

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrNUBEQA®**

Darolutamide tablets

Tablet, 300 mg, oral

Anti-androgen

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Mississauga, Ontario  
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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

NUBEQA (darolutamide) is indicated for:

- the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

NUBEQA has not been studied in patients with nmCRPC at low risk of developing metastases (see [14 CLINICAL TRIALS](#)). The benefit and risk profile in these patients is unknown.

- the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC) in combination with docetaxel.

#### 1.1 Pediatrics

**Pediatrics (<18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics

**Geriatrics (≥ 65 years of age):** Evidence from clinical studies does not suggest clinically relevant differences in safety or efficacy associated with the use of NUBEQA in the geriatric population (see [7.1 Special Populations](#), [7.1.4 Geriatrics](#)).

### 2 CONTRAINDICATIONS

NUBEQA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

- Patients receiving NUBEQA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.
- Patients with mCSPC should take NUBEQA in combination with docetaxel. The first cycle of docetaxel should be administered within 6 weeks after the start of NUBEQA treatment. Docetaxel should be administered every 3 weeks for up to 6 cycles. Treatment with NUBEQA should be continued until disease progression or unacceptable toxicity even if the administration of docetaxel is delayed, interrupted, or discontinued before completion of 6 cycles.

#### 4.2 Recommended Dose and Dosage Adjustment

The recommended dose is 600 mg (two film-coated tablets of 300 mg) NUBEQA taken twice daily, equivalent to a total daily dose of 1200 mg. NUBEQA should be continued until disease progression or unacceptable toxicity.

If a patient experiences a Grade 3 or higher toxicity or an intolerable adverse reaction, dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Then treatment may be resumed at a dose of 600 mg twice daily.

Dose reduction below 300 mg twice daily is not recommended. The maximum daily dose is 1200 mg (600 mg twice daily).

When NUBEQA is used in combination with docetaxel, dosage and administration recommendations in the docetaxel product monograph should be followed.

### ***Pediatrics (<18 years of age)***

Health Canada has not authorized an indication for pediatric use.

### ***Patients with hepatic impairment***

No dose adjustment is necessary for patients with mild hepatic impairment.

The recommended dose for patients with moderate hepatic impairment (Child-Pugh B) is 300 mg NUBEQA twice daily (see [10.3 Pharmacokinetics](#)).

The effect of severe hepatic impairment (Child-Pugh C) on NUBEQA pharmacokinetics has not been studied.

### ***Patients with renal impairment***

No dose adjustment is necessary for patients with mild or moderate renal impairment.

The recommended dose for patients with severe renal impairment not receiving hemodialysis (estimated glomerular filtration rate (eGFR) of 15 to 29 mL/min/1.73m<sup>2</sup>) is 300 mg NUBEQA twice daily (see [10.3 Pharmacokinetics](#)). Clinical experience in patients with severe renal impairment is limited.

The pharmacokinetics of NUBEQA has not been studied in patients with end-stage renal disease receiving dialysis (eGFR <15 mL/min/1.73 m<sup>2</sup>).

## **4.4 Administration**

For oral use.

The tablets should be taken whole with food (see [10.3 Pharmacokinetics](#)).

## **4.5 Missed Dose**

If a dose of NUBEQA is missed, the dose should be taken as soon as the patient remembers prior to the next scheduled dose. The patient should not take two doses together to make up for a missed dose.

## **5 OVERDOSAGE**

There is no specific antidote for NUBEQA and symptoms of overdose are not established.

The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

In the event of an overdose, closely monitor patients for signs and symptoms of adverse reactions, and initiate appropriate symptomatic and supportive treatment (see [8 ADVERSE REACTIONS](#); [10 CLINICAL PHARMACOLOGY](#); [16 NON-CLINICAL TOXICOLOGY](#)).

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet, 300 mg	Calcium hydrogen phosphate, croscarmellose sodium, hypromellose 15 cP, lactose monohydrate, Macrogol 3350, magnesium stearate, povidone K 30, titanium dioxide

NUBEQA (darolutamide) 300 mg tablet is presented as white to off-white film-coated oval tablets. The tablets are marked with BAYER on one side and with 300 on the other side. The product is supplied in 120 mL bottles of 120 tablets or blisters containing 112 tablets.

