92× |
| M1 | 193 | 0.17× | 0.19× | 0.44× | 0.54× | 1.66× | 1.51× |
| M2 | 278 | 0.02× | 0.004× | 0.06× | 0.01× | 0.12× | 0.04× |

Exposure multiples: $AUC_{24h}$ in each sex animals/$AUC_{24h}$ in humans.

M1: metabolite MDPC0001, a carboxylic acid derivative; M2: metabolite MDPC0002, *N*-desmethyl-enzalutamide.

† Day 49 after administration of enzalutamide 160 mg (9785-CL-0007)

## 2.2.4. Ecotoxicity/environmental risk assessment

*Table 2: Summary of main study results*

| **Substance (INN/Invented Name): Enzalutamide (Xtandi)** | | | |
|---|---|---|---|
| **CAS-number (if available): 873857-62-6** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 | 2.99 at pH7 | Potential PBT (No) |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | 2.99 at pH7 | not B |
| | BCF | Not determined | |
| Persistence | DT50 or ready biodegradability | < 40 days fresh water >180 days in fresh sediment | vP |
| **PBT-statement :** | The compound is not considered vP | | |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 0.047 | µg/L | > 0.01 threshold |
| Other concerns (e.g. chemical class) | | | Potential endocrine disruptor |
| ***Phase II Physical-chemical properties and fate*** | | | |
| **Study type** | **Test protocol** | **Results** | **Remarks** |
| Adsorption-Desorption | OECD 106 | $K_{oc}$ (sandy loam) =436<br>$K_{oc}$ (clay loam) =612<br>$K_{oc}$ (clay loam) =238<br>$K_{oc}$ (Sludge)=945<br>$K_{oc}$ (Sludge)=870 | Phase II Tier B terrestrial compartment studies are not necessary |
| Ready Biodegradability Test | OECD 301 | Not conducted | Considered not ready biodegradable |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | <u>Calwich Abbey lake</u><br>$DT_{50,\ water\ (20°)}$ =21.2 d<br>$DT_{50,\ sediment\ (20°)}$ =178 d<br>$DT_{50,\ whole\ system\ (20°)}$ =242 d<br>$DT_{50,\ water\ (12°)}$ =44.9 d<br>$DT_{50,\ sediment\ (12°)}$ =378.8 d<br>$DT_{50,\ whole\ system\ (12°)}$ =515 d<br><br>Swiss lake<br>$DT_{50,\ water\ (20°)}$ =24.9 d<br>$DT_{50,\ whole\ system\ (20°)}$ =198 d<br>$DT_{50,\ water\ (12°)}$ =53 d<br>$DT_{50,\ whole\ system\ (12°)}$ =421 d | vP in the aquatic environment |

| | | | | | |
|---|---|---|---|---|---|
| | | % shifting to sediment =57.5% and 51.9% at D103 | | | |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*Species* | OECD 201 | NOEC | 1370 | µg/L | *Pseudokirchneriella subcapitata.* |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | 318 | µg/L | *Daphnia magna* |
| Fish, Early Life Stage Toxicity Test/*Species* | OECD 210 | NOEC | 971 | µg/L | *Brachydanio rerio* |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | NOEC | $1x10^6$ | µg/L | |
| Fish Sexual Development Test | OECD 234 | NOEC | 890 | µg/L | *Pimephales promelas* |
| ***Phase IIb Studies*** | | | | | |
| Sediment dwelling organism | OECD 218 | NOEC | 23.4 | mg/ kg | *Chironomus riparius* |

Enzalutamide is not a PBT substance.

Considering the above data, enzalutamide is not expected to pose a risk to the environment.

## 2.2.5. Discussion on non-clinical aspects

No additional nonclinical pharmacology and pharmacokinetic studies were submitted. This is acceptable since the nonclinical data available from previous submissions are considered sufficient to support the newly claimed indication.

With regards to carcinogenicity, the daily oral administration of enzalutamide for 26 weeks did not demonstrate any neoplastic findings, indicative of a lack of carcinogenic potential in the Tg rasH2 mice at a dose of ≤ 20 mg/kg per day. However, taking into account that the plasma exposure levels at 20 mg/kg/day (348 µg.h/mL and 286 µg.h/mL, in females and males respectively) were similar to the clinical exposure in metastatic CRPC patients receiving 160 mg/kg/day (322 µg.h/mL) and, the AUC24h for M1 and M2 ranged from 0.08 to 0.21-fold of those in humans, the carcinogenicity potential of enzalutamide cannot be discarded.

In the 13-week DRF study in Wistar Han (WH) rats, enzalutamide was found to be well-tolerated. Based on the saturation of absorption, as evidenced by a lack of a dose-dependent exposure increase and generally similar findings at 100 and 200 mg/kg/day, the 100 mg/kg/day was selected as the high dose for the 104-week carcinogenicity study, with the low (10 mg/kg/day) and mid (30 mg/kg/day) dose levels selected to cover a wide range of clinical exposure margins and study dose responses.

A 2 year carcinogenicity study in rats Wistar Han (both sexes) has been completed in line with ICH S1A guideline. In this study (dose levels: 0, 10, 30 and 100 mg/kg per day), the increased incidences of the following tumours were considered treatment-related in male Wistar Han (WH) rats: Leydig cell tumour in the testis (≥10 mg/kg per day); benign thymoma in the thymus (≥10 mg/kg per day); and urothelial papilloma/carcinoma in the urinary bladder, adenoma of pars distalis in the pituitary and fibroadenoma in the mammary gland (100 mg/kg per day).

In female WH rats, treatment-related increases in adenoma of pars distalis in the pituitary (≥ 30 mg/kg per day) and benign granulosa cell tumour in the ovary (100 mg/kg per day) were noted.

Except for the urinary bladder, these tumours were observed in organs that are regulated via the hypothalamic-pituitary-gonadal hormone axis and may be related to the pharmacological activity of enzalutamide. Leydig cell tumours in rats are generally accepted as not relevant to humans [Cook et al, 1999]. The human relevance of thymoma, pituitary adenoma, granulosa cell tumour in the ovary and mammary fibroadenoma in rats cannot be ruled out.

Urothelial papilloma/carcinoma in the urinary bladder could be induced by continuous local irritation of the epithelium by crystals or calculi that consist of excreted carboxylic acid metabolite. Calculi and crystals were observed in rat urinary bladders. However, no obvious mechanistic rationale to explain specifically this malignancy can be established. At 10, 30 and 100 mg/kg per day, the exposure multiples of enzalutamide in male rats were 0.28-, 0.76- and 1.4-fold, respectively, of the exposure in humans taking enzalutamide 160 mg/day, while those of the inactive carboxylic acid metabolite were 0.17-, 0.44- and 1.7-fold, respectively. At all dose levels, the exposure multiple of the active metabolite, N-desmethyl enzalutamide, in male rats was less than 0.12-fold. In conclusion, taking into account that exposure levels, based on AUC, achieved in the study, for enzalutamide plus its metabolite M2, were less than or similar to those in prostate cancer patients at the recommended dose of 160 mg/day (322 µg.h/mL), urinary bladder carcinogenicity potential of enzalutamide in human cannot be excluded . Results of PROSPER clinical trial, assessed as part of the procedure EMEA/H/C/002639/II/0049, support that the clinical relevance of these types of tumours observed in rats cannot be ruled out. The results of the carcinogenicity study have been reflected in section 5.3 of the SmPC as part of variation EMEA/H/C/002639/II/0049.

The MAH has submitted an updated ERA to consider the potential impact of the increased patient population from the new indication on the environmental risk assessment of enzalutamide. Furthermore, in the original ERA, the degradation half-lives in aquatic sediment systems were reported at 20°C. The current guidance is to report half-lives at 12°C which more accurately reflects the temperature of European surface waters. This amendment quotes the degradation half-lives at 12°C and considers the environmental impact of these extrapolated half-lives. Based on the assessment of the updated ERA, enzalutamide is unlikely to represent a risk to the aquatic or terrestrial environments.

### 2.2.6. Conclusion on the non-clinical aspects

Overall, the non-clinical package is considered adequate to support this application to extend the indication to patients with metastatic hormone sensitive prostate cancer.

Considering the above data, enzalutamide is not expected to pose a risk to the environment.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

*Table 3: Tabular overview of clinical studies*

| Study Identifier | Clinical Phase and Blinding | Study Population | No. Treated Patients | Study Drugs and Dose | Primary Endpoints | Safety Data Collected |
|---|---|---|---|---|---|---|
| ARCHES | Phase 3 Double-blind | Patients with mHSPC | 572 enzalutamide+ADT, 574 placebo+ADT | enzalutamide 160 mg/day, placebo | rPFS† | Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death |
| AFFIRM‡ | Phase 3 Double-blind and open-label | Patients with progressive CRPC who have been previously treated with docetaxel-based chemotherapy | 800 enzalutamide, 399 placebo | enzalutamide 160 mg/day, placebo | OS | Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death |
| PREVAIL§ | Phase 3 Double-blind and open-label | Chemotherapy-naïve patients with asymptomatic or mildly symptomatic progressive metastatic CRPC | 871 enzalutamide, 844 placebo | enzalutamide 160 mg/day, placebo | OS, rPFS | Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death |
| Asian PREVAIL (excl. site 105) | Phase 3 Double-blind | Chemotherapy-naïve patients who have progressive, metastatic prostate cancer after ADT | 198 enzalutamide, 190 placebo | enzalutamide 160 mg/day, placebo | TTPP¶ | Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death |
| TERRAIN†† | Phase 2 Double-blind and open-label | Patients with metastatic prostate cancer whose disease has progressed while on LHRH agonist/antagonist or after receiving a bilateral orchiectomy | 183 enzalutamide, 189 bicalutamide | enzalutamide 160 mg/day, bicalutamide 50 mg/day | PFS‡‡ | Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death |
| STRIVE§§ | Phase 2 Double-blind and open-label | Patients with metastatic and nonmetastatic prostate cancer whose disease has progressed while on LHRH agonist/antagonist or after receiving a bilateral orchiectomy | 197 enzalutamide, 198 bicalutamide | enzalutamide 160 mg/day bicalutamide 50 mg/day | PFS¶¶ | Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death |
| PROSPER | Phase 3 Double-blind | Patients with nonmetastatic CRPC | 930 enzalutamide, 465 placebo | enzalutamide 160 mg/day, placebo | MFS††† | Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death |
| ENZAMET | Phase 3 Open-label | Patients with mHSPC receiving treatment with first-line medical or surgical ADT and optional concurrent docetaxel | 563 enzalutamide, 558 nonsteroidal antiandrogen‡‡‡ | enzalutamide 160 mg/day, nonsteroidal antiandrogen ‡‡‡ | OS | Drug exposure, grade 3 or 4 AEs and SAEs of any grade, laboratory assessment§§§, death |

Data cutoff dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; TERRAIN: 17 Feb 2018, STRIVE: 30 May 2018 and ENZAMET: 28 Feb 2019.

### 2.3.2. Clinical Pharmacology

No new pharmacology data were submitted in support of this application.

### 2.3.3. Discussion and conclusion on clinical pharmacology

No additional data have been provided with this submission which is considered acceptable as the clinical pharmacology properties of enzalutamide were described in detail in the original marketing application and previous supplemental applications with new clinical data consistent with results in the original marketing application. All studies included in support of this application used enzalutamide at the approved dose of 160 mg/day, which has been established as a generally safe and efficacious dose in patients with CRPC and mHSPC. Available clinical pharmacology data are considered sufficient to support this application.

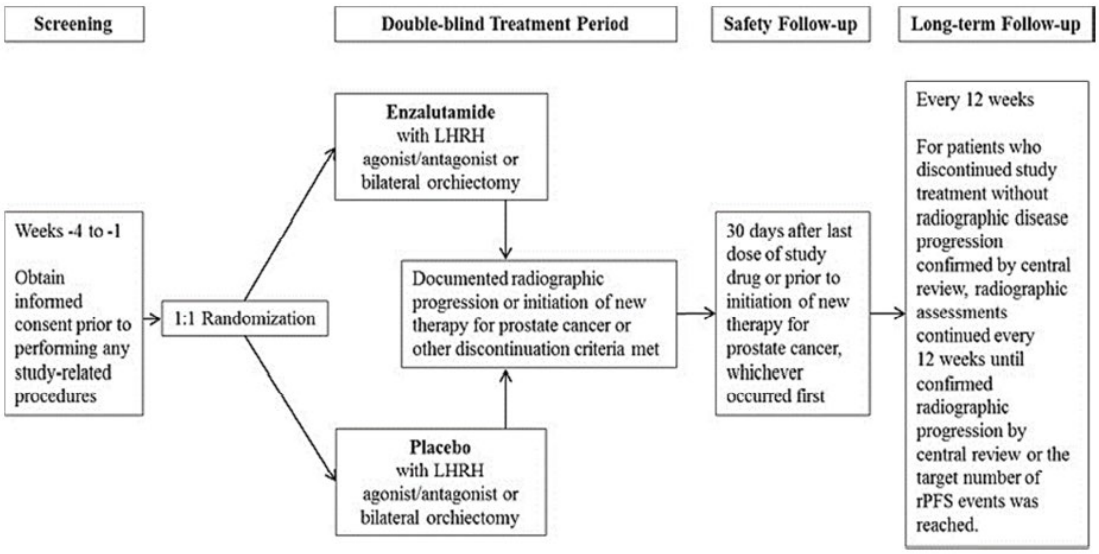
## *2.4. Clinical efficacy*

### 2.4.1. Dose response study

No new dose responses studies were submitted with this application. The posology for the proposed indication (enzalutamide 160 mg administered orally once daily) is the daily dose authorised for other indications.

## 2.4.2. Main study

**<u>ARCHES (Study 9785-CL-0335)</u>: a multinational, Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of enzalutamide plus ADT vs placebo plus ADT in patients with mHSPC**




While on study treatment, patients returned to the study site at weeks 5 and 13 and every 12 weeks thereafter. At week 5, general activities included brief physical examination, vital signs, clinical laboratory and PSA testing, assessment of ECOG performance status, adverse events, concomitant medications reviews and study drug dispensing. At week 13 and every 12 weeks thereafter until treatment discontinuation, general activities included radiographic assessments (including a chest x-ray or CT/MRI), testosterone testing and completion of patient-reported outcome questionnaires in addition to the activities performed at week 5.

CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; LHRH: luteinizing hormone-releasing hormone; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival

*Figure 1: ARCHES Study Schematic*

## *Methods*

## Study participants

<u>Inclusion criteria</u>

1. Approved written informed consent and privacy language as per national regulations must have been obtained from the patient or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Patient was considered an adult according to local regulation at the time of signing informed consent.
3. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell or small cell histology. Specific to patients enrolled in France, histological diagnosis was required.
4. Metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue). Patients whose disease spread was limited to regional pelvic lymph nodes were not eligible.

5. Once randomized at day 1, patient maintained ADT with an LHRH agonist or antagonist during study treatment or had a history of bilateral orchiectomy (i.e., medical or surgical castration).
6. ECOG performance status of 0 or 1 at screening.
7. Estimated life expectancy of ≥ 12 months as assessed by the investigator.
8. Patient able to swallow the study drug and comply with study requirements.
9. Used 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) from screening through 3 months after the last dose of study drug
10. Used a condom throughout the study if engaging in sexual intercourse with a pregnant woman.
11. Agreement of not to donate sperm from first dose of study drug through 3 months after the last dose of study drug.
12. Agreement of not to participate in another interventional study while on treatment.

Exclusion criteria

1. Patient had received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer (the following exceptions are permitted):
    - Up to 3 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1, with no radiographic evidence of disease progression or rising PSA levels prior to day 1;
    - Patient could have had 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease (M1) if it was administered at least 4 weeks prior to day 1;
    - Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy;
    - Up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day1 if patient was treated with docetaxel, with no radiographic evidence of disease progression or rising PSA levels prior to day 1;
    - Prior ADT given for < 39 months in duration and > 9 months before randomization as neoadjuvant/adjuvant therapy.
2. Major surgery within 4 weeks prior to day 1.
3. Treatment with 5-α reductase inhibitors (finasteride, dutasteride) within 4 weeks prior to day 1.
4. Patient had received treatment with estrogens, cyproterone acetate or androgens within 4 weeks prior to day 1.
5. Treatment with systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone within 4 weeks prior to day 1, intended for the treatment of prostate cancer.
6. Treatment with herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels within 4 weeks prior to day 1.

7. Prior aminoglutethimide, ketoconazole, abiraterone acetate or enzalutamide for the treatment of prostate cancer or participation in a clinical study of an investigational agent that inhibits the AR or androgen synthesis.

8. Patient received investigational agent within 4 weeks prior to day 1.

9. Known or suspected brain metastasis or active leptomeningeal disease

10. History of another invasive cancer within 3 years of screening, with the exception of fully treated cancers with a remote probability of recurrence based on investigator assessment.

11. Absolute neutrophil count < 1500/µL, platelet count < 100000/µL or haemoglobin <10 g/dL (6.2 mmol/L) at screening. NOTE: May not have received any growth factors within 7days or blood transfusions within 28 days prior to the haematology values obtained at screening.

12. Total bilirubin ≥ 1.5 x the upper limit of normal (ULN) (except patients with documented Gilbert's disease), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 x the ULN at screening. Creatinine > 2 mg/dL (177 µmol/L) at screening. Albumin < 3.0 g/dL (30 g/L) at screening.

13. Creatinine > 2 mg/dL (177 µmol/L) at screening

14. Albumin < 3.0 g/dL (30 g/L) at screening

15. History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma, brain arteriovenous malformation).

16. History of loss of consciousness or transient ischemic attack within 12 months prior to day 1.

17. Clinically significant cardiovascular disease, including the following: Myocardial infarction within 6 months prior to screening; Unstable angina within 3 months prior to screening; New York Heart Association class III or IV congestive heart failure or a history of New York Heart Association class III or IV congestive heart failure unless a screening echocardiogram or multigated acquisition scan performed within 3 months before the randomization date demonstrates a left ventricular ejection fraction ≥45%; History of clinically significant ventricular arrhythmias (e.g., sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes); History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place; Hypotension as indicated by systolic blood pressure < 86 mmHg at screening; Bradycardia as indicated by a heart rate of ≤ 45 beats per minute on the screening ECG; Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mmHg or diastolic blood pressure >105mmHg at screening.

18. Gastrointestinal disorder affecting absorption

19. Concurrent disease, infection or comorbid condition that interfered with the ability of the patient to participate in the study,

20. Patient had received bisphosphonates or denosumab within 2 weeks prior to day 1 unless administered at stable dose or to treat diagnosed osteoporosis.

21. Hypersensitivity reaction to the active pharmaceutical ingredient or any of the study capsule components

## Treatments

Study drug consisted of enzalutamide provided as 40-mg capsules or tablets to be taken as 160 mg (4 capsules or tablets) orally once daily or enzalutamide-matching placebo. Treatment was to be continued until the radiographic disease progression was documented, the patient started another investigational agent or new therapy for treatment of prostate cancer, unacceptable toxicity or any other discontinuation criteria were met. All subjects were required to maintain ADT during study treatment, either using an LHRH agonist/antagonist or having a history of bilateral orchiectomy.

During the study, subjects who experience a National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) guidelines (version 4.03) grade 3 or higher AE (except liver function test [LFT] AE) toxicity that is attributed to the study drug and cannot be ameliorated by the use of adequate medical intervention and/or dose reduction may interrupt study drug treatment for 1 week or until the toxicity grade improves to grade 2 or lower in severity. Study drug may be restarted at the original dose (160 mg/day) or a reduced dose (120 mg or 80 mg/day) in consultation with the Medical Monitor. After dose reduction, based on subject tolerance, study drug may be increased to a maximum dose of 160 mg/day per Investigator discretion.

Enzalutamide must be interrupted during the evaluation of symptoms suspicious of posterior reversible encephalopathy syndrome (PRES) (headache, lethargy, confusion, blindness and other visual and neurological disturbances, with or without associated hypertension).

Restarting treatment at a reduced dose or after treatment interruption for > 2 weeks must be discussed with the Medical Monitor.

## Objectives

Primary objective

The primary objective was to determine the benefit of enzalutamide plus ADT as compared to placebo plus ADT as assessed by radiographic progression-free survival (rPFS) based on Independent Central Review (ICR).

Secondary objectives

Key secondary objectives of the study were to evaluate the benefit of enzalutamide plus ADT compared with placebo plus ADT as measured by Overall Survival (OS), time to PSA progression, time to start of new antineoplastic therapy, PSA undetectable (< 0.2 ng/mL) rate, Overall Response Rate (ORR) and time to deterioration of urinary symptoms.

Additional secondary objectives were to compare time to first symptomatic skeletal event (SSE); time to castration resistance; Quality of Life (QoL) as measured by Quality of Life Questionnaire-Prostate 25 (QLQ-PR25), Functional Assessment of Cancer Therapy – Prostate (FACT-P) and EuroQoL Group 5-Dimension 5-Level (EQ-5D-5L), and in particular the time to deterioration in QoL using the FACT-P global score; worsening of pain assessed by Brief Pain Inventory-Short Form (BPI-SF); and to evaluate safety of enzalutamide plus ADT as compared to placebo plus ADT.

Exploratory objective (North America sites only)

The study also included an exploratory objective to determine gene mutations potentially related to resistance of enzalutamide plus ADT as assessed by DNA mutation testing (i.e., sequence analysis of

circulating free tumour DNA) in plasma. This objective was limited to patients who signed a separate genotyping informed consent form at North American sites.

## Outcomes/endpoints

Primary endpoint

The primary endpoint was rPFS (based on central review), where rPFS events were defined as objective evidence of radiographic progression disease (rPD) as assessed by ICR or death, as follows:

- Death from any cause within 24 weeks (2 scan cycles) from study drug discontinuation.
- rPD was defined by RECIST 1.1 for soft tissue disease or the appearance of 2 or more new bone lesions on bone scan. Unconfirmed disease progression on a bone scan at week 13 was not to be considered an event. The study-specified documentation and confirmation required for the determination of rPD are listed in Table 4. The date of rPD was the date the first objective evidence of rPD was documented rPFS (based on central review).

*Table 4 Study-specified Documentation for Radiographic Evidence of Disease Progression vs PCWG2 Criteria*

| Date Progression Detected (Visit)† | ARCHES-specified Primary Endpoint Definition | | | PCWG2 Criteria for Primary Endpoint |
|---|---|---|---|---|
| | Criteria for Progression | Criteria for Confirmation of Progression (Requirement and Timing) | Criteria for Documentation of Disease Progression on Confirmatory Scan | |
| Week 13 | Bone lesions: ≥ 2 new lesions compared to baseline bone scan | Timing: ≥ 6 weeks after progression identified or at week 25 visit | ≥ 2 new bone lesions on bone scan compared to week 13 scan (≥ 4 new lesions compared to baseline bone scan)† | No change |
| | Soft tissue lesions: progressive disease on CT or MRI by RECIST 1.1 | No confirmatory scan required for soft tissue disease progression | Not applicable | Not applicable |
| Week 25 or Later | Bone lesions: ≥ 2 new lesions on bone scan **compared to best response on treatment** (i.e., smallest number bone lesions on bone scan during treatment period) | No confirmatory scan required | Not applicable | Bone lesions: ≥ 2 new lesions on bone scan **compared to baseline** (or compared to week 13 in case of ≥ 2 new bone lesions appearing at week 13) |
| | Soft tissue lesions: progressive disease on CT or MRI by RECIST 1.1 | No confirmatory scan required for soft tissue disease progression | Not applicable | Not applicable |

CT: computed tomography; MRI: magnetic resonance imaging; PCWG2: Prostate Cancer Clinical Trials Working Group 2; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1.

† Progression detected by bone scan at an unscheduled visit prior to week 25 required the same criteria for documentation of disease progression as week 13 with a confirmatory scan at least 6 weeks later or at the next scheduled scan.

In patients with an rPFS event, rPFS was to be calculated as the time from the date of randomisation to the first objective evidence of rPD at any time or death up to 24 weeks after study drug discontinuation without documented radiographic progression, whichever occurred first. In patients with no rPFS event, rPFS was to be censored on the date of last evaluable radiographic assessment prior to the data analysis cut-off date. In patients with no baseline radiographic assessment, with no postbaseline radiographic assessments or with all postbaseline radiographic assessments documented as "not evaluable (NE)," the rPFS was to be censored on the date of randomisation.

Key Secondary endpoints

- Overall survival (OS)

OS was defined as the time from randomisation to death from any cause. All events of death were included. For patients who were alive at the time of the data cut-off date, OS time was to be censored on the last date the patient was known to be alive or the cut-off date, whichever occurred first.

- Time to PSA progression

Time to PSA progression was calculated as the time from randomisation to the date of first observation of PSA progression. A PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir (i.e., lowest PSA value observed postbaseline or at baseline), which was confirmed by a second consecutive value at least 3 weeks later. Only results from PSA samples taken before the start of any new prostate cancer therapy after the start of study drug were to be considered.

- Time to start of new antineoplastic therapy

Time to start of new antineoplastic therapy was defined as the time from randomisation to the date of first dose administration of the first antineoplastic therapy. In patients with no new antineoplastic therapy initiated for prostate cancer after randomisation, time to start of new antineoplastic therapy was to be censored on the last visit date or the date of randomisation, whichever occurred last.

- PSA undetectable rate

PSA undetectable rate was defined as the percentage of patients with detectable (≥0.2 ng/mL) PSA at baseline, which became undetectable (<0.2 ng/mL) during study treatment. Only results from PSA samples taken before the start of any new prostate cancer therapy were to be considered.

- Overall response rate (ORR)

This was defined as the percentage of intent-to-treat (ITT) patients with measurable disease at baseline who achieved a complete response (CR) or partial response (PR) (unconfirmed responses) in their soft tissue disease using the RECIST 1.1 criteria. In addition to ORR, the best overall response was also determined for each patient based on a combined response assessment. The best combined (i.e., overall) response was the best response assessment, based on the RECIST 1.1 assessment for soft tissue lesions on CT/MRI and the response assessment for bone lesions on bone scans, reported at any time during the study. Bone lesions were assessed for CR, non-CR/non-PD and PD. As bone lesions were evaluated differently than soft tissue lesions, the possible categories changed when considering bone and soft tissue responses together. "CR" reflects patients with CR for all pre-existing metastases and "PD" reflects patients with PD in either soft tissue or bone. In this setting, "PR" includes patients with CR or PR in soft tissue and who remained non-CR/non-PD in bone lesions and those patients with PR in soft tissue-only disease.

- Time to deterioration of urinary symptoms

The deterioration of urinary symptoms was based on responses to a selected subset of symptoms from the "urinary symptoms" subscale of the QLQ-PR25 questionnaire (3 items: Q31 to Q33). Deterioration in urinary symptoms was defined as an increase in the urinary symptoms' subscale score by ≥ 50% of the standard deviation observed in the urinary symptoms' subscale score at baseline. The time to confirmed deterioration in urinary symptoms was defined as the time interval to the first deterioration in urinary symptoms that was confirmed by a second consecutive assessment of the deterioration.

<u>Other secondary endpoints</u>

- Time to castration resistance: defined as the time from randomisation to the first castration resistance event. A castration resistance event was defined as the occurrence of rPD by ICR, PSA progression, or SSE, whichever occurred first, with castrate levels of testosterone (<50 ng/dL).

- Time to Deterioration of Quality of Life (FACT-P): The time to deterioration of QoL was defined as the time interval from the date of randomization to the first date a decline from baseline of 10 points or more in the FACT-P total score was recorded.
- Time to first symptomatic skeletal event (SSE): an SSE was defined as radiation to bone, surgery to bone, a clinically apparent pathological bone fracture or a spinal cord compression. In patients with an SSE, the time to the first SSE was defined as the time from randomisation to the occurrence of the first SSE prior to the data analysis cut-off date.
- Time to pain progression: defined as time from randomization to the first pain progression event, which was an increase of ≥ 30% from baseline in the average Brief Pain Inventory-Short Form (BPI-SF) item scores.
- Patient reported outcomes (PRO) using FACT-P, EQ-5D-5L, QLQ-PR25, BPI-SF.

## Sample size

Approximately 1,100 patients (550 patients per treatment group) were planned to be randomised in the study. The final analysis of the primary endpoint (rPFS) was to be conducted when a minimum of 262 progression events had occurred, based on the following considerations:

1. A target hazard ratio (HR) was 0.67. The expected median rPFS for the placebo plus ADT group was 20 months as measured from the date of randomisation. Under the assumption of an exponential distribution, a target HR of 0.67 corresponds to approximately 50% increase in median rPFS for the enzalutamide plus ADT group relative to the placebo plus ADT group (approximately 30 vs 20 months).
2. 262 rPFS events (radiographic progression at any time or death from any cause within 24 weeks after study drug discontinuation, whichever occurred first) provide 90% power to detect the target HR based on a 2-sided log-rank test and a significance level of 0.05.

In addition, the study was powered for OS. Specifically, 342 death events were required to provide 80% power to detect a target HR of 0.73 with a target difference in Kaplan-Meier estimated median of approximately 15 months (40 months for placebo plus ADT vs 55 months for enzalutamide plus ADT) at the 0.04 significance level under the assumption of an exponential distribution. This significance level was chosen to apply a parallel testing strategy between OS and some other secondary endpoints (with allocated type I error rate of 0.01).

## Randomisation

Randomisation was performed via the Interactive Response Technology (IRT) system and treatment assigned in a 1:1 ratio to enzalutamide 160 mg/day or placebo. Subjects were to be stratified by prior docetaxel (None, 1-5 cycles, 6 cycles) and disease volume (low versus high). High-volume disease was defined as metastases involving the viscera or, in the absence of visceral lesions, the presence of 4 or more bone lesions, at least 1 of which in a bony structure beyond the vertebral column and pelvic bone. Prior docetaxel therapy was defined as 1 or more cycles of docetaxel but no more than 6 cycles.

The categories '1-5 cycles' and '6 cycles' used at randomisation for the stratification factor 'prior docetaxel use' were regrouped in the stratified analyses because of the small number of randomized patients with 1 to 5 cycles of docetaxel as prior medication. This stratification factor therefore became prior docetaxel use (yes versus no) in the stratified analyses.

## Blinding (masking)

This was a double-blind study.

Based on substantial Amendment 2 (dated 14 Dec 2017), unblinding of study treatment assignment could be performed to determine the next course of therapy if a patient discontinued due to disease progression.

At the time of primary endpoint analysis and recommendation of the Data Safety Monitoring Board (DSMB) on study continuation, patients were eligible to transition to an optional open-label extension portion of the current study. The open-label extension period was added in Substantial Amendment 3 to the study protocol.

## Statistical methods

The following analysis sets were used for the analyses:

1. The ITT population, defined as all patients who were randomised in this study. The ITT population was analysed by treatment group as randomised (i.e., treatment group based on randomization assignment) regardless of study drug administration. Unless otherwise specified, efficacy analyses were performed on the ITT population.
2. The safety population, defined as all randomised patients who received at least 1 dose of study drug. The safety population was used to conduct safety analyses by treatment group as treated (i.e., based on the actual study drug the patient received for the greater number of days rather than the study drug to which the patient was randomised).

Primary efficacy endpoint: rPFS

The effect of enzalutamide plus ADT compared to placebo plus ADT was tested using a stratified log-rank test at the level of significance of 0.05 (2-sided). The stratification factors were prior docetaxel use (yes vs no) and disease volume (low vs high); both factors were used at randomisation. The analysis was to be conducted when at least 262 rPFS events had occurred.

Kaplan-Meier methods were used to estimate the distribution of rPFS events by treatment group. The median rPFS was estimated using the corresponding $50^{th}$ percentile of Kaplan-Meier estimates. A 2-sided 95% Confidence interval (CI) was provided for this estimate by use of the Brookmeyer and Crowley method. The benefit of enzalutamide plus ADT compared to placebo plus ADT was summarised by a single HR with its 95% CI based on a Cox regression model stratified for prior docetaxel use and disease volume.

The following sensitivity analyses were performed to evaluate the robustness of the rPFS results:

- Sensitivity analysis 1: impact of study drug discontinuation as an additional event.
- Sensitivity analysis 2: impact of new antineoplastic therapy and occurrence of an SSE as additional events.
- Sensitivity analysis 3: impact of all deaths (with no time limit) as events
- Sensitivity analysis 4: impact of rPD documented between per-protocol visits
- Sensitivity analysis 5: 'missing' data impact – last scan not documented as not evaluable
- Sensitivity analysis 6: 'missing' data impact – absence of 2 consecutive scans
- Sensitivity analysis 7: censoring rPD on competing risks: new antineoplastic therapy and occurrence of an SSE

- Sensitivity analysis 8: 'missing' data impact and censoring rPD on competing risks: new antineoplastic therapy, occurrence of an SSE and study drug discontinuation in patients with M1 based on ICR assessments
- Sensitivity analysis 9: limited to M1 patients who were identified from the baseline assessments made by ICR
- Sensitivity analysis 10: impact of rPD documented by the investigators
- Sensitivity analysis 11: impact of rPD according to PCWG2 criteria [Ryan et al, 2012] and documented by the investigators
- Sensitivity analysis 12: impact of rPD according to PCWG2 criteria and documented by ICR

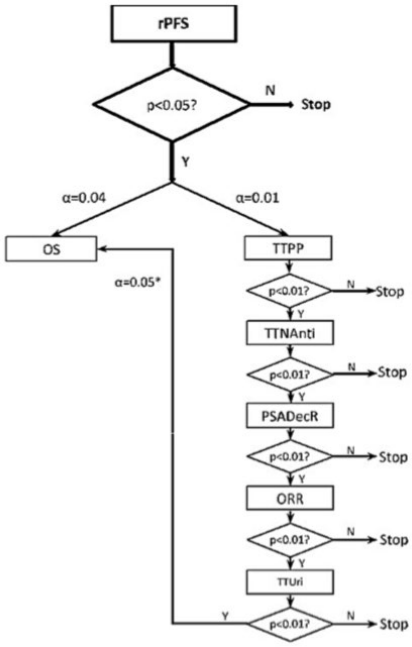
These sensitivity analyses were conducted on the ITT population using the same analysis methods as described for the primary analysis.

Subgroup analyses of rPFS were performed to determine whether the treatment effect was concordant among subgroups. Subgroup analyses were not adjusted for the stratification factors used at randomisation. Subgroup assessments included the following: age (<65 years vs ≥65years), geographic region, Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0 vs 1), Gleason score at initial diagnosis (<8 vs ≥8), disease location at baseline (bone only, soft tissue only, both bone and soft tissue), baseline PSA (≤ overall median vs > overall median), volume of disease at baseline (low vs high), prior docetaxel use (yes vs no) and prior use of ADT or orchiectomy (yes vs no).

Key secondary efficacy endpoint analyses

All secondary endpoint analyses were performed at the time of the rPFS final analysis (i.e., when at least 262 rPFS events had occurred).

The primary rPFS endpoint was tested at a 0.05 (2-sided) significance level. Once testing confirmed this primary endpoint was statistically significant, the 6 key secondary endpoints were tested utilizing a method to preserve the family-wise 2-sided type I error rate at 0.05. A parallel testing strategy was used to test OS with an allocated type I error rate of 0.04 and the remaining 5 key secondary endpoints (time to PSA progression, time to start of a new antineoplastic therapy, rate of PSA decline to <0.2ng/mL, ORR and time to deterioration in urinary symptoms from the QLQ-PR25) with an allocated type I error rate of 0.01.




ORR: objective response rate; OS: overall survival; PSA: prostate-specific antigen; PSADecR: rate of PSA decline to < 0.2 ng/mL; rPFS: radiographic progression-free survival; TTNAnti: time to start of new antineoplastic therapy; TTPP: time to PSA progression; TTUri: time to deterioration in urinary symptoms from the Quality of Life Questionnaire-Prostate 25 module

*OS was tested at 0.05 only, if all other 5 key secondary endpoint analyses were statistically significant at 0.01.

*Figure 2: Testing Strategy for the Primary and Key Secondary Efficacy Endpoints*

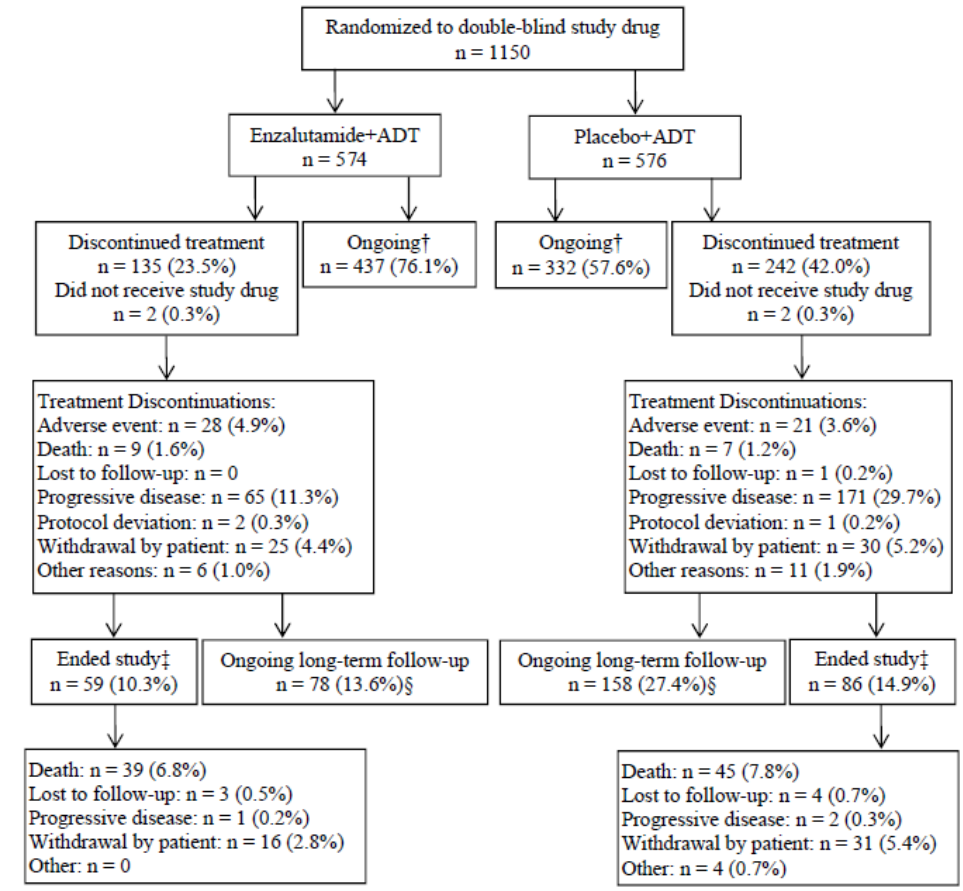
One interim analysis and a final analysis were planned for OS. The interim analysis of OS was to be performed at the time of the rPFS final analysis (i.e., when at least 262 rPFS events had occurred). The exact significance level for this analysis, calculated using the O'Brien-Fleming alpha spending function [Lan & DeMets, 1983], was used to determine the stopping boundaries based on the number of events observed at the interim analysis and control the overall 2-sided alpha at 0.05 or at 0.04. If the interim analysis of OS was not statistically significant, the final analysis of OS was planned for when approximately 342 deaths were observed to ensure an adequate number of events. At the time of the planned final analysis of OS, no additional analyses of other efficacy endpoints were to be conducted.