## 7 WARNINGS AND PRECAUTIONS

### Cardiovascular

Ischemic heart disease, including fatal cases, occurred in patients receiving NUBEQA.

In a randomized study of patients with nmCRPC, ischemic heart disease occurred in 3.2% of patients treated with NUBEQA and in 2.5% of patients treated with placebo, including Grade 3-4 events in 1.7% and 0.4%, respectively.

In a randomized study of patients with mCSPC, ischemic heart disease occurred in 2.9% of patients treated with NUBEQA+docetaxel and 2.0% of patients treated with placebo+docetaxel, including Grade 3-4 events in 1.3% and 1.1%, respectively. Fatal ischemic events occurred only in the NUBEQA+docetaxel arm in 0.3% of patients.

Patients should be monitored for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia.

### Hepatic/Biliary/Pancreatic

Serious cases of drug-induced liver injury (DILI), including Hy's law cases, with increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to  $\geq 5x$  and  $\geq 20x$  upper limit of normal (ULN), including with concomitant bilirubin elevations  $\geq 2x$  ULN, have been reported in patients treated with NUBEQA. Time to onset ranged from 1 month to 12 months after initiation of NUBEQA. The liver function test abnormalities were reversible upon NUBEQA discontinuation. Monitor serum transaminases and bilirubin as per routine clinical practice. In case of liver function test abnormalities suggestive of idiosyncratic drug-induced liver injury, permanently discontinue NUBEQA.

### Monitoring and Laboratory Tests

Monitoring for laboratory or clinical parameters should be conducted as per routine practice and the following are recommended for patients treated with NUBEQA.

- Patients should be monitored for signs and symptoms of ischemic heart disease.

- Serum transaminases and bilirubin should be measured as clinically indicated.

Patients should be monitored for disease progression radiographically in addition to Prostate Specific Antigen (PSA). In the ARAMIS trial in nmCRPC, 141 out of 246 patients treated with NUBEQA who reported radiographic progression (distant metastasis) did not have PSA progression. In the ARASENS trial in mCSPC, 100 out of 225 patients treated with NUBEQA plus docetaxel who reported radiographic progression did not have PSA progression.

## Neurologic

Seizure occurred in patients receiving NUBEQA. Patients with a history of seizure were permitted to enroll in the clinical trials. However, all seizure events in patients receiving NUBEQA occurred in patients without prior history of seizure. In clinical trials, none of the patients permanently discontinued therapy due to seizure.

In a randomized study of patients with nmCRPC, seizure (grade 1-2) occurred in 0.2% of patients receiving NUBEQA or placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA.

In a randomized study of patients with mCSPC, seizure occurred in 0.6% of patients receiving NUBEQA+docetaxel, including one grade 3 event, and 0.2% of patients receiving placebo+docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA.

Consider withholding NUBEQA in patients who develop a seizure during treatment.

## Reproductive Health: Female and Male Potential

### *Teratogenic Risk*

Based on the mechanism of action, darolutamide can cause harm to the developing fetus or lead to loss of pregnancy. If the patient is engaged in sexual activity with a pregnant woman, a condom should be used during and for 3 months after completion of treatment with NUBEQA.

If the patient is engaged in sexual activity with a woman of childbearing potential, a highly effective contraceptive method (<1% failure rate per year) should be used during and for 3 months after completion of treatment with NUBEQA to prevent pregnancy.

### *Fertility*

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential (see [16 NON-CLINICAL TOXICOLOGY](#)). Male patients should not donate sperm during treatment and for 3 months after the last dose of NUBEQA.

## 7.1 Special Populations

### 7.1.1 Pregnant Women

NUBEQA is not indicated in women. There are no human data on the use of NUBEQA in pregnant women. Animal embryo fetal toxicology studies have not been performed. However, based on the mechanism of action, NUBEQA can cause embryo/fetal harm or loss of pregnancy. Therefore, NUBEQA is not to be used in women who are or may become pregnant.

### 7.1.2 Breast-feeding

NUBEQA is not indicated in women. No data exist on the presence of NUBEQA or its metabolites in human milk, its effects on the breast fed infant, or the effect on milk production. However,

because many drugs are excreted in human milk, NUBEQA is not to be used in women who are breast-feeding.