Additional secondary endpoint analyses

Time to first SSE, time to castration resistance, time to deterioration of QoL based on FACT-P and time to pain progression were to be analysed using the same analysis methods as for rPFS. All QoL assessment data were also summarized descriptively by study visit.

## *Results*

### Participant flow




Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy.

† Patients were still on-treatment by the cutoff date (or no documentation of treatment discontinuation was received).

‡ Includes patients who did not complete any long-term follow-up visits or ended their participation in the long-term follow-up.

§ Patients in long-term follow-up after treatment discontinuation

**Figure 1.** Patient disposition (All randomised patients)

A total of 1146 (99.7%) patients received at least 1 dose of study drug (572 [99.7%] in the enzalutamide plus ADT group and 574 [99.7%] in the placebo plus ADT group) and were included in the safety population. A total of 769 (66.9%) patients remained on study drug as of the data cut-off date (437 [76.1%] in the enzalutamide plus ADT group and 332 [57.6%] in the placebo plus ADT group.

### Recruitment

From 21 March 2016 to 14 October 2018 (the study data cut-off date), 1150 patients were randomly assigned at a 1:1 ratio to treatment with enzalutamide plus ADT (574 patients) or placebo plus ADT (576 patients); 1146 patients received at least 1 dose of enzalutamide plus ADT (572 patients) or placebo plus

ADT (574 patients). There were 204 study sites in 24 countries in North and South America, Europe, the Asia-Pacific region and Israel that randomised patients in this study. The countries with the highest patient enrolment were the Russian Federation (139, 12.1%), the US (122, 10.6%), Japan (92, 8.0%) and Slovakia (81,7.0%). Enrolment by site ranged from 1 to 40 patients.

## Conduct of the study

Analysis sets

*Table 5 Analysis Sets (All Randomised Patients)*

| | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) | Total (n = 1150) |
|---|---|---|---|
| ITT Population†, n (%) | 574 (100) | 576 (100) | 1150 (100) |
| Safety Population ‡, n (%) | 572 (99.7) | 574 (99.7) | 1146 (99.7) |

Data cutoff date: 14 Oct 2018

All randomized patients. The denominator for percentages is the number of patients randomized for each treatment group and overall.

ADT: androgen deprivation therapy; ITT: intent-to-treat.

† All randomized patients as assigned at randomization.

‡ All randomized patients who took at least 1 dose of study drug (based on the actual treatment received).

Protocol amendments

The original study protocol was dated 10 Nov 2015. There were 6 amendments to the protocol, including 3 substantial amendments. Major changes from the substantial amendments are summarised below.

*Substantial Amendment 1* (dated 02 Jun 2016) included the following major changes:

1. Added 2 exclusion criteria to exclude patients who had not received bisphosphonates or denosumab at a stable dose (unless diagnosed with osteoporosis) and exclude patients who had shown a hypersensitivity reaction to any of the study capsule components.
2. Revised test drug information to remove information related to tablet formulations and add information related to the capsule formulation of study drug and placebo (chemical name, physical description and storage requirements).

*Substantial Amendment 2* (dated 14 Dec 2017) included the following major changes:

1. Revised the number of events required for the primary endpoint to reflect that primary analysis was to occur when 262 rPD events were confirmed by independent central imaging review. All secondary endpoints were to be evaluated at the time of primary analysis
2. Specified a step-wise approach for the statistical testing of the key secondary endpoints. To maintain the family-wise 2-sided type I error rate at 0.05, a parallel testing strategy between OS (with allocated type I error rate 0.04) and the other 4 endpoints (with allocated type I error rate 0.01) was developed. If the interim results of the OS analysis were statistically significant, no further analysis of OS would be completed.
3. Specified that unblinding of study treatment assignment could have been performed if a patient discontinued due to disease progression and in the investigator's opinion this information was necessary to determine the next course of therapy.

*Substantial Amendment 3* (dated 10 Dec 2018) included the following major changes:

1. Added an open-label extension period. Following unblinding at the end of the double-blind period and demonstration of a statistically significant advantage of enzalutamide over placebo when added to

ADT, as assessed by the primary endpoint, all eligible patients could be treated on study with open-label enzalutamide at the discretion of the patient and investigator.

2. Specific QoL assessments related to deterioration of urinary symptoms and QoL were added to the secondary endpoints.

The majority of patients were enrolled under Protocol Version 2.0 incorporating Substantial Amendment 1 Table 6.

*Table 6. Number of Patients Enrolled by Protocol Version (All Patients)*

| Protocol Version | Enzalutamide +ADT (n = 574) n (%) | Placebo +ADT (n = 576) n (%) | Screen Failures (n = 282) n (%) | Total (n = 1432) n (%) |
|---|---|---|---|---|
| Version 1.0, Original Protocol | 2 (0.3) | 2 (0.3) | 4 (1.4) | 8 (0.6) |
| Version 2.0, Substantial Amendment 1 | 572 (99.7) | 574 (99.7) | 278 (98.6) | 1424 (99.4) |

Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy.

Three country-specific non-substantial protocol amendments were implemented during the study. A non-substantial amendment was implemented on 21 Apr 2016 to require a histological diagnosis of adenocarcinoma of the prostate (in inclusion criterion 3) for entry into the study in France. A second non-substantial amendment was also implemented on 21 Apr 2016 to provide a concise summary of risk-benefit assessment and modify the risk mitigation strategy that the sponsor would maintain throughout the study to ensure safety of the subjects. A third and final non-substantial amendment was implemented on 04 Oct 2017 for Canada and the US. An exploratory objective to assess genetic mutations related to resistance of enzalutamide plus ADT was added to the study protocol. Gene mutations were to be assessed in plasma samples requiring an additional 10mL of blood to be collected at randomization, week 49, and at study treatment discontinuation. This applied only to those patients who consented to participate in this optional, exploratory analysis.

Protocol deviations

A total of 152 (13.2%) patients, 70 (12.2%) in the enzalutamide plus ADT group and 82 (14.2%) in the placebo plus ADT group, had 1 or more major protocol deviations during the study.

Major protocol deviations are grouped into the following 4 categories:

1. PD1 Entered into the study even though they did not satisfy entry criteria
2. PD2 Developed withdrawal criteria during the study and was not withdrawn
3. PD3 Received wrong treatment or incorrect dose
4. PD4 Received excluded concomitant treatment

*Table 7. Summary of Major Protocol Deviations (All Randomized Patients)*

| Protocol Deviation, n (%) | Enzalutamide +ADT (n = 574) | Placebo +ADT (n = 576) | Total (n = 1150) |
|---|---|---|---|
| Any Major Deviation | 70 (12.2) | 82 (14.2) | 152 (13.2) |
| PD1: Entered into the study even though they did not satisfy entry criteria | 51 (8.9) | 50 (8.7) | 101 (8.8) |
| PD2: Developed withdrawal criteria during the study and was not withdrawn | 2 (0.3) | 7 (1.2) | 9 (0.8) |
| PD3: Received wrong treatment or incorrect dose | 4 (0.7) | 2 (0.3) | 6 (0.5) |
| PD4: Received excluded concomitant treatment | 16 (2.8) | 28 (4.9) | 44 (3.8) |

Data cutoff date: 14 Oct 2018

Additionally, after database lock the sponsor was notified that 2 patients at 1 site each received the incorrect treatment (1 patient in the placebo group received enzalutamide, 1 patient in the enzalutamide group received placebo) for approximately 3 months between 2 study visits.

Protocol deviations categorised with respect to violations of inclusion/exclusion criteria are presented in Table 8. The most frequently violated criterion was exclusion criterion 1 (Patient had received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer) occurring in 38 (3.3%) patients in total, followed by exclusion criterion 17 (Patient had clinically significant cardiovascular disease) in 12 (1.0%) patients, inclusion criterion 4 (Patient had metastatic prostate cancer documented by positive bone scan or metastatic lesions on CT or MRI scan) in 12 (1.0%) patients and exclusion criterion 11 (Patient had absolute neutrophil count <1500/µL, platelet count <100000/µL or haemoglobin <10 g/dL [6.2 mmol/L] at screening) in 11 (1.0%) patients. All other inclusion/exclusion criteria violations occurred in <1% of patients in total.

*Table 8. Summary of Inclusion and Exclusion Criteria Deviations (All Randomized Patients)*

| Number (%) of Patients Reporting at Least 1 Deviation | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) | Total (n = 1150) |
|---|---|---|---|
| **Any Inclusion/Exclusion Criteria Deviation** | 51 (8.9) | 50 (8.7) | 101 (8.8) |
| **Inclusion Criterion** | | | |
| 3 | 0 | 2 (0.3) | 2 (0.2) |
| 4 | 9 (1.6) | 3 (0.5) | 12 (1.0) |
| 5 | 6 (1.0) | 1 (0.2) | 7 (0.6) |
| 8 | 1 (0.2) | 0 | 1 (0.1) |
| 12 | 0 | 1 (0.2) | 1 (0.1) |
| **Exclusion Criterion** | | | |
| 1 | 12 (2.1) | 26 (4.5) | 38 (3.3) |
| 3 | 4 (0.7) | 3 (0.5) | 7 (0.6) |
| 4 | 1 (0.2) | 0 | 1 (0.1) |
| 6 | 2 (0.3) | 1 (0.2) | 3 (0.3) |
| 11 | 6 (1.0) | 5 (0.9) | 11 (1.0) |
| 12 | 4 (0.7) | 2 (0.3) | 6 (0.5) |
| 13 | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| 14 | 1 (0.2) | 2 (0.3) | 3 (0.3) |
| 15 | 5 (0.9) | 1 (0.2) | 6 (0.5) |
| 17 | 5 (0.9) | 7 (1.2) | 12 (1.0) |
| 20 | 2 (0.3) | 2 (0.3) | 4 (0.3) |

Data cutoff date: 14 Oct 2018

## Baseline data

*Table 9. Arches study. Demographic and baseline characteristics. Data Cut-off 14 October 2018*

| Parameter Statistics/Criteria | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) | Total (n = 1150) |
|---|---|---|---|
| **Age category (years), n (%)** | | | |
| < 65 | 148 (25.8) | 152 (26.4) | 300 (26.1) |
| 65 to < 75 | 256 (44.6) | 255 (44.3) | 511 (44.4) |
| ≥ 75 | 170 (29.6) | 169 (29.3) | 339 (29.5) |
| **Age (years)** | | | |
| Mean (SD) | 69.5 (8.0) | 69.5 (8.4) | 69.5 (8.2) |
| Median (minimum, maximum) | 70.0 (46, 92) | 70.0 (42, 92) | 70.0 (42, 92) |
| **Race†, n (%)** | | | |
| White | 466 (81.2) | 460 (79.9) | 926 (80.5) |
| Black or African American | 8 (1.4) | 8 (1.4) | 16 (1.4) |
| Asian | 75 (13.1) | 80 (13.9) | 155 (13.5) |
| Other | 2 (0.3) | 3 (0.5) | 5 (0.4) |
| Missing | 23 (4.0) | 25 (4.3) | 48 (4.2) |
| **Ethnicity†, n (%)** | | | |
| Hispanic or Latino | 46 (8.0) | 37 (6.4) | 83 (7.2) |
| Not Hispanic or Latino | 504 (87.8) | 514 (89.2) | 1018 (88.5) |
| Missing | 24 (4.2) | 25 (4.3) | 49 (4.3) |
| **Weight (kg)** | | | |
| n | 573 | 575 | 1148 |
| Mean (SD) | 81.25 (16.17) | 81.26 (16.22) | 81.26 (16.19) |
| Median (minimum, maximum) | 80.00 (42.7, 163.0) | 80.00 (39.1, 157.5) | 80.00 (39.1, 163.0) |
| **Body mass index (kg/m$^2$)** | | | |
| n | 567 | 570 | 1137 |
| Mean (SD) | 27.20 (4.44) | 27.21 (4.61) | 27.20 (4.53) |
| Median (minimum, maximum) | 26.65 (16.7, 45.2) | 26.91 (16.4, 48.8) | 26.81 (16.4, 48.8) |

All patients who were randomized in the study (ITT population).

Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy; ITT: intent-to-treat

† Race/ethnicity was not collected in France, per country regulations.

*Table 10. Prostate cancer disease history*

| Parameter Statistics/Criteria | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) | Total (n = 1150) |
|---|---|---|---|
| **ECOG performance status at study entry, n (%)** | | | |
| 0 | 448 (78.0) | 443 (76.9) | 891 (77.5) |
| 1 | 125 (21.8) | 133 (23.1) | 258 (22.4) |
| **Baseline serum PSA† (ng/mL)** | | | |
| n | 572 | 574 | 1146 |
| Mean (SD) | 75.37 (356.36) | 104.78 (834.48) | 90.10 (641.90) |
| Median (minimum, maximum) | 5.36 (0.0, 4823.5) | 5.07 (0.0, 19000.0) | 5.21 (0.0, 19000.0) |
| **Total Gleason score at initial diagnosis, n (%)** | | | |
| < 8 | 171 (29.8) | 187 (32.5) | 358 (31.1) |
| ≥ 8 | 386 (67.2) | 373 (64.8) | 759 (66.0) |
| **Volume of disease‡, n (%)** | | | |
| Low | 220 (38.3) | 203 (35.2) | 423 (36.8) |
| High | 354 (61.7) | 373 (64.8) | 727 (63.2) |
| **Prior docetaxel therapy‡, n (%)** | | | |
| None | 471 (82.1) | 474 (82.3) | 945 (82.2) |
| 1 to 5 cycles | 14 (2.4) | 11 (1.9) | 25 (2.2) |
| 6 cycles | 89 (15.5) | 91 (15.8) | 180 (15.7) |
| **Previous use of ADT, n (%)** | | | |
| None | 39 (6.8) | 61 (10.6) | 100 (8.7) |
| ≤ 3 months | 414 (72.1) | 394 (68.4) | 808 (70.3) |
| > 3 months | 121 (21.1) | 120 (20.8) | 241 (21.0) |
| Unknown§ | 0 | 1 (0.2) | 1 (0.1) |
| **Duration of prostate cancer (months)¶** | | | |
| n | 572 | 575 | 1147 |
| Mean (SD) | 17.56 (37.47) | 19.99 (41.40) | 18.78 (39.49) |
| Median (minimum, maximum) | 3.47 (0.26, 267.89) | 3.38 (0.39, 259.09) | 3.45 (0.26, 267.89) |
| **Duration of metastatic disease (months)††** | | | |
| n | 562 | 571 | 1133 |
| Mean (SD) | 3.40 (6.66) | 3.77 (8.34) | 3.59 (7.55) |
| Median (minimum, maximum) | 2.07 (0.20, 82.83) | 2.07 (0.03, 141.21) | 2.07 (0.03, 141.21) |
| **Metastasis based on ICR, n (%)‡‡** | | | |
| Yes | 536 (93.4) | 531 (92.2) | 1067 (92.8) |
| No | 34 (5.9) | 45 (7.8) | 79 (6.9) |
| Unknown | 4 (0.7) | 0 | 4 (0.3) |
| **Location of metastasis based on ICR, n (%)** | | | |
| Bone only | 268 (46.7) | 245 (42.5) | 513 (44.6) |
| Soft tissue only | 51 (8.9) | 45 (7.8) | 96 (8.3) |
| Bone and soft tissue | 217 (37.8) | 241 (41.8) | 458 (39.8) |
| **Location of metastasis based on investigator assessment, n (%)** | | | |
| Bone only | 249 (43.4) | 241 (41.8) | 490 (42.6) |
| Soft tissue only | 64 (11.1) | 72 (12.5) | 136 (11.8) |
| Bone and soft tissue | 254 (44.3) | 258 (44.8) | 512 (44.5) |

| | | | |
|---|---|---|---|
| **Total number of bone lesions based on ICR, n (%)** | | | |
| 1 | 83 (14.5) | 70 (12.2) | 153 (13.3) |
| 2 to 4 | 151 (26.3) | 142 (24.7) | 293 (25.5) |
| 5 to 9 | 95 (16.6) | 106 (18.4) | 201 (17.5) |
| 10 to 19 | 111 (19.3) | 114 (19.8) | 225 (19.6) |
| ≥ 20 (including too numerous to count) | 45 (7.8) | 54 (9.4) | 99 (8.6) |
| **Total number of bone lesions based on investigator assessment, n (%)** | | | |
| 1 | 72 (12.5) | 59 (10.2) | 131 (11.4) |
| 2 to 4 | 124 (21.6) | 126 (21.9) | 250 (21.7) |
| 5 to 9 | 77 (13.4) | 74 (12.8) | 151 (13.1) |
| 10 to 19 | 26 (4.5) | 28 (4.9) | 54 (4.7) |
| ≥ 20 | 23 (4.0) | 23 (4.0) | 46 (4.0) |
| Too numerous to count§§ | 181 (31.5) | 189 (32.8) | 370 (32.2) |

All patients who were randomized in the study (ITT population).

The analysis data cutoff date was 14 Oct 2018.

ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; ICR: independent central review; ITT: intent-to-treat; PSA: prostate-specific antigen

† PSA levels of 0 were observed, which could have been due to prior treatment with docetaxel and/or use of ADT within 3 months of study start. One patient receiving placebo plus ADT had a baseline PSA level of > 19000 ng/mL, which impacted the calculation of mean baseline PSA for this group.

‡ Volume of disease and prior docetaxel therapy were stratification factors at randomization.

§ The patient had ADT; however, the duration of ADT use was not known.

¶ Duration of prostate cancer (months) = [(date of randomization - date of initial diagnosis) + 1]/(365.25/12)

†† Duration of metastatic disease (months) = [(date of randomization - date of diagnosis of metastatic disease) + 1]/(365.25/12)

‡‡ Enrollment was based on investigator assessment of metastatic disease; ICR confirmation of this assessment was not required prior to entry into the study.

§§ The instructions to the investigators allowed the selection of "too numerous to count" as an alternative to an exact bone lesion count.

*Table 11. Radiation and surgical prostate cancer treatment History*

| Parameter | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) | Total (n = 1150) |
|---|---|---|---|
| **Previous radiation, n (%)** | | | |
| No | 480 (83.6) | 480 (83.3) | 960 (83.5) |
| Yes | 94 (16.4) | 96 (16.7) | 190 (16.5) |
| **Area radiated, n (%)** | | | |
| Bone | 16 (2.8) | 23 (4.0) | 39 (3.4) |
| Lymph node | 2 (0.3) | 3 (0.5) | 5 (0.4) |
| Prostate gland | 63 (11.0) | 57 (9.9) | 120 (10.4) |
| Bone marrow | 0 | 2 (0.3) | 2 (0.2) |
| Other | 21 (3.7) | 28 (4.9) | 49 (4.3) |
| **Reason for radiation, n (%)** | | | |
| Primary disease | 62 (10.8) | 60 (10.4) | 122 (10.6) |
| Palliative | 21 (3.7) | 34 (5.9) | 55 (4.8) |
| Other | 19 (3.3) | 19 (3.3) | 38 (3.3) |
| **Previous surgery, n (%)** | | | |
| No | 366 (63.8) | 399 (69.3) | 765 (66.5) |
| Yes | 208 (36.2) | 177 (30.7) | 385 (33.5) |
| **Previous surgeries/procedures, n (%)** | | | |
| Radical prostatectomy | 72 (12.5) | 89 (15.5) | 161 (14.0) |
| Bilateral orchiectomy | 46 (8.0) | 27 (4.7) | 73 (6.3) |
| Transurethral resection of the prostate | 62 (10.8) | 34 (5.9) | 96 (8.3) |
| Cryoablation | 1 (0.2) | 2 (0.3) | 3 (0.3) |
| Pelvic lymph node dissection | 12 (2.1) | 13 (2.3) | 25 (2.2) |
| Other | 58 (10.1) | 64 (11.1) | 122 (10.6) |

All patients who were randomized in the study (ITT population).

The analysis data cutoff date was 14 Oct 2018.

ADT: androgen deprivation therapy; ITT: intent-to-treat

*Table 12. Prior Drug Therapies for Prostate Cancer (in at Least 5% of Patients in Either Treatment Group)*

| ATC Level 2 Description<br>Preferred WHO Name | Number of Patients (%) | | |
|---|---|---|---|
| | Enzalutamide+ADT (n = 572) | Placebo+ADT (n = 574) | Total (n = 1146) |
| **Overall** | **514 (89.9)** | **505 (88.0)** | **1019 (88.9)** |
| **Endocrine therapy** | **508 (88.8)** | **504 (87.8)** | **1012 (88.3)** |
| Bicalutamide† | 195 (34.1) | 215 (37.5) | 410 (35.8) |
| Leuprorelin‡ | 196 (34.3) | 191 (33.3) | 387 (33.8) |
| Degarelix§ | 128 (22.4) | 141 (24.6) | 269 (23.5) |
| Goserelin‡ | 95 (16.6) | 101 (17.6) | 196 (17.1) |
| Triptorelin‡ | 89 (15.6) | 85 (14.8) | 174 (15.2) |
| **Antineoplastic agents** | **103 (18.0)** | **102 (17.8)** | **205 (17.9)** |
| Docetaxel¶ | 103 (18.0) | 102 (17.8) | 205 (17.9) |

All randomized patients who received at least 1 dose of study drug (safety population).

The analysis data cutoff date was 14 Oct 2018.

Sorting order: alphabetical order by ATC level 2 and decreasing order of frequency of preferred WHO name. Patients taking the same medication multiple times were counted once per medication and period.

ADT: androgen deprivation therapy; ATC: Anatomical Therapeutic Chemical

† ATC Level 4: antiandrogens

‡ ATC Level 4: gonadotropin releasing hormone analogues

§ ATC Level 4: other hormone antagonists and related agents

¶ ATC Level 4: taxanes

## Numbers analysed

The final analysis of rPFS was conducted with 287 rPFS events. The data cut-off date for the final analysis was 14 Oct 2018.

## Outcomes and estimation

Primary endpoint

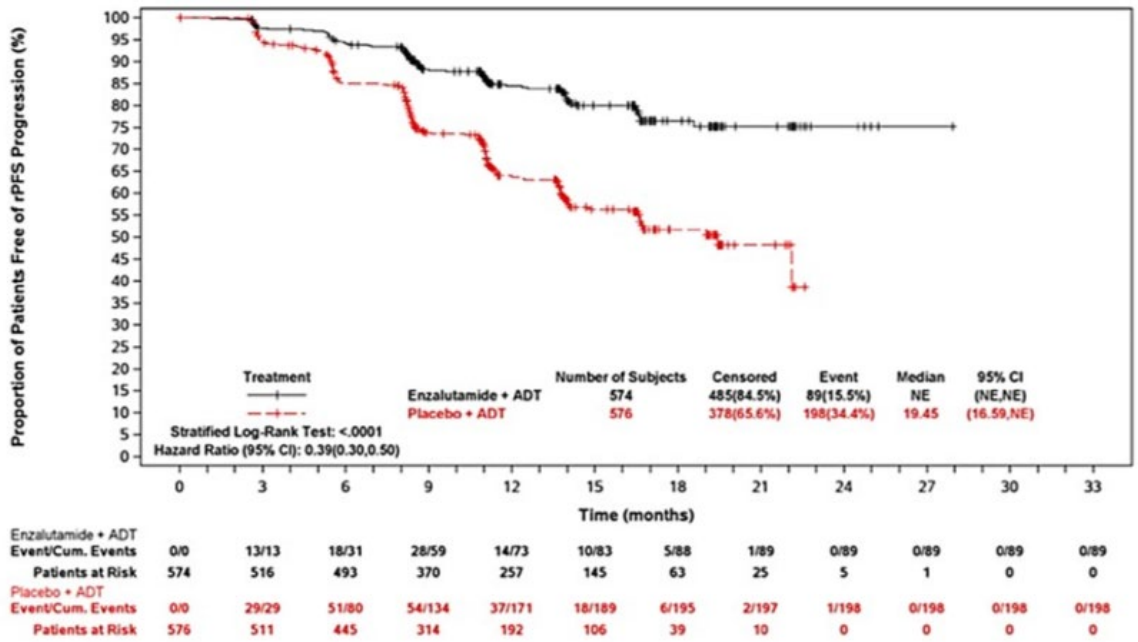
rPD was defined by RECIST 1.1 for soft tissue disease or the appearance of 2 or more new bone lesions on bone scan. Unconfirmed disease progression on a bone scan at week 13 was not to be considered an event. The study-specified documentation and confirmation required for the determination of rPD are listed in Table 4. However, the ICR did not follow Table 4 for bone scans and reported disease progression based on bone scan according to PCWG2 criteria [Scher et al, 2008] instead. The ICR assessed radiographic progression on bone scan solely on the appearance of bone lesion(s) which were new compared to baseline of week 13.

Treatment with enzalutamide plus ADT demonstrated a statistically significant 61% reduction in the risk of a patient experiencing an rPFS event compared with placebo plus ADT treatment (HR=0.39 [95% CI: 0.30, 0.50]; P<0.0001). This analysis is based upon the data provided by the ICR..

rPFS data were censored for a higher proportion of patients in the enzalutamide plus ADT group compared with the placebo plus ADT group (84.49% vs 65.63%). In both treatment groups, the most frequent reason for censoring rPFS data was that there was no evidence of radiographic disease progression at the data cut-off date (448/485 [92.37%] for the enzalutamide plus ADT group vs 348/378 [92.06%] for the placebo plus ADT group).

*Table 13. rPFS -Primary Efficacy Analysis Based on ICR Assessment (ITT Population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT<br>(n = 574) | Placebo+ADT<br>(n = 576) |
|---|---|---|
| **Events, n (%)†** | 89 (15.51) | 198 (34.38) |
| **Kaplan-Meier estimates (months)** | | |
| 25th percentile | NR | 8.5 |
| Median (95% CI)‡ | NR | 19.4 (16.59, NR) |
| 75th percentile | NR | NR |
| Kaplan-Meier event-free rate at 12 months | 84.45% | 63.71% |
| **Treatment comparison: enzalutamide+ADT vs placebo+ADT** | | |
| Cox HR (95% CI)§ | 0.39 (0.30, 0.50) | |
| Log-rank P value§ | < 0.0001 | |
| **Individual components in rPFS events, n (%)¶** | | |
| rPD | 77 (13.41) | 185 (32.12) |
| Death within 24 weeks after treatment discontinuation | 12 (2.09) | 13 (2.26) |
| **Censoring, n (%)†** | | |
| Censored | 485 (84.49) | 378 (65.63) |
| First censored reason | | |
| No baseline assessment | 4 (0.82) | 0 |
| No postbaseline assessment | 9 (1.86) | 16 (4.23) |
| All postbaseline assessments were "Not Evaluable" | 24 (4.95) | 14 (3.70) |
| No rPFS event before the data cutoff date | 448 (92.37) | 348 (92.06) |




Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.
The analysis data cutoff date was 14 Oct 2018.

*Figure 3 Kaplan-Meier Plot of rPFS Based on ICR Assessment in ARCHES (ITT Population)*

Secondary endpoints

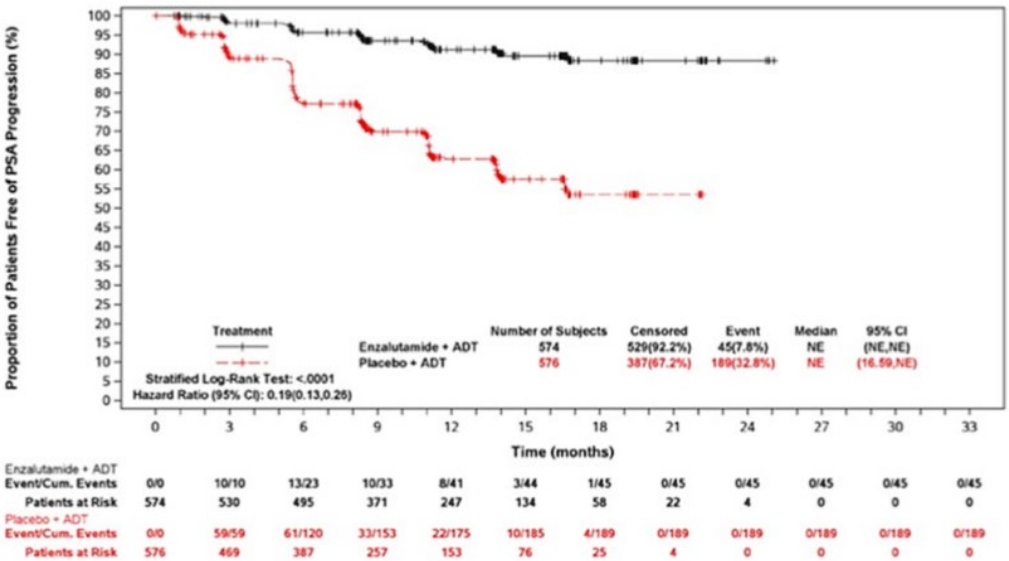
- Time to PSA progression

*Table 14 Time to PSA progression – Key secondary efficacy analysis (ITT population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT<br>(n = 574) | Placebo+ADT<br>(n = 576) |
|---|---|---|
| **PSA progression events†, n (%)** | 45 (7.84) | 189 (32.81) |
| **Kaplan-Meier estimates for time to PSA progression (months)** | | |
| 25th percentile | NR | 8.3 |
| Median (95% CI)‡ | NR | NR (16.59, NR) |
| 75th percentile | NR | NR |
| Kaplan-Meier event-free rate at 12 months | 91.19% | 62.79% |
| **Treatment comparison: enzalutamide vs placebo** | | |
| Cox HR (95% CI)§ | 0.19 (0.13, 0.26) | |
| Log-rank P value§ | < 0.0001 | |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cutoff date was 14 Oct 2018.




Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cut-off date was 14 Oct 2018.

*ADT: androgen deprivation therapy; CI: confidence interval; Cum: cumulative; ITT: intent-to-treat; NE: not estimable; PSA: prostate-specific antigen*

*Figure 4. Kaplan-Meier Plot of time to PSA progression – Key secondary efficacy analysis (ITT population)*

- Time to start of new antineoplastic therapy

*Table 15. Time to start of new antineoplastic therapy – Key secondary efficacy analysis (ITT population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT<br>(n = 574) | Placebo+ADT<br>(n = 576) |
|---|---|---|
| **Patients with new antineoplastic therapy†, n (%)** | 46 (8.01%) | 133 (23.09%) |
| **Kaplan-Meier estimates for time to start of antineoplastic therapy (months)** | | |
| 25th percentile | 30.2 | 13.9 |
| Median (95% CI)‡ | 30.2 (NR, NR) | NR (21.06, NR) |
| 75th percentile | 30.2 | NR |
| Kaplan-Meier event-free rate at 12 months | 94.09% | 80.41% |
| **Treatment comparison: enzalutamide vs placebo** | | |
| Cox HR (95% CI)§ | 0.28 (0.20, 0.40) | |
| Log-rank P value§ | < 0.0001 | |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

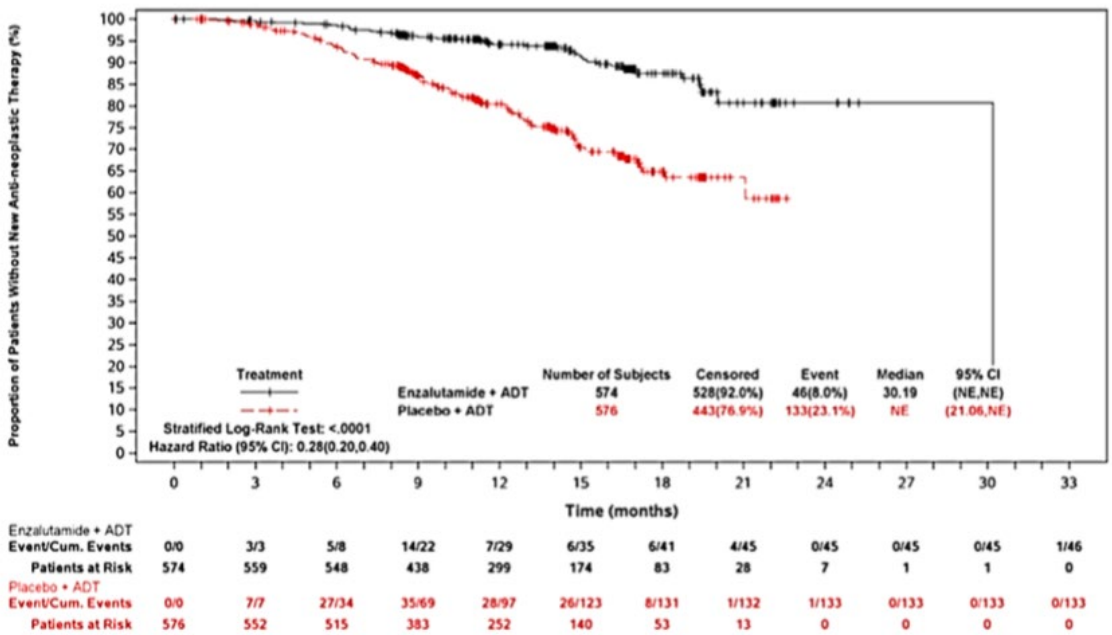
Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; NR: not reached

† In patients with a new (systemic) antineoplastic therapy initiated for prostate cancer after randomization, time to start of a new antineoplastic therapy was defined as the time interval from randomization to the date of the first dose administration of the first antineoplastic therapy. In patients with no new antineoplastic therapy initiated for prostate cancer after randomization, time to start of new antineoplastic therapy was censored on the last visit date or the date of randomization, whichever occurred last.

‡ Calculated by Brookmeyer and Crowley method

§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)




Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

Data cut-off date: 14 Oct 2018

ADT: androgen deprivation therapy; CI: confidence interval; Cum: cumulative; ITT: intent-to-treat; NE: not estimable

*Figure 5. Kaplan-Meier Plot of time to start of new antineoplastic therapy – Key secondary efficacy analysis (ITT population)*

*Table 16. Selected new systemic antineoplastic therapies for prostate cancer (ITT population)*

| Therapy, n (%) | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) |
|---|---|---|
| **Overall** | **46 (8.0)** | **133 (23.1)** |
| Docetaxel | 11 (1.9) | 52 (9.0) |
| Abiraterone acetate | 13 (2.3) | 28 (4.9) |
| Enzalutamide | 4 (0.7) | 28 (4.9) |
| Bicalutamide | 4 (0.7) | 12 (2.1) |
| Other | 14 (2.4) | 15 (2.6) |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cutoff date was 14 Oct 2018.

The table shows the first new antineoplastic prostate cancer therapy used on or after the date of last dose. One patient in the placebo plus ADT group received a combination of docetaxel and carboplatin and another patient in the placebo plus ADT group received a combination of docetaxel with blinded therapy. Both of these patients were counted in both the docetaxel and the "other" categories.

ADT: androgen deprivation therapy; ITT: intent-to-treat.

- PSA undetectable rate

*Table 17. PSA undetectable rate – Key secondary efficacy analysis (ITT population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) |
|---|---|---|
| **Patients from ITT population with PSA detectable at baseline (n)** | 511 | 506 |
| **Patients from ITT population with PSA undetectable at baseline (n)** | 61† | 68† |
| **Lowest PSA value during the treatment period, n (%)** | | |
| Undetectable‡ | 348/511 (68.1) | 89/506 (17.6) |
| 95% CI for rate§ | 63.9, 72.1 | 14.4, 21.2 |
| Difference in rate (95% CI)§ | 50.5% (45.3, 55.7) | |
| P value¶ | < 0.0001 | |
| Detectable | 159/511 (31.1) | 415/506 (82.0) |
| No postbaseline | 4/511 (0.8) | 2/506 (0.4) |
| **Week 13, n (%)** | | |
| Patients with detectable PSA at baseline and available PSA at specified visit | 483/511 (94.5) | 472/506 (93.3) |
| Undetectable‡ | 226/483 (46.8) | 52/472 (11.0) |
| Detectable | 257/483 (53.2) | 420/472 (89.0) |
| **Week 25, n (%)** | | |
| Patients with detectable PSA at baseline and available PSA at specified visit | 466/511 (91.2) | 440/506 (87.0) |
| Undetectable‡ | 278/466 (59.7) | 68/440 (15.5) |
| Detectable | 188/466 (40.3) | 372/440 (84.5) |
| **Week 37, n (%)** | | |
| Patients with detectable PSA at baseline and available PSA at specified visit | 446/511 (87.3) | 390/506 (77.1) |
| Undetectable‡ | 288/446 (64.6) | 71/390 (18.2) |
| Detectable | 158/446 (35.4) | 319/390 (81.8) |
| **Week 61, n (%)** | | |
| Patients with detectable PSA at baseline and available PSA at specified visit | 218/511 (42.7) | 176/506 (34.8) |
| Undetectable‡ | 152/218 (69.7) | 38/176 (21.6) |
| Detectable | 66/218 (30.3) | 138/176 (78.4) |
| **Week 85, n (%)** | | |
| Patients with detectable PSA at baseline and available PSA at specified visit | 47/511 (9.2) | 33/506 (6.5) |
| Undetectable‡ | 38/47 (80.9) | 7/33 (21.2) |
| Detectable | 9/47 (19.1) | 26/33 (78.8) |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cutoff date was 14 Oct 2018.