### **7.1.3 Pediatrics**

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### **7.1.4 Geriatrics**

Evidence from clinical studies do not suggest clinically relevant differences in safety or efficacy associated with the use of NUBEQA in the geriatric population.

## **8 ADVERSE REACTIONS**

### **8.1 Adverse Reaction Overview**

The safety of NUBEQA has been assessed in two randomized, double-blind, placebo-controlled, multi-centre clinical studies: ARAMIS, consisting of 1509 patients with non-metastatic castration-resistant prostate cancer (nmCRPC), and ARASENS, consisting of 1306 patients with metastatic castration-sensitive prostate cancer (mCSPC) (see [14 CLINICAL TRIALS](#)).

#### **Non-Metastatic Castration Resistant Prostate Cancer (nmCRPC)**

The most frequently observed adverse reaction ( $\geq 10\%$ ) in patients receiving NUBEQA was fatigue.

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in  $\geq 1\%$  of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Permanent discontinuation due to adverse reactions occurred in 8.9% of patients treated with NUBEQA and 8.7% of patients who received placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%)

Adverse reactions leading to dose interruption occurred in 12.5% of patients treated with NUBEQA and in 8.8% of patients who received placebo. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Adverse reactions leading to dose reduction occurred in 4.8% of patients treated with NUBEQA and in 1.6% of patients who received placebo. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

#### **Metastatic Castration-Sensitive Prostrate Cancer (mCSPC)**

The most frequently observed adverse reactions ( $\geq 20\%$ ) in patients receiving NUBEQA+docetaxel were alopecia (40.5%), fatigue (33.1%), anemia (27.8%), arthralgia (27.3%), edema peripheral (26.5%), neutrophil count decreased (26.1%), diarrhea (25.6%), white blood cell count decreased (23.8%), and constipation (22.5%), and were reported at similar incidence in the placebo+docetaxel arm.



Serious adverse reactions occurred in 44.8% of patients receiving NUBEQA+docetaxel and in 42.3% of patients receiving placebo+docetaxel. Serious adverse reactions in  $\geq 2\%$  of patients who received NUBEQA+docetaxel included febrile neutropenia (6.1%), neutrophil count decreased (2.8%), and pneumonia (2.5%). Overall, 4.1% of patients receiving NUBEQA+docetaxel and 4.0% receiving placebo+docetaxel died from adverse reactions. Deaths reported in  $\geq 2$  patients in the NUBEQA+docetaxel arm included COVID-19/COVID-19 pneumonia (0.8%), myocardial infarction (0.3%), and sudden death (0.3%).

Permanent discontinuation of study drug due to adverse reactions occurred in 13.5% of patients who received NUBEQA+docetaxel and 10.6% of patients who received placebo+docetaxel. The most frequent adverse reactions requiring discontinuation in patients who received NUBEQA+docetaxel included rash (1.1%), aspartate aminotransferase (AST) increased (0.9%), and alanine aminotransferase (ALT) increased (0.8%).

Dose interruption of study drug due to adverse reactions occurred in 22.9% of patients treated with NUBEQA+docetaxel and in 15.7% of patients who received placebo+docetaxel. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA+docetaxel included ALT increased (3.2%), AST increased (3.1%), and febrile neutropenia (2.1%).

Dose reductions of study drug due to adverse reactions occurred in 8.7% of patients treated with NUBEQA+docetaxel and in 4.3% of patients who received placebo+docetaxel. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA+docetaxel included ALT increased (2.8%), and AST increased (2.5%).

## 8.2 Clinical Trial Adverse Reactions

*Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.*

### Non-Metastatic Castration Resistant Prostate Cancer (nmCRPC) (ARAMIS)

ARAMIS, a phase III, randomized (2:1), double-blind, placebo-controlled, multi-centre clinical study, enrolled patients who had nmCRPC. In this study, patients received either NUBEQA at a dose of 600 mg twice a day, or a placebo. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Patients with uncontrolled hypertension or recent (in the past 6 months) stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, congestive heart failure New York Heart Association (NYHA) Class III or IV were excluded from the study. 64.4% of patients on NUBEQA and 36.1% of patients on placebo were receiving ongoing treatment at the time of the primary analysis. The median duration of exposure at the time of the primary analysis was 14.8 months (range: 0.0 to 44.3 months) in patients who received NUBEQA and 11.0 months (range: 0.1 to 40.5 months) in patients who received placebo.