ADT: androgen deprivation therapy; CI: confidence interval; ITT: intent-to-treat; PSA: prostate-specific antigen

† In addition, 2 patients in each treatment group had a missing PSA value at baseline.

‡ The PSA undetectable rate was defined as the percentage of patients with undetectable (< 0.2 ng/mL) PSA values at any time during study treatment, of those patients with detectable (≥ 0.2 ng/mL) PSA values at baseline.

§ 95% CI was computed using Clopper-Pearson method based on exact binomial distribution; the asymptotic one was provided on the difference.

¶ Cochran-Mantel-Haenszel score test, stratified by volume of disease and previous docetaxel use.

- Objective response rate (ORR)

*Table 18. ORR – Key secondary efficacy analysis (ITT population)*

| Best RECIST 1.1 Overall Response | ICR | | Investigator | |
|---|---|---|---|---|
| | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) |
| **Patients with measurable disease at baseline (n)** | 177 | 182 | 178 | 202 |
| **Objective response† n (%)** | 147 (83.1) | 116 (63.7) | 138 (77.5) | 118 (58.4) |
| 95% CI for rate‡ | (76.7, 88.3) | (56.3, 70.7) | (70.7, 83.4) | (51.3, 65.3) |
| Difference in rate (95% CI)‡ | 19.3 (10.4, 28.2) | | 19.1 (10.0, 28.3) | |
| P value§ | < 0.0001 | | 0.0005 | |
| **Categories, n (%)** | | | | |
| CR | 65 (36.7) | 42 (23.1) | 50 (28.1) | 27 (13.4) |
| PR | 82 (46.3) | 74 (40.7) | 88 (49.4) | 91 (45.0) |
| Stable disease | 17 (9.6) | 43 (23.6) | 31 (17.4) | 73 (36.1) |
| Non-CR/Non-PD | 0 | 0 | 0 | 0 |
| PD | 7 (4.0) | 9 (4.9) | 2 (1.1) | 5 (2.5) |
| NA¶ | 1 (0.6) | 5 (2.7) | 0 | 0 |
| Not evaluable | 5 (2.8) | 9 (4.9) | 7 (3.9) | 6 (3.0) |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cutoff date was 14 Oct 2018.

The best RECIST overall response corresponded to the best assessment made at any time during the treatment period, up to the start of any other prostate cancer therapy after the last dose of study treatment. Patients with no postbaseline assessment at any visit were reported in the "not evaluable" category.

ADT: androgen deprivation therapy; CI: confidence interval; CR: complete response; ICR: independent central review; ITT: intent-to-treat; NA: not applicable; ORR: objective response rate; PD: progressive disease; PR: partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1

† Objective response: the patient achieved a CR or PR in their soft tissue disease using the RECIST 1.1 criteria.

‡ 95% CI was computed using Clopper-Pearson method based on exact binomial distribution; the asymptotic one was provided on the difference.

§ Cochran-Mantel-Haenszel score test, stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no).

¶ The ICR reassessed the baseline tumor status of these patients during postbaseline time points.

- Time to deterioration of urinary symptoms

*Table 19. Time to deterioration of urinary symptoms based on QLQ-PR25 Score – Key secondary efficacy analysis (ITT population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) |
|---|---|---|
| **Patients with events†, n (%)** | 184 (32.06) | 201 (34.90) |
| **Kaplan-Meier estimates for time to deterioration of QLQ-PR25 score (months)** | | |
| 25th percentile | 5.6 | 5.6 |
| Median (95% CI)‡ | NR (19.35, NR) | 16.8 (14.06, NR) |
| 75th percentile | NR | NR |
| Kaplan-Meier event-free rate at 12 months | 64.79% | 61.67% |
| **Treatment comparison: enzalutamide vs placebo** | | |
| Cox HR (95% CI)§ | 0.88 (0.72, 1.08) | |
| Log-rank P value§ | 0.2162 | |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

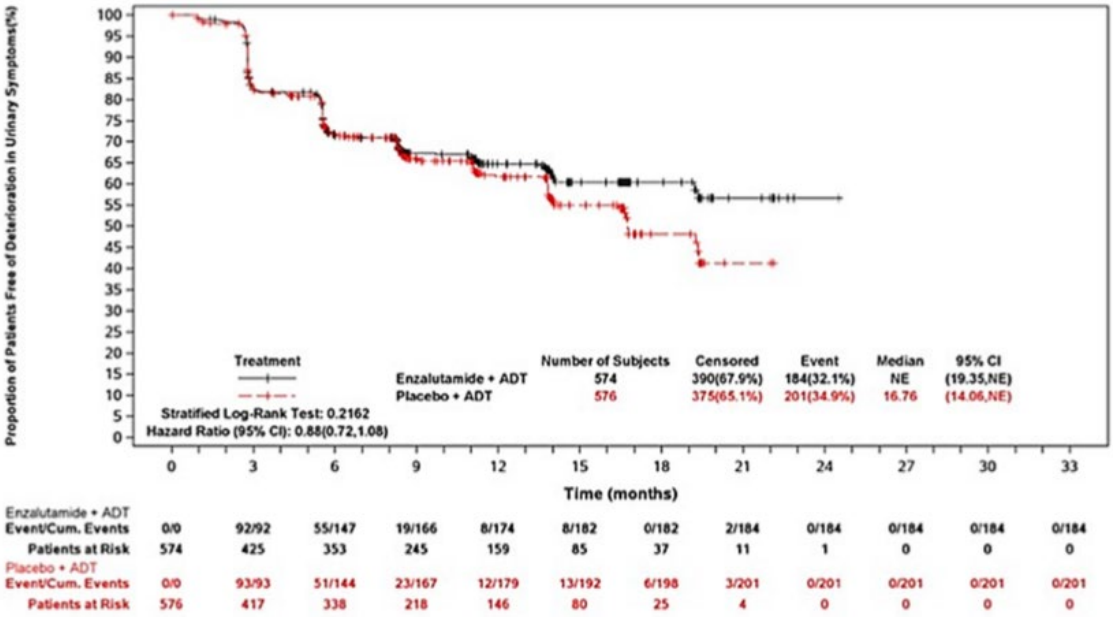
The analysis data cutoff date was 14 Oct 2018.

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; NR: not reached; QLQ-PR25: Quality of Life Questionnaire-Prostate 25

† A deterioration in urinary symptoms was defined as an increase in the QLQ-PR25 modified urinary symptoms score (i.e., Q31 to Q33) by ≥ 50% of the standard deviation observed in the QLQ-PR25 modified urinary symptoms score at baseline. In patients with a deterioration, the time to deterioration was defined as the time interval between randomization and the first deterioration in urinary symptoms at any postbaseline visit. In patients without a deterioration in urinary symptoms, the time to deterioration in urinary symptoms was censored on the date the last urinary symptoms QLQ-PR25 score was calculable.

‡ Calculated by Brookmeyer and Crowley method

§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)




Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cut-off date was 14Oct2018.

A deterioration in urinary symptoms was defined as an increase in the QLQ-PR25 modified urinary symptoms score (i.e., Q31 to Q33) by ≥ 50% of the standard deviation observed in the QLQ-PR25 modified urinary symptoms score at baseline. In patients with a deterioration, the time to deterioration was defined as the time interval between randomization and the first deterioration in urinary symptoms at any postbaseline visit. In patients without a deterioration in urinary symptoms, the time to deterioration in urinary symptoms was censored on the date the last urinary symptom QLQ-PR25 score was calculable.

*ADT: androgen deprivation therapy; ITT: intent-to-treat; NE: not estimated; QLQ-PR25: Quality of Life Questionnaire-Prostate25*

*Figure 6 Kaplan-Meier curves for time to deterioration of urinary symptoms based on QLQ-PR25 Score - Key secondary efficacy analysis (ITT Population)*

- Overall survival

The prespecified interim analysis of the OS endpoint was planned to occur at the time of the final rPFS analysis. The results of the interim analysis of OS (data cut off 14 Oct 2018) based on a total of 84 deaths (24.6% of the 342 events required for the final analysis) are presented below. The stopping boundary for OS at the interim analysis was 0.0000054.

*Table 20. Overall survival – Key secondary efficacy analysis (ITT population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT<br>(n = 574) | Placebo+ADT<br>(n = 576) |
|---|---|---|
| **Deaths by any cause, n (%)** | 39 (6.79) | 45 (7.81) |
| **Kaplan-Meier estimates† (months)** | | |
| 25th percentile | NR | NR |
| Median (95% CI)‡ | NR | NR |
| 75th percentile | NR | NR |
| Kaplan-Meier event-free rate at 12 months | 95.54% | 93.90% |
| **Treatment comparison: enzalutamide+ADT vs placebo+ADT** | | |
| Cox HR (95% CI)§ | 0.81 (0.53, 1.25) | |
| Log-rank P value§ | 0.3361 | |
| **Primary reason for death, n (%)** | | |
| Radiographic progression | 26 (4.53) | 29 (5.03) |
| Other | 13 (2.26) | 16 (2.78) |
| **Median follow-up (months)** | 14.4 | |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

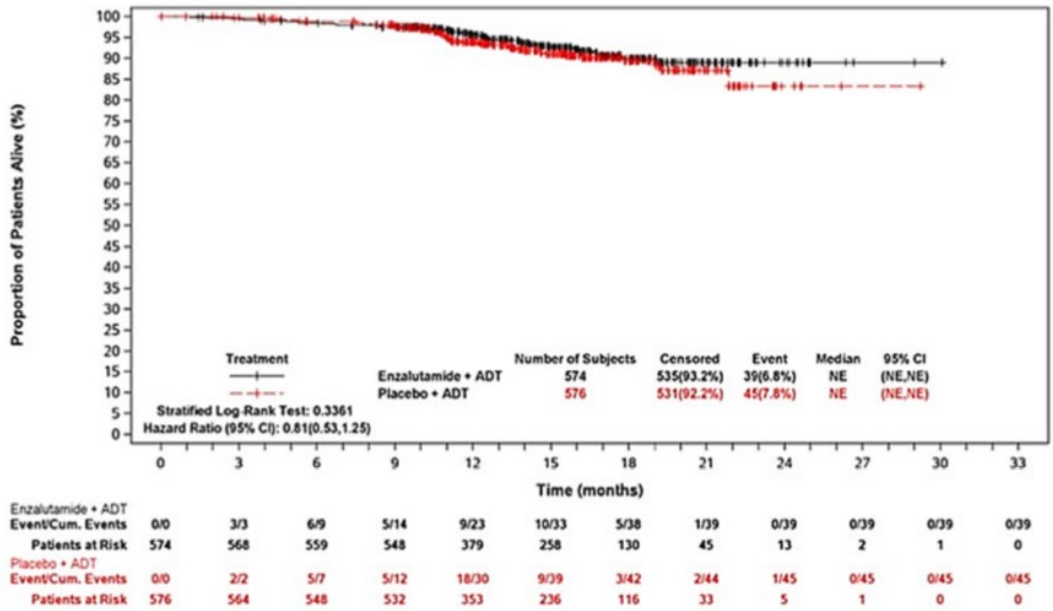
The analysis data cutoff date was 14 Oct 2018.

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; NR: not reached

† Time from randomization to death from any cause. For patients still alive at the date of the analysis cutoff point, overall survival was censored on the last date the patient was known to be alive.

‡ Calculated by Brookmeyer and Crowley method

§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)




Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

Data cut-off date: 14 Oct 2018

Time from randomization to death from any cause. For patients still alive at the date of the analysis cut-off point, overall survival was censored on the last date the patient was known to be alive.

ADT: androgen deprivation therapy; CI: confidence interval; Cum.: cumulative; ITT: intent-to-treat; NE: not estimable

*Figure 7 Kaplan-Meier Plot of Overall Survival –Key Secondary Efficacy Analysis (ITT Population)*

Additional secondary endpoints

In the analyses of other secondary endpoints, nominal P values were provided for descriptive purposes only.

- Time to first SSE

*Table 21. Time to first SSE (ITT population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT<br>(n = 574) | Placebo+ADT<br>(n = 576) |
|---|---|---|
| **Patients with SSE events†, n (%)** | 31 (5.40) | 56 (9.72) |
| **Kaplan-Meier estimates for time to first SSE (months)** | | |
| 25th percentile | NR | NR |
| Median (95% CI)‡ | NR | NR |
| 75th percentile | NR | NR |
| Kaplan-Meier event-free rate at 12 months | 94.43% | 90.91% |
| **Treatment comparison: enzalutamide vs placebo** | | |
| Cox HR (95% CI) | 0.52 (0.33, 0.80) | |
| Log-rank P value, nominal | 0.0026 | |

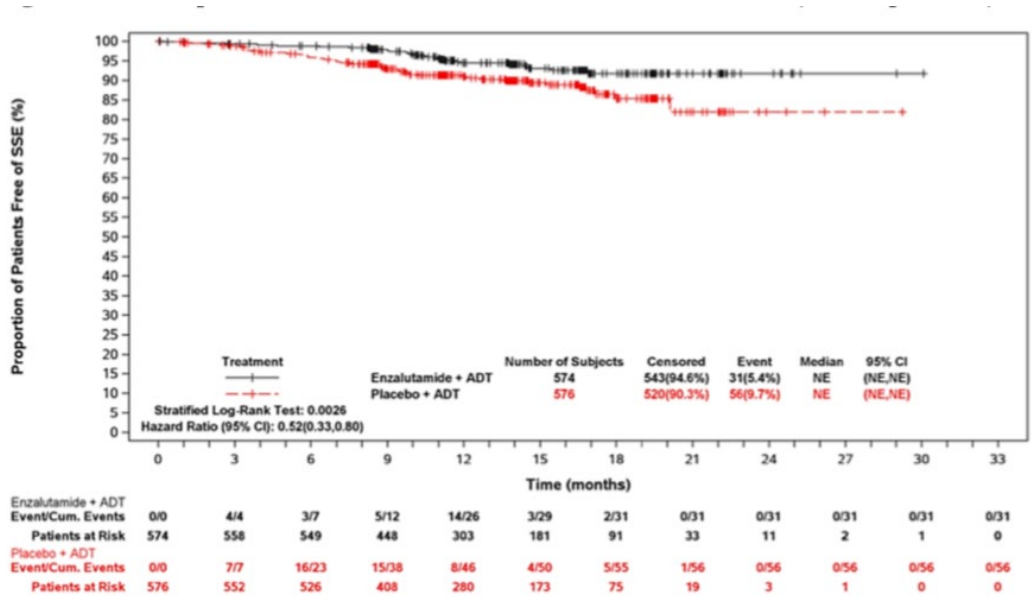
Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cutoff date was 14 Oct 2018.

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; NR: not reached; SSE: symptomatic skeletal event

† A SSE was defined as a radiation or surgery to bone, clinically apparent pathological bone fracture and spinal cord compression, whichever occurred first. Time to first SSE was the time from randomization to the occurrence of the first SSE. In patients with no SSE by the time of the data cut-off point, time to SSE was censored on the last visit date or the date of randomization, whichever occurred last.

‡ Calculated by Brookmeyer and Crowley method.




Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cut-off date was 14 Oct 2018.

An SSE was defined as a radiation or surgery to bone, clinically apparent pathological bone fracture and spinal cord compression, whichever occurred first. Time to first SSE was the time from randomization to the occurrence of the first SSE. In patients with no SSE by the time of the data cut-off point, time to SSE was censored on the last visit date or the date of randomization, whichever occurred last.

*ADT: androgen deprivation therapy; CI: confidential interval; Cum: cumulative; ITT: intent-to-treat; NE: not estimated; SSE: symptomatic skeletal event*

*Figure 8. Kaplan-Meier Plot of time to first SSE (ITT population)*

- Time to castration resistance

*Table 22. Time to castration resistance (ITT population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT<br>(n = 574) | Placebo+ADT<br>(n = 576) |
|---|---|---|
| **Patients with castration resistance events†, n (%)** | 90 (15.68) | 257 (44.62) |
| **Kaplan-Meier estimates (months)** | | |
| 25th percentile | NR | 5.6 |
| Median (95% CI)‡ | NR | 13.9 (11.40, 17.18) |
| 75th percentile | NR | NR |
| Kaplan-Meier event-free rate at 12 months | 84.20% | 53.33% |
| **Treatment comparison: enzalutamide+ADT vs placebo+ADT** | | |
| Cox HR (95% CI) | 0.28 (0.22, 0.36) | |
| Log-rank P value, nominal | < 0.0001 | |
| **Individual components for castration resistance events (i.e., events that occurred with castration levels of testosterone [< 50 ng/dL]), n (%)** | | |
| PSA progression | 32 (5.57) | 143 (24.83) |
| Radiographic progression of disease and PSA progression | 2 (0.35) | 3 (0.52) |
| Radiographic progression of disease | 38 (6.62) | 86 (14.93) |
| SSE | 18 (3.14) | 25 (4.34) |

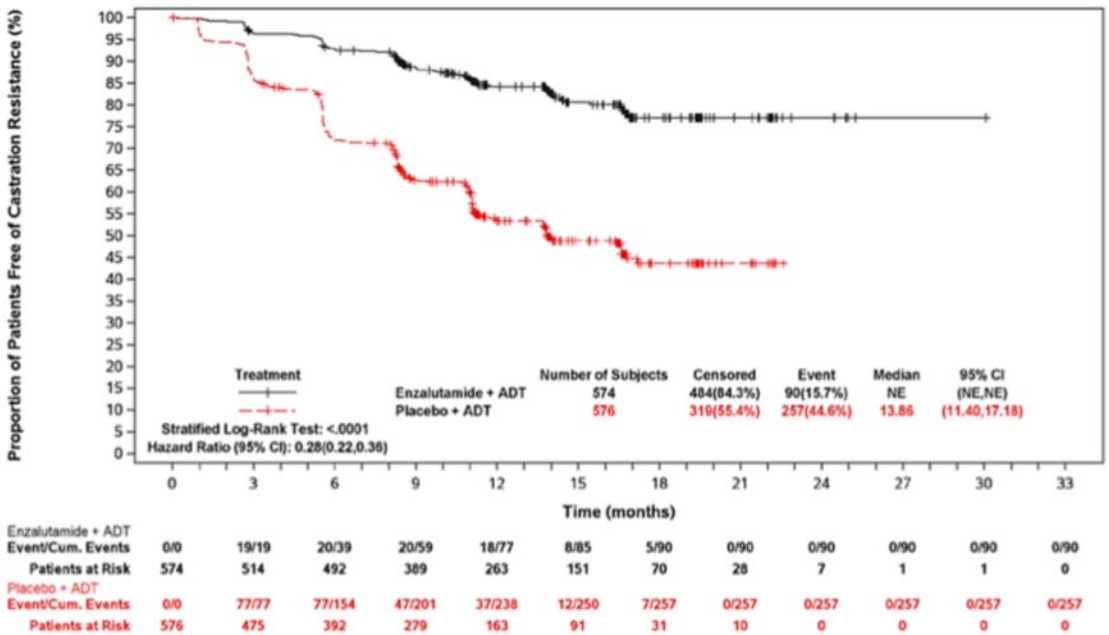
Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cut-off date was 14Oct2018.

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; ICR: independent central review; ITT: intent-to-treat; NR: not reached; PSA: prostate-specific antigen; SSE: symptomatic skeletal event

† A castration-resistance event was defined as any of the following in the presence of castration levels of testosterone (<50ng/dL): radiographic disease progression by ICR, PSA progression or SSE, whichever occurred first. In patients with castration resistance event, time to castration resistance was defined as the time from randomization to the first castration-resistant event. In patients with no documented castration resistance event, the time to castration resistance was censored on the latest date from: the date of last radiologic assessment, the last PSA sample taken prior to the start of any new prostate cancer therapy and prior to 2 or more consecutive missed PSA assessments (if applicable), and the last visit date performed.

‡ Calculated by Brookmeyer and Crowley method



Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

Data cut-off date: 14 Oct 2018

ADT: androgen deprivation therapy; CI: confidence interval; Cum.: cumulative; ICR: independent central review; ITT: intent-to-treat; NE: not estimated; PSA: prostate-specific antigen; SSE: symptomatic skeletal event.

*Figure 9. Kaplan-Meier Plot of time to castration resistance (ITT population)*

- Time to deterioration of QoL

*Table 23. Time to deterioration of QoL based on FACT-P Total Score (ITT population)*

| **Category**<br>Parameter/Statistics | **Enzalutamide+ADT (n = 574)** | **Placebo+ADT (n = 576)** |
|---|---|---|
| **Patients with deterioration of QoL†, n (%)** | 280 (48.78) | 274 (47.57) |
| **Kaplan-Meier estimates for time to deterioration of QoL based on FACT-P total score (months)** | | |
| 25th percentile | 5.5 | 3.2 |
| Median (95% CI)‡ | 11.3 (11.04, 13.83) | 11.1 (8.48, 13.83) |
| 75th percentile | NR | NR |
| Kaplan-Meier event-free rate at 12 months | 46.87% | 47.30% |
| **Treatment comparison: enzalutamide vs placebo** | | |
| Cox HR (95% CI) | 0.96 (0.81, 1.14) | |
| Log-rank P value, nominal | 0.6548 | |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy; CI: confidence interval; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: hazard ratio; ITT: intent-to-treat; NR: not reached; QoL: quality of life

† A deterioration of QoL was defined as a decrease of at least 10 points in the FACT-P total score from baseline. In patients with QoL deterioration, the time to deterioration of QoL was defined as the time interval from the date of randomization to the first date a decline from baseline of 10 points or more in the FACT-P total score was recorded. In patients without FACT-P progression, the time to deterioration of QoL was censored on the date of the last FACT-P total score was calculable.

‡ Calculated by Brookmeyer and Crowley method

- Time to pain progression

*Table 24. Time to pain progression (ITT population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT<br>(n = 574) | Placebo+ADT<br>(n = 576) |
|---|---|---|
| **Patients with pain progression†, n (%)** | 324 (56.45) | 329 (57.12) |
| **Kaplan-Meier estimates for time to pain progression (months)** | | |
| 25th percentile | 2.9 | 2.8 |
| Median (95% CI)‡ | 8.3 (8.25, 10.91) | 8.3 (5.65, 8.38) |
| 75th percentile | 19.5 | 19.4 |
| Kaplan-Meier event-free rate at 12 months | 37.83% | 35.04% |
| **Treatment comparison: enzalutamide vs placebo** | | |
| Cox HR (95% CI) | 0.92 (0.78, 1.07) | |
| Log-rank P value, nominal | 0.2715 | |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat

† Pain progression was defined an increase of ≥ 30% from baseline in the average BPI-SF item scores. In patients with pain progression, time to pain progression was defined as time from randomization to the first pain progression event. In patients with no pain progression event, time to pain progression was censored on the last visit date where BPI-SF was collected.

‡ Calculated by Brookmeyer and Crowley method

Other efficacy results

- Combined response (soft tissue lesions and bone lesions)

*Table 25. Best overall response (ITT population)*

| Best Overall Response | ICR | | Investigator | |
|---|---|---|---|---|
| | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) |
| Categories, n (%) | | | | |
| CR | 56 (9.8) | 31 (5.4) | 66 (11.5) | 36 (6.3) |
| PR | 155 (27.0) | 127 (22.0) | 142 (24.7) | 120 (20.8) |
| Stable disease | 16 (2.8) | 39 (6.8) | 30 (5.2) | 70 (12.2) |
| Non-CR/non-PD† | 254 (44.3) | 257 (44.6) | 298 (51.9) | 299 (51.9) |
| Unconfirmed PD | 1 (0.2) | 0 | 0 | 0 |
| PD | 11 (1.9) | 35 (6.1) | 10 (1.7) | 26 (4.5) |
| NA‡ | 28 (4.9) | 40 (6.9) | 0 | 0 |
| NE | 25 (4.4) | 16 (2.8) | 5 (0.9) | 7 (1.2) |
| No overall response assessment | 28 (4.9) | 31 (5.4) | 23 (4.0) | 18 (3.1) |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

Data cutoff date: 14 Oct 2018

The best overall response corresponded to the best of the overall response assessments derived by ICR or calculated programmatically from investigator data at any time during the treatment period. For patients still on treatment by the data cut-off date, the best overall response corresponded to the best of the overall time point response reported up to the data cut-off date. Patients with no postbaseline assessment at any visit are reported in the NE category.

ADT: androgen deprivation therapy; CR: complete response; ICR: independent central review; ITT: intent-to-treat; NA: not applicable; NE: not evaluable; PD: progressive disease; PR: partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1

† In patients without measurable disease at baseline, non-CR/non-PD refers to assessments that were evaluable and were neither CR nor PD.

‡ The ICR reassessed the baseline tumor status of these patients during postbaseline time points.

- PSA reduction

*Table 26. PSA reductions from baseline (ITT population)*

| Parameter | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) |
|---|---|---|
| Maximal PSA reduction†, % | | |
| n | 567 | 572 |
| Mean (SD) | -87.07 (45.66) | -44.01 (66.13) |
| Median | -97.70 | -63.80 |
| Minimum, maximum | -100.0, 858.0 | -100.0, 471.4 |
| PSA reduction ≥ 50%‡, n (%) | | |
| Yes | 533 (92.9) | 327 (56.8) |
| No | 41 (7.1) | 249 (43.2) |
| PSA reduction ≥ 90%‡, n (%) | | |
| Yes | 418 (72.8) | 173 (30.0) |
| No | 156 (27.2) | 403 (70.0) |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

Data cutoff date: 14 Oct 2018

ADT: androgen deprivation therapy; ITT: intent-to-treat; PSA: prostate-specific antigen

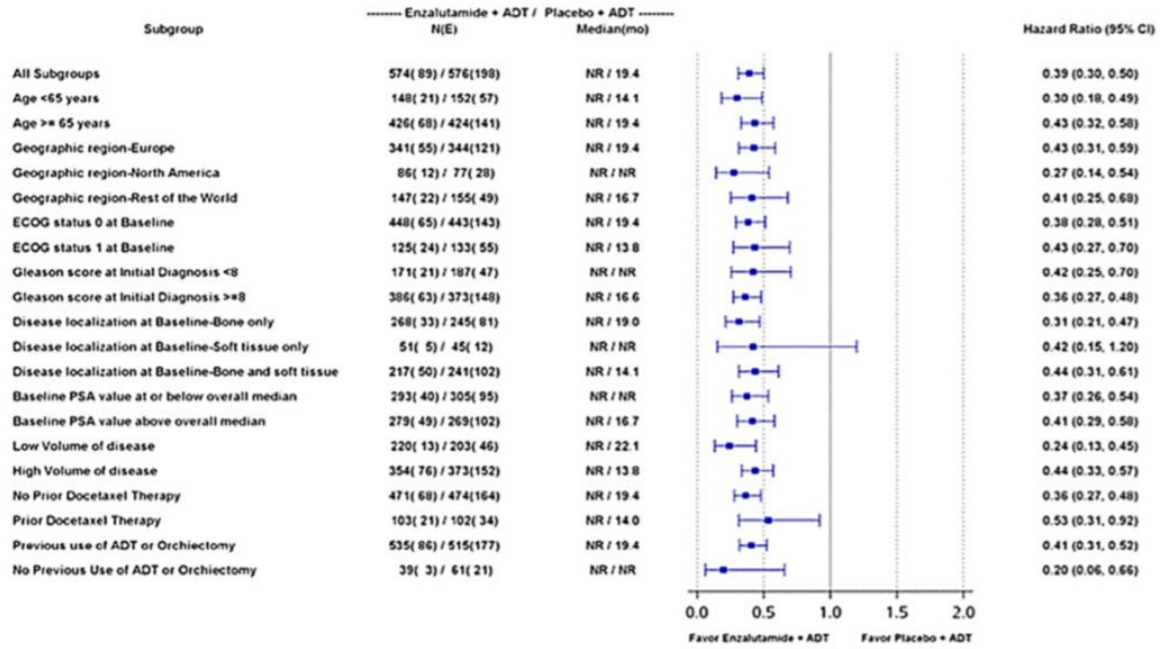
† The maximal PSA reduction postbaseline was defined as the largest decrease from baseline in PSA that occurred at any point after the start of treatment, expressed as the percentage change of PSA from baseline. For patients with no decrease from baseline in PSA, the smallest increase from baseline in PSA was used. For patients with no postbaseline PSA values, the largest decrease from baseline in PSA was set to missing.

‡ PSA reductions of ≥ 50% and ≥ 90% from baseline were defined as binary variables for achieving this criterion based on the lowest PSA value observed postbaseline. For patients with no postbaseline PSA value, the variable was set to missing (no).

## Ancillary analyses

Subgroup analyses of rPFS

*Figure 10 Forest Plot of rPFS – Subgroup analyses (ITT population)*




Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cutoff date was 14 Oct 2018.

ADT: androgen deprivation therapy; CI: confidence interval; E: number of events; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; NR: not reached; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival.

Sensitivity analyses of rPFS

*Table 27. Summary of rPFS Sensitivity Analyses (ITT Population)*

| Analyses | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) |
|---|---|---|
| **Primary rPFS analysis†** | | |
| Events, n (%) | 89 (15.51) | 198 (34.38) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 19.4 (16.59, NR) |
| Cox HR (95% CI)§ | 0.39 (0.30, 0.50) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 1 - Modified rPFS events (inclusion of study drug discontinuation)** | | |
| Events, n (%) | 153 (26.66) | 282 (48.96) |
| Kaplan-Meier median (95% CI)‡ (months) | 22.9 (19.58, NR) | 13.8 (12.32, 14.78) |
| Cox HR (95% CI)§ | 0.47 (0.39, 0.58) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 2 - Modified rPFS events (inclusion of new antineoplastic therapy and occurrence of an SSE)** | | |
| Events, n (%) | 116 (20.21) | 249 (43.23) |
| Kaplan-Meier median (95% CI)‡ (months) | 30.2 (NR, NR) | 14.9 (13.73, 17.22) |
| Cox HR (95% CI)§ | 0.38 (0.31, 0.48) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 3 - Inclusion of all deaths** | | |
| Events, n (%) | 91 (15.85) | 201 (34.90) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 19.0 (16.39, NR) |
| Cox HR (95% CI)§ | 0.39 (0.30, 0.50) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 4 - Impact of radiographic disease progression documented between visits** | | |
| Events, n (%) | 89 (15.51) | 198 (34.38) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 19.0 (16.59, NR) |
| Cox HR (95% CI)§ | 0.39 (0.30, 0.50) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 5 – 'Missing' data impact: censoring on date of last evaluable scan** | | |
| Events, n (%) | 89 (15.51) | 198 (34.38) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 19.0 (16.59, NR) |
| Cox HR (95% CI)§ | 0.38 (0.30, 0.49) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 6 – 'Missing' data impact: censoring prior to any period with 2 missing consecutive scans** | | |
| Events, n (%) | 88 (15.33) | 198 (34.38) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 19.4 (16.59, NR) |
| Cox HR (95% CI)§ | 0.38 (0.30, 0.49) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 7 – Censoring radiographic disease progression on new antineoplastic therapy and occurrence of an SSE** | | |
| Events, n (%) | 81 (14.11) | 175 (30.38) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 19.4 (16.62, NR) |
| Cox HR (95% CI)§ | 0.38 (0.29, 0.50) | |
| Log-rank P value§ | < 0.0001 | |

| Analyses | Enzalutamide+ADT (n = 574) | Placebo+ADT (n = 576) |
|---|---|---|
| **Sensitivity 8 – 'Missing' data impact and censoring on new antineoplastic therapy, occurrence of an SSE and study drug discontinuation** | | |
| n¶ | 536 | 531 |
| Events, n (%) | 77 (14.37) | 169 (31.83) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 16.8 (14.78, NR) |
| Cox HR (95% CI)§ | 0.36 (0.28, 0.48) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 9 - rPFS in patients with ICR-assessed metastasis at baseline** | | |
| n¶ | 536 | 531 |
| Events, n (%) | 88 (16.42) | 195 (36.72) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 16.7 (14.06, NR) |
| Cox HR (95% CI)§ | 0.37 (0.29, 0.48) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 10 - rPFS based on investigator's assessment** | | |
| Events, n (%) | 102 (17.77) | 192 (33.33) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 19.3 (16.53, NR) |
| Cox HR (95% CI)§ | 0.46 (0.36, 0.59) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 11 - rPFS based on PCWG2 criteria and investigator's assessment** | | |
| Events, n (%) | 102 (17.77) | 194 (33.68) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 19.0 (16.53, NR) |
| Cox HR (95% CI)§ | 0.46 (0.36, 0.58) | |
| Log-rank P value§ | < 0.0001 | |
| **Sensitivity 12 - rPFS based on PCWG2 criteria and ICR** | | |
| Events, n (%) | 90 (15.68) | 199 (34.55) |
| Kaplan-Meier median (95% CI)‡ (months) | NR | 19.3 (16.53, NR) |
| Cox HR (95% CI)§ | 0.39 (0.30, 0.50) | |
| Log-rank P value§ | < 0.0001 | |

Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cutoff date was 14 Oct 2018.

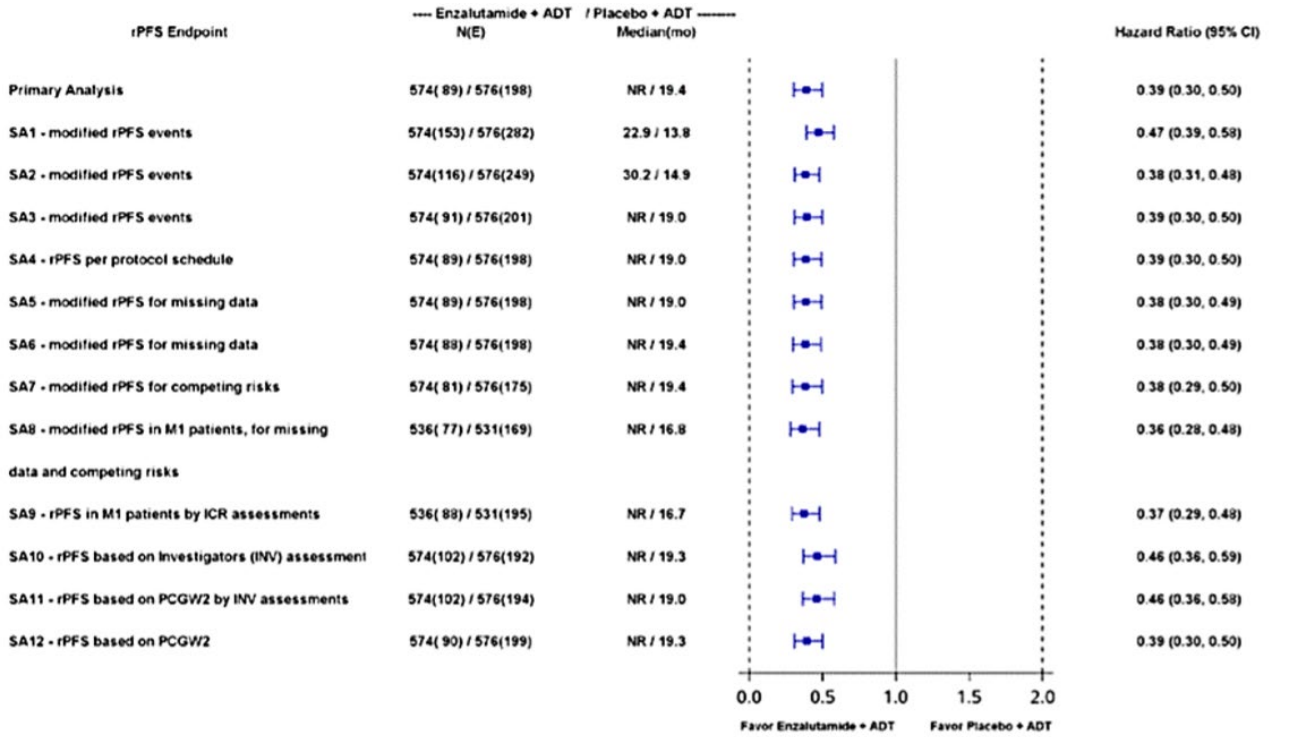
ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; ICR: independent central review; ITT: intent-to-treat; NR: not reached; PCWG2: Prostate Cancer Clinical Trials Working Group 2; rPFS: radiographic progression-free survival; SSE: symptomatic skeletal event

† A progression event was defined as objective evidence of radiographic disease progression based on the assessments by ICR or death by any cause within 24 weeks from study drug discontinuation, whichever occurred first. The time to event was calculated from the date of randomization to the date of occurrence of the first progression event. For patients with no documented progression event, rPFS was censored on the date of the last radiologic assessment performed before the cutoff date.

‡ Calculated by Brookmeyer and Crowley method

§ Stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)

¶ Analysis was conducted in patients with metastatic disease based on ICR assessments.




Unless otherwise specified, efficacy analyses were performed on the ITT population, which was defined as all patients who were randomized in the study.

The analysis data cutoff date was 14 Oct 2018.

ADT: androgen deprivation therapy; CI: confidence interval; E: number of events; ICR: independent central review; INV: investigator; ITT: intent-to-treat; M1: metastatic disease; NR: not reached; PCWG2: Prostate Cancer Clinical Trials Working Group 2; PSA: prostate-specific antigen; rPD: radiographic disease progression; rPFS: radiographic progression-free survival; SSE: symptomatic skeletal event; SA: sensitivity analysis as follows:

SA1: impact of treatment discontinuation as additional rPFS event

SA2: impact of new antineoplastic therapy and SSE as additional rPFS event

SA3: impact of all deaths with (no time limit) as rPFS event

SA4: impact of rPD documented between per protocol visits

SA5: 'missing' data impact - last scan not documented as not evaluable

SA6: 'missing' data impact – absence of 2 consecutive scans

SA7: censoring rPD on competing risks of new antineoplastic therapy and occurrence of an SSE

SA8: 'missing' data impact and censoring rPD on competing risks of new antineoplastic therapy, occurrence of an SSE and study drug discontinuation in metastatic disease patients based on ICR assessments

SA9: rPFS in M1 patients based on ICR assessments

SA10: impact of rPD documented by INV

SA11: impact of rPD according to PCWG2 criteria and documented by the investigator

SA12: impact of rPD according to PCWG2 criteria and documented by ICR

*Figure 11. Forest Plot of rPFS sensitivity analyses (ITT population)*

## *Summary of main study*

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

*Table 28. Summary of Efficacy for trial ARCHES (Study 9785-CL-0335)*

| **Title: ARCHES, a multinational, Phase 3, randomised, double-blind, placebo-controlled efficacy and safety study of enzalutamide plus androgen deprivation therapy (ADT) versus placebo plus ADT in patients with metastatic hormone sensitive prostate cancer (mHSPC)** | |
|---|---|
| Study identifier | Protocol number 9785-CL-0335; Phase 3; EudraCT 2015-003869-28 |

| | | | |
|---|---|---|---|
| Design | Randomised, double-blind | | |
| Hypothesis | Superiority | | |
| Treatments groups | Enzalutamide + ADT | | Enzalutamide 160 mg once daily + ADT until radiographic Disease Progression, start of another therapy for prostate cancer, unacceptable toxicity or any other discontinuation criteria are met; n=574 |
| | Placebo + ADT | | Placebo for enzalutamide + ADT until radiographic DP, start of another therapy for prostate cancer, unacceptable toxicity or any other discontinuation criteria are met; n=576 |
| Endpoints and definitions | Primary endpoint | rPFS | Time from the date of randomisation to the date of first objective evidence of rPD at any time or death from any cause within 24 weeks from study drug discontinuation, whichever occurs first. rPD was defined as progressive disease by RECIST 1.1 for soft tissue disease or by appearance of 2 or more new lesions on bone scan |
| | Secondary endpoint | OS | Time from randomisation to death from any cause |
| | Secondary endpoint | Time to PSA progression | Time from randomisation to the date of first observation of PSA progression, defined as a ≥25% increase and an absolute increase of ≥2 ng/ml above the nadir, confirmed by a second consecutive value at least 3 weeks later. |
| | Secondary Endpoint | Time to start of new antineoplastic therapy | Time from randomisation to the date of first dose administration of the first antineoplastic therapy. |
| | Secondary endpoint | PSA undetectable rate | Percentage of patients with detectable (≥0.2 ng /ml) PSA at baseline which became undetectable (<0.2 ng/ml) during study treatment. |
| | Secondary endpoint | ORR | Percentage of ITT patients with measurable disease at baseline who achieved a CR or PR (unconfirmed responses) in their soft tissue disease using RECIST 1.1 criteria |
| | Secondary endpoint | Time to deterioration of urinary symptoms | Increase in the urinary symptoms' subscale score of the QLQ-PR25 questionnaire (3 items: Q31 to Q33) by ≥50% of the standard deviation observed in the urinary symptoms' subscale score at baseline. |
| Database lock | 14 Oct 2018 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat | | |
| Descriptive statistics and estimate variability | Treatment group | Enzalutamide + ADT | Placebo + ADT |
| | Number of subjects | 574 | 576 |

| | | | |
|---|---|---|---|
| | rPFS* (Median – months) | NR | 19.0 |
| | 95% CI | NR | (16.59, 22.24) |
| | Time to PSA Progression (Median – months) | NR | NR |
| | 95% CI | (NR, NR) | (16.59, NR) |
| | Time to Start of New Antineoplastic Therapy (Median – months) | 30.2 | NR |
| | 95% CI | (NR, NR) | (21.06, NR) |
| | PSA Undetectable Rate (Patients with detectable PSA at baseline) | 511 | 506 |
| | n (%) | 348 (68.1) | 89 (17.6) |
| | Objective Response Rate (Patients with measurable disease) | 177 | 182 |
| | n (%) | 147 (83.1) | 116 (63.7) |
| | Time to Deterioration of Urinary Symptoms (Median – months) | NR | 16.8 |
| | 95% CI | (19.35, NR) | (14.06, NR) |
| | Overall Survival (Median – months) | NR | NR |
| | 95% CI | NR | NR |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint: rPFS | Comparison groups | <1 favours Enza+ADT |
| | | Hazard Ratio | 0.39 |
| | | (95% CI) | (0.30, 0.50) |
| | | P-value | <0.0001 |
| | Key Secondary: Time to PSA Progression | Comparison groups | <1 favours Enza+ADT |
| | | Hazard Ratio | 0.19 |
| | | (95% CI) | (0.13, 0.26) |
| | | P-value | <0.0001 |
| | Key Secondary: Time to Start of New Antineoplastic Therapy | Comparison groups | <1 favours Enza+ADT |
| | | Hazard Ratio | 0.28 |
| | | (95% CI) | (0.20, 0.40) |
| | | P-value | <0.0001 |
| | Key Secondary: PSA Undetectable Rate | Comparison groups | |
| | | Difference | 50.5% |
| | | (95% CI) | (45.3, 55.7) |
| | | P-value | <0.0001 |
| | Key Secondary: Objective Response Rate | Comparison groups | |
| | | Difference in Response Rates | 19.3% |
| | | (95% CI) | (10.4, 28.2) |
| | | P-value | <0.0001 |

| | | | |
|---|---|---|---|
| | Key Secondary: Time to Deterioration of Urinary Symptoms | Comparison groups | |
| | | Hazard Ratio | 0.88 |
| | | (95% CI) | (0.72, 1.08) |
| | | P-value | 0.2162 |
| | Key Secondary: Overall Survival | Comparison groups | |
| | | Hazard Ratio | 0.81 |
| | | (95% CI) | (0.53, 1.25) |
| | | P-value | 0.3361 |

* per protocol-specified criteria

## *Analysis performed across trials (pooled analyses and meta-analysis)*

Side-by-side comparisons of the efficacy results for ARCHES and ENZAMET, both of which were conducted in patients with mHSPC, and the previous placebo-controlled phase 3 studies in patients with metastatic CRPC (AFFIRM, PREVAIL, Asian PREVAIL) and nonmetastatic CRPC (PROSPER) are presented in this section.

*Table 29. Key elements in the study design for Phase 3 enzalutamide studies in patients with prostate cancer*

| Study Characteristic | ARCHES (9785-CL-0335) (n = 1150) | ENZAMET (ANZUP 1304) (n = 1125) | AFFIRM (CRPC2) (n = 1199) | PREVAIL (MDV3100-03) (n = 1717) | Asian PREVAIL (9785-CL-0232) (n = 388) | PROSPER (MDV3100-14) (n = 1401) |
|---|---|---|---|---|---|---|
| Multinational | Yes | Yes | Yes | Yes | Yes† | Yes |
| Blinded study | Yes | No (open-label) | Yes | Yes | Yes | Yes |
| Population | Patients with mHSPC | Patients with mHSPC | Patients with metastatic CRPC | Patients with metastatic CRPC | Patients with metastatic CRPC | Patients with nonmetastatic CRPC |
| Comparator | Placebo | NSAA | Placebo | Placebo | Placebo | Placebo |
| Prior docetaxel use | Up to 6 cycles allowed, to be completed within 2 months of day 1 | Up to 2 cycles allowed prior to randomization | Required | Prohibited | Prohibited | Prohibited |
| Concurrent docetaxel allowed | No | Yes; total of 6 cycles allowed | No | No | No | No |
| Planned assessments | Every 12 weeks | Every 12 weeks (imaging only at progression)§ | Every 12 weeks | Every 12 weeks | Every 12 weeks | Every 16 weeks |
| Assessment of radiographic disease progression | ICR | Investigator review | ICR | ICR | ICR | ICR |
| Primary efficacy endpoint | rPFS‡ | OS¶ | OS¶ | OS¶ and rPFS‡ | Time to PSA progression†† | MFS‡‡ |
| OS as endpoint | Yes | Yes | Yes | Yes | Yes | Yes |

CRPC: castration-resistant prostate cancer; CSR: clinical study report; ICR: independent central review; MFS: metastasis-free survival; mHSPC: metastatic hormone-sensitive prostate cancer; NSAA: nonsteroidal antiandrogen; OS: overall survival; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival

† Asian multinational study

‡ rPFS was defined as the time from randomization to the first objective evidence of radiographic disease progression as assessed by central review, or death (defined as death from any cause within 24 weeks from study drug discontinuation), whichever occurred first.

§ Clinical assessments, blood tests, quality of life assessments and reviews of adverse events were performed every 12 weeks. Imaging with computed tomography and whole body bone scans were performed at baseline and at evidence of PSA or clinical progression (whichever occurred first).

¶ OS was defined as the time from randomization to death from any cause.

†† Time to PSA progression was defined as the time from randomization to PSA progression, where progression was defined according to the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2.

‡‡ MFS was defined as the time from randomization to the first date of radiographic progression (assessed by ICR) at any time or death within 112 days of treatment discontinuation without evidence of radiographic progression, whichever occurred first.

*Table 30. Key elements in the patient population for Phase 3 enzalutamide studies in patients with prostate cancer*

| Patient Populations | ARCHES (9785-CL-0335) (n = 1150) | ENZAMET (ANZUP 1304) (n = 1125) | AFFIRM (CRPC2) (n = 1199) | PREVAIL (MDV3100-03) (n = 1717) | Asian PREVAIL (9785-CL-0232) (n = 388) | PROSPER (MDV3100-14) (n = 1401) |
|---|---|---|---|---|---|---|
| Population description | Patients with metastatic hormone-sensitive prostate cancer | Patients with metastatic hormone-sensitive prostate cancer | Patients with metastatic CRPC whose disease progressed after 1 or 2 prior chemotherapy regimens, 1 of which was docetaxel-based | Chemotherapy-naïve, asymptomatic or mildly symptomatic patients with metastatic CRPC | Chemotherapy-naïve, asymptomatic or mildly symptomatic patients with metastatic CRPC | Patients with nonmetastatic CRPC at high risk of disease progression based on baseline PSA level and short PSA doubling time |
| Median age, years | 70 | 69 | 69 | 71 | 71 | 74 |
| Baseline ECOG performance status of 0, % | 77.5 | 72.0 | 37.9 | 68.1 | 61.1 | 80.6 |
| Baseline pain score of 0 or 1, % | 57.7 enzalutamide+ADT<br>58.0 placebo+ADT | NA | NR† | 66.2 enzalutamide<br>67.5 placebo | 68.7 enzalutamide<br>65.8 placebo | 68.5 enzalutamide<br>71.8 placebo |
| Median baseline PSA level, ng/mL | 5.21 | 8.06 | 111.2 | 49.6 | 60.2 | 10.7 |

All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (safety population).

Data cutoff dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 25 Sep 2011; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 28 Jun 2017

CRPC: castration-resistant prostate cancer; ECOG: Eastern Cooperative Oncology Group; NA: not applicable; NR: not reported; PSA: prostate-specific antigen

† A summary by baseline pain score of 0 or 1 was not provided; however, 71.6% of patients had a baseline pain score < 4.

Comparison of efficacy results

*Table 31. Interim overall survival results in patients with mHSPC: ARCHES and ENZAMET*

| Parameter Statistics | ARCHES (9785-CL-0335) | | ENZAMET (ANZUP 1304) | |
|---|---|---|---|---|
| | Enzalutamide +ADT (n = 574) | Placebo +ADT (n = 576) | Enzalutamide +ADT (n = 563) | Conventional NSAA+ADT (n = 562) |
| **Overall survival (months)†** | | | | |
| 25th percentile | NR | NR | 45.73 | 34.79 |
| Median (95% CI) | NR | NR | NR | NR |
| 75th percentile | NR | NR | NR | NR |
| Cox HR (95% CI)† | 0.81 (0.53, 1.25) | | 0.669 (0.518, 0.862) | |
| Log-rank P value† | 0.3361 | | 0.0018 | |
| **Median follow-up (months)** | 14.4 | | 33.84 | |

All patients randomly assigned to treatment (ITT Population).

The analysis data cutoff date for ARCHES was 14 Oct 2018; the analysis data cutoff date for ENZAMET was 28 Feb 2019.

ADT: androgen-deprivation therapy; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; NR: not reached; NSAA: nonsteroidal antiandrogen

† The analysis of overall survival was based on a Cox proportional hazards model. In ARCHES, an adjusted Cox model was used which included the stratification factors (volume of disease [low, high] and prior docetaxel use [yes, no]) as covariates. The primary analysis of overall survival in ENZAMET used an unadjusted Cox model.

*Table 32. Comparison of Selected Efficacy Endpoints in Patients with mHSPC (ARCHES) and Patients with Metastatic CRPC (AFFIRM, PREVAIL, Asian PREVAIL) or Nonmetastatic CRPC (PROSPER)*

| Parameter | mHSPC | | Metastatic CRPC | | | | | | Nonmetastatic CRPC | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ARCHES (9785-CL-0335) | | AFFIRM (CRPC2) | | PREVAIL (MDV3100-03) | | Asian PREVAIL (9785-CL-0232) | | PROSPER (MDV3100-14) | |
| Statistics/ Category | Enza (n = 574) | Placebo (n = 576) | Enza (n = 800) | Placebo (n = 399) | Enza (n = 872) | Placebo (n = 845) | Enza (n = 198) | Placebo (n = 190) | Enza (n = 933) | Placebo (n = 468) |
| **rPFS† (months)** | | | | | | | | | | |
| 25th percentile | NR | 8.5 | 3.1 | 2.7 | 9.5 | 1.9 | 8.25 | 1.91 | 21.6 | 7.2 |
| Median (95% CI) | NR | 19.4 (16.59, NR) | 8.3 (8.2, 9.4) | 2.9 (2.8, 3.4) | NR (13.8, NR) | 3.9 (3.7, 5.4) | NR (10.97, NR) | 5.29 (3.61, 11.33) | 36.6 (33.1, NR) | 14.7 (14.2, 15.0) |
| 75th percentile | NR | NR | 14.7 | 6.1 | NR | 8.3 | NR | 11.33 | NR | 33.0 |
| P value‡ | < 0.0001 | | < 0.0001 | | < 0.0001 | | < 0.0001 | | < 0.0001 | |
| HR (95% CI)‡ | 0.39 (0.30, 0.50) | | 0.40 (0.35, 0.47) | | 0.19 (0.15, 0.23) | | 0.31 (0.20, 0.46) | | 0.29 (0.24, 0.35) | |
| **OS (months)** | | | | | | | | | | |
| 25th percentile | NR | NR | 10.1 | 6.8 | 22.0 | 17.4 | NR | 11.33 | NR | 34.0 |
| Median (95% CI) | NR | NR | 18.4 (17.3, NR) | 13.6 (11.3, 15.8) | 35.5 (33.5, 38.0) | 31.4 (28.9, 33.8) | NR (NR, NR) | NR (11.70, NR) | NR (NR, NR) | NR (NR, NR) |
| 75th percentile | NR | NR | NR | NR | 62.5 | 55.4 | NR | NR | NR | NR |
| P value‡ | 0.3361§ | | < 0.0001 | | 0.0008¶ | | 0.0015 | | 0.1519§ | |
| HR (95% CI)‡ | 0.81 (0.53, 1.25) | | 0.63 (0.53, 0.75) | | 0.83 (0.75, 0.93)§ | | 0.33 (0.16, 0.67) | | 0.80 (0.58, 1.09) | |
| **Time to PSA progression (months)** | | | | | | | | | | |
| 25th percentile | NR | 8.3 | 4.6 | 2.8 | 5.7 | 2.8 | 4.63 | 2.79 | 18.5 | 3.7 |
| Median (95% CI) | NR | NR (16.59, NR) | 8.3 (5.8, 8.3) | 3.0 (2.9, 3.7) | 11.2 (11.1, 13.7) | 2.8 (2.8, 2.9) | 8.31 (5.72, 10.25) | 2.86 (2.83, 4.63) | 37.2 (33.1, NR) | 3.9 (3.8, 4.0) |
| 75th percentile | NR | NR | 14.0 | 4.7 | NR | 4.6 | NR | 8.31 | NR | 7.5 |
| P value‡ | < 0.0001 | | < 0.0001 | | < 0.0001 | | < 0.0001 | | < 0.0001 | |
| HR (95% CI)‡ | 0.19 (0.13, 0.26) | | 0.25 (0.20, 0.30) | | 0.17 (0.15, 0.20) | | 0.38 (0.27, 0.52) | | 0.07 (0.05, 0.08) | |

| Parameter | mHSPC | | Metastatic CRPC | | | | | | Nonmetastatic CRPC | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ARCHES (9785-CL-0335) | | AFFIRM (CRPC2) | | PREVAIL (MDV3100-03) | | Asian PREVAIL (9785-CL-0232) | | PROSPER (MDV3100-14) | |
| Statistics/ Category | Enza (n = 574) | Placebo (n = 576) | Enza (n = 800) | Placebo (n = 399) | Enza (n = 872) | Placebo (n = 845) | Enza (n = 198) | Placebo (n = 190) | Enza (n = 933) | Placebo (n = 468) |
| **≥ 50% Decrease in PSA level (confirmed)** | | | | | | | | | | |
| n/N (%) | 533/574 (92.9) | 327/576 (56.8) | 395/731 (54.0) | 5/330 (1.5) | 666/854 (78.0) | 27/777 (3.5) | 120/182 (65.9) | 15/148 (10.1) | 712/933†† (76.3) | 11/468†† (2.4) |
| 95% CI for response rate | NA‡‡ | NA‡‡ | 50.3, 57.7 | 0.5, 3.5 | 75.1, 80.7 | 2.3, 5.0 | 58.6, 72.8 | 5.8, 16.2 | 73.5, 79.0 | 1.2, 4.2 |
| Difference in response rates (95% CI) | NA‡‡ | | 52.5 (48.7, 56.4) | | 74.51 (71.45, 77.57) | | 55.8 (47.4, 64.2) | | 73.96 (70.91, 77.02) | |
| P value | NA‡‡ | | < 0.0001§§ | | < 0.0001§§ | | < 0.0001§§ | | < 0.0001§§ | |
| **PSA undetectable** | | | | | | | | | | |
| n/N (%) | 348/511¶¶ (68.1) | 89/506¶¶ (17.6) | NA | | NA | | NA | | 90/933†† (9.6) | 0 |
| 95% CI for response rate | 63.9, 72.1 | 14.4, 21.2 | | | | | | | 7.8, 11.7 | 99.2, 100.0 |
| Difference in response rates (95% CI) | 50.5 (45.3, 55.7) | | | | | | | | 9.65 (7.75, 11.54) | |
| P value | < 0.0001§§ | | | | | | | | < 0.0001§§ | |

All patients randomly assigned to study treatment (ITT population)

Data cutoff dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 25 Sep 2011; PREVAIL: 30 Sep 2017 for OS, 06 May 2012 for rPFS, 16 Sep 2013 for all other efficacy analyses; Asian PREVAIL: 20 Sep 2015; PROSPER: 28 Jun 2017

CI: confidence interval; CRPC: castration-resistant prostate cancer; Enza: enzalutamide; HR: hazard ratio; ITT: intent-to-treat; mHSPC: metastatic hormone-sensitive prostate cancer; NA: not applicable; NR: not reached; OS: overall survival; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival.

† In PROSPER, metastasis-free survival was measured rather than rPFS; the measure of metastasis-free survival for patients with nonmetastatic CRPC is analogous to the measure of rPFS in patients with metastatic CRPC.

‡ HR and its 95% CI from a Cox proportional hazards model with treatment group as a covariate. P value from a stratified log rank test in ARCHES and PROSPER; P value from an unstratified log rank test in AFFIRM, PREVAIL and Asian PREVAIL.

§ For ARCHES and PROSPER, analyses are interim, pending future interim or final analyses. The OS results from the interim analyses are presented.

¶ For PREVAIL, 5-year updated OS results are presented.

†† In PROSPER, the number of evaluable patients with a baseline PSA value and at least 1 postbaseline PSA value was 887 in the enzalutamide group and 439 in the placebo group. The percentages are provided are based on the full ITT population.

‡‡ Statistics were not calculated for the PSA responder rate in ARCHES. The endpoint for ARCHES was a PSA decline to < 0.2 ng/mL (undetectable).

§§ P value was based on a stratified Cochran-Mantel-Haenszel mean score test ARCHES and PROSPER and on an unistratified test in AFFIRM, PREVAIL and Asian PREVAIL.

¶¶ Patients must have had a detectable PSA level at baseline to be included in this analysis.

## *Clinical studies in special populations*

N/A

## *Supportive studies*

### Study ENZAMET (ANZUP 1304)

This is a multicenter, open-label, randomised, phase 3 study in 1,125 patients with mHSPC starting first-

line ADT for metastatic prostate cancer. The study is being led by ANZUP Cancer Trials Group in collaboration with the University of Sydney (sponsor) acting through the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC).

*Methods*

Patients were randomized 1:1 to enzalutamide 160 mg daily by mouth or a conventional nonsteroidal antiandrogen -NSAA (bicalutamide, nilutamide or flutamide) by mouth; all patients were also treated with an LHRH analogue or surgical castration. Patients were allowed up to 6 cycles of concomitant docetaxel (75 mg/m$^2$), as long as the decision to use early docetaxel was made and specified prior to randomisation and the patients received no more than 2 cycles prior to randomisation.

Treatment was to continue until disease progression or prohibitive toxicity.

Randomisation was stratified for volume of disease (high vs low), study site, concomitant antiresorptive therapy (yes vs no), comorbidities according to the Adult Comorbidity Evaluation [ACE-27] score (0 to 1 vs 2 to 3) and early planned use of docetaxel (yes vs no). High volume of disease was defined as 4 or more bone metastases, 1 of which was outside the vertebral column and pelvis and/or visceral metastases. Lymph node involvement of bladder invasion did not qualify as visceral disease. Antiresorptive therapy referred to concomitant therapy to delay skeletal-related events when commencing ADT (denosumab, zoledronic acid or any other therapy at doses proven to prevent skeletal-related events). ACE-27 score intervals of 0 to 1 vs 2 to 3 were used for the stratification. Early planned use of docetaxel was defined as the use of docetaxel in conjunction with initiation of ADT.

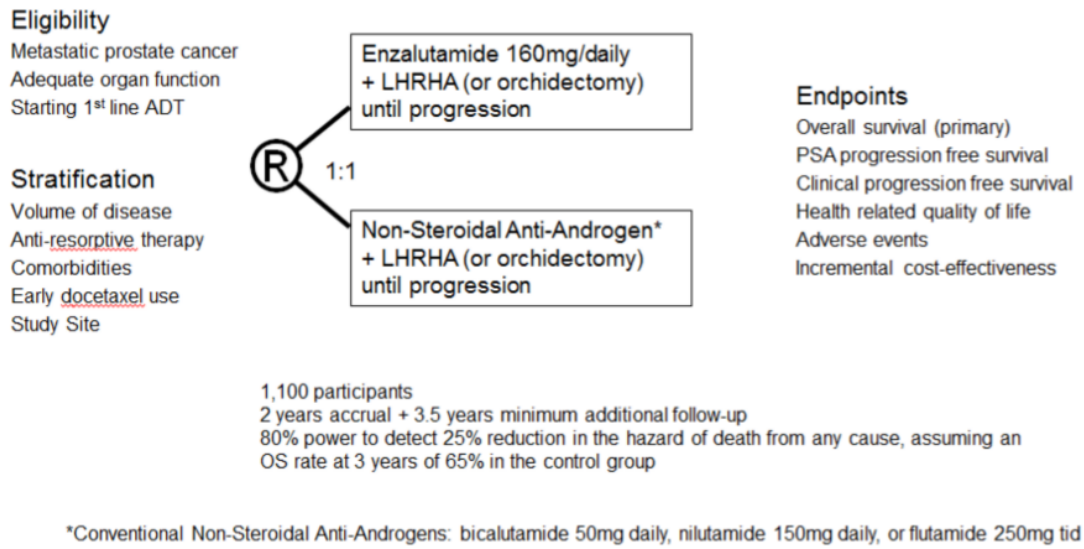



Figure 12. ENZAMET study schematic

Eligible patients had metastatic adenocarcinoma of the prostate defined by documented histopathology or cytopathology of prostate adenocarcinoma from a biopsy of a metastatic site; or documented histopathology of prostate adenocarcinoma from a transrectal ultrasound-guided biopsy, radical prostatectomy or transurethral resection of the prostate and metastatic disease consistent with prostate cancer; or metastatic disease typical of prostate cancer (i.e., involving bone or pelvic lymph nodes or

para-aortic lymph nodes) and a serum PSA concentration that is rising and is >20 ng/mL, have received prior ADT or prior cytotoxic chemotherapy for prostate cancer, with the following exceptions:

- ADT could have been started <12 weeks prior to randomization, with PSA stable or falling.
- Prior ADT was allowed in the adjuvant setting, where the completion of adjuvant hormonal therapy was >12 months prior to randomisation and the total duration of hormonal treatment did not exceed 24 months.
- Up to 2 cycles of docetaxel chemotherapy for metastatic disease were permitted prior to randomisation; continued treatment with docetaxel was allowed for a total of up to 6cycles.

The primary objective was to determine the effect of enzalutamide plus ADT on OS (defined as death from any cause). Secondary objectives were to determine the effects of enzalutamide plus ADT on the following: PSA PFS (based on the first evidence of PSA progression, clinical progression or death from any cause), clinical PFS (based on evidence of radiographic progression using PCWG2 for bone lesions and RECIST 1.1 for soft tissue, development of symptoms attributable to cancer progression or initiation of another anticancer treatment for prostate cancer), Adverse Events (AEs) and HRQoL (utilizing European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, QLQ-PR25 and EQ-5D-5L health questionnaires).

The primary analysis population for efficacy was the ITT population, defined as all randomised patients. The ITT population was analysed by treatment group according to study treatment assigned at the time of randomization.

The study design included a provision for up to 3 interim efficacy analyses on OS at 50%, 67% and 80% of the maximum number of events being sought (i.e., 470). The interim analyses allowed for early rejection of the null hypothesis according to an alpha spending function with an O'Brien-Fleming boundary shape.

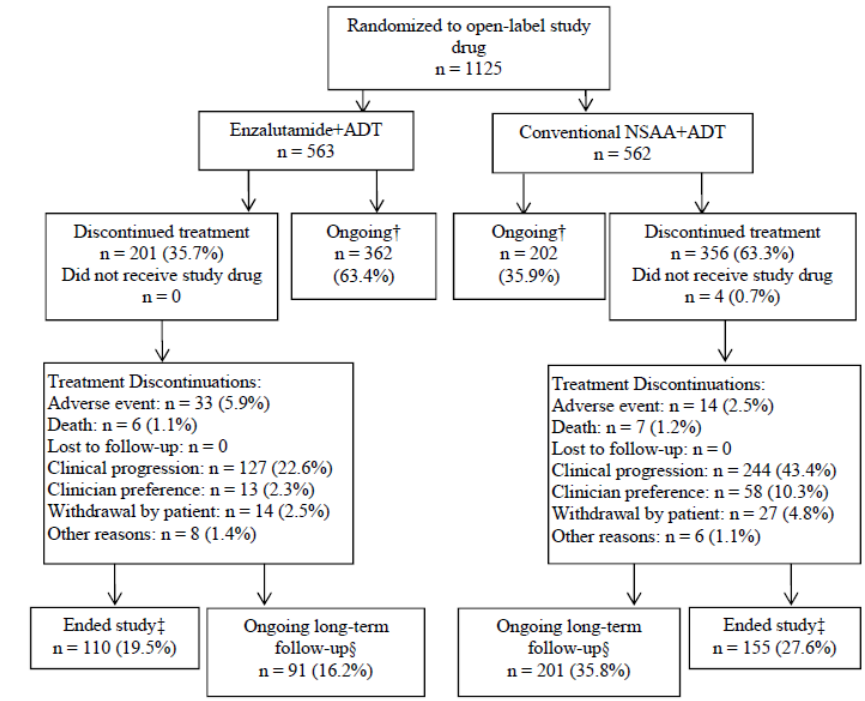
*Table 33. Indicative Boundary for Rejection of the Null Hypothesis*

| Stage | Proportion of Required Events | Z Score Boundary Rejection of the Null Hypothesis† | 2-Sided P-value Corresponding to Boundary |
|---|---|---|---|
| 1 | 0.5 | ±2.96 | 0.003 |
| 2 | 0.67 | ±2.53 | 0.011 |
| 3 | 0.8 | ±2.32 | 0.020 |
| 4 | 1 | ±2.03 | 0.042 |

† Calculated using SAS code

*Results*

From 31 Mar 2014 to 24 Mar 2017 (the last date of randomisation), 1,125 patients were randomly assigned at a 1:1 ratio to treatment with enzalutamide plus ADT (563 patients) or NSAA plus ADT (562 patients); 1121 patients received at least 1 dose of enzalutamide plus ADT (563 patients) or NSAA plus ADT (558 patients) Figure 13. There were 79 study sites in 6 countries (Australia, Canada, Ireland, New Zealand, UK and the US) in 3 regions: Australia/New Zealand, Europe and North America.




Data cutoff date: 28 Feb 2019

ADT: androgen deprivation therapy; NSAA: nonsteroidal antiandrogen

† Patients were still on-treatment by the cutoff date (or no documentation of treatment discontinuation was received).

‡ Includes patients who did not complete any long-term follow-up visits or ended their participation in long-term follow-up.

§ Patients in long-term follow-up after treatment discontinuation

Figure 13. Patient Disposition (All Randomised Patients)

The original study protocol (dated 11 Nov 2013) was amended twice (07 Nov 2014 and 01 Mar 2018). Use of docetaxel was introduced with amendment 1 of the protocol.

There were 134 patients (11.9%) who had at least 1 major protocol deviation. Protocol deviations were more frequent in the enzalutamide arm compared to the NSAA arm (16.2% vs 7.7%). Differences were mainly driven by PD4 (i.e. received excluded concomitant treatment) with only 2 (0.4%) patients in the control arm and 34 patients (6.0%) in the experimental arm. The higher number of protocol deviations observed in the enzalutamide arm was due to patients continuing prior anti-androgen therapy post-randomisation (31 of the 34 deviations). In the majority of the cases (28/31), ADT therapy was discontinued within 7 days after randomisation.

*Table 34. Demographic Characteristics for Patients in ENZAMET*

| Parameter<br>Statistics/Criteria | Enzalutamide+ADT<br>(n = 563) | Conventional NSAA+ADT<br>(n = 562) | Total<br>(n = 1125) |
|---|---|---|---|
| **Sex** | | | |
| Male | 563 (100) | 562 (100) | 1125 (100) |
| **Age category (years), n (%)** | | | |
| < 65 | 177 (31.4) | 174 (31.0) | 351 (31.2) |
| ≥ 65 | 386 (68.6) | 388 (69.0) | 774 (68.8) |
| < 70 | 306 (54.4) | 305 (54.3) | 611 (54.3) |
| ≥ 70 | 257 (45.6) | 257 (45.7) | 514 (45.7) |
| < 75 | 434 (77.1) | 437 (77.8) | 871 (77.4) |
| ≥ 75 | 129 (22.9) | 125 (22.2) | 254 (22.6) |
| **Age (years)** | | | |
| Mean (SD) | 68.4 (8.1) | 68.3 (8.3) | 68.3 (8.2) |
| Median (min, max) | 69.0 (47, 90) | 68.0 (40, 95) | 69.0 (40, 95) |
| **Weight (kg)** | | | |
| n | 561 | 560 | 1121 |
| Mean (SD) | 87.1 (16.4) | 85.9 (16.0) | 86.5 (16.2) |
| Median (min, max) | 85.0 (51, 154) | 84.0 (42, 156) | 85.0 (42, 156) |
| **Body mass index (kg/m$^2$)** | | | |
| n | 561 | 559 | 1120 |
| Mean (SD) | 28.48 (4.95) | 28.12 (4.82) | 28.30 (4.89) |
| Median (min, max) | 27.78 (17.6, 47.9) | 27.73 (16.3, 54.6) | 27.76 (16.3, 54.6) |
| **Body surface area (m$^2$)** | | | |
| n | 520 | 518 | 1038 |
| Mean (SD) | 2.02 (0.19) | 2.01 (0.19) | 2.01 (0.19) |
| Median (min, max) | 2.01 (1.6, 2.7) | 1.99 (1.4, 2.6) | 2.01 (1.4, 2.7) |
| **Region†, n (%)** | | | |
| Europe | 102 (18.1) | 93 (16.5) | 195 (17.3) |
| Australia/New Zealand | 344 (61.1) | 340 (60.5) | 684 (60.8) |
| North America | 117 (20.8) | 129 (23.0) | 246 (21.9) |
| **Site country, n (%)** | | | |
| Australia | 324 (57.5) | 321 (57.1) | 645 (57.3) |
| Canada | 97 (17.2) | 107 (19.0) | 204 (18.1) |
| Ireland | 39 (6.9) | 43 (7.7) | 82 (7.3) |
| New Zealand | 20 (3.6) | 19 (3.4) | 39 (3.5) |
| United Kingdom | 63 (11.2) | 50 (8.9) | 113 (10.0) |
| United States | 20 (3.6) | 22 (3.9) | 42 (3.7) |

All randomized patients (ITT population)

Data cutoff date: 28 Feb 2019

Body mass index = weight (kg)/height (m$^2$).

ADT: androgen deprivation therapy; ITT: intent-to-treat; max: maximum; min: minimum; NSAA: nonsteroidal antiandrogen

† Europe includes Ireland and the United Kingdom; North America includes Canada and the United States

*Table 35. Prostate Cancer Disease History*

| Parameter Statistics/Criteria | Enzalutamide+ADT (n = 563) | Conventional NSAA+ADT (n = 562) | Total (n = 1125) |
|---|---|---|---|
| **ECOG performance status, n (%)** | | | |
| 0 | 405 (71.9) | 405 (72.1) | 810 (72.0) |
| 1 | 150 (26.6) | 151 (26.9) | 301 (26.8) |
| 2 | 8 (1.4) | 6 (1.1) | 14 (1.2) |
| **Gleason score group, n (%)** | | | |
| < 8 | 152 (27.0) | 163 (29.0) | 315 (28.0) |
| ≥ 8 | 335 (59.5) | 321 (57.1) | 656 (58.3) |
| Unknown or missing | 76 (13.5) | 78 (13.9) | 154 (13.7) |
| **Volume of disease strata†, n (%)** | | | |
| High | 291 (51.7) | 297 (52.8) | 588 (52.3) |
| Low | 272 (48.3) | 265 (47.2) | 537 (47.7) |
| **Docetaxel chemotherapy strata†, n (%)** | | | |
| No | 309 (54.9) | 313 (55.7) | 622 (55.3) |
| Yes | 254 (45.1) | 249 (44.3) | 503 (44.7) |
| **Antiresorptive therapy strata†, n (%)** | | | |
| No | 508 (90.2) | 504 (89.7) | 1012 (90.0) |
| Yes | 55 (9.8) | 58 (10.3) | 113 (10.0) |
| **ACE-27 strata†, n (%)** | | | |
| 0 to 1 | 422 (75.0) | 419 (74.6) | 841 (74.8) |
| 2 to 3 | 141 (25.0) | 143 (25.4) | 284 (25.2) |
| **Prior ADT status‡, n (%)** | | | |
| No | 505 (89.7) | 522 (92.9) | 1027 (91.3) |
| Yes | 58 (10.3) | 40 (7.1) | 98 (8.7) |
| **Duration of previous ADT, n (%)** | | | |
| > 0 to ≤ 6 months | 15 (2.7) | 8 (1.4) | 23 (2.0) |
| > 6 to ≤ 12 months | 16 (2.8) | 11 (2.0) | 27 (2.4) |
| > 12 to ≤ 24 months | 13 (2.3) | 10 (1.8) | 23 (2.0) |
| > 24 months | 8 (1.4) | 8 (1.4) | 16 (1.4) |
| Unknown | 6 (1.1) | 4 (0.7) | 10 (0.9) |
| **Baseline PSA (ng/mL)** | | | |
| n | 559 | 558 | 1117 |
| Mean (SD) | 61.91 (265.28) | 90.53 (815.75) | 76.21 (606.23) |
| Median (min, max) | 8.00 (0, 3592.00) | 8.11 (0.02, 18380.00) | 8.06 (0, 18380.00) |
| **Local disease prostate, n (%)** | | | |
| No | 119 (21.1) | 123 (21.9) | 242 (21.5) |
| Yes | 444 (78.9) | 439 (78.1) | 883 (78.5) |
| **Local disease bladder invasion, n (%)** | | | |
| No | 510 (90.6) | 520 (92.5) | 1030 (91.6) |
| Yes | 53 (9.4) | 42 (7.5) | 95 (8.4) |
| **Visceral metastases§, n (%)** | | | |
| No | 501 (89.0) | 495 (88.1) | 996 (88.5) |
| Yes | 62 (11.0) | 67 (11.9) | 129 (11.5) |
| **Distant metastases first diagnosed prior to randomization, n (%)** | | | |
| Within 12 weeks | 425 (75.5) | 408 (72.6) | 833 (74.0) |
| > 12 weeks | 136 (24.2) | 151 (26.9) | 287 (25.5) |
| More than 6 months | 32 (5.7) | 40 (7.1) | 72 (6.4) |
| More than 12 months | 16 (2.8) | 16 (2.8) | 32 (2.8) |

All randomized patients (ITT population)

Data cutoff date: 28 Feb 2019

ACE: Adult Comorbidity Evaluation; ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; max: maximum; min: minimum; NSAA: nonsteroidal antiandrogen; PSA: prostate specific antigen

† Volume of disease, planned early use of docetaxel, antiresorptive therapy and comorbidities based on ACE-27 score were stratification factors at randomization; summaries were based on data from the centralized randomization system.