[Table 2](#) shows the incidence of adverse drug reactions reported in patients treated with NUBEQA in ARAMIS that occurred with a  $\geq 2\%$  absolute increase in frequency compared to placebo.

**Table 2: Incidence of adverse drug reactions reported in patients treated with NUBEQA in ARAMIS that occurred with a  $\geq 2\%$  absolute increase in frequency compared to placebo**

System/Organ Class Preferred Term MedDRA Version 21.0	NUBEQA (n=954)		Placebo (n=554)	
	Grade		Grade	
	All n (%)	3-4 n (%)	All n (%)	3-4 n (%)
<b>General disorders and administration site conditions</b>				
Fatigue <sup>a</sup>	151 (16%)	6 (0.6%)	63 (11%)	6 (1%)
<b>Musculoskeletal and connective tissue disorders</b>				
Pain in Extremity	55 (6%)	0	18 (3%)	1 (0.2%)
<b>Skin and subcutaneous tissue disorders</b>				
Rash <sup>b</sup>	28 (3%)	1 (0.1%)	5 (0.9%)	0

a includes Asthenia, Fatigue, Malaise, Lethargy

b includes Rash, Rash macular, Rash maculo-papular, Rash papular, Rash pustular, Erythema, Dermatitis

At the final analysis, the median treatment duration was 25.8 months (range: 0.0 to 58.9) in patients who received NUBEQA and 11.6 months (range: 0.1 to 45.1 months) in patients who received placebo. The safety profile of NUBEQA remained consistent with the data presented in the primary analysis.

### Cardiovascular

Heart failure occurred in 1.9% of patients treated with NUBEQA and in 0.9% of patients treated with placebo. Grade 3 or 4 reactions occurred only in the NUBEQA arm in 0.5% of patients.

### Fractures

At the final analysis of the ARAMIS study, during the double-blind period, bone fractures occurred in 5.5% of patients treated with NUBEQA and in 3.6% of patients treated with placebo. Grade 3 or 4 reactions occurred in 1.0% of patients treated with NUBEQA and 0.9% of patients treated with placebo. Bone fractures occurred in 8.3% of patients treated in the combined double blind and open label period with NUBEQA and Grade 3 or 4 reactions occurred in 1.4% of patients. No Grade 4 bone fracture reactions were reported with NUBEQA.

### Metastatic Castration-Sensitive Prostrate Cancer (mCSPC) (ARASENS)

ARASENS, a phase III, randomized (1:1), double-blind, placebo-controlled, multi-centre clinical study, enrolled patients who had mCSPC. In this study, patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day in combination with 75 mg/m<sup>2</sup> docetaxel every 21 days for 6 cycles. All patients received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 41.0 months (range: 0.13 to 56.5 months) in patients who received NUBEQA and 16.7 months (range: 0.26 to 55.8 months) in patients who received placebo.

Table 3 shows the incidence of adverse drug reactions reported in patients treated with NUBEQA+docetaxel in ARASENS that occurred in  $\geq 10\%$  of patients with a  $\geq 2\%$  absolute increase in frequency compared to placebo+docetaxel.

**Table 3: Adverse drug reactions that occurred at an incidence of  $\geq 10\%$  in patients treated with NUBEQA+docetaxel with a  $\geq 2\%$  absolute increase in frequency compared to placebo+docetaxel in ARASENS<sup>a</sup>**

System/Organ Class Preferred Term MedDRA Version 24.1	NUBEQA+docetaxel (n=652)		Placebo+docetaxel (n=650)	
	Grade		Grade	
	All n (%)	3-4 n (%)	All n (%)	3-4 n (%)
<b>Gastrointestinal disorders</b>				
Constipation <sup>b</sup>	147 (23%)	2 (0.3%)	130 (20%)	2 (0.3%)
<b>Investigations</b>				
Weight increased	116 (18%)	14 (2%)	102 (16%)	8 (1%)
<b>Metabolism and nutrition disorders</b>				
Decreased appetite <sup>b</sup>	121 (19%)	1 (0.2%)	85 (13%)	4 (0.6%)
<b>Musculoskeletal and connective tissue disorders</b>				
Pain in extremity <sup>b</sup>	98 (15%)	2 (0.3%)	78 (12%)	2 (0.3%)
<b>Vascular disorders</b>				
Hemorrhage <sup>c</sup>	115 (18%)	9 (1%)	85 (13%)	9 (1%)
Hypertension <sup>d</sup>	90 (14%)	43 (7%)	61 (9%)	24 (4%)
<b>Skin and subcutaneous tissue disorders</b>				
Rash <sup>b,e</sup>	125 (19%)	12 (2%)	98 (15%)	1 (0.2%)