‡ Included adjuvant ADT, but did not include ADT for metastatic disease started within 12 weeks prior to randomization or bilateral orchiectomy.

§ Visceral metastases included lung, pleura, liver, adrenal and others; lymph node involvement or bladder invasion did not qualify as visceral disease.

The majority of the patients included in the ENZAMET study received ADT in the metastatic setting (79% of patients on the enzalutamide arm versus 81.5% in the control arm)h, i.e., within 12 weeks prior to

randomisation, according to inclusion/exclusion criteria  Furthermore, there were around 9% of patients that received adjuvant ADT.

*Table 36. Radiation and surgical treatment history for prostate cancer (ITT population)*

| Parameter | Enzalutamide+ADT (n = 563) | Conventional NSAA+ADT (n = 562) | Total (n = 1125) |
|---|---|---|---|
| **Prior local treatment†, n (%)** | | | |
| Yes | 238 (42.3) | 235 (41.8) | 473 (42.0) |
| Missing | 325 (57.7) | 327 (58.2) | 652 (58.0) |
| **Prior radiotherapy‡, n (%)** | | | |
| No | 380 (67.5) | 412 (73.3) | 792 (70.4) |
| Yes | 183 (32.5) | 150 (26.7) | 333 (29.6) |
| **Prior local radiotherapy§, n (%)** | | | |
| No | 450 (79.9) | 462 (82.2) | 912 (81.1) |
| Yes | 113 (20.1) | 100 (17.8) | 213 (18.9) |
| **Bilateral orchiectomy, n (%)** | | | |
| No | 558 (99.1) | 554 (98.6) | 1112 (98.8) |
| Yes | 5 (0.9) | 8 (1.4) | 13 (1.2) |
| **Prior surgery related to the primary tumor¶, n (%)** | | | |
| No | 85 (15.1) | 89 (15.8) | 174 (15.5) |
| Yes | 478 (84.9) | 473 (84.2) | 951 (84.5) |
| **Type of surgery††, n (%)** | | | |
| Radical prostatectomy | 128 (22.7) | 122 (21.7) | 250 (22.2) |
| TURP | 64 (11.4) | 69 (12.3) | 133 (11.8) |
| Biopsy | 365 (64.8) | 342 (60.9) | 707 (62.8) |
| Other | 30 (5.3) | 30 (5.3) | 60 (5.3) |
| Missing | 85 (15.1) | 90 (16.0) | 175 (15.6) |
| **Surgery for metastatic disease, n (%)** | | | |
| No | 513 (91.1) | 520 (92.5) | 1033 (91.8) |
| Yes | 50 (8.9) | 42 (7.5) | 92 (8.2) |
| Bone | 14 (2.5) | 12 (2.1) | 26 (2.3) |
| Other | 36 (6.4) | 30 (5.3) | 66 (5.9) |

All randomized patients (ITT population)

Data cutoff date: 28 Feb 2019

ADT: androgen deprivation therapy; ITT: intent-to-treat; NSAA: nonsteroidal antiandrogen; TURP: transurethral resection of the prostate

† Included local surgeries (radical prostatectomy, TURP), local radiotherapy (for the prostate including lymph nodes, for the prostate not including lymph nodes) or other local treatment (nanoknife, green light laser prostatectomy, low dose rate brachytherapy, high-intensity focused ultrasound or laser cryoablation).

‡ Included adjuvant radiotherapy, radiotherapy started prior to randomization or up to 6 weeks after commencing study treatment.

§ Irradiated sites included 'prostate including lymph nodes' and 'prostate not including lymph nodes.'

¶ Included all prostate-related surgeries and biopsies.

†† Type of surgery refers to treatment of the primary tumor.  Patients who reported results in more than 1 category were counted once in each applicable category.  Percentages were calculated based on the total number of patients in each treatment group.

*Table 37. Prior drug therapy for prostate cancer (ITT population)*

| Parameter | Enzalutamide+ADT (n = 563) | Conventional NSAA+ADT (n = 562) | Total (n = 1125) |
|---|---|---|---|
| **Prior cytotoxic chemotherapy†, n (%)** | | | |
| No | 511 (90.8) | 513 (91.3) | 1024 (91.0) |
| Yes | 10 (1.8) | 7 (1.2) | 17 (1.5) |
| Missing | 42 (7.5) | 42 (7.5) | 84 (7.5) |
| **Docetaxel for metastatic disease prior to randomization, n (%)** | | | |
| No | 426 (75.7) | 436 (77.6) | 862 (76.6) |
| Yes | 95 (16.9) | 83 (14.8) | 178 (15.8) |
| Missing | 42 (7.5) | 43 (7.7) | 85 (7.6) |
| **NSAA for metastatic disease within 12 weeks prior to randomization, n (%)** | | | |
| No | 278 (49.4) | 246 (43.8) | 524 (46.6) |
| Yes | 285 (50.6) | 316 (56.2) | 601 (53.4) |
| **LHRHA for metastatic disease within 12 weeks prior to randomization, n (%)** | | | |
| No | 152 (27.0) | 144 (25.6) | 296 (26.3) |
| Yes | 411 (73.0) | 418 (74.4) | 829 (73.7) |

All randomized patients (ITT population)

Data cutoff date: 28 Feb 2019

ADT: androgen deprivation therapy; ITT: intent-to-treat; LHRHA: luteinizing hormone releasing analogue; NSAA: nonsteroidal antiandrogen

† Included adjuvant chemotherapy, but did not include docetaxel chemotherapy for metastatic prostate cancer.

For the analysis of OS, a total of 245 deaths occurred and included 102 deaths (18.1%) in the enzalutamide plus ADT group and 143 deaths (25.4%) in the NSAA plus ADT group. A statistically significant 33% reduction in the risk of death was observed in patients treated with enzalutamide plus ADT compared with a conventional NSAA plus ADT, with an HR of 0.67 (95%CI:0.52,0.86; P=0.002) Table 38]. This interim analysis, based on a median follow-up of 33.8 months, showed that the efficacy stopping boundary was crossed. There were not enough death events in either arm to estimate the median OS. Survival at 36 months was 79.7% in the enzalutamide plus ADT group vs 72.4% in the NSAA plus ADT group. A sensitivity analysis using a stratified log-rank test and Cox regression model showed an HR of 0.68 (95% CI: 0.52, 0.87, P=0.0008).

The patients continue on-study and continue to be followed for survival; an updated OS analysis is currently planned when at least 470 deaths have been reported.

*Table 38. Interim analysis of overall survival (ITT population)*

| Category<br>Parameter/Statistics | Enzalutamide+ADT<br>(n = 563) | Conventional NSAA+ADT<br>(n = 562) |
|---|---|---|
| **Deaths, n (%)** | 102 (18.1) | 143 (25.4) |
| **Censored at the cutoff date, n (%)** | 461 (81.9) | 419 (74.6) |
| **Overall survival, Kaplan-Meier estimate (months)** | | |
| 25th percentile (95% CI) | 45.73 (38.83, NE) | 34.79 (30.82, 37.62) |
| Median (95% CI) | NE (NE, NE) | NE (NE, NE) |
| 75th percentile (95% CI) | NE (NE, NE) | NE (NE, NE) |
| **Treatment comparison: enzalutamide+ADT vs NSAA+ADT** | | |
| **Unstratified analysis** | | |
| Cox HR (95% CI) † | 0.669 (0.518, 0.862) | |
| Log-rank 2-sided P value | 0.0018 | |
| **Stratified analysis‡** | | |
| Cox HR (95% CI) § | 0.675 (0.522, 0.870) | |
| Log-rank 2-sided P value | 0.0008 | |
| **Overall survival rate, % (95% CI)¶** | | |
| Month 12 | 96.6 (94.7, 97.8) | 95.7 (93.6, 97.1) |
| Month 24 | 89.1 (86.2, 91.4) | 84.7 (81.4, 87.4) |
| Month 36 | 79.7 (75.4, 83.3) | 72.4 (67.8, 76.4) |
| **Median follow-up in months** | 33.68 | 33.84 |
| **Combined median follow-up in months** | 33.84 | |

All patients randomly assigned to treatment (ITT Population).

Data cutoff date: 28 Feb 2019

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; NE: not estimable; NSAA: nonsteroidal antiandrogen

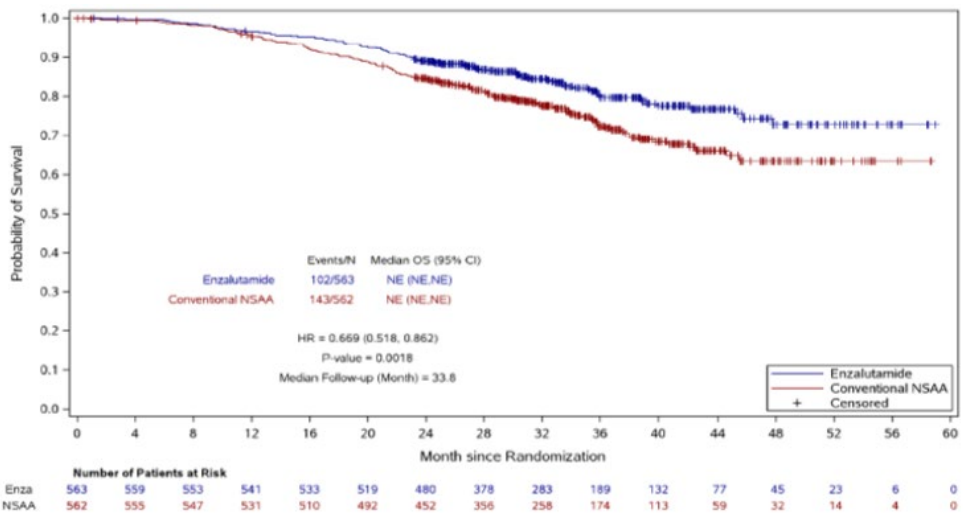
Overall survival in months was defined as (death [or censoring] date - randomization date)/30.4375.

† Based on a Cox proportional hazards model. Assuming proportional hazards, HR < 1 indicated a reduction in hazard rate in favor of the enzalutamide arm.

‡ Stratification factors were volume of disease (high, low), use of early docetaxel planned (yes, no), use of antiresorptive therapy (yes, no), Adult Comorbidity Evaluation score (0 to 1, 2 to 3) and region (Europe, Australia and New Zealand, North America). If patients were incorrectly stratified at the time of randomization, data in the electronic case report form corrected by the site were used in analysis.

§ Based on an adjusted Cox model that included the stratification factors as covariates. Assuming proportional hazards, HR < 1 indicated a reduction in hazard rate in favor of the enzalutamide arm.

¶ Survival rate and 95% CI were estimated using the Kaplan-Meier method and Greenwood formula.




All patients randomly assigned to treatment (ITT Population).

Data cutoff date: 28 Feb 2019

Enza: enzalutamide; HR: hazard ratio; ITT: intent-to-treat; NE: not estimable; NSAA: nonsteroidal antiandrogen; OS: overall survival

P values < 0.05 suggested violation of the proportional hazards assumption.

*Figure 14 Kaplan-Meier Plot of Overall Survival (ITT Population)*

Prespecified subgroup analyses included the following: Gleason score (<8, ≥8), age (<70 years, ≥70 years), ECOG performance status (0, 1 to 2), visceral disease (no, yes), prior local treatment (missing, yes), docetaxel chemotherapy (no, yes), volume of disease (high, low), antiresorptive therapy (no, yes), ACE-27 (0 to 1, 2 to 3), region (Europe, Australia/New Zealand, North America).

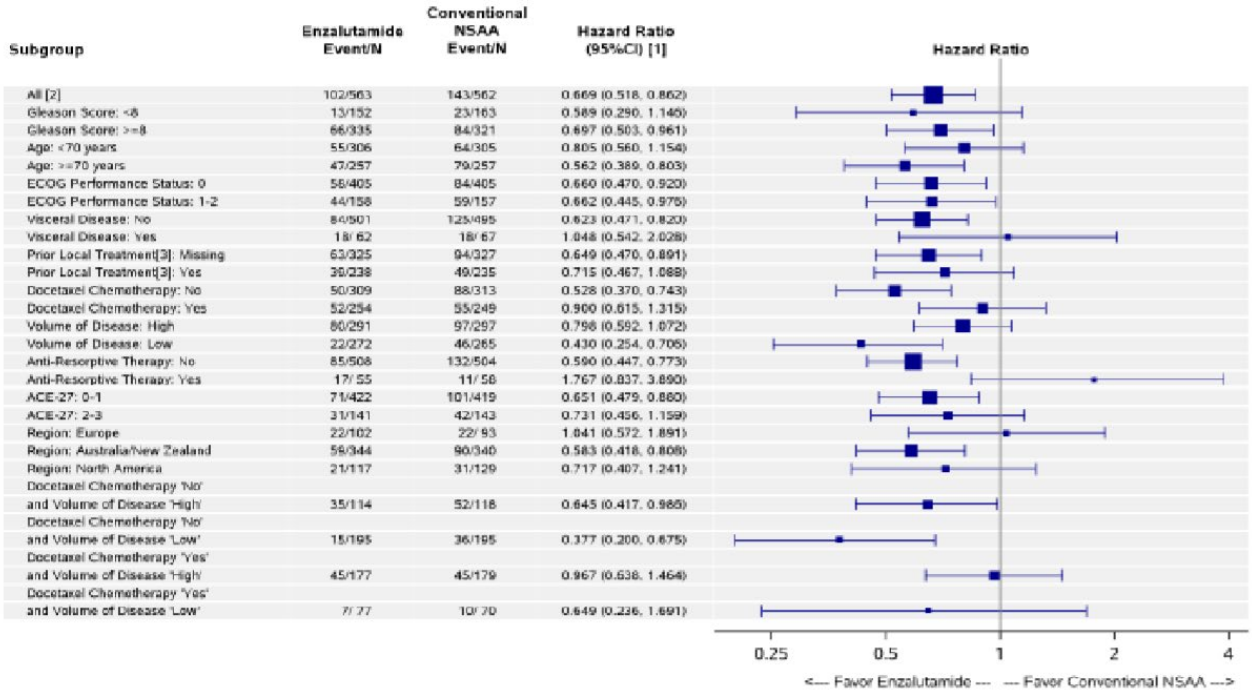



*Figure 15 Forest Plot of OS – Subgroup analyses (ITT population)*

**Study PREVAIL (MDV3100-03)**

In addition to the extension of indication to include mHSPC the MAH has provided updated 5-year OS results from study PREVAIL in chemo-naïve mCRPC to update section 5.1 of the SmPC.

PREVAIL was a multinational, randomised, double-blind, Phase 3, placebo-controlled study of enzalutamide in chemotherapy-naïve patients with mCRPC. The coprimary efficacy endpoints were OS and rPFS.

The first patient was randomly assigned on 28 Sep 2010 and the last patient was randomly assigned on 07 Sep 2012. On 21 Oct 2013, after a protocol-specified interim analysis was performed following 540 death events, the external independent Data Monitoring Committee (DMC) offered access to open-label enzalutamide to patients randomly assigned to placebo. In Jan 2014, placebo-treated patients began crossing over to enzalutamide treatment in the open-label period of the study.

As of the 5-year analysis data cut-off date of 30 Sep 2017, a total of 871 patients in the enzalutamide group, 844 patients in the placebo group and 234 patients on placebo who crossed over to enzalutamide received at least 1 dose or partial dose of study drug.

The number of patients enrolled in the open-label extension or long-term follow-up of PREVAIL as of the 5-year analysis data cut-off date of 30 Sep 2017 was 520 patients (59.6%) in the enzalutamide group and 435 patients (51.5%) in the placebo group.

As of the 5-year analysis data cut-off date of 30 Sep 2017, 62 patients (7.1%) in the enzalutamide group and 26 placebo patients (11.1%) who crossed over to enzalutamide were still receiving study treatment.

As of the 5-year analysis data cut-off date, the number of patients who had come off their primary treatment and continued in long-term follow-up for OS included 157 patients (18.0%) in the enzalutamide group, 53 patients (6.3%) in the placebo group and 63 placebo patients (26.9%) who crossed over to enzalutamide.

*Table 39. Summary of Patients Enrolled in the PREVAIL Open-label Extension*

| Parameter, n (%) | Enzalutamide (n = 872) | Placebo (n = 845) | Total (n = 1717) |
|---|---|---|---|
| Number of patients enrolled in OLE or in LTFU | 520 (59.6) | 435 (51.5) | 955 (55.6) |
| Patients received study drug in OLE | 231 (26.5) | 234 (27.7) | 465 (27.1) |
| Patients enrolled in OLE but not dosed by data cutoff date | 1 (0.1) | 0 | 1 (< 0.1) |
| Patients in LTFU | 288 (33.0) | 201 (23.8) | 489 (28.5) |
| Number of patients not enrolled in OLE | 352 (40.4) | 410 (48.5) | 762 (44.4) |
| Patients died prior to OLE | 342 (39.2) | 395 (46.7) | 737 (42.9) |
| Patients not transitioned to OLE | 10 (1.1) | 15 (1.8) | 25 (1.5) |
| Patients only receiving study drug in blinded phase | 10 (1.1) | 15 (1.8) | 25 (1.5) |

All patients randomly assigned to treatment (ITT population).
The analysis data cutoff date was 30 Sep 2017.
ITT: intent-to-treat; LTFU: long-term follow-up; OLE: open-label extension.

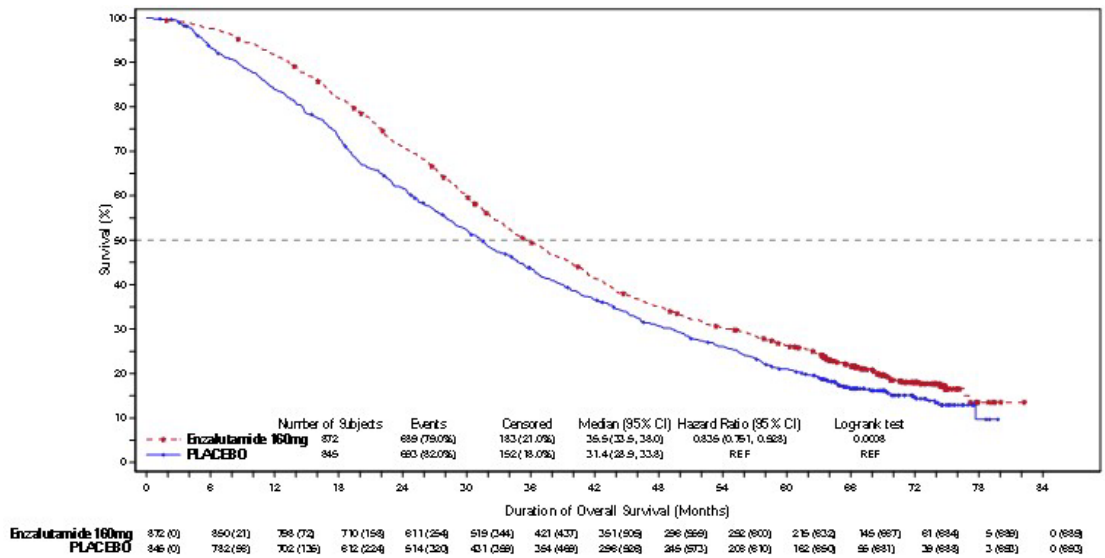
The median treatment duration was 17.7 months for the enzalutamide group, 4.6 months for the placebo group and 9.8 months on enzalutamide for patients who crossed over from placebo. Most patients in the enzalutamide group (591[67.9%]) received study drug for at least 12 months and most patients in the placebo group (526 [62.3%]) received study drug for less than 6 months. Approximately 37% of enzalutamide-treated patients received study drug for at least 2 years. Approximately 20% of placebo patients who crossed over to enzalutamide received enzalutamide for at least 2 years.
Results of OS as of the data cut-off date of 30 Sep 2017 are presented in Table 40. Table 38

*Table 40 . Updated Analysis of Overall Survival in PREVAIL – 5-Year Follow-up*

| Overall Survival | Enzalutamide (n = 872) | Placebo (n = 845) |
|---|---|---|
| Survival status, n (%) | | |
| Death | 689 (79.0) | 693 (82.0) |
| Censored† | 183 (21.0) | 152 (18.0) |
| Alive at data analysis cutoff date | 160 (18.3) | 117 (13.8) |
| Lost to follow-up | 8 (0.9) | 9 (1.1) |
| Withdrawal of consent | 15 (1.7) | 26 (3.1) |
| Overall survival†‡ | | |
| Censored, n (%) | 183 (21.0) | 152 (18.0) |
| 25th percentile (months) | 22.0 | 17.4 |
| Median (months) (95% CI) | 35.5 (33.5, 38.0) | 31.4 (28.9, 33.8) |
| 75th percentile (months) | 62.5 | 55.4 |
| Treatment comparison: enzalutamide vs placebo | | |
| P value§ | 0.0008 | |
| Hazard ratio (95% CI)§ | 0.835 (0.751, 0.928) | |
| Observed follow-up time (in months) for censored patients¶ | | |
| n | 183 | 152 |
| 25th percentile | 63.6 | 62.8 |
| Median | 67.2 | 66.5 |
| 75th percentile | 73.0 | 71.7 |
| Range | 1.9, 82.3 | 1.3, 79.8 |
| Follow-up time (in months) based on reverse Kaplan-Meier Estimates for all patients | | |
| 25th percentile | 66.2 | 65.0 |
| Median | 69.5 | 68.8 |
| 75th percentile | 74.4 | 74.0 |
| Probability of being event free at:‡ | | |
| Year 2 (95% CI) | 0.71 (0.68, 0.74) | 0.62 (0.58, 0.65) |
| Year 3 (95% CI) | 0.49 (0.46, 0.53) | 0.44 (0.40, 0.47) |
| Year 5 (95% CI) | 0.26 (0.23, 0.29) | 0.21 (0.18, 0.24) |

All patients randomly assigned to treatment (ITT population).
The analysis data cut-off date was 30 Sep 2017.
CI: confidence interval; ITT: intent-to-treat
† Patients who were not known to have died at the analysis date were censored at date last known alive or data analysis cut-off date, whichever occurred first.
‡ Based on Kaplan-Meier estimates.
§ P value was based on an unstratified log-rank test. Hazard ratio was based on an unstratified Cox regression model (with treatment as the only covariate) and was relative to placebo with < 1 favouring enzalutamide.
¶ Calculated as (date last known alive or data analysis cut-off date, whichever occurred first – randomization date + 1)/30.4375.

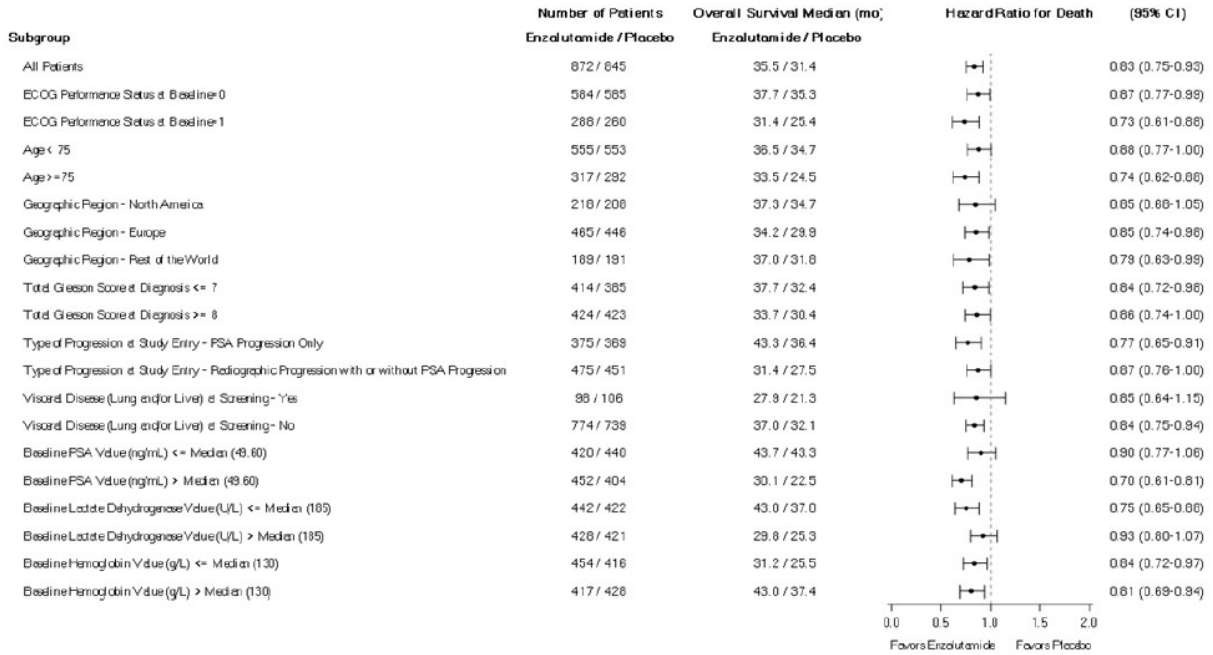
*Table 41. Updated Kaplan-Meier Plot of Overall Survival in PREVAIL – 5-Year Follow-up*




All patients randomly assigned to treatment (ITT population).

The analysis data cut-off date was 30 Sep 2017.
Hazard ratio was based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with <1 favouring enzalutamide.
CI: confidence interval; ITT: intent-to-treat; REF: reference

*Table 42. Updated Forest Plot for Duration of Overall Survival: Subgroup Analysis in PREVAIL*




All patients randomly assigned to treatment (ITT population).
The analysis data cutoff date was 30 Sep 2017.
Hazard ratio was based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring enzalutamide.
CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; PSA: prostate-specific antigen

The incidence of subsequent antineoplastic therapy use for prostate cancer was lower in the enzalutamide group (610 patients [70.0%]) compared with the placebo group (678 patients [80.2%]), reflective of the higher proportion of patients in the placebo group who had disease progression compared with the enzalutamide group The most common subsequent antineoplastic therapies for prostate cancer were docetaxel (481 enzalutamide patients [55.2%], 520 placebo patients [61.5%]), abiraterone acetate (362 enzalutamide patients [41.5%], 431 placebo patients [51.0%]) and cabazitaxel (151 enzalutamide patients [17.3%], 172 placebo patients [20.4%]).

*Table 43. Selected Subsequent Antineoplastic Therapy Use in PREVAIL*

| Subsequent Therapy, n (%) | Enzalutamide (n = 872) | Placebo (n = 845) | Placebo Patients Crossover to Enzalutamide (n = 234) |
|---|---|---|---|
| Number of patients taking at least 1 subsequent antineoplastic treatment | 610 (70.0) | 678 (80.2) | 99 (42.3) |
| Number of patients taking at least 1 of the 6 subsequent therapies below | 583 (66.9) | 632 (74.8) | 90 (38.5) |
| Abiraterone acetate† | 362 (41.5) | 431 (51.0) | 38 (16.2) |
| Cabazitaxel | 151 (17.3) | 172 (20.4) | 39 (16.7) |
| Docetaxel | 481 (55.2) | 520 (61.5) | 40 (17.1) |
| Enzalutamide‡ | 53 (6.1) | 130 (15.4) | 8 (3.4) |
| Radium-223 | 57 (6.5) | 42 (5.0) | 23 (9.8) |
| Sipuleucel-T | 20 (2.3) | 12 (1.4) | 0 |

All patients randomly assigned to treatment (ITT population).

The analysis data cutoff date was 30 Sep 2017.

ITT: intent-to-treat

† Concomitant abiraterone use was allowed before study drug discontinuation in patients with confirmed radiographic progression or a skeletal-related event.

‡ Placebo patients who received enzalutamide in the open-label extension period were included in the "Placebo Patients Crossover to Enzalutamide 160 mg" column.

## 2.4.3. Discussion on clinical efficacy

Enzalutamide is currently approved for the treatment of patients with metastatic (pre and post chemotherapy) and non-metastatic CRPC (see SmPC section 4.1). Enzalutamide is an androgen receptor inhibitor that targets the AR signalling pathway. Within this application the MAH is seeking approval for the treatment of patients with metastatic prostate cancer prior to development of castration resistant disease (i.e., hormone-sensitive prostate cancer) in combination with ADT.
Additionally, the MAH proposes an update in section 5.1 of the SmPC based on the 5-year overall survival (OS) results obtained from the PREVAIL (MD V310003) study, a phase 3 study of enzalutamide in chemotherapy naïve patients with metastatic prostate cancer that progressed on ADT.

## Design and conduct of clinical studies

The submission of this type II variation for the extension of indication is based on the Study 9785-CL-0335 (ARCHES), a Phase 3, randomised, double-blind, placebo-controlled study of enzalutamide plus ADT versus placebo plus ADT in 1,150 patients with mHSPC. Additionally, OS results from the first interim analysis of the study ENZAMET, a Phase 3, randomised, open-label, active-comparator study of enzalutamide plus ADT versus nonsteroidal antiandrogen (NSAA) plus ADT led by ANZUP Cancer Trials Group in collaboration with the University of Sydney as sponsor, have been provided as supportive information.

Focusing on the Study ARCHES, eligibility criteria allowed the inclusion of patients with metastatic adenocarcinoma of the prostate (newly diagnosed or diagnosed in a previous stage), regardless of volume disease. Patients with an ECOG performance status >1 and those with known or suspected brain metastasis or active leptomeningeal disease and with history of seizure or any condition that may predispose to seizure were excluded from the study. Patients who have received up to 6 cycles of docetaxel and prior treatment with ADT (either LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens), up to 3 months (6 months if patient was treated with docetaxel), and patients who have received prior ADT in the neoadjuvant/adjuvant setting (up to 39 months in duration)were allowed in the trial. Moreover, 1 course of palliative radiation or surgical therapy to treat

symptoms from metastatic disease were allowed. No other prior treatment for the metastatic disease was allowed.

Patients were randomised in a 1:1 ratio to enzalutamide (160 mg once daily) + ADT or matching placebo + ADT. While the use of ADT alone as comparator could be acceptable in this setting, the add-on of docetaxel might have been a preferable choice, as it was suggested in the CHMP scientific advice (EMA/CHMP/SAWP/596561/2015). Based on the STAMPEDE and CHAARTED trials, in which docetaxel plus ADT improved OS in men with metastatic, hormone-naïve disease (Sweeney C, 2014; James ND, 2015), ADT plus docetaxel with or without prednisone or prednisolone is currently authorised for the treatment of patients with metastatic hormone-sensitive prostate cancer (Docetaxel EPAR).

Patients were stratified by prior docetaxel (none, 1-5 cycles, 5 cycles), and disease volume (low vs high).

Radiographic PFS (rPFS), as assessed by ICR, was chosen as the primary endpoint. Radiographic progression disease (rPD) was defined by RECIST 1.1 criteria for soft tissue and by the appearance of 2 or more new bone lesions on bone scan. The assessment of rPFS was performed at week 13 and thereafter every 12 weeks. As per protocol, if progression was identified at week 13 (bone lesion), confirmation was required ≥ 6 weeks after that or at week 25 visit. The latter is considered appropriate to avoid false positive of progression. Progression was to be confirmed if there were ≥ 2 new bone lesions on bone scan compared to week 13 scan (≥ 4 new lesions compared to baseline bone scan). At week 25 or later no confirmatory scan was required for bone lesions and rPD on bone scans was planned to be assessed by comparison to best response on treatment. However, according to the applicant the ICR assessed rPD on bone scan solely on the appearance of bone lesion(s) which were new compared to baseline or to week 13 (i.e. according to PCWG2 criteria – Scher et al, 2008). This analysis was initially planned as a sensitivity analysis but not as the primary analysis. This was considered a major deviation from the protocol and statistical analysis plan (SAP), and matter of concern. According to the MAH this change in the method of analysis was due to an unintentional error which affected 66 of the 1150 patients included in the ARCHES study. A GCP inspection was conducted and no findings impacting negatively the data quality were identified.

Overall, secondary endpoints are considered acceptable, although the addition of PFS2 as a secondary endpoint would have been informative. It should be pointed out that "time to deterioration in urinary symptoms" was added as a secondary endpoint with amendment 3 (dated 10 Dec 2018), after the data cut-off. Nevertheless, according to the MAH the inclusion of "time to deterioration in urinary symptoms" as a secondary endpoint was included in the final version of the SAP, dated 15 Nov 2018, while data were still unblinded (database lock 14 Dec 2018).

Overall, the statistical methods seem appropriate. The efficacy analyses were performed on the ITT population. The primary efficacy endpoint is the rPFS with a multiplicity control for the 6 key secondary endpoints, including OS once rPFS was demonstrated to be statistically significant. Key secondary endpoints, other than OS, were sequentially tested at a 1% significance level.

A total of 152 (13.2%) patients (70 [12.2%] in the enzalutamide arm and 82 [14.2%] in the placebo arm) had 1 or more major protocol deviations during the study and the majority of them were related to violation of inclusion criteria. Overall, percentages of major protocol deviations were balanced between treatment arms, apart from the violation of the exclusion criterion 1 (Patient had received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer), where the proportion of patients in the control arm was double compared to the enzalutamide arm (26 [4.5%] vs 12 [2.1%], respectively. Exclusion criterion 1 deviations more frequent in the placebo plus ADT group compared to the enzalutamide plus ADT group were: treated with docetaxel and received >6 months ADT prior to day 1, received > 3 months of ADT prior to day 1,and had final administration of docetaxel >2 months prior to day 1. No patterns have been identified to explain the larger number of deviations in the placebo plus

ADT group vs enzalutamide plus ADT group. Taking into account the small number of patients and the results observed, this imbalance does not appear to have a great impact on the results.

Regarding baseline characteristics, the population was balanced between treatment arms. The median age was 70 years (range: 42, 92), with nearly 30% of patients being 75 years or older. The majority of patients were white (80.5%) and had a good performance status (77.5% ECOG 0). The majority of patients had high volume of disease (63%) and a Gleason score at initial diagnosis ≥8 (66%). Median serum PSA was 5.21 ng/ml, with some patients with a PSA level of 0. The mean PSA at baseline for enzalutamide group was 75.37 ng/ml which may question whether the population was castration sensitive. However, patients with evidence of disease progression (i.e. radiographic or PSA) in the context of ADT were excluded from the study, thus the population included in study ARCHES can be considered castration sensitive.

Most of the patients had distant metastasis at diagnosis (66.7%). The majority of patients received prior treatment with ADT (90%) and around 18% of patients received prior treatment with docetaxel. Other prior therapies included radiation (16.5%) and surgery (33.5%). A high number of patients received subsequent antineoplastic therapy for prostate cancer in the control arm compared to the enzalutamide arm (8.0% vs 23.1%), which seems reasonable taking into account the results of the primary analysis. Docetaxel (1.9% vs 9.0%), abiraterone (2.3% vs 4.9%) and enzalutamide (0.7% vs 4.9%) were the most commonly used subsequently in the control arm.

The study ENZAMET included a total of 1,125 patients who were randomised 1:1 to treatment with enzalutamide plus ADT (563 patients) or NSAA plus ADT (562 patients). Randomisation was stratified for volume of disease (high vs low), study site, concomitant antiresorptive therapy (yes vs no), comorbidities according to the ACE-27 score (0 to 1 vs 2 to 3) and early planned use of docetaxel (yes vs no).

The primary endpoint was OS without multiplicity control for the secondary endpoints. Three interim analyses were proposed for OS, once 50%, 67% and 80% of the required events were observed. An alpha spending function with an O'Brien-Fleming boundary shape was used with a final alpha value of 0.042. The ENZAMET study design is overall considered adequate.

The population included in the study ENZAMET is not completely comparable to the population of ARCHES study. Patients in the study ENZAMET could receive early docetaxel use (i.e. a total of 6 cycles of docetaxel, of which 0-2 cycles were allowed before randomisation) while in the study ARCHES treatment with docetaxel was only allowed prior randomisation (i.e. up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1) (see Table 29). According to the data provided by the MAH, 45.1% of patients in the enzalutamide arm in study ENZAMET had early docetaxel use (i.e. use of docetaxel in conjunction with initiation of ADT), of whom approximately 43% received at least 1 dose of early docetaxel. Moreover, 15.8% of patients received docetaxel for metastatic disease prior to randomisation.

**Efficacy data and additional analyses**

The primary analysis of study ARCHES was performed at the data cut-off date of 14 Oct 2018. This was the only planned analysis for rPFS (primary endpoint) and the first interim analysis for OS (secondary endpoint).

With 287 rPFS events (89 [15.51%] in the enzalutamide arm and 198 [34.38%] in the placebo arm), based on ICR assessment, the study met its primary objective with a HR of 0.39 (95% CI: 0.3, 0.5). Median rPFS was not reached in the enzalutamide arm and was of 19.4 months in the placebo arm. According to Kaplan-Meier plot, the benefit of adding enzalutamide to ADT treatment is observed after the third month, when the curves separate and maintained separated thereafter. rPFS data is however not

very mature, with nearly 85% and 66% censoring in the enzalutamide and placebo arms, respectively. The main reason for censoring in both arms was no rPFS event at the data cut-off date.

As previously mentioned, results of the primary analysis were based on IRC assessment as per PCWG2 criteria (against of what was specified in the protocol). A reanalysis of rPFS as per protocol was also provided. Results of this analysis were in line with the primary analysis (HR 0.39 [95% CI: 0.30, 0.50]), with 91 events (15.85%) in the enzalutamide plus ADT group and 201 (34.9%) in the placebo plus ADT group. Median PFS was not reached in the enzalutamide arm and was 19.0 months [95% CI: 16.59, 22.24].

Subgroup analyses for the primary endpoint showed consistent results in all subgroup analysed, including the subgroup of patients previously treated with docetaxel. The MAH was requested to provide rPFS data for both newly diagnosed patients (i.e. patients whose initial diagnosis of prostate cancer was within 3 months of the first dose of randomized treatment) and recurrent disease patients (i.e. patients with prior local treatment) (data not shown). Overall, rPFS results in both subgroups were consistent with that of the overall population.

Moreover, several sensitivity analyses of rPFS were performed and all of them supported the primary analysis. The sensitivity analysis analysing rPFS based on investigator´s assessment, in principle according to the protocol-specified criteria, showed a HR of 0.46 [95% CI: 0.36, 0.59]), with a concordance rate between the ICR and the investigator of around 90%.

OS was a secondary endpoint in study ARCHES. OS was assessed based on an allocated 2-sided alpha of 0.04. For the first interim analysis the stopping boundary was 0.0000054. At the time of the data cut-off date, the number of deaths was 84 (39 [6.8%] in the enzalutamide arm and 45 [7.8%] in the placebo arm). Considering the immaturity of data, median OS was not reached in any arm and while a detrimental effect on OS is excluded, the statistical significance was not reached (HR 0.81 [95% CI: 0.53, 1.25]; p=0.3361). Therefore, the MAH is recommended to provide updated OS data when available. Final OS results are expected by March 2022 (REC).

Other main secondary endpoints were: time to PSA progression, time to start of a new antineoplastic therapy, PSA undetectable rate, ORR and time to deterioration in urinary symptoms. The prespecified level of significance for these key secondary endpoints was 0.01. Overall, all these secondary endpoints favoured the enzalutamide arm, with statistically significant results, except for the time to deterioration in urinary symptoms (HR 0.88 [95% CI: 0.72, 1.08]; p=0.2162) where no statistically significant differences were observed between treatment arms.

In addition, time to symptomatic skeletal event, time to castration resistance, quality of life and time to pain progression (assessed by BPI-SF) were also assessed as secondary endpoints, although the "p" values provided were only for descriptive purposes and should not be used to assess statistical significance. Adding enzalutamide to ADT treatment appears to delay time to castration resistance and time to first symptomatic skeletal event. However, there seems to be no differences in terms of time to deterioration of QoL or time to progression between treatments arms.

The ENZAMET study has been provided to support the results of the ARCHES study. Within this application the MAH is providing results of the first OS interim analysis. No additional efficacy data have been submitted.

This first interim analysis for OS was conducted when 245 events had occurred (52% of 470 planned events for the final analysis). OS analysis was statistically significant, since the pre-specified alpha boundary of 0.003 was crossed (HR 0.669 [95% CI: 0.518, 0.862]; p=0.0018; unstratified analysis).

However, these data are considered immature (82% and 75% of censures in the experimental and control arm, respectively) and median OS had not been reached in either treatment arm. At the time of the data cut-off, the median follow-up time was 14.4 months in ARCHES vs. 33.8 months in ENZAMET.

With regard to subgroup analysis, an apparently lack of benefit was observed in the subgroup of patients receiving early treatment with docetaxel (HR 0.9 [95% CI: 0.615, 1.315]), especially in those patients with high volume of disease (HR 0.967 [95% CI: 0.638, 1.464]). Moreover, a similar pattern is observed in the subgroup of patients with visceral disease (HR 1.048 [95% CI: 0.542, 2.028]), concomitant use of anti-resorptive therapy (HR 1.767 [95% CI: 0.837, 3.890]) and the subgroup of European patients (HR 1.041 [95% CI: 0.572, 1.891]). However, data are limited due to the low number of events.

In the subgroup of patients not receiving early treatment with docetaxel, which may be more similar to the population of study ARCHES, the results were in line with the primary analysis (HR 0.528 [95% CI: 0,370, 0,743]).

Despite the inherent limitations of subgroup analyses, it is considered that the data from the subgroup of patients without planned early use of docetaxel can be considered convincing in accordance with the Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013) and therefore supportive of the current application.

Within this submission the MAH has also provided 5-year OS data from the study PREVAIL. The study PREVAIL was a randomised, double-blind, Phase 3 study in 1,717 patients with metastatic castration resistant prostate cancer (mCRPC) who were chemotherapy naïve. Patients were randomised in a 1:1 ratio to receive either enzalutamide [160 mg once daily] (n=872) or placebo (n=845). In this study, OS and rPFS were co-primary efficacy endpoints.

An interim analysis for OS was performed when 540 events had occurred, in which enzalutamide demonstrated a statistically significant improvement in OS compared to placebo (HR 0.706 [95% CI: 0.60, 0.84]). After this specified interim analysis, the patients randomly assigned to placebo have been offered by the independent DMC to pass to the enzalutamide treatment in the open-label period of the study.

Through this variation, the MAH has provided 5-year OS data based on data cut-off date of 30 Sep 2017. At the data cut-off, the number of patients enrolled in the open-label extension period was 520 (59.6%) in the enzalutamide arm and 435 (51.5%) in the placebo arm. There were 234 patients (27,7%) on placebo who crossed over to enzalutamide and received at least one dose or partial dose of study drug.

Results of this final analysis, when 1,382 deaths had occurred (689 [79.0%] in the enzalutamide arm and 693 [82%] in the placebo arm), were statistically significant, with a HR of 0.835 [95% CI: 0.751, 0.928] and a OS median of 35.5 months in the enzalutamide arm versus 31.4% in the placebo arm.

These results confirm the clinical benefit of enzalutamide over placebo in the treatment of patients with mCRPC chemotherapy naïve.

These results do not change the benefit/risk ratio (B/R) for enzalutamide and have been adequately reflected in section 5.1 of the SmPC. The B/R of enzalutamide remains positive.

## 2.4.4. Conclusions on the clinical efficacy

In study ARCHES a statistically significant 61% reduction in the risk of an rPFS event was observed for enzalutamide + ADT compared to placebo + ADT [HR = 0.39 (95% CI: 0.30, 0.50); p < 0.0001].

There is no indication of detrimental effect in survival. Nevertheless, the OS data are immature and the MAH is recommended to provide updated OS data from study ARCHES.

The results of study ARCHES are supported by preliminary results from a subgroup of patients from study ENZAMET which is close to the population enrolled in study ARCHES.

Regarding results of study PREVAIL, data with a 5-year follow up confirm the clinical benefit of enzalutamide in the treatment of patients with mCRPC chemotherapy naïve.

## *2.5. Clinical safety*

### Introduction

The safety profile of enzalutamide (MDV3100, ASP9785) in support of its use for the treatment of patients with mHSPC, is based on the safety results from the pivotal study ARCHES (9785-CL-0335). In addition to the ARCHES study, safety data from the following studies have been included:

- A Phase 3 randomized, placebo-controlled study in patients with metastatic CRPC previously treated with docetaxel-based chemotherapy (AFFIRM [CRPC2]).
- Two phase 3 randomised, placebo-controlled, studies in chemotherapy-naïve patients with metastatic CRPC (PREVAIL [MDV3100-03] and Asian PREVAIL [9785-CL-0232]). The PREVAIL study provides long-term follow-up data (after all patients have been followed for a minimum of 5 years, died, or were otherwise lost to follow-up or had withdrawn consent). In the Asian PREVAIL study, data from Site 105 was excluded due to data quality concerns.
- Two randomised, bicalutamide-controlled, phase 2 studies in patients with metastatic CRPC (TERRAIN [9785-CL-0222]) and with nonmetastatic or metastatic CRPC (STRIVE [MDV3100-09]).
- A phase 3 randomised, placebo-controlled study in patients with nonmetastatic CRPC (PROSPER [MDV3100-14]).
- A phase 3 randomised, study in patients with mHSPC receiving treatment with first-line medical or surgical ADT and optional concurrent docetaxel for metastatic prostate cancer (ENZAMET). As ENZAMET was an investigator-initiated study conducted by a collaborative group (Australian and New Zealand Urogenital and Prostate Cancer Trials Group Ltd. [ANZUP]) that maintains the database for the study, these data are presented standalone as the safety data in this study were not collected/handled in the same way as the other studies. Only grade 3 and 4 adverse events (AEs), serious adverse events (SAEs) of any severity and death data are presented for the ENZAMET study.

Safety data are summarised for ARCHES and 2 pools of studies with the presentation of a total of 5 groups in order to provide a comprehensive summary of the clinical safety of enzalutamide in these studies.

*Table 44. Description of Integrated Safety Groups*

| **Study or Pool** | **Studies Included** | **Treatment Groups Presented** |
|---|---|---|
| ARCHES (placebo-controlled) | ARCHES | Enzalutamide +ADT (n = 572)<br>Placebo+ADT (n = 574) |

| | | |
|---|---|---|
| Other phase 3 studies (placebo-controlled) | AFFIRM<br>PREVAIL<br>Asian PREVAIL<br>PROSPER | Enzalutamide (n = 2799)<br><br>Placebo (n = 1898) |
| Total enzalutamide (phase 2 and 3 studies) | ARCHES<br>AFFIRM<br>PREVAIL<br>Asian PREVAIL<br>TERRAIN<br>STRIVE<br>PROSPER | Enzalutamide (n = 4081) |

Together these studies of enzalutamide plus standard of care included 4081 patients treated with enzalutamide 160 mg/per day that make up the integrated safety population and 2474 patients treated with placebo plus standard of care.

## Patient exposure

In the ARCHES enzalutamide plus ADT group, 572 patients received at least 1 dose or partial dose of enzalutamide. In the phase 3 CRPC enzalutamide group and in the total enzalutamide group, 2799 and 4081 patients, respectively, received at least 1 dose or partial dose of enzalutamide.

*Table 45. Extent of Exposure- Across all groups*

| Category | mHSPC | | CRPC | | |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Total‡ Enzalutamide (n = 4081) |
| **Treatment duration, months** | | | | | |
| Mean (SD) | 13.16 (5.05) | 11.85 (5.08) | 16.86 (12.29) | 8.09 (7.65) | 17.96 (15.05) |
| Median | 12.80 | 11.55 | 14.00 | 5.14 | 13.80 |
| Minimum, Maximum | 0.2, 26.6 | 0.2, 24.6 | 0, 87.6 | 0.1, 44.8 | 0, 87.6 |
| **Treatment duration category (months), n (%)** | | | | | |
| < 3 | 24 (4.2) | 29 (5.1) | 255 (9.1) | 508 (26.8) | 361 (8.8) |
| ≥ 3 to < 6 | 26 (4.5) | 53 (9.2) | 349 (12.5) | 583 (30.7) | 488 (12.0) |
| ≥ 6 to < 12 | 193 (33.7) | 224 (39.0) | 617 (22.0) | 397 (20.9) | 961 (23.5) |
| ≥ 12 to < 24 | 323 (56.5) | 267 (46.5) | 787 (28.1) | 309 (16.3) | 1241 (30.4) |
| ≥ 24 | 6 (1.0) | 1 (0.2) | 791 (28.3) | 101 (5.3) | 1030 (25.2) |
| **Number of dose modifications (includes interruptions or reductions) n (%)** | | | | | |
| 0 | 511 (89.3) | 529 (92.2) | 2358 (84.2) | 1673 (88.1) | 3488 (85.5) |
| 1 | 43 (7.5) | 32 (5.6) | 257 (9.2) | 165 (8.7) | 371 (9.1) |
| 2 | 16 (2.8) | 8 (1.4) | 93 (3.3) | 39 (2.1) | 141 (3.5) |
| 3 | 1 (0.2) | 3 (0.5) | 46 (1.6) | 11 (0.6) | 64 (1.6) |
| 4 | 0 | 2 (0.3) | 20 (0.7) | 4 (0.2) | 26 (0.6) |
| 5 | 1 (0.2) | 0 | 5 (0.2) | 3 (0.2) | 10 (0.2) |
| 6 | 0 | 0 | 6 (0.2) | 2 (0.1) | 6 (0.1) |
| > 6 | 0 | 0 | 14 (0.5) | 1 (0.1) | 17 (0.4) |
| **Number of dosing interruptions, n (%)** | | | | | |
| 0 | 525 (91.8) | 536 (93.4) | 2390 (85.4) | 1680 (88.5) | 3544 (86.8) |
| 1 | 44 (7.7) | 32 (5.6) | 305 (10.9) | 181 (9.5) | 435 (10.7) |
| 2 | 3 (0.5) | 5 (0.9) | 55 (2.0) | 28 (1.5) | 85 (2.1) |
| 3 | 0 | 0 | 31 (1.1) | 7 (0.4) | 37 (0.9) |
| 4 | 0 | 1 (0.2) | 10 (0.4) | 1 (0.1) | 14 (0.3) |
| 5 | 0 | 0 | 0 | 1 (0.1) | 0 |
| 6 | 0 | 0 | 4 (0.1) | 0 | 4 (0.1) |
| > 6 | 0 | 0 | 4 (0.1) | 0 | 4 (0.1) |
| **Reason for dosing interruption§, n (%)** | | | | | |
| Adverse event | 38 (6.6) | 30 (5.2) | 385 (13.8) | 193 (10.2) | 537 (13.2) |
| Other | 10 (1.7) | 8 (1.4) | 40 (1.4) | 32 (1.7) | 70 (1.7) |
| **Number of dose reductions** | | | | | |
| 0 | 539 (94.2) | 559 (97.4) | 2656 (94.9) | 1860 (98.0) | 3901 (95.6) |
| 1 | 29 (5.1) | 12 (2.1) | 88 (3.1) | 26 (1.4) | 141 (3.5) |
| 2 | 3 (0.5) | 1 (0.2) | 31 (1.1) | 6 (0.3) | 50 (1.2) |
| 3 | 0 | 2 (0.3) | 11 (0.4) | 2 (0.1) | 14 (0.3) |
| 4 | 1 (0.2) | 0 | 5 (0.2) | 2 (0.1) | 8 (0.2) |
| 5 | 0 | 0 | 5 (0.2) | 1 (0.1) | 6 (0.1) |
| 6 | 0 | 0 | 1 (0.1) | 0 | 1 (0.0) |
| > 6 | 0 | 0 | 2 (0.1) | 1 (0.1) | 2 (0.0) |
| **Reason for dose reduction§** | | | | | |
| Adverse event | 26 (4.5) | 11 (1.9) | 135 (4.8) | 35 (1.8) | 203 (5.0) |
| Other | 10 (1.7) | 4 (0.7) | 17 (0.6) | 6 (0.3) | 37 (0.9) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population).*
*Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN:*
*17 Feb 2018 and STRIVE: 30 May 2018.*
*Treatment duration was defined as [(the date of last dosing) - (the date of first dosing) +1] / 30.4375 for patients who discontinued treatment and [(the data cut-off date)-(the date of first*
*dosing) +1] / 30.4375 for patients still on treatment by the data cut-off date.*
*ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer.*
*† The phase 3 CRPC studies include PREVAIL, AFFIRM, Asian PREVAIL and PROSPER.*
*‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of studies ARCHES, PROSPER, PREVAIL, AFFIRM, Asian PREVAIL, TERRAIN,*
*STRIVE and open-label phase of studies PREVAIL, AFFIRM, TERRAIN and STRIVE.*
*§ Patients with multiple reasons for dosing interruptions/reductions were counted only once for each reason.*

*Table 46. ENZAMET Treatment Exposure- (Safety Population)*

| Measure | Enzalutamide+ADT (n = 563) | Conventional NSAA+ADT (n = 558) |
|---|---|---|
| **Duration of study drug exposure (months)†** | | |
| Mean (SD) | 28.31 (12.66) | 22.14 (12.83) |
| Median (min, max) | 29.47 (0.1, 58.4) | 22.06 (0.0, 58.6) |
| **Proportion of days patient did not take study drug (enzalutamide or conventional NSAA)‡** | | |
| **At 4 weeks, n (%)** | 558 (99.1) | 537 (96.2) |
| 0 to 10% (0 to 2 missed days since day 1) | 546 (97.0) | 535 (95.9) |
| 11% to 20% (3 to 5 missed days since day 1) | 10 (1.8) | 0 |
| > 20% (6 or more missed days since day 1) | 2 (0.4) | 2 (0.4) |
| Missing | 5 (0.9) | 21 (3.8) |
| **At 12 weeks, n (%)** | 546 (97.0) | 523 (93.7) |
| 0 to 10% (0 to 5 missed days since day 29) | 526 (93.4) | 516 (92.5) |
| 11% to 20% (6 to 11 missed days since day 29) | 13 (2.3) | 2 (0.4) |
| > 20% (12 or more missed days since day 29) | 7 (1.2) | 5 (0.9) |
| Missing | 17 (3.0) | 35 (6.3) |

*All randomized patients who received at least 1 administration of study drug, in which study drug includes enzalutamide and conventional NSAA (Safety Population) Data cut-off date: 28 Feb 2019. ADT: androgen deprivation therapy; max: maximum; min: minimum; NSAA: non-steroidal antiandrogen Patient medication compliance was formally determined by a count of tablets performed at the time of clinic review and out of sight of the patient at week 4 and at week 12 after randomization. † Duration of study drug in months = (min [cut-off date, last dose date] - first dose date)/ (365.25/12). ‡ Included only incidentally missed days; did not include prescribed treatment interruptions. Source: ENZAMET End-of-Text Tables 12.2.1 and 12.2.3*

*Table 47. Docetaxel Exposure (ENZAMET Safety Population)*

| Measure | Enzalutamide+ADT (n = 563) | Conventional NSAA+ADT (n = 558) |
|---|---|---|
| **Number of patients who were stratified to early docetaxel use†‡, n (%)** | | |
| Planned | 254 (45.1) | 246 (44.1) |
| **Number of patients who received at least 1 dose of early docetaxel†‡, n (%)** | | |
| Overall§ | 243 (43.2) | 235 (42.1) |
| Since randomization | 241 (42.8) | 235 (42.1) |
| **Duration of docetaxel exposure (months)¶** | | |
| n | 241 | 235 |
| Mean (SD) | 3.43 (0.97) | 3.62 (0.87) |
| Median (min, max) | 3.48 (0.7, 5.5) | 4.11 (0.7, 5.1) |
| **Number of cycles of docetaxel received‡§, n (%)** | | |
| 0 | 320 (56.8) | 323 (57.9) |
| 1 | 8 (1.4) | 5 (0.9) |
| 2 | 10 (1.8) | 6 (1.1) |
| 3 | 17 (3.0) | 13 (2.3) |
| 4 | 20 (3.6) | 8 (1.4) |
| 5 | 29 (5.2) | 22 (3.9) |
| 6 | 157 (27.9) | 180 (32.3) |
| > 6 | 2 (0.4) | 1 (0.2) |

*All randomized patients who received at least 1 administration of study drug, in which study drug includes enzalutamide and conventional NSAA (Safety Population). Data cut-off date: 28 Feb 2019*
*ADT: androgen deprivation therapy; max: maximum; min: minimum; NSAA: nonsteroidal antiandrogen*
*† Although patients were stratified based on planned docetaxel use, 11 patients in each of the enzalutamide plus ADT and NSAA plus ADT treatment groups in the planned docetaxel group did not receive early docetaxel.*
*‡ Percentage was calculated based on the total number of patients in each treatment group*
*§ Docetaxel commenced prior to study entry is included.*
*¶ Duration of docetaxel (months) = (min [cut-off date, last dose date of docetaxel + 21] - first dose date of docetaxel since randomization)/ (365.25/12).*

## Adverse events

*Table 48. Overall Summary of Treatment-emergent Adverse Events*

| Category, n patients (%) | mHSPC | | CRPC | | |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Total‡ Enzalutamide (n = 4081) |
| Any TEAE | 487 (85.1) | 493 (85.9) | 2628 (93.9) | 1699 (89.5) | 3783 (92.7) |
| TEAE within the first 30 days | 289/572 (50.5) | 260/574 (45.3) | 1697/2799 (60.6) | 1131/1898 (59.6) | 2389/4081 (58.5) |
| TEAE between 31 to 180 days | 356/571 (62.3) | 360/573 (62.8) | 2141/2788 (76.8) | 1400/1885 (74.3) | 3023/4066 (74.3) |
| TEAE between 181 to 365 days | 267/526 (50.8) | 274/503 (54.5) | 1479/2264 (65.3) | 509/909 (56.0) | 2101/3345 (62.8) |
| TEAE between 366 to 540 days | 114/331 (34.4) | 104/281 (37.0) | 902/1618 (55.7) | 220/427 (51.5) | 1250/2336 (53.5) |
| TEAE between 541 to 730 days | 24/104 (23.1) | 15/78 (19.2) | 632/1147 (55.1) | 107/233 (45.9) | 820/1528 (53.7) |
| TEAE as primary reason for study drug discontinuation§ | 28 (4.9) | 21 (3.7) | 265 (9.5) | 155 (8.2) | 381 (9.3) |
| TEAE leading to study drug discontinuation¶ | 41 (7.2) | 30 (5.2) | 473 (16.9) | 362 (19.1) | 708 (17.3) |
| TEAE leading to dosing interruption of study drug | 42 (7.3) | 36 (6.3) | 403 (14.4) | 205 (10.8) | 572 (14.0) |
| TEAE leading to dose reduction of study drug | 25 (4.4) | 11 (1.9) | 137 (4.9) | 34 (1.8) | 205 (5.0) |
| Grade ≥ 3 TEAE†† | 139 (24.3) | 147 (25.6) | 1208 (43.2) | 700 (36.9) | 1730 (42.4) |
| Grade ≥ 3 TEAE onset within the first 30 days | 18/572 (3.1) | 21/574 (3.7) | 190/2799 (6.8) | 152/1898 (8.0) | 285/4081 (7.0) |
| Grade ≥ 3 TEAE onset between 31 to 180 days | 70/571 (12.3) | 64/573 (11.2) | 517/2788 (18.5) | 462/1885 (24.5) | 771/4066 (19.0) |
| Grade ≥ 3 TEAE onset between 181 to 365 days | 52/526 (9.9) | 61/503 (12.1) | 357/2264 (15.8) | 130/909 (14.3) | 520/3345 (15.5) |
| Grade ≥ 3 TEAE onset between 366 to 540 days | 13/331 (3.9) | 23/281 (8.2) | 227/1618 (14.0) | 58/427 (13.6) | 303/2336 (13.0) |
| Grade ≥ 3 TEAE onset between 541 to 730 days | 4/104 (3.8) | 2/78 (2.6) | 161/1147 (14.0) | 27/233 (11.6) | 211/1528 (13.8) |
| Serious TEAE | 104 (18.2) | 112 (19.5) | 954 (34.1) | 521 (27.4) | 1368 (33.5) |
| Grade ≥ 3 serious TEAE†† | 84 (14.7) | 90 (15.7) | 838 (29.9) | 460 (24.2) | 1200 (29.4) |
| TEAE leading to death | 14 (2.4) | 10 (1.7) | 127 (4.5) | 57 (3.0) | 207 (5.1) |
| Study drug-related TEAE‡‡ | 303 (53.0) | 268 (46.7) | 1816 (64.9) | 955 (50.3) | 2553 (62.6) |
| Study drug-related grade ≥ 3 TEAE††‡‡ | 56 (9.8) | 35 (6.1) | 309 (11.0) | 138 (7.3) | 460 (11.3) |
| Study drug-related serious TEAE‡‡ | 22 (3.8) | 16 (2.8) | 105 (3.8) | 61 (3.2) | 173 (4.2) |
| Study drug-related TEAEs leading to death‡‡ | 0 | 1 (0.2) | 5 (0.2) | 1 (0.1) | 9 (0.2) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018. Number of patients (n) reporting and percentage of patients (%) are shown. ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; TEAE: treatment-emergent adverse event. † The phase 3 CRPC studies include PREVAIL, AFFIRM, Asian PREVAIL and PROSPER. ‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of studies ARCHES, PROSPER, PREVAIL, AFFIRM, Asian PREVAIL, TERRAIN, STRIVE and open-label phase of studies PREVAIL, AFFIRM, TERRAIN, STRIVE.*
*§ TEAE identified as primary reason for study drug discontinuation is from the treatment discontinuation case report form.*
*¶ TEAE leading to study drug discontinuation is from adverse event case report form and includes TEAEs with action taken of permanent discontinuation.*
*†† Grade ≥ 3, based on National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.*
*‡‡ Study drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably, or definitely related to study drug.*

*Table 49. Overall Summary of Grade 3 or 4 AEs, SAEs of Any Grade and Deaths in ENZAMET*

| Category, n patients (%) | Enzalutamide+ADT (n = 563) | Conventional NSAA+ADT (n = 558) |
|---|---|---|
| AEs grade 3 or 4 and SAE of any grade | 332 (59.0) | 262 (47.0) |
| AEs grade 3 or 4 | 320 (56.8) | 237 (42.5) |
| SAEs | 235 (41.7) | 189 (33.9) |
| SAE grade 3 or 4 | 208 (36.9) | 154 (27.6) |
| Grade 3 or higher SAEs | 209 (37.1) | 159 (28.5) |
| Study drug-related † SAE | 17 (3.0) | 2 (0.4) |
| Study drug-related † SAE leading to discontinuation of study drug | 12 (2.1) | 1 (0.2) |
| SAEs leading to discontinuation of study drug | 61 (10.8) | 50 (9.0) |
| SAEs leading to dose interruption | 45 (8.0) | 11 (2.0) |
| SAEs leading to dose reduction | 11 (2.0) | 13 (2.3) |
| Fatal SAEs | 8 (1.4) | 13 (2.3) |
| Study drug-related † fatal SAE | 0 | 0 |
| Death‡ | 102 (18.1) | 143 (25.6) |

All randomized patients who received at least 1 administration of study drug, in which study drug includes enzalutamide and conventional NSAA (safety population).

The analysis data cutoff date was 28 Feb 2019.

ADT: androgen deprivation therapy; AE: adverse event; NSAA: nonsteroidal antiandrogen; SAE: serious adverse event

† Possible or probable, as assessed by the investigator, or records where relationship was missing.

‡ Deaths that occurred prior to or on the data cutoff date.

**Common TEAEs**

*Table 50. Treatment-emergent Adverse Events Experienced by ≥ 5% of Patients in the ARCHES Enzalutamide plus ADT Group by SOC and Preferred Term*

| SOC (MedDRA v 21.0)<br>Preferred Term, n (%) | mHSPC<br>ARCHES Enzalutamide+ADT (n = 572) | mHSPC<br>ARCHES Placebo+ADT (n = 574) | CRPC<br>Phase 3† Enzalutamide (n = 2799) | CRPC<br>Phase 3† Placebo (n = 1898) | Total‡ Enzalutamide (n = 4081) |
|---|---|---|---|---|---|
| Gastrointestinal Disorders | 66 (11.5) | 55 (9.6) | 878 (31.4) | 558 (29.4) | 1135 (27.8) |
| Nausea | 37 (6.5) | 29 (5.1) | 605 (21.6) | 409 (21.5) | 775 (19.0) |
| Diarrhoea | 34 (5.9) | 33 (5.7) | 438 (15.6) | 240 (12.6) | 562 (13.8) |
| General Disorders and Administration Site Conditions | 157 (27.4) | 141 (24.6) | 1372 (49.0) | 657 (34.6) | 1828 (44.8) |
| Fatigue | **112 (19.6)** | **88 (15.3)** | 946 (33.8) | 414 (21.8) | 1288 (31.6) |
| Asthenia | 31 (5.4) | 28 (4.9) | 364 (13.0) | 172 (9.1) | 453 (11.1) |
| Oedema peripheral | 29 (5.1) | 38 (6.6) | 283 (10.1) | 144 (7.6) | 377 (9.2) |
| Investigations | 35 (6.1) | 44 (7.7) | 24 (0.9) | 10 (0.5) | 66 (1.6) |
| Weight increased | 35 (6.1) | 44 (7.7) | 24 (0.9) | 10 (0.5) | 66 (1.6) |
| Musculoskeletal and Connective Tissue Disorders | 121 (21.2) | 122 (21.3) | 1025 (36.6) | 578 (30.5) | 1391 (34.1) |
| Arthralgia | 70 (12.2) | 61 (10.6) | 485 (17.3) | 255 (13.4) | 666 (16.3) |
| Back pain | 43 (7.5) | 62 (10.8) | 591 (21.1) | 338 (17.8) | 776 (19.0) |
| Musculoskeletal pain | **36 (6.3)** | **23 (4.0)** | 287 (10.3) | 132 (7.0) | 391 (9.6) |
| Nervous System Disorders | 29 (5.1) | 20 (3.5) | 253 (9.0) | 107 (5.6) | 354 (8.7) |
| Dizziness | 29 (5.1) | 20 (3.5) | 253 (9.0) | 107 (5.6) | 354 (8.7) |
| Vascular Disorders | 184 (32.2) | 151 (26.3) | 716 (25.6) | 213 (11.2) | 1060 (26.0) |
| Hot Flush | **155 (27.1)** | **128 (22.3)** | 451 (16.1) | 146 (7.7) | 684 (16.8) |
| Hypertension | **46 (8.0)** | **32 (5.6)** | 336 (12.0) | 73 (3.8) | 480 (11.8) |

All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population).

Data cutoff dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Patients with multiple events for a given preferred term or SOC were counted only once for each preferred term and SOC. Number of patients (n) reporting and percentage of patients (%) are shown. The preferred terms were coded by MedDRA v 21.0. Events are sorted by SOC alphabetically and then by decreasing frequency of preferred term in the enzalutamide plus ADT group in the ARCHES study.

Preferred term frequencies highlighted in **bold** are TEAEs that occurred in ≥ 5% of patients in the ARCHES enzalutamide plus ADT group and ≥ 2% higher incidence than the ARCHES placebo plus ADT group.

ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; TEAE: treatment-emergent adverse event.

† The phase 3 CRPC studies include PREVAIL, AFFIRM, Asian PREVAIL and PROSPER.

‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of studies ARCHES, PROSPER, PREVAIL, AFFIRM, Asian PREVAIL, TERRAIN, STRIVE and open-label phase of studies PREVAIL, AFFIRM, TERRAIN, STRIVE.

**Grade 3 or Higher TEAEs**

In the ARCHES study, the incidence of grade ≥ 3 TEAEs was 24.3% in the enzalutamide plus ADT group and 25.6% in the placebo plus ADT group. The incidence of grade ≥ 3 TEAEs in the phase 3 CRPC enzalutamide group was 43.2%.

In the phase 3 studies, there were 20 preferred terms noted as grade ≥ 3 TEAEs occurring in ≥ 1% of patients in the enzalutamide or placebo groups [Table 51].

*Table 51. Grade ≥ 3 Treatment-emergent Adverse Events Experienced by ≥ 1% of Patients in the Phase 3 Enzalutamide or Placebo Groups*

| Preferred Term (MedDRA v 21.0) n (%) | mHSPC | | CRPC | | Total‡ |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Enzalutamide (n = 4081) |
| Hypertension | 19 (3.3) | 10 (1.7) | **140 (5.0)** | **34 (1.8)** | 209 (5.1) |
| Asthenia | 6 (1.0) | 3 (0.5) | **49 (1.8)** | **20 (1.1)** | 67 (1.6) |
| Syncope | 6 (1.0) | 1 (0.2) | **36 (1.3)** | **14 (0.7)** | 56 (1.4) |
| Anaemia | 5 (0.9) | 6 (1.0) | 107 (3.8) | 77 (4.1) | 156 (3.8) |
| Back Pain | 5 (0.9) | 3 (0.5) | 67 (2.4) | 44 (2.3) | 89 (2.2) |
| Fatigue | 5 (0.9) | 6 (1.0) | **103 (3.7)** | **48 (2.5)** | 137 (3.4) |
| Haematuria | 5 (0.9) | 2 (0.3) | 46 (1.6) | 34 (1.8) | 67 (1.6) |
| Bone pain | 4 (0.7) | 4 (0.7) | 40 (1.4) | 40 (2.1) | 50 (1.2) |
| Spinal cord compression | 3 (0.5) | 5 (0.9) | **94 (3.4)** | **41 (2.2)** | 115 (2.8) |
| Arthralgia | 2 (0.3) | 4 (0.7) | 37 (1.3) | 21 (1.1) | 49 (1.2) |
| Fall | 2 (0.3) | 1 (0.2) | **34 (1.2)** | **9 (0.5)** | 50 (1.2) |
| Hydronephrosis | 2 (0.3) | 2 (0.3) | 10 (0.4) | 24 (1.3) | 23 (0.6) |
| Pain in extremity | 2 (0.3) | 2 (0.3) | 23 (0.8) | 20 (1.1) | 31 (0.8) |
| Pneumonia | 2 (0.3) | 3 (0.5) | **44 (1.6)** | **16 (0.8)** | 66 (1.6) |
| Urinary retention | 2 (0.3) | 6 (1.0) | 18 (0.6) | 26 (1.4) | 27 (0.7) |
| Cancer pain | 1 (0.2) | 2 (0.3) | 47 (1.7) | 28 (1.5) | 65 (1.6) |
| Decreased appetite | 1 (0.2) | 0 | 28 (1.0) | 12 (0.6) | 31 (0.8) |
| General physical health deterioration | 1 (0.2) | 2 (0.3) | **46 (1.6)** | **20 (1.1)** | 65 (1.6) |
| Urinary tract obstruction | 1 (0.2) | 1 (0.2) | 27 (1.0) | 22 (1.2) | 38 (0.9) |
| Urinary tract infection | 0 | 1 (0.2) | 36 (1.3) | 18 (0.9) | 50 (1.2) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.*
*Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) reporting and percentage of patients (%) are shown. The preferred terms were coded by MedDRA v 21.0. Preferred term values highlighted in bold are grade ≥ 3 TEAEs that occurred in ≥ 1% of patients in the phase 3 enzalutamide group and ≥ 0.5% higher incidence than the phase 3 placebo group.*
*ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer.*

*† The phase 3 CRPC studies include PREVAIL, AFFIRM, Asian PREVAIL and PROSPER.*
*‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of studies ARCHES, PROSPER, PREVAIL, AFFIRM, Asian PREVAIL, TERRAIN, STRIVE and open-label phase of studies PREVAIL, AFFIRM, TERRAIN, STRIVE.*

In the phase 3 studies, the median time to first grade ≥ 3 TEAE was 24.9 months for the enzalutamide group and 17.7 months for the placebo group.

*Table 52. Grade 3 or Grade 4 AEs by Preferred Term Experienced by ≥ 1% of Patients in the Enzalutamide Plus ADT or NSAA Plus ADT Group in ENZAMET*

| MedDRA v21.0 Preferred Tem | Overall Incidence, n (%) | | | | | |
|---|---|---|---|---|---|---|
| | Enzalutamide+ADT | | | Conventional NSAA+ADT | | |
| | With Early Docetaxel† (n = 243) | Without Early Docetaxel (n = 320) | Total (n = 563) | With Early Docetaxel† (n = 235) | Without Early Docetaxel (n = 323) | Total (n = 558) |
| **Overall‡** | 145 (59.7) | 175 (54.7) | 320 (56.8) | 123 (52.3) | 114 (35.3) | 237 (42.5) |
| Febrile neutropenia | 34 (14.0) | 2 (0.6) | **36 (6.4)** | 32 (13.6) | 0 | **32 (5.7)** |
| Hypertension | 18 (7.4) | 25 (7.8) | **43 (7.6)** | 11 (4.7) | 14 (4.3) | **25 (4.5)** |
| Neutrophil count decreased | 30 (12.3) | 1 (0.3) | **31 (5.5)** | 15 (6.4) | 1 (0.3) | **16 (2.9)** |
| Fatigue | 14 (5.8) | 17 (5.3) | **31 (5.5)** | 2 (0.9) | 2 (0.6) | **4 (0.7)** |
| Syncope | 10 (4.1) | 11 (3.4) | **21 (3.7)** | 4 (1.7) | 2 (0.6) | ***6* (1.1)** |
| Erectile dysfunction | 6 (2.5) | 6 (1.9) | 12 (2.1) | 7 (3.0) | 5 (1.5) | 12 (2.2) |
| Back pain | 5 (2.1) | 6 (1.9) | 11 (2.0) | 3 (1.3) | 7 (2.2) | 10 (1.8) |
| Lung infection | ***3* (1.2)** | ***7* (2.2)** | 10 (1.8) | 4 (1.7) | 5 (1.5) | 9 (1.6) |
| Arthritis | ***2* (0.8)** | ***6* (1.9)** | 8 (1.4) | 5 (2.1) | 4 (1.2) | 9 (1.6) |
| Pain | ***3* (1.2)** | ***7* (2.2)** | **10 (1.8)** | 4 (1.7) | 1 (0.3) | **5 (0.9)** |
| Skin infection | 2 (0.8) | 4 (1.3) | 6 (1.1) | 4 (1.7) | 4 (1.2) | 8 (1.4) |
| Cataract | 2 (0.8) | 5 (1.6) | 7 (1.2) | ***1* (0.4)** | ***5* (1.5)** | 6 (1.1) |
| Sepsis | 4 (1.6) | 1 (0.3) | *5 (0.9)* | 5 (2.1) | 3 (0.9) | *8 (1.4)* |
| Urinary tract infection | 4 (1.6) | 3 (0.9) | 7 (1.2) | 2 (0.9) | 4 (1.2) | 6 (1.1) |
| Urinary tract obstruction | 5 (2.1) | 3 (0.9) | **8 (1.4)** | 3 (1.3) | 2 (0.6) | **5 (0.9)** |
| Fracture | 5 (2.1) | 4 (1.3) | **9 (1.6)** | 1 (0.4) | 2 (0.6) | **3 (0.5)** |
| Haematuria | 2 (0.8) | 5 (1.6) | 7 (1.2) | 3 (1.3) | 2 (0.6) | 5 (0.9) |
| Hyperglycaemia | 3 (1.2) | 3 (0.9) | 6 (1.1) | 4 (1.7) | 2 (0.6) | 6 (1.1) |
| Urinary retention | 3 (1.2) | 3 (0.9) | 6 (1.1) | 1 (0.4) | 4 (1.2) | 5 (0.9) |
| Pyramidal tract syndrome | 2 (0.8) | 1 (0.3) | *3 (0.5)* | 4 (1.7) | 2 (0.6) | *6 (1.1)* |
| Fall | 2 (0.8) | 4 (1.3) | **6 (1.1)** | 0 | 2 (0.6) | **2 (0.4)** |

All randomized patients who received at least 1 administration of study drug, in which study drug includes enzalutamide and conventional NSAA (safety population).