a Adverse drug reaction incidence presented in Table 3 may not be attributable to NUBEQA alone but may contain contributions from other medicinal products used in combination

b The incidence was highest during the first 6 months of treatment

c Includes hematuria, epistaxis, anal hemorrhage, hemorrhoidal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, hemorrhagic stroke, subarachnoid hemorrhage, lower gastrointestinal hemorrhage, cystitis hemorrhagic, gastrointestinal hemorrhage, hemorrhage subcutaneous, intra-abdominal hemorrhage, nail bed bleeding, subdural hemorrhage

d Includes hypertension, blood pressure increased, hypertensive crisis, hypertensive emergency

e Includes rash, rash maculo-papular, palmar-plantar erythrodysesthesia syndrome, eczema, dermatitis, skin exfoliation, dermatitis acneiform, drug eruption, rash pruritic, rash erythematous, erythema multiforme, rash macular, dermatitis exfoliative generalized, penile rash, dyshidrotic eczema, rash papular, dermatitis bullous, rash follicular, rash pustular, rash vesicular, toxic skin eruption

### 8.3 Less Common Clinical Trial Adverse Reactions

The following are selected less common clinically significant adverse reactions reported in patients receiving NUBEQA and with higher incidences reported than the placebo arm, in the ARASENS study:

Cardiac disorders: ischemic heart disease (3.2%)

Hepatobiliary disorders: drug induced liver injury (0.3%)

Nervous system disorders: seizures (0.6%)

#### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

[Table 4](#) shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

**Table 4: Laboratory test abnormalities in NUBEQA-Treated Patients Occurring at a Higher Incidence than Placebo (Between Arm Difference of >5%) in ARAMIS (nmCRPC)**

Laboratory parameter	NUBEQA (N=954) <sup>a</sup>		Placebo (N=554) <sup>a</sup>	
	All Grades <sup>b</sup> (%)	Grade 3/4 <sup>b</sup> (%)	All Grades <sup>b</sup> (%)	Grade 3/4 <sup>b</sup> (%)
<b>Blood and lymphatic system disorders</b>				
Neutrophil count decreased	20	4	9	0.5
<b>Hepatobiliary disorders</b>				
Bilirubin increased	16	0.1	7	0
AST increased	23	0.5	14	0.2

a The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.

b Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Only laboratory values (no clinical assessments) were used for the grading. Grade 4 laboratory test values were limited to neutrophil count decreased.

[Table 5](#) shows laboratory test abnormalities related to NUBEQA+docetaxel treatment and reported more frequently in NUBEQA+docetaxel-treated patients compared to placebo+docetaxel-treated patients in the ARASENS study.

**Table 5: Laboratory test abnormalities occurring in ≥30% of NUBEQA+docetaxel - Treated Patients and at a Higher Incidence than Placebo+docetaxel in ARASENS<sup>a</sup> (mCSPC)**

Laboratory parameter	NUBEQA+docetaxel (N=652) <sup>b</sup>		Placebo+docetaxel (N=650) <sup>b</sup>	
	All Grades <sup>c</sup> (%)	Grade 3/4 <sup>c</sup> (%)	All Grades <sup>c</sup> (%)	Grade 3/4 <sup>c</sup> (%)
<b>Blood and lymphatic system disorders</b>				
Anemia	96	6	94	7
<b>Investigations</b>				
White blood cell count decreased	56	27	52	26
Neutrophil count decreased	51	34	46	31
ALT increased	42	4	38	3
AST increased	44	4	39	2
<b>Metabolism and nutrition disorders</b>				
Hyperglycemia	75	9	71	12
Hypocalcemia	35	3	31	2

a Laboratory test abnormalities presented in Table 5 may not be attributable to NUBEQA, but may contain contributions from other medicinal products used in combination.

b The number of patients tested for a specific laboratory test parameter may be different. The incidence of each laboratory test abnormality was calculated accordingly.

c Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Only laboratory test values (no clinical assessments) were used for the grading.