The analysis data cutoff date was 28 Feb 2019.

Preferred term frequencies highlighted in **bold** are grade 3 or 4 AEs that occurred in ≥ 1% of patients in the enzalutamide plus ADT group and ≥ 0.5% higher incidence than the NSAA plus ADT group.

Preferred term frequencies that are *italicized* are grade 3 or 4 AEs that occurred in ≥ 1% of patients in the NSAA plus ADT group and ≥ 0.5% higher incidence than the enzalutamide plus ADT group.

Preferred term frequencies that are shaded occurred with a ≥ 1% higher incidence in patients receiving docetaxel than those without docetaxel, within treatment groups.

Preferred term frequencies highlighted in ***bold, italicized and underlined*** occurred with a ≥ 1% higher incidence in patients who did not receive early docetaxel than those receiving early docetaxel, within treatment groups.

ADT: androgen deprivation therapy; AE: adverse event; NSAA: nonsteroidal antiandrogen

† Patients who actually received at least 1 dose of docetaxel during the study. Administrations commenced prior to study entry, as specified in the study protocol, were included.

‡ Based on the safety population and independent of the ≥ 1% patient cutoff used in this table.

## Study Drug-related TEAEs

Study drug-related TEAEs were TEAEs of any grade that were assessed by the investigator as possibly, probably or definitely related to study drug. The proportion of patients with any study drug-related TEAE is presented in the table below.

*Table 53. Study Drug-related Treatment-emergent Adverse Events Experienced by ≥ 2% of Patients in the ARCHES Enzalutamide plus ADT or Placebo plus ADT Groups*

| Preferred Term (MedDRA v 21.0) n (%) | mHSPC | | CRPC | | Total‡ Enzalutamide (n = 4081) |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | |
| Overall | 303 (53.0) | 268 (46.7) | 1816 (64.9) | 955 (50.3) | 2553 (62.6) |
| Hot flush | 117 (20.5) | 104 (18.1) | 342 (12.2) | 110 (5.8) | 524 (12.8) |
| Fatigue | 85 (14.9) | 63 (11.0) | 695 (24.8) | 278 (14.6) | 970 (23.8) |
| Arthralgia | 29 (5.1) | 18 (3.1) | 72 (2.6) | 38 (2.0) | 114 (2.8) |
| Nausea | 28 (4.9) | 15 (2.6) | 364 (13.0) | 241 (12.7) | 464 (11.4) |
| Hypertension | 27 (4.7) | 19 (3.3) | 142 (5.1) | 28 (1.5) | 214 (5.2) |
| Weight increased | 27 (4.7) | 24 (4.2) | 11 (0.4) | 3 (0.2) | 41 (1.0) |
| Asthenia | 21 (3.7) | 18 (3.1) | 222 (7.9) | 89 (4.7) | 273 (6.7) |
| Dizziness | 19 (3.3) | 7 (1.2) | 116 (4.1) | 41 (2.2) | 169 (4.1) |
| Gynaecomastia | 17 (3.0) | 7 (1.2) | 49 (1.8) | 13 (0.7) | 78 (1.9) |
| Decreased appetite | 16 (2.8) | 8 (1.4) | 257 (9.2) | 127 (6.7) | 314 (7.7) |
| Constipation | 12 (2.1) | 8 (1.4) | 130 (4.6) | 68 (3.6) | 162 (4.0) |
| Memory impairment | 12 (2.1) | 4 (0.7) | 24 (0.9) | 6 (0.3) | 41 (1.0) |
| Oedema peripheral | 12 (2.1) | 12 (2.1) | 83 (3.0) | 32 (1.7) | 115 (2.8) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population).Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018. Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) reporting and percentage of patients (%) are shown. The preferred terms were coded by MedDRA v 21.0. Events are sorted by decreasing frequency of preferred term in the enzalutamide group in the ARCHES study. Study drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably, or definitely related to study drug.*

*ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; TEAE: treatment-emergent adverse event.*
*† The phase 3 CRPC studies include AFFIRM, PREVAIL, Asian PREVAIL and PROSPER.*
*‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE, PROSPER, and open-label phase of studies PREVAIL, AFFIRM, TERRAIN and STRIVE.*

**Adverse events of special interest (AEOSIs)**

The prespecified TEAEs of special interest described are convulsions (seizure), hypertension, neutrophil count decreased, cognitive and memory impairment, ischemic heart disease, other selected cardiovascular events (Haemorrhagic Central Nervous System Vascular Conditions, Ischemic Central Nervous System Vascular Conditions and Cardiac Failure), posterior reversible encephalopathy syndrome (PRES), second primary malignancies, falls, fracture, fatigue, loss of consciousness, thrombocytopenia, musculoskeletal events, severe cutaneous adverse reactions, angioedema, and rash. In addition, TEAEs of hepatic and renal disorders are described as TEAEs of clinical interest.

*Table 54. Overall Summary of TEAEs of Special Interest*

| | mHSPC | | CRPC | | |
|---|---|---|---|---|---|
| **Category, n (%)** | **ARCHES Enzalutamide+ADT (n = 572)** | **ARCHES Placebo+ADT (n = 574)** | **Phase 3† Enzalutamide (n = 2799)** | **Phase 3† Placebo (n = 1898)** | **Total‡ Enzalutamide (n = 4081)** |
| Convulsions (seizure) | 2 (0.3) | 2 (0.3) | 11 (0.4) | 1 (0.1) | 21 (0.5) |
| Hypertension | 49 (8.6) | 36 (6.3) | 352 (12.6) | 82 (4.3) | 509 (12.5) |
| Neutrophil count decreased | 5 (0.9) | 4 (0.7) | 36 (1.3) | 8 (0.4) | 51 (1.2) |
| Cognitive and memory impairment | 26 (4.5) | 12 (2.1) | 146 (5.2) | 29 (1.5) | 227 (5.6) |
| Ischemic heart disease | 10 (1.7) | 8 (1.4) | 85 (3.0) | 25 (1.3) | 124 (3.0) |
| Other selected cardiovascular events | 13 (2.3) | 9 (1.6) | 117 (4.2) | 39 (2.1) | 186 (4.6) |
| Posterior reversible encephalopathy syndrome | 0 | 0 | 0 | 0 | 0 |
| Fatigue-related events | 138 (24.1) | 112 (19.5) | 1257 (44.9) | 570 (30.0) | 1665 (40.8) |
| Second primary malignancies excluding non-melanoma skin cancer | 10 (1.7) | 11 (1.9) | 80 (2.9) | 18 (0.9) | 123 (3.0) |
| Falls | 21 (3.7) | 15 (2.6) | 299 (10.7) | 72 (3.8) | 413 (10.1) |
| Fractures | 37 (6.5) | 24 (4.2) | 289 (10.3) | 78 (4.1) | 394 (9.7) |
| Loss of consciousness-related events§ | 9 (1.6) | 1 (0.2) | 74 (2.6) | 23 (1.2) | 114 (2.8) |
| Thrombocytopenia | 3 (0.5) | 3 (0.5) | 46 (1.6) | 26 (1.4) | 64 (1.6) |
| Musculoskeletal events | 151 (26.4) | 159 (27.7) | 1249 (44.6) | 748 (39.4) | 1704 (41.8) |
| Severe cutaneous adverse reactions | 0 | 1 (0.2) | 5 (0.2) | 2 (0.1) | 6 (0.1) |
| Angioedema | 7 (1.2) | 1 (0.2) | 40 (1.4) | 17 (0.9) | 56 (1.4) |
| Rash | 15 (2.6) | 9 (1.6) | 122 (4.4) | 54 (2.8) | 181 (4.4) |

All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (safety population).

Data cutoff dates were as follow: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; TEAE: treatment-emergent adverse event.

† The previous phase 3 studies include AFFIRM, PREVAIL, Asian PREVAIL and PROSPER.

‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE, PROSPER, and open-label phase of studies PREVAIL, AFFIRM, TERRAIN and STRIVE.

§ In addition to 'loss of consciousness", the preferred terms of 'syncope' and 'pre-syncope' were also evaluated.

Other selected cardiovascular events: Cardiac failure, Cardiac failure chronic, Cardiopulmonary failure, Carotid arteriosclerosis, Carotid artery stenosis Cerebellar infarction, Cerebral arteriosclerosis Cerebral haemorrhage Cerebral infarction Cerebral ischaemia Cerebrovascular accident Cerebrovascular disorder Ischaemic stroke Pulmonary oedema Subarachnoid haemorrhage Subdural haematoma Transient ischaemic attack

*Table 55. Overall Summary of Grade 3 or 4 AEs of Special Interest and All SAEs of Special Interest in ENZAMET*

| Category† | Overall Incidence, n (%) | | | | | |
|---|---|---|---|---|---|---|
| | Enzalutamide+ADT | | | Conventional NSAA+ADT | | |
| | With Early Docetaxel‡ (n = 243)) | Without Early Docetaxel (n = 320) | Total (n = 563) | With Early Docetaxel‡ (n = 235) | Without Early Docetaxel (n = 323) | Total (n = 558) |
| Convulsion | 2 (0.8) | 4 (1.3) | 6 (1.1) | 0 | 0 | 0 |
| Hypertension | 18 (7.4) | 26 (8.1) | 44 (7.8) | 11 (4.7) | 14 (4.3) | 25 (4.5) |
| Neutropenia/neutrophil count decreased | 63 (25.9) | 3 (0.9) | 66 (11.7) | 45 (19.1) | 1 (0.3) | 46 (8.2) |
| Cognitive/memory impairment | 1 (0.4) | 0 | 1 (0.2) | 0 | 0 | 0 |
| Ischemic heart disease | 2 (0.8) | 12 (3.8) | 14 (2.5) | 3 (1.3) | 6 (1.9) | 9 (1.6) |
| Other selected cardiovascular events | 5 (2.1) | 10 (3.1) | 15 (2.7) | 3 (1.3) | 6 (1.9) | 9 (1.6) |
| Posterior reversible encephalopathy syndrome | 0 | 0 | 0 | 0 | 0 | 0 |
| Fatigue | 14 (5.8) | 17 (5.3) | 31 (5.5) | 2 (0.9) | 2 (0.6) | 4 (0.7) |
| Fall | 2 (0.8) | 4 (1.3) | 6 (1.1) | 0 | 2 (0.6) | 2 (0.4) |
| Fractures | 9 (3.7) | 11 (3.4) | 20 (3.6) | 2 (0.9) | 6 (1.9) | 8 (1.4) |
| Loss of consciousness-related events | 14 (5.8) | 11 (3.4) | 25 (4.4) | 8 (3.4) | 3 (0.9) | 11 (2.0) |
| Thrombocytopenia | 1 (0.4) | 0 | 1 (0.2) | 0 | 0 | 0 |
| Musculoskeletal events | 8 (3.3) | 13 (4.1) | 21 (3.7) | 8 (3.4) | 9 (2.8) | 17 (3.0) |
| Severe cutaneous adverse reactions | 0 | 0 | 0 | 0 | 1 (0.3) | 1 (0.2) |
| Angioedema | 0 | 0 | 0 | 0 | 0 | 0 |
| Rash | 3 (1.2) | 1 (0.3) | 4 (0.7) | 1 (0.4) | 0 | 1 (0.2) |
| Second primary malignancies | 5 (2.1) | 4 (1.3) | 9 (1.6) | 2 (0.9) | 8 (2.5) | 10 (1.8) |

All randomized patients who received at least 1 administration of study drug, in which study drug includes enzalutamide and conventional NSAA (safety population).
The analysis data cutoff date was 28 Feb 2019.
ADT: androgen deprivation therapy; AE: adverse event; NSAA: nonsteroidal antiandrogen; SAE: serious adverse event
† Definitions of categories used MedDRA v 21.0.
‡ Patients who actually received at least 1 dose of docetaxel during the study. Administrations commenced prior to study entry, as specified in the study protocol, were included.

## Serious adverse event/deaths/other significant events

### Deaths

In the ARCHES study, the proportion of patients who died on-treatment and during survival follow-up was 6.8% (39/572) in the enzalutamide plus ADT group and 7.8% (45/574) in the placebo plus ADT group.

The proportion of patients who died on-treatment and during survival follow-up in the phase 3 CRPC enzalutamide group was 49.8% (1393/2799). Differences in treatment duration as well as difference in the follow-up for OS and the corresponding safety reporting periods were observed between the studies.

*Table 56. Summary of All Deaths*

| Deaths, n (%) | mHSPC | | CRPC | | Total‡ |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Enzalutamide (n = 4081) |
| Total number of deaths | 39 (6.8) | 45 (7.8) | 1393 (49.8) | 1107 (58.3) | 1634 (40.0) |
| Cause of death | | | | | |
| Disease progression | 26 (4.5) | 29 (5.1) | 1138 (40.7) | 939 (49.5) | 1321 (32.4) |
| Other§ | 13 (2.3) | 16 (2.8) | 189 (6.8) | 130 (6.8) | 242 (5.9) |
| Unknown | 0 | 0 | 66 (2.4) | 36 (1.9) | 71 (1.7) |
| Missing | 0 | 0 | 0 | 2 (0.1) | 0 |
| Deaths within 30 days after the first dose date of study drug | 0 | 0 | 4 (0.1) | 4 (0.2) | 5 (0.1) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018. All deaths up to and including the analysis data cut-off date are included. Number of patients (n) reporting and percentage of patients (%) are shown. Table is based on data from the end-of-study CRF. ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer. † The phase 3 CRPC studies include AFFIRM, PREVAIL and Asian PREVAIL and PROSPER. ‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE, PROSPER, and open-label phase of studies PREVAIL, AFFIRM, TERRAIN, STRIVE. § All known primary causes of death other than disease progression*

Overall, the most common cause of death was disease progression. The cause of death was generally categorized as due to disease progression, other or unknown.

In the ARCHES study, TEAEs leading to death were reported in 14 (2.4%) patients in the enzalutamide plus ADT group and 10 (1.7%) patients in the placebo plus ADT group. No patient in the enzalutamide plus ADT group had a fatal TEAE that was considered to be study drug-related. One patient in the placebo plus ADT group had a TEAE leading to death that was considered by the investigator to be study drug-related (general physical health deterioration).

In the phase 3 studies in patients with CRPC, TEAEs leading to death were reported in 127 (4.5%) patients in the enzalutamide group; 5 patients had TEAEs leading to death that were considered by the investigator to be study drug-related.

In the ARCHES study, preferred terms leading to death in ≥ 2 patients were malignant neoplasm progression (4 [0.7%] patients in the enzalutamide plus ADT group and 2 [0.3%] patients in the placebo plus ADT group) and pulmonary embolism (2 [0.3%] patients in the enzalutamide plus ADT group).

*Table 57. Treatment-emergent Adverse Events Resulting in Death by Preferred Term in ≥ 2 Patients in the Total Enzalutamide Group*

| Preferred Term (MedDRA v 21.0) n (%) | mHSPC | | CRPC | | Total‡ |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Enzalutamide (n = 4081) |
| Patients with ≥ 1 TEAE resulting in death, overall n (%) | 14 (2.4) | 10 (1.7) | 127 (4.5) | 57 (3.0) | 207 (5.1) |
| Malignant neoplasm progression | 4 (0.7) | 2 (0.3) | 0 | 0 | 4 (0.1) |
| Pulmonary embolism | 2 (0.3) | 0 | 2 (0.1) | 1 (0.1) | 4 (0.1) |
| Cardio-respiratory arrest | 1 (0.2) | 1 (0.2) | 1 (0.0) | 0 | 3 (0.1) |
| Cardiopulmonary failure | 1 (0.2) | 0 | 2 (0.1) | 0 | 3 (0.1) |
| Death | 1 (0.2) | 0 | 7 (0.3) | 3 (0.2) | 8 (0.2) |
| General physical health deterioration | 1 (0.2) | 1 (0.2) | 18 (0.6) | 9 (0.5) | 25 (0.6) |
| Myocardial infarction | 1 (0.2) | 0 | 4 (0.1) | 1 (0.1) | 6 (0.1) |
| Sepsis | 1 (0.2) | 1 (0.2) | 2 (0.1) | 0 | 4 (0.1) |
| Septic shock | 1 (0.2) | 0 | 3 (0.1) | 2 (0.1) | 4 (0.1) |
| Acute kidney injury | 0 | 0 | 0 | 2 (0.1) | 3 (0.1) |
| Acute myocardial infarction | 0 | 0 | 6 (0.2) | 0 | 7 (0.2) |
| Arteriosclerosis coronary artery | 0 | 0 | 1 (0.0) | 1 (0.1) | 2 (0.0) |
| Cachexia | 0 | 0 | 2 (0.1) | 1 (0.1) | 2 (0.0) |
| Cardiac arrest | 0 | 0 | 2 (0.1) | 2 (0.1) | 3 (0.1) |
| Cardiac failure | 0 | 0 | 7 (0.3) | 0 | 10 (0.2) |
| Cardiac failure congestive | 0 | 0 | 1 (0.0) | 1 (0.1) | 4 (0.1) |
| Cerebrovascular accident | 0 | 1 (0.2) | 4 (0.1) | 0 | 4 (0.1) |
| Disease progression | 0 | 0 | 12 (0.4) | 6 (0.3) | 26 (0.6) |
| Disseminated intravascular coagulation | 0 | 0 | 1 (0.0) | 0 | 2 (0.0) |
| Haemorrhage intracranial | 0 | 0 | 1 (0.0) | 0 | 2 (0.0) |
| Hepatic failure | 0 | 0 | 2 (0.1) | 0 | 3 (0.1) |
| Infection | 0 | 0 | 1 (0.0) | 0 | 2 (0.0) |
| Metastases to liver | 0 | 0 | 1 (0.0) | 0 | 2 (0.0) |
| Multiple organ dysfunction syndrome | 0 | 0 | 3 (0.1) | 1 (0.1) | 3 (0.1) |
| Pneumonia | 0 | 0 | 6 (0.2) | 1 (0.1) | 12 (0.3) |
| Pneumonia aspiration | 0 | 0 | 1 (0.0) | 0 | 3 (0.1) |
| Prostate cancer | 0 | 0 | 1 (0.0) | 1 (0.1) | 2 (0.0) |
| Prostate cancer metastatic | 0 | 0 | 0 | 2 (0.1) | 2 (0.0) |
| Subdural haematoma | 0 | 0 | 1 (0.0) | 1 (0.1) | 2 (0.0) |
| Urosepsis | 0 | 0 | 1 (0.0) | 0 | 2 (0.0) |
| Ventricular fibrillation | 0 | 0 | 1 (0.0) | 0 | 2 (0.0) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018. Number of patients (n) reporting and percentage of patients (%) are shown. The preferred terms were coded by MedDRA v 21.0. Events are sorted by decreasing frequency of preferred term in the enzalutamide group in the ARCHES study. ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; TEAE: treatment-emergent adverse event. † The phase 3 CRPC studies include AFFIRM, PREVAIL, Asian PREVAIL and PROSPER. ‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE, PROSPER, and open-label phase of studies PREVAIL, AFFIRM, TERRAIN and STRIVE.*

**Serious adverse events**

In the ARCHES study, the incidence of serious TEAEs was 18.2% in the enzalutamide plus ADT group and 19.5% in the placebo plus ADT group. The incidence of serious TEAEs in the phase 3 CRPC enzalutamide group was 34.1% and 27.4% in the placebo group.

*Table 58. Serious Treatment-emergent Adverse Events Reported in at Least 0.5% of Patients in Either Treatment Group (Safety Population)*

| MedDRA v21.0 Preferred Term | Overall Incidence, n (%) | |
|---|---|---|
| | Enzalutamide+ADT (n = 572) | Placebo+ADT (n = 574) |
| **Overall** | **104 (18.2)** | **112 (19.5)** |
| Anaemia | 4 (0.7) | 3 (0.5) |
| Atrial fibrillation | 2 (0.3) | 4 (0.7) |
| Sepsis | 3 (0.5) | 3 (0.5) |
| Fall | 3 (0.5) | 2 (0.3) |
| Malignant neoplasm progression | 6 (1.0) | 3 (0.5) |
| Basal cell carcinoma | 4 (0.7) | 4 (0.7) |
| Spinal cord compression | 3 (0.5) | 6 (1.0) |
| Syncope | 3 (0.5) | 0 |
| Hydronephrosis | 4 (0.7) | 3 (0.5) |
| Urinary retention | 3 (0.5) | 4 (0.7) |
| Haematuria | 4 (0.7) | 2 (0.3) |
| Pulmonary embolism | 3 (0.5) | 3 (0.5) |

Data cutoff date: 14 Oct 2018

All randomized patients who received at least 1 dose of study drug (safety population).

Sorting order: ascending order by system organ class code and descending by the number of patients of total group by preferred term. In case of ties ascending order by preferred term code is applied.

ADT: androgen deprivation therapy.

Serious TEAEs were considered drug-related by the investigator in 22 (3.8%) patients in the enzalutamide plus ADT group and 16 patients (2.8%) patients in the placebo plus ADT group.

*Table 59. Drug-related Serious Treatment-emergent Adverse Events Reported in at Least 2 Patients in Either Treatment Group (Safety Population)*

| MedDRA v21.0 Preferred Term | Overall Incidence, n (%) | |
|---|---|---|
| | Enzalutamide+ADT (n = 572) | Placebo+ADT (n = 574) |
| **Overall** | **22 (3.8)** | **16 (2.8)** |
| Fatigue | 2 (0.3) | 0 |
| Myocardial infarction | 0 | 2 (0.3) |
| General physical health deterioration | 0 | 2 (0.3) |
| Alanine aminotransferase increased | 2 (0.3) | 0 |
| Aspartate aminotransferase increased | 2 (0.3) | 0 |
| Seizure | 2 (0.3) | 1 (0.2) |
| Spinal cord compression | 2 (0.3) | 0 |
| Syncope | 2 (0.3) | 0 |

Data cutoff date: 14 Oct 2018

All randomized patients who received at least 1 dose of study drug (safety population).

Sorting order: ascending order by system organ class code and descending by the number of patients of total group by preferred term. In case of ties ascending order by preferred term code is applied.

ADT: androgen deprivation therapy.

*Table 60. Serious Adverse Events of Any Grade Experienced by ≥ 1% of Patients in the Enzalutamide plus ADT or NSAA plus ADT Groups (ENZAMET Safety Population)*

| MedDRA v 21.0 Preferred Tem | Overall Incidence, n (%) | | | | | |
|---|---|---|---|---|---|---|
| | Enzalutamide+ADT | | | Conventional NSAA+ADT | | |
| | With Early Docetaxel† (n = 243) | Without Early Docetaxel (n = 320) | Total (n = 563) | With Early Docetaxel† (n = 235) | Without Early Docetaxel (n = 323) | Total (n = 558) |
| **Overall** | 111 (45.7) | 124 (38.8) | 235 (41.7) | 95 (40.4) | 94 (29.1) | 189 (33.9) |
| Febrile neutropenia | 34 (14.0) | 1 (0.3) | **35 (6.2)** | 31 (13.2) | 0 | **31 (5.6)** |
| Lung infection | ***3 (1.2)*** | ***7 (2.2)*** | 10 (1.8) | 4 (1.7) | 6 (1.9) | 10 (1.8) |
| Arthritis | ***0*** | ***6 (1.9)*** | *6 (1.1)* | 5 (2.1) | 6 (1.9) | *11 (2.0)* |
| Fracture | 4 (1.6) | 6 (1.9) | **10 (1.8)** | 1 (0.4) | 4 (1.2) | **5 (0.9)** |
| Haematuria | 4 (1.6) | 5 (1.6) | **9 (1.6)** | 2 (0.9) | 4 (1.2) | **6 (1.1)** |
| Sepsis | 3 (1.2) | 1 (0.3) | *4 (0.7)* | 6 (2.6) | 4 (1.2) | *10 (1.8)* |
| Skin infection | 2 (0.8) | 4 (1.3) | 6 (1.1) | 5 (2.1) | 3 (0.9) | 8 (1.4) |
| Urinary tract infection | 4 (1.6) | 3 (0.9) | 7 (1.2) | ***1 (0.4)*** | ***5 (1.5)*** | 6 (1.1) |
| Back pain | 1 (0.4) | 4 (1.3) | 5 (0.9) | 2 (0.9) | 5 (1.5) | 7 (1.3) |
| Urinary tract obstruction | 4 (1.6) | 4 (1.3) | **8 (1.4)** | 2 (0.9) | 2 (0.6) | **4 (0.7)** |
| Pain | ***1 (0.4)*** | ***6 (1.9)*** | **7 (1.2)** | 4 (1.7) | 0 | **4 (0.7)** |
| Urinary retention | 2 (0.8) | 3 (0.9) | 5 (0.9) | ***1 (0.4)*** | ***5 (1.5)*** | 6 (1.1) |
| Pyrexia | 6 (2.5) | 0 | 6 (1.1) | 4 (1.7) | 0 | 4 (0.7) |
| Syncope | 3 (1.2) | 3 (0.9) | **6 (1.1)** | 1 (0.4) | 2 (0.6) | **3 (0.5)** |
| Fall | 2 (0.8) | 4 (1.3) | **6 (1.1)** | 0 | 2 (0.6) | **2 (0.4)** |
| Acute kidney injury | 5 (2.1) | 1 (0.3) | **6 (1.1)** | 0 | 1 (0.3) | **1 (0.2)** |
| Spinal fracture | 4 (1.6 ) | 3 (0.9) | **7 (1.2)** | 0 | 0 | **0** |
| Seizure | 2 (0.8) | 4 (1.3) | **6 (1.1)** | 0 | 0 | **0** |

All randomized patients who received at least 1 administration of study drug, in which study drug includes enzalutamide and conventional NSAA (Safety Population).
Data cutoff date: 28 Feb 2019
Preferred term frequencies highlighted in **bold** are SAEs that occurred in ≥ 1% of patients in the enzalutamide plus ADT group and ≥ 0.5% higher incidence than the NSAA plus ADT group.
Preferred term frequencies that are *italicized* are SAEs that occurred in ≥ 1% of patients in the NSAA plus ADT group and ≥ 0.5% higher incidence than the enzalutamide plus ADT group.
Preferred term frequencies shaded occurred with a ≥ 1% higher incidence in patients receiving early docetaxel than those without early docetaxel, within treatment groups.
Preferred term frequencies highlighted in ***bold, italicized and underlined*** occurred with a ≥ 1% higher incidence in patients who did not receive early docetaxel than those receiving early docetaxel, within treatment groups.
ADT: androgen deprivation therapy; NSAA: nonsteroidal antiandrogen; SAEs: serious adverse events
†Patients who actually received at least 1 dose of docetaxel during the study. Administrations commenced prior to study entry, as specified in the study protocol, were included.

The proportion of patients with any study drug-related SAE was 3.0% in the enzalutamide plus ADT group and 0.4% in the NSAA plus ADT group. No study drug-related SAEs were fatal. Most SAEs occurred in 1 patient, the events that occurred in ≥ 2 patients in the enzalutamide plus ADT group were seizure (5 [0.9%] patients), hypertension (3 [0.5%] patients) and fatigue (2 [0.4%] patients). Two preferred terms (alanine aminotransferase increased and pneumonitis) were noted as study drug-related SAEs in the NSAA plus ADT group.

## Laboratory findings

Haematology

A summary of postbaseline grade 3 and 4 haematology laboratory abnormalities is provided in Table 62

*Table 61. Haematology Results: Summary of Grade 3 and 4 Postbaseline Laboratory Abnormalities*

| Parameter (Unit) [Direction of Criteria], n (%) | mHSPC | | CRPC | | Total‡ |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Enzalutamide (n = 3751) |
| Hemoglobin (g/L) [low] | 3 (0.5) | 5 (0.9) | 64 (2.3) | 38 (2.0) | 75 (2.0) |
| Hemoglobin (g/L) [high] | 0 | 0 | 2 (0.1) | 1 (0.1) | 2 (0.1) |
| Lymphocytes ($10^6$/L) [low] | 3 (0.5) | 10 (1.7) | 110 (3.9) | 70 (3.7) | 125 (3.3) |
| Neutrophils ($10^6$/L) [low] | 5 (0.9) | 4 (0.4) | 25 (0.9) | 6 (0.3) | 32 (0.9) |
| Platelets ($10^9$/L) [low] | 1 (0.2) | 1 (0.2) | 8 (0.3) | 8 (0.4) | 12 (0.3) |
| Leukocytes ($10^9$/L) [low] | 1 (0.2) | 2 (0.3) | 13 (0.5) | 3 (0.2) | 15 (0.4) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.*
*Grade 3 and 4 toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. Patients were generally counted only once for each parameter. However, for parameters with both high and low criteria, patients were counted only once for each criterion (high or low), so a single patient could count towards both high and low criteria if the patient had laboratory values meeting each criterion. Summaries are based on all test results collected in the treatment-emergent period.ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer. † The phase 3 CRPC studies include PREVAIL, AFFIRM, Asian PREVAIL and PROSPER.*

*‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE and PROSPER;the open-label phase of PREVAIL, AFFIRM, TERRAIN and STRIVE are not included.*

Chemistry

A summary of postbaseline grade 3 and 4 chemistry laboratory abnormalities is provided in Table 63 In the ARCHES study, the most frequently reported grade 3 and 4 postbaseline chemistry laboratory abnormality was high ALP (in the enzalutamide plus ADT group was 4.2% compared to 8.0% in the placebo plus ADT group).

*Table 62. Blood Chemistry Results: Summary of Grade 3 and 4 Postbaseline Laboratory Abnormalities*

| Parameter (Unit) [Direction of Criteria], n (%) | mHSPC | | CRPC | | Total‡ |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Enzalutamide (n = 3751) |
| Albumin (g/L) [low] | 0 | 0 | 10 (0.4) | 5 (0.3) | 10 (0.3) |
| Alkaline phosphatase (U/L) [high] | 24 (4.2) | 46 (8.0) | 158 (5.6) | 160 (8.4) | 193 (5.1) |
| Alanine aminotransferase (U/L) [high] | 9 (1.6) | 3 (0.5) | 6 (0.2) | 2 (0.1) | 19 (0.5) |
| Aspartate aminotransferase (U/L) [high] | 5 (0.9) | 3 (0.5) | 7 (0.3) | 7 (0.4) | 15 (0.4) |
| Bilirubin (µmol/L) [high] | 0 | 1 (0.2) | 2 (0.1) | 0 | 2 (0.1) |
| Calcium (mmol/L) [high] | 2 (0.3) | 0 | 2 (0.1) | 0 | 4 (0.1) |
| Calcium (mmol/L) [low] | 1 (0.2) | 0 | 18 (0.6) | 18 (0.9) | 19 (0.5) |
| Creatinine (µmol/L) [high] | 0 | 2 (0.3) | 4 (0.1) | 7 (0.4) | 4 (0.1) |
| Glucose (mmol/L) [low] | 0 | 0 | 0 | 0 | 1 (0.0) |
| Glucose (mmol/L) [high] | 21 (3.7) | 28 (4.9) | 82 (2.9) | 43 (2.3) | 132 (3.5) |
| Magnesium (mmol/L) [low] | 0 | 0 | 1 (0.0) | 1 (0.1) | 2 (0.1) |
| Magnesium (mmol/L) [high] | 0 | 0 | 5 (0.2) | 9 (0.5) | 5 (0.1) |
| Phosphate (mmol/L) [low] | 2 (0.3) | 2 (0.3) | 42 (1.5) | 20 (1.1) | 48 (1.3) |
| Potassium (mmol/L) [low] | 0 | 2 (0.3) | 10 (0.4) | 11 (0.6) | 12 (0.3) |
| Potassium (mmol/L) [high] | 2 (0.3) | 1 (0.2) | 6 (0.2) | 6 (0.3) | 11 (0.3) |
| Sodium (mmol/L) [low] | 2 (0.3) | 8 (1.4) | 42 (1.5) | 27 (1.4) | 51 (1.4) |
| Sodium (mmol/L) [high] | 0 | 0 | 2 (0.1) | 2 (0.1) | 2 (0.1) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018. Patients were generally counted only once for each parameter. However, for parameters with both high and low criteria, patients were counted only once for each criterion (high or low), so a single patient could count towards both high and low criteria if the patient had laboratory values meeting each criterion. Summaries are based on all test results collected in the treatment-emergent period. ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer. † The phase 3 CRPC studies include PREVAIL, AFFIRM, Asian PREVAIL and PROSPER. ‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE and PROSPER; the open-label phase of PREVAIL, AFFIRM, TERRAIN and STRIVE are not included.*

In the ARCHES study, the investigator or the central laboratory was required to report any occurrences of severe liver function test abnormalities, defined as ALT or AST > 3 × ULN and total bilirubin > 2 × ULN.

One patient in the ARCHES placebo plus ADT group had ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN. Overall, no patients in the ARCHES study met Hy's Law case criteria. One patient in the placebo plus ADT group had ALT 11.0 × ULN, AST 11.3 × ULN and total bilirubin 3.3 × ULN; this patient did not meet the criteria for Hy's Law.

*Table 63. Treatment-emergent Liver Function Test Elevations*

| Parameter<br>Criteria, n (%) | mHSPC | | CRPC | | Total‡ |
|---|---|---|---|---|---|
| | ARCHES<br>Enzalutamide+ADT<br>(n = 572) | ARCHES<br>Placebo+ADT<br>(n = 574) | Phase 3†<br>Enzalutamide<br>(n = 2799) | Phase 3†<br>Placebo<br>(n = 1898) | Enzalutamide<br>(n = 3751) |
| **ALT** | | | | | |
| n | 569 | 571 | 2750 | 1859 | 3696 |
| ≥ 3 × ULN | 16 (2.8) | 16 (2.8) | 20 (0.7) | 15 (0.8) | 42 (1.1) |
| ≥ 3 × ULN and worse than baseline | 16 (2.8) | 16 (2.8) | 20 (0.7) | 15 (0.8) | 42 (1.1) |
| ≥ 5 × ULN | 9 (1.6) | 3 (0.5) | 6 (0.2) | 2 (0.1) | 19 (0.5) |
| ≥ 10 × ULN | 4 (0.7) | 2 (0.4) | 0 | 0 | 6 (0.2) |
| ≥ 20 × ULN | 1 (0.2) | 0 | 0 | 0 | 2 (0.1) |
| **AST** | | | | | |
| n | 569 | 571 | 2748 | 1858 | 3694 |
| ≥ 3 × ULN | 12 (2.1) | 11 (1.9) | 33 (1.2) | 21 (1.1) | 50 (1.4) |
| ≥ 3 × ULN and worse than baseline | 12 (2.1) | 11 (1.9) | 33 (1.2) | 20 (1.1) | 50 (1.4) |
| ≥ 5 × ULN | 5 (0.9) | 3 (0.5) | 7 (0.3) | 7 (0.4) | 15 (0.4) |
| ≥ 10 × ULN | 2 (0.4) | 1 (0.2) | 1 (0.0) | 1 (0.1) | 4 (0.1) |
| ≥ 20 × ULN | 0 | 0 | 0 | 0 | 0 |
| **ALT or AST** | | | | | |
| ≥ 3 × ULN | 18/569 (3.2) | 22/571 (3.9) | 39/2750 (1.4) | 26/1859 (1.4) | 64/3696 (1.7) |
| **Total bilirubin** | | | | | |
| ≥ 2 × ULN | 2/569 (0.4) | 1/571 (0.2) | 4/2751 (0.1) | 1/1859 (0.1) | 7/3697 (0.2) |
| **ALP** | | | | | |
| ≥ 1.5 × ULN | 110/569 (19.3) | 143/571 (25.0) | 673/2751 (24.5) | 549/1860 (29.5) | 846/3697 (22.9) |
| **ALT and/or AST and total bilirubin** | | | | | |
| ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN | 0 | 1/571 (0.2) | 2/2751 (0.1) | 0 | 2/3697 (0.1) |
| **ALT and/or AST and total bilirubin and ALP** | | | | | |
| ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and < 2 × ULN for ALP | 0 | 0 | 1/2751 (0.0) | 0 | 1/3697 (0.0) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018. ADT: androgen deprivation therapy; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; ULN: upper limit of normal. † The phase 3 CRPC studies include PREVAIL, AFFIRM, Asian PREVAIL and PROSPER.*
*‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE and PROSPER; the open-label phase of PREVAIL, AFFIRM, TERRAIN and STRIVE are not included.*

## Safety in special populations

The impacts of demographic subgroups of age (data not shown), baseline weight, geographic region, history of hypertension and history of significant cardiovascular disease on the safety of enzalutamide were evaluated in the ARCHES and the integrated safety group.

*Table 64. Treatment-emergent Adverse Events by Age Group Safety related to drug-drug interactions and other interactions*

| Category, n (%) | mHSPC | | CRPC | | |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Total‡ Enzalutamide (n = 4081) |
| Age group§ | | | | | |
| < 65 years | 148 (25.9) | 151 (26.3) | 578 (20.7) | 425 (22.4) | 887 (21.7) |
| 65 to 74 years | 256 (44.8) | 254 (44.3) | 1193 (42.6) | 808 (42.6) | 1768 (43.3) |
| 75 to 84 years | 153 (26.7) | 159 (27.7) | 887 (31.7) | 569 (30.0) | 1240 (30.4) |
| ≥ 85 years | 15 (2.6) | 10 (1.7) | 141 (5.0) | 96 (5.1) | 186 (4.6) |
| Patients with any TEAE | | | | | |
| < 65 years | 120/148 (81.1) | 132/151 (87.4) | 536/578 (92.7) | 377/425 (88.7) | 806/887 (90.9) |
| 65 to 74 years | 221/256 (86.3) | 218/254 (85.8) | 1122/1193 (94.0) | 728/808 (90.1) | 1641/1768 (92.8) |
| 75 to 84 years | 133/153 (86.9) | 135/159 (84.9) | 836/887 (94.3) | 509/569 (89.5) | 1159/1240 (93.5) |
| ≥ 85 years | 13/15 (86.7) | 8/10 (80.0) | 134/141 (95.0) | 85/96 (88.5) | 177/186 (95.2) |
| Patients with any grade ≥ 3 TEAE | | | | | |
| < 65 years | 36/148 (24.3) | 36/151 (23.8) | 226/578 (39.1) | 140/425 (32.9) | 334/887 (37.7) |
| 65 to 74 years | 48/256 (18.8) | 63/254 (24.8) | 497/1193 (41.7) | 303/808 (37.5) | 715/1768 (40.4) |
| 75 to 84 years | 49/153 (32.0) | 45/159 (28.3) | 409/887 (46.1) | 215/569 (37.8) | 578/1240 (46.6) |
| ≥ 85 years | 6/15 (40.0) | 3/10 (30.0) | 76/141 (53.9) | 42/96 (43.8) | 103/186 (55.4) |
| Patients with any serious TEAE | | | | | |
| < 65 years | 22/148 (14.9) | 18/151 (11.9) | 169/578 (29.2) | 104/425 (24.5) | 245/887 (27.6) |
| 65 to 74 years | 34/256 (13.3) | 51/254 (20.1) | 390/1193 (32.7) | 208/808 (25.7) | 557/1768 (31.5) |
| 75 to 84 years | 42/153 (27.5) | 39/159 (24.5) | 330/887 (37.2) | 173/569 (30.4) | 476/1240 (38.4) |
| ≥ 85 years | 6/15 (40.0) | 4/10 (40.0) | 65/141 (46.1) | 36/96 (37.5) | 90/186 (48.4) |

All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population).

Data cutoff dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

ADT: androgen deprivation therapy; bpm: beats per minute; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; TEAE: treatment-emergent adverse event

† The phase 3 CRPC studies include PREVAIL, AFFIRM, Asian PREVAIL and PROSPER.

‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE, PROSPER, and open-label phase of studies PREVAIL, AFFIRM, TERRAIN and STRIVE.

§ The n value provided in these age group rows represents the denominator used to calculate the percentages of the respective age subgroups.

## Discontinuation due to adverse events

In the ARCHES study, the incidence of TEAEs leading to permanent study drug discontinuation was 7.2% in the enzalutamide plus ADT group and 5.2% in the placebo plus ADT group. The incidence of TEAEs leading to study drug discontinuation in the phase 3 CRPC enzalutamide group was 16.9%.

*Table 65. Treatment-emergent Adverse Events Reported as the Primary Reason for Permanent Treatment Discontinuation in ≥ 1 Patient in the ARCHES Enzalutamide plus ADT or Placebo plus ADT Groups*

| Preferred Term (MedDRA v 21.0) n (%) | mHSPC | | CRPC | | |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Total‡ Enzalutamide (n = 4801) |
| TEAE as primary reason for study drug discontinuation§ | 28 (4.9) | 21 (3.7) | 265 (9.5) | 155 (8.2) | 381 (9.3) |
| Anaemia | 5 (0.9) | 3 (0.5) | 2 (0.1) | 3 (0.2) | 9 (0.2) |
| Decreased appetite | 5 (0.9) | 4 (0.7) | 3 (0.1) | 2 (0.1) | 15 (0.4) |
| Diarrhoea | 5 (0.9) | 2 (0.3) | 2 (0.1) | 1 (0.1) | 11 (0.3) |
| Fatigue | 5 (0.9) | 4 (0.7) | 26 (0.9) | 11 (0.6) | 44 (1.1) |
| Hot flush | 4 (0.7) | 5 (0.9) | 0 | 0 | 7 (0.2) |
| Weight decreased | 4 (0.7) | 2 (0.3) | 2 (0.1) | 0 | 10 (0.2) |
| Abdominal distension | 3 (0.5) | 0 | 0 | 1 (0.1) | 4 (0.1) |
| Hypertension | 3 (0.5) | 1 (0.2) | 4 (0.1) | 0 | 9 (0.2) |
| Insomnia | 3 (0.5) | 1 (0.2) | 0 | 0 | 4 (0.1) |
| Alanine aminotransferase increased | 2 (0.3) | 0 | 1 (0.0) | 0 | 5 (0.1) |
| Aspartate aminotransferase increased | 2 (0.3) | 0 | 0 | 1 (0.1) | 2 (0.0) |
| Back pain | 2 (0.3) | 2 (0.3) | 3 (0.1) | 4 (0.2) | 6 (0.1) |
| Blood alkaline phosphatase increased | 2 (0.3) | 0 | 0 | 0 | 2 (0.0) |
| Bone pain | 2 (0.3) | 2 (0.3) | 6 (0.2) | 7 (0.4) | 9 (0.2) |
| Cardiac failure | 2 (0.3) | 1 (0.2) | 6 (0.2) | 1 (0.1) | 10 (0.2) |
| Constipation | 2 (0.3) | 2 (0.3) | 1 (0.0) | 0 | 6 (0.1) |
| Dizziness | 2 (0.3) | 2 (0.3) | 3 (0.1) | 1 (0.1) | 8 (0.2) |
| Haematuria | 2 (0.3) | 0 | 3 (0.1) | 4 (0.2) | 7 (0.2) |
| Muscle spasms | 2 (0.3) | 0 | 1 (0.0) | 1 (0.1) | 4 (0.1) |
| Oedema peripheral | 2 (0.3) | 2 (0.3) | 0 | 2 (0.1) | 5 (0.1) |
| Pyrexia | 2 (0.3) | 0 | 1 (0.0) | 3 (0.2) | 3 (0.1) |
| Seizure | 2 (0.3) | 1 (0.2) | 5 (0.2) | 0 | 12 (0.3) |
| Urinary tract infection | 2 (0.3) | 1 (0.2) | 2 (0.1) | 0 | 5 (0.1) |
| Arthralgia | 1 (0.2) | 3 (0.5) | 0 | 2 (0.1) | 2 (0.0) |
| Pain in extremity | 1 (0.2) | 2 (0.3) | 1 (0.0) | 0 | 3 (0.1) |
| Chronic obstructive pulmonary disease | 0 | 2 (0.3) | 1 (0.0) | 1 (0.1) | 1 (0.0) |
| Pain | 0 | 2 (0.3) | 0 | 0 | 1 (0.0) |
| Transient ischaemic attack | 0 | 2 (0.3) | 4 (0.1) | 0 | 6 (0.1) |

All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.
Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) reporting and percentage of patients (%) are shown. The preferred terms were coded by MedDRA v 21.0. Events are sorted by decreasing frequency of preferred term in the enzalutamide group in the ARCHES study. ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; TEAE: treatment-emergent adverse event.
† The phase 3 CRPC studies include AFFIRM, PREVAIL, Asian PREVAIL and PROSPER.
‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE, PROSPER, and open-label phase of studies PREVAIL, AFFIRM, TERRAIN and STRIVE.
§ TEAE identified as primary reason for study drug discontinuation is from the treatment discontinuation case report form.

## Treatment-emergent Adverse Events Leading to Dose Modification

### Dosing Interruptions

*Table 66. Treatment-emergent Adverse Events Leading to a Dosing Interruption Reported in ≥ 2 Patients in the ARCHES Enzalutamide plus ADT or Placebo plus ADT Groups*

| Preferred Term (MedDRA v 21.0) n (%) | mHSPC | | CRPC | | |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Total‡ Enzalutamide (n = 4081) |
| TEAE leading to dosing interruption of study drug | 42 (7.3) | 36 (6.3) | 403 (14.4) | 205 (10.8) | 572 (14.0) |
| Alanine aminotransferase increased | 4 (0.7) | 3 (0.5) | 3 (0.1) | 3 (0.2) | 8 (0.2) |
| Aspartate aminotransferase increased | 3 (0.5) | 3 (0.5) | 2 (0.1) | 4 (0.2) | 6 (0.1) |
| Fatigue | 3 (0.5) | 1 (0.2) | 46 (1.6) | 10 (0.5) | 68 (1.7) |
| Hypertension | 3 (0.5) | 1 (0.2) | 22 (0.8) | 6 (0.3) | 35 (0.9) |
| Asthenia | 2 (0.3) | 4 (0.7) | 19 (0.7) | 3 (0.2) | 28 (0.7) |
| Decreased appetite | 2 (0.3) | 1 (0.2) | 21 (0.8) | 14 (0.7) | 28 (0.7) |
| Diarrhoea | 2 (0.3) | 3 (0.5) | 17 (0.6) | 6 (0.3) | 25 (0.6) |
| Nausea | 2 (0.3) | 0 | 33 (1.2) | 21 (1.1) | 40 (1.0) |
| Pneumonia | 2 (0.3) | 0 | 10 (0.4) | 3 (0.2) | 16 (0.4) |
| Urinary tract infection | 2 (0.3) | 0 | 5 (0.2) | 4 (0.2) | 7 (0.2) |
| Dizziness | 1 (0.2) | 2 (0.3) | 12 (0.4) | 4 (0.2) | 17 (0.4) |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018. Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) reporting and percentage of patients (%) are shown. The preferred terms were coded by MedDRA v 21.0. Events are sorted by decreasing frequency of preferred term in the enzalutamide group in the ARCHES study. ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; TEAE: treatment-emergent adverse event. † The phase 3 CRPC studies include AFFIRM, PREVAIL, Asian PREVAIL and PROSPER. ‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE, PROSPER, and open-label phase of studies PREVAIL, AFFIRM, TERRAIN and STRIVE.*

Dose Reductions

*Table 67. Treatment-emergent Adverse Events Leading to Dose Reduction in the ARCHES Enzalutamide plus ADT or Placebo plus ADT Groups*

| Preferred Term (MedDRA v 21.0) n (%) | mHSPC | | CRPC | | Total‡ |
|---|---|---|---|---|---|
| | ARCHES Enzalutamide+ADT (n = 572) | ARCHES Placebo+ADT (n = 574) | Phase 3† Enzalutamide (n = 2799) | Phase 3† Placebo (n = 1898) | Enzalutamide (n = 4081) |
| TEAE leading to dose reduction of study drug | 25 (4.4) | 11 (1.9) | 137 (4.9) | 34 (1.8) | 205 (5.0) |
| Fatigue | 8 (1.4) | 3 (0.5) | 49 (1.8) | 5 (0.3) | 76 (1.9) |
| Asthenia | 4 (0.7) | 1 (0.2) | 15 (0.5) | 2 (0.1) | 25 (0.6) |
| Nausea | 3 (0.5) | 0 | 11 (0.4) | 5 (0.3) | 18 (0.4) |
| Diarrhoea | 2 (0.3) | 0 | 6 (0.2) | 2 (0.1) | 11 (0.3) |
| Hot flush | 2 (0.3) | 0 | 1 (0.0) | 0 | 3 (0.1) |
| Memory impairment | 2 (0.3) | 0 | 0 | 0 | 2 (0.0) |
| Alanine aminotransferase increased | 1 (0.2) | 0 | 2 (0.1) | 1 (0.1) | 3 (0.1) |
| Amnesia | 1 (0.2) | 0 | 1 (0.0) | 0 | 2 (0.0) |
| Arthralgia | 1 (0.2) | 1 (0.2) | 0 | 3 (0.2) | 3 (0.1) |
| Aspartate aminotransferase increased | 1 (0.2) | 0 | 0 | 2 (0.1) | 1 (0.0) |
| Depression | 1 (0.2) | 0 | 1 (0.0) | 0 | 2 (0.0) |
| Disturbance in attention | 1 (0.2) | 0 | 0 | 0 | 1 (0.0) |
| Dizziness | 1 (0.2) | 1 (0.2) | 7 (0.3) | 2 (0.1) | 8 (0.2) |
| Headache | 1 (0.2) | 0 | 5 (0.2) | 1 (0.1) | 11 (0.3) |
| Hypertension | 1 (0.2) | 0 | 9 (0.3) | 1 (0.1) | 14 (0.3) |
| Muscular weakness | 1 (0.2) | 0 | 3 (0.1) | 2 (0.1) | 5 (0.1) |
| Urticaria | 1 (0.2) | 0 | 0 | 0 | 1 (0.0) |
| Vomiting | 1 (0.2) | 0 | 5 (0.2) | 1 (0.1) | 6 (0.1) |
| Weight decreased | 1 (0.2) | 0 | 2 (0.1) | 0 | 3 (0.1) |
| Arthritis | 0 | 1 (0.2) | 0 | 0 | 0 |
| Back pain | 0 | 1 (0.2) | 0 | 0 | 0 |
| Cognitive disorder | 0 | 1 (0.2) | 1 (0.0) | 0 | 1 (0.0) |
| Oedema peripheral | 0 | 1 (0.2) | 0 | 0 | 0 |
| Pleural effusion | 0 | 1 (0.2) | 0 | 0 | 0 |

*All enrolled patients who received any amount of study drug (enzalutamide or placebo) in their respective study (Safety Population). Data cut-off dates were as follows: ARCHES: 14 Oct 2018; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 20 Sep 2015; PROSPER: 29 Sep 2017; TERRAIN:17 Feb 2018 and STRIVE: 30 May 2018. Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) reporting and percentage of patients (%) are shown. The preferred terms were coded by MedDRA v 21.0. Events are sorted by decreasing frequency of preferred term in the enzalutamide group in the ARCHES study. ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; TEAE: treatment-emergent adverse event. † The phase 3 CRPC studies include AFFIRM, PREVAIL, Asian PREVAIL and PROSPER. ‡ Total enzalutamide summarizes all enzalutamide-treated patients from double-blind phase of ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN, STRIVE, PROSPER, and open-label phase of studies PREVAIL, AFFIRM, TERRAIN and STRIVE.*

## Post marketing experience

In Europe, enzalutamide was initially approved in June 2013, but was made available in France through a temporary authorization for use from April 2013.

The enzalutamide post-marketing exposure estimates are based on internal sales data for all countries.

*Table 68. Cumulative Exposure in Patient Treatment-years by Region*

| Region | Cumulative Patient Treatment-years (Sep 2012 to 30 Aug 2018) |
|---|---|
| Total America | 88849 |
| US | 63695 |
| US Patient Assistance Program | 12317 |
| Canada | 5344 |
| Latin America | 7493 |
| Europe | 102248 |
| Total Asia | 76906 |
| Japan | 67277 |
| Other Asian countries | 9629 |
| **Total** | **268003** |

Seven PSURs for Xtandi (enzalutamide) have been submitted to regulatory authorities since August 2012. In the current PSUR (dated 29 October 2018), a cumulative review and evaluation of post-marketing ADRs for enzalutamide was performed for all cases reported through 30 August 2018. Cumulatively, a total of 107540 ADRs have been reported from post-marketing data sources. During the reporting period for PSUR (dated 29 October 2018), an assessment of post-marketing events revealed no safety concerns related to the following important identified risks (seizure, PRES, hypertension, neutrophil count decreased, cognitive/memory impairment, fall and nonpathological fracture) and the following important identified interactions (interactions with strong inhibitors or inducers of cytochrome P450 (CYP) 2C8 and interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19) listed in the current enzalutamide EU risk management plan (v 12.5, 15 November 2018).

## 2.5.1. Discussion on clinical safety

The safety profile of enzalutamide in patients with mHSPC is based mainly on data from the pivotal Phase 3 study ARCHES in which 1,146 patients were treated with either enzalutamide + ADT (n=572) or placebo + ADT (n=574). Additionally, pooled data from 6 additional clinical trials (four Phase 3 placebo-controlled studies in patients with CRPC and two Phase 2 studies in metastatic CRPC) have been provided. In total, the integrated safety population includes 4,081 patients treated with enzalutamide 160 mg/day plus standard of care. Of these, 24.7% had nonmetastatic prostate cancer and 75.3% had metastatic disease. Moreover, safety data from the Phase 3 study ENZAMET, have been provided separately. In study ENZAMET 563 patients were treated with enzalutamide + ADT and 558 patients with nonsteroidal antiandrogen + ADT.

In the study ARCHES the median duration of treatment was 12.8 months in the enzalutamide arm and 11.55 months in the placebo arm, with nearly 57% and 47% of patients being exposed ≥12 months to <24 months, in the enzalutamide and placebo arm, respectively. Only 7 patients (6 enzalutamide and 1 placebo) received study drug ≥24 months. In the Phase 3 studies pool, the extent of exposure was longer, with 791 (28%) patients being exposed ≥24 months. To adjust for the duration of treatment, the event rate of AEs per 100 patient-years of exposure was also analysed (data not shown). At the time of the data cut-off date 76% of patients in the enzalutamide arm and 57% in the placebo arm were still on treatment.

The study ARCHES included patients with a median age of 70 years [range: 42, 92] (30% were ≥ 75 years). The majority of patients were White and had a good performance status (77.5% had ECOG 0). More than half of patients had a medical history of hypertension. Patients with any clinically significant cardiovascular disease as well as those with past history of seizure or any condition that may predispose to seizure were excluded from the study (see SmPC section 4.4).

Overall incidence of treatment emergent adverse events (TEAEs) was similar between treatment arms (>85%) although TEAEs considered related to study drug were more frequent in the enzalutamide arm (53% vs 47%). The most commonly reported (≥10%) TEAEs in the enzalutamide group were hot flush (27.1% enzalutamide vs 22.3% placebo), fatigue (19.6% vs 15.3%) and arthralgia (12.2% vs 10.6%).

Grade 3 or higher TEAEs were reported in 24.3% of patients in the enzalutamide arm and 25.6% in the placebo arm. The most frequently reported TEAEs of grade ≥3 were hypertension (3.3% enzalutamide vs 1.7% placebo), asthenia (1% vs 0.5%), malignant neoplasm progression (1% vs 0.5%) and syncope (1% vs 0.2%).

TEAEs of special interest for enzalutamide are: seizure, hypertension, neutrophil count decreased, cognitive and memory impairment, ischemic heart disease, other selected cardiovascular events, PRES, secondary primary malignancies, falls, fracture, fatigue, loss of consciousness, thrombocytopenia, musculoskeletal events, severe cutaneous adverse reactions, angioedema and rash. TEAEs of special interest with a higher incidence (>2% or double) in the enzalutamide arm compared to placebo arm were: hypertension (8.6% vs 6.3%), cognitive and memory impairment (4.5% vs 2.1%), fatigue (24.1% vs 19.5%), fractures (6.5% vs 4.2%), loss of consciousness (1.6% vs 0.2%) and angioedema (1.2% vs 0.2%). At study entry, more than half of patients had hypertension at baseline. Among these, the incidence of hypertension was 9% in the enzalutamide arm compared to 5.3% in the placebo arm.

No events of PRES or severe cutaneous reactions were reported in the enzalutamide arm and there was one event of dermatitis bullous in the placebo arm.

There were 2 (0.3%) events of seizure in each treatment arm. In the enzalutamide arm both events were considered to be related to study drug and led to treatment discontinuation. A warning on seizure is included in current the SmPC.

Ischemic heart disease is included as an ADR in the SmPC. In study ARCHES, 10 (1.7%) patients in the enzalutamide arm (8 [1.4%] in the placebo arm) reported an event of ischemic heart disease, being angina pectoris the most frequently reported (4 [0.7%] enzalutamide vs none in the placebo arm). Additionally, there were 12 (2.3%) patients that reported other selected cardiovascular event, with cardiac failure as the most commonly reported. Cardiac failure was reported in 7 [1.2%] patients in the enzalutamide arm and 3 (0.5%) patients in the placebo arm. In most of these cases several confounding factors were present. However, the potential contribution of enzalutamide to events of cardiac failure cannot be ruled out taking into account that patients with clinically significant cardiovascular disease were excluded from the study. Nevertheless, it is not possible to draw any conclusion on the possible causal relationship with enzalutamide based on the available data. Cardiac failure should be monitored through routine pharmacovigilance activities.

In patients with a baseline history of other selected cardiovascular events (23.3% in the enzalutamide arm and 19.9% in the placebo arm), no differences were observed between treatment arms whereas in patients without a baseline history the incidence was higher in the enzalutamide arm (8 [1.4%] vs 3 [0.5%]). Overall, the incidence of cardiovascular adverse events in study ARCHES was low, however, it should be taken into account that patients with clinically significant cardiovascular disease (i.e. myocardial infarction within 6 months prior to screening, unstable angina within 3 months prior to screening, etc) were excluded from the study (See SmPC section 4.4).

In the ARCHES study second primary malignancies were reported in 10 (1.7%) patients in the enzalutamide arm and 11 (1.9%) patients in the placebo arm. In previous Phase 3 clinical trials, the incidence of second primary malignancies in the enzalutamide arm compared to placebo was 2.9% vs 0.9%, respectively. Despite the number of events reported is low, it should be kept in mind that enzalutamide has shown to be carcinogenic in non-clinical trials (see discussion on non-clinical aspects). In non-clinical trials, the most prominent neoplastic findings were benign Leydig cell tumours, urothelium

papilloma, and carcinoma of urinary bladder. A similar pattern is observed in clinical trials. In the total enzalutamide population (n=4081) bladder cancer was the most frequently reported malignancy (9 [0.2%]). The mechanism is not completely elucidated. Although a causal relationship is not formally established, the potential risk of enzalutamide to develop second primary malignancies, especially urinary bladder cancer, cannot be ruled out. Section 4.4 of the SmPC was recently updated (EMEA/H/C/002639/II/0049) to include a warning mentioning that patients should be advised to promptly seek the attention of their physician if they notice signs of gastrointestinal bleeding, macroscopic haematuria, or other symptoms such as dysuria or urinary urgency develop during treatment with enzalutamide.

With regard to deaths, at the time of data cut-off, 39 (6.8%) patients in the enzalutamide arm and 45 (7.8%) patients in the placebo arm had died. Disease progression was the leading cause in both treatment arms (4.5% vs 7.8%, enzalutamide and placebo, respectively). Deaths due to TEAEs were slightly higher in the enzalutamide arm (14 [2.4%] vs 10 [1.7%]). Malignant neoplasm progression was the leading cause (4 [0.7%] and there were 3 deaths related to cardiac disorders (cardio-respiratory arrest, cardiopulmonary failure and myocardial infarction). No patient in the enzalutamide plus ADT group had a fatal TEAE that was considered to be study drug-related.

Serious TEAEs were reported by 18.2% of patients in the enzalutamide arm and 19.5% in the placebo group. In the enzalutamide arm, malignant neoplasm progression was the only serious TEAE reported in at least 1% of patients. Serious TEAEs were considered drug-related by the investigator in 22 (3.8%) patients in the enzalutamide plus ADT group and 16 patients (2.8%) patients in the placebo plus ADT group.

Overall, enzalutamide appears to be well tolerated, taking into account the relatively low rate of treatment discontinuations (7.2% enzalutamide vs 5.2% placebo) as well as dose reductions (4.4% enzalutamide vs 1.9% placebo) and dose interruptions (7.3% enzalutamide vs 6.3% placebo).

Regarding safety in special populations, no major differences in terms of TEAEs, SAEs and Grade ≥3 TEAEs according to baseline weight, geographic region, history of hypertension, age and history of significant CV disease were observed (data not shown) Considering TEAEs of special interest, in the study ARCHES a slightly higher incidence of memory impairment was reported in the subgroup of patients ≥85 years treated with enzalutamide. Memory impairment is a common adverse reaction included in section 4.8 of the SmPC.

During the procedure, updated safety data, with three months of additional follow-up, were provided for study ARCHES. At the time of the new data cut-off (3 Jan 2019), median treatment exposure in the enzalutamide+ADP arm was of 15.90 months and 13.80 months in the placebo+ADT arm (data not shown). No major differences were observed in the safety profile of enzalutamide plus ADT compared to previous data submitted, apart from a slight increase in the incidence of several TEAEs. However, this is not unexpected since updated data add only 3 months of additional follow-up. Therefore, and taking into account that a high percentage of patients remained on treatment at the time of the data cut-off (around 71% in the enzalutamide plus ADT group) the MAH is recommended to provide an updated safety analysis with final results of the ARCHES study (REC).

Overall, the safety profile of enzalutamide in the ARCHES study was in line with its already known safety profile. The incidence of adverse events was generally lower in the ARCHES study compared to Phase 3 studies. Pharmacovigilance activities in place are considered sufficient to address the risks associated with enzalutamide. Within this application the MAH is also proposing a minor change in section 4.7 Effects on ability to drive and use machines of the SmPC which is considered in line with the safety profile of Xtandi.

Moreover section point 6.6 of the SmPC has been updated to clarify to precaution of handling for woman who are or might become pregnant, in line with section 5.3 of the SmPC.

### 2.5.2. Conclusions on clinical safety

Overall, the safety profile of enzalutamide in combination with ADT in the treatment of patients with mHSPC was in line with the already known safety profile of enzalutamide and no worrisome findings have been identified. However, considering a high number of patients remained on treatment at the time of the new data cut-off, an updated safety analysis is recommended to be provided with the final results of the ARCHES study.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The CHMP endorsed the Risk Management Plan version 13.0 with the following content:

### *Safety concerns*

*Table 69.* Summary of the Safety Concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Seizure<br>Fall<br>Non-pathological fracture<br>Ischemic heart disease |
| Important potential risks | None |
| Missing information | None |

### *Pharmacovigilance plan*

*Table 70.* Ongoing and planned additional pharmacovigilance activities

| **Study Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| **Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| Not applicable | | | | |
| **Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| Not applicable | | | | |
| **Category 3 – Required additional pharmacovigilance activities** | | | | |
| Not applicable | | | | |

### *Risk minimisation measures*

*Table 71.*Summary table of pharmacovigilance activities and risk minimization activities by safety concern.

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| Seizure | Routine risk communication:<br>• SmPC sections 4.4, 4.7, 4.8, and 4.9;<br>• PL sections 2 and 4;<br>• Recommendation that the decision to continue treatment in patients who develop seizure should be taken case by case, is provided in SmPC Section 4.4 and PL sections 2 and 4;<br>• Concomitant medications associated with higher risk of seizure are described in PL Section 2.<br>Additional risk minimization measures:<br>• None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None.<br>Additional pharmacovigilance activities:<br>• None. |
| Fall | Routine risk communication:<br>• SmPC Section 4.8;<br>• PL Section 4.<br>Additional risk minimization measures:<br>• None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• Fall TDQ and Fracture TDQ in clinical trials;<br>• Safety analyses of events of fall in CSRs of individual enzalutamide clinical trials.<br>Additional pharmacovigilance activities:<br>• None. |
| Non-pathological fracture | Routine risk communication:<br>• SmPC Section 4.8;<br>• PL Section 4.<br>Additional risk minimization measures:<br>• None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• Fall TDQ and Fracture TDQs in clinical trials;<br>• Safety analyses of events of fracture in CSRs of individual enzalutamide clinical trials.<br>Additional pharmacovigilance activities:<br>• None. |
| Ischemic heart disease | Routine risk communication:<br>• SmPC Section 4.8;<br>• PL Section 4.<br>Additional risk minimization measures:<br>• None. | Routine pharmacovigilance activities include safety analyses of events of ischemic heart disease in CSRs of individual enzalutamide clinical trials.<br>Additional pharmacovigilance activities:<br>• None. |

CSR: Clinical Study Report; PL: package leaflet; SmPC: Summary of Product Characteristics; TDQ: targeted data questionnaire.

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 5.1, and 6.6 of the SmPC have been updated.

The Package Leaflet has been updated accordingly.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: Results from the readability testing study of the parent package leaflet can be extrapolated to the daughter package leaflet as the differences between the two have little impact on readability.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The claimed indication is for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).

For patients with this advanced stage of the disease, the aim of treatment is to improve the symptoms in particular pain and to extend the time during which the disease can be controlled with androgen deprivation therapy to delay progression.

### 3.1.2. Available therapies and unmet medical need

ADT has been the basis for the treatment of patients with locally advanced and metastatic HSPC. ADT is defined as surgical castration by bilateral orchiectomy or medical castration with gonadotropin-releasing hormone (GnRH) agonists or antagonists. The aim of ADT treatment is to reduce testosterone concentrations. Even though the majority of patients have an initial response to treatment with ADT, most men progress to castration-resistant prostate cancer.

Treatment options for men with mHSPC have expanded beyond ADT alone. Docetaxel (75 mg/$m_2$ every 3 weeks for 6 cycles) has been shown to improve overall survival (OS) and failure-free survival (FFS) in patients with mHSPC in multiple studies, including CHAARTED and Arm C of the STAMPEDE trial and has been approved for the treatment of mHSPC.

Furthermore, abiraterone in combination with ADT and prednisone or prednisolone was authorised in EU for the treatment of adult men with newly diagnosed high risk metastatic hormone sensitive prostate cancer.

Recently apalutamide has also been approved in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) (see EPAR Erleada).

### 3.1.3. Main clinical studies

The efficacy data in support of this application for the extension of indication is based mainly on the Study 9785-CL-0335 (ARCHES), a Phase 3, randomised, double-blind, placebo-controlled study of enzalutamide plus ADT versus placebo plus ADT in 1,150 patients with mHSPC.

Patients received enzalutamide at 160 mg once daily (N=574) or placebo (N=576). Patients with metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue) were eligible. Patients whose disease spread was limited to regional pelvic lymph nodes were not eligible. Patients were allowed to receive up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy.

Radiographic progression-free survival (rPFS), based on independent central review, was the primary endpoint defined as the time from randomisation to the first objective evidence of radiographic disease progression or death whichever occurred first.

## *3.2. Favourable effects*

Results from the study ARCHES at the data cut-off date of 14 Oct 2018 include the main planned analysis for rPFS based on independent central review assessment (primary endpoint) and the first interim analysis for OS (secondary endpoint).

A statistically significant treatment effect on rPFS in favour of enzalutamide was observed, with a HR of 0.39 (95% CI: 0.3, 0.5). At the time of data cut-off median rPFS was not reached in the enzalutamide arm and was of 19.0 months in the placebo arm. Overall, subgroup analysis and several sensitivity analyses performed support the results of the primary analysis.

To adjust for multiplicity, a parallel testing strategy was used to test OS with an allocated type I error rate of 0.04 and the remaining 5 key secondary endpoints (time to PSA progression, time to start of a new antineoplastic therapy, rate of PSA decline to <0.2 ng/mL, ORR and time to deterioration in urinary symptoms from the QLQ-PR25) with an allocated type I error rate of 0.01.

Statistically significant improvements in patients treated with enzalutamide compared to placebo were observed for all key secondary endpoints except time to deterioration in urinary symptoms from the QLQ-PR25.

Regarding OS, at the time of data cut-off, data were still immature and the statistical significance was not reached (HR 0.81 [95% CI: 0.53, 1.25]; p=0.3361). A trend in favour of enzalutamide was observed.

## *3.3. Uncertainties and limitations about favourable effects*

Based on OS analysis submitted at the data cut off 14 Oct 2018 on a total of 84 deaths (24.6% of the 342 events required for the final analysis) the effect of enzalutamide on OS is uncertain. Nevertheless, based on the totality of data (effect on rPFS and secondary endpoint) a detrimental effect on OS can be excluded. Further OS data are expected to be submitted as soon as available (REC).

## *3.4. Unfavourable effects*

In the study ARCHES, the median duration of treatment was 12.8 months in the enzalutamide arm and 11.55 months in the placebo arm.

The most frequently reported (≥10%) TEAES in the enzalutamide arm were hot flush (27.1% enzalutamide vs 22.3% placebo) and fatigue (19.6% vs 15.3%).

Grade 3 or higher TEAEs were reported by 24.3% of patients in the enzalutamide arm and 25.6% in the placebo arm. The most frequently reported TEAEs of grade ≥3 were hypertension (3.3% enzalutamide vs 1.7% placebo), asthenia (1% vs 0.5%), malignant neoplasm progression (1% vs 0.5%) and syncope (1% vs 0.2%).

Serious TEAEs were reported by 18.2% of patients in the enzalutamide arm and 19.5% in the placebo group. Serious TEAEs were considered drug-related by the investigator in 22 (3.8%) patients in the enzalutamide plus ADT group and 16 patients (2.8%) patients in the placebo plus ADT group.

Treatment was discontinued due to a TEAE in 7.2% of patients in the enzalutamide arm and 5.2% in the placebo arm. Decreased appetite, diarrhoea and fatigue were the main TEAEs that led to treatment discontinuation.

Dose reductions and dose interruptions were required, respectively, in 4.4% and 7.3% of patients in the enzalutamide arm compared to 1.9% and 6.3% of patients in the placebo arm.

TEAEs of special interest for enzalutamide are: seizure, hypertension, neutrophil count decreased, cognitive and memory impairment, ischemic heart disease, other selected cardiovascular events (Hemorrhagic Central Nervous System Vascular Conditions, Ischemic Central Nervous System Vascular Conditions and Cardiac Failure), PRES, secondary primary malignancies, falls, fracture, fatigue, , thrombocytopenia, musculoskeletal events, severe cutaneous adverse reactions and rash.

## 3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

## 3.6. Effects Table

*Table 72 Effects Table for Xtandi in the treatment of mHSPC patients along with ADT (data cut-off: 14 Oct 2018)*

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| rPFS* | Time from randomisation to the date of first objective evidence of radiographic progressive disease or death due to any cause within 24 weeks from study drug discontinuation | Median - months (CI 95%) | NR | 19.0 (16.59, 22.24) | HR 0.39 (95% CI: 0.30, 0.50) | ARCHES (Study 9785-CL-0335) |
| OS | Time from randomisation to death from any cause | Median - months (CI 95%) | NR | NR | HR 0.81 (95% CI: 0.53, 1.25)<br><br>First interim analysis.<br>OS data immature | |
| **Unfavourable Effects** | | | | | | |
| TEAEs | Overall incidence of AEs | % | 85.1 | 85.9 | | ARCHES (Study 9785-CL-0335) |
| Grade ≥ 3 TEAEs | Incidence of AEs of grade ≥3<br>All causality<br>Drug-related | % | <br>24.3<br>9.8 | <br>25.6<br>6.1 | | |
| Discontinuatio | Incidence of | % | 7.2 | 5.2 | | |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| n | AEs leading to discontinuation | | | | | |
| | | | | | | |
| Seizure | AE special interest | % | 0.3 | 0.3 | | |
| Hypertension | AE special interest | % | 8.6 | 6.3 | | |
| Cognitive and memory impairment | AE special interest | | 4.5 | 2.1 | | |
| Ischemic heart disease | AE special interest | % | 1.7 | 1.4 | | |
| | | | | | | |
| | | | | | | |
| Falls | AE special interest | % | 3.7 | 2.6 | | |
| Fractures | AE special interest | | 6.5 | 4.2 | | |
| Second primary malignancies | AE special interest | % | 1.7 | 1.9 | | |

Abbreviations: NR: not reached; ORR: objective response rate

Notes: The primary efficacy endpoint is the rPFS with a multiplicity control for the 6 key secondary endpoints. Key secondary endpoints, other than OS, were sequentially tested at a 1% significance level

* per protocol-specified criteria

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Enzalutamide plus ADT has shown a clinically relevant increase in terms of rPFS. These results are supported by almost all key secondary endpoints and several sensitivity analyses.

Nevertheless, the OS data are immature and the MAH is recommended to provide updated OS data from study ARCHES.

Despite the immaturity of survival data, there is no indication of detrimental effect in survival.. In support of the results of study ARCHES, OS results from study ENZAMET at the first interim analysis were submitted.. Despite the inherent limitations of subgroup analyses, results in the subgroup of patients without planned early docetaxel treatment were considered convincing in accordance with the Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013) and thus supportive of the results from study ARCHES.

The overall safety profile of enzalutamide in the treatment of adult men with mHSPC is consistent with the already known safety profile of enzalutamide in other settings and no new unexpected findings have been identified.

### 3.7.2. Balance of benefits and risks

The use of enzalutamide in combination with ADT has led to a substantial longer rPFS based on the results of study ARCHES. Even though there are uncertainties on the magnitude of the benefit in terms of OS, the results are considered clinically relevant. Overall, the risks associated with enzalutamide in this setting are considered manageable and in line with the already known safety profile of the drug. In view of the favourable effects, the benefit-risk balance is considered positive.

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

## *3.8. Conclusions*

The overall B/R of Xtandi in the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

| **Variations accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I |

C.1.6: Extension of Indication to include the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) for Xtandi in combination with androgen deprivation therapy based on the data of study 9785-CL-0335 (ARCHES). As a consequence, sections 4.1, 4.2, 5.1, and 6.6 of the SmPC are updated. Furthermore the MAH took the opportunity to make corrections to section 4.7. The Package Leaflet is updated in accordance.
The RMP version 13.0 is approved.

C.1.4: Update of section 5.1 of the SmPC based the 5-year Overall Survival (OS) results obtained from the PREVAIL study (MDV310003), a phase 3 study of enzalutamide in chemotherapy naïve patients with metastatic prostate cancer that progressed on ADT.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

In view of the data submitted with the group of variations, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.