Clinically relevant laboratory test abnormalities in < 30% of patients who received NUBEQA with docetaxel included blood bilirubin increased (all Grades 20%, Grade 3-4 0.5%) compared to placebo with docetaxel (all Grades 10%, Grades 3-4 0.3%).

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

Darolutamide is primarily metabolized by CYP3A4, which can be induced or inhibited by concomitant medications. Darolutamide is also a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Concomitant use of darolutamide with combined P-gp and strong CYP3A4 inducers can decrease darolutamide exposure. Concomitant use of darolutamide with combined P-gp, BCRP and strong inhibitors of CYP3A4 can increase darolutamide exposure.

Darolutamide is also an inhibitor of BCRP, Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 and P-gp *in vitro*. Co-administration of darolutamide with a BCRP substrate can significantly increase exposure of the BCRP substrate. Co-administration of darolutamide with OATP1B1 and OATP1B3 substrates may increase exposure of the OATP1B1 and OATP1B3 substrates. Co-administration of darolutamide with a P-gp substrate (i.e. dabigatran etexilate) does not result in a clinically significant drug-drug interaction. This indicates that NUBEQA may be given concomitantly with P-gp substrates.

Darolutamide is a weak inducer of CYP3A4. Co-administration of darolutamide with a CYP3A4 substrate does not result in a clinically significant drug-drug interaction.

In vitro data indicate darolutamide administration may inhibit OAT3, MATE1, MATE2K and intestinal MRP2. Darolutamide does not inhibit the transporters BSEP, OAT1, OCTs, OATP2B1 and NTCP at clinically relevant concentrations.

Administration of darolutamide in combination with docetaxel did not result in clinically relevant changes in the pharmacokinetics of either docetaxel or darolutamide in mCSPC patients.

#### 9.4 Drug-Drug Interactions

The drugs listed in this table are based on drug interaction studies.

**Table 6: Established or Potential Drug-drug Interactions**

Proper / Common name	Source of Evidence	Effect	Clinical Comment
Effect of CYP3A4 and P-gp inducers on darolutamide			
Rifampicin (600 mg)	CT	AUC ↓ 72% C <sub>max</sub> ↓ 52%	Avoid concomitant use of strong CYP3A4 inducers and P-gp inducers during treatment with NUBEQA, unless there is no therapeutic alternative.
Effect of CYP3A4, P-gp and BCRP inhibitors on darolutamide			
Itraconazole (200 mg twice daily on day 1 and once daily on the following 7 days)	CT	AUC ↑ 1.7-fold C <sub>max</sub> ↑ 1.4-fold	Consider alternative therapies that do not strongly inhibit CYP3A4 and/or P-gp activity. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for darolutamide related adverse events.
Effect of darolutamide on BCRP, OATP1B1 and OATP1B3 substrates			
Rosuvastatin (5 mg)	CT	AUC ↑ 5-fold C <sub>max</sub> ↑ 5-fold	BCRP substrates: Avoid concomitant use if clinically feasible. If co-administration with NUBEQA is required, the related recommendation and monitoring advice in the Product Monograph of the BCRP substrate should be followed. OATP1B1 and OATP1B3 substrates: Concomitant use of NUBEQA may increase plasma exposure, therefore, the related recommendation and monitoring advice in the Product Monograph of the OATP1B1 and OATP1B3 substrates should be followed.
Effect of darolutamide on CYP3A4 substrates			
Midazolam (1 mg)	CT	AUC ↓ 29% C <sub>max</sub> ↓ 32%	NUBEQA may be given concomitantly with CYP3A4 substrates.

Legend: CT=Clinical Trial

## 9.5 Drug-Food Interactions

Administration of darolutamide (2 x 300 mg) with a high-fat high-calorie meal resulted in a 2.5 fold increase in  $AUC_T$  and a 2.0 fold increase in  $C_{max}$  relative to administration of darolutamide (2 x 300 mg) under fasted conditions.

Administration of darolutamide (2 x 300 mg) with a low-fat low-calorie meal resulted in a 2.5 fold increase in  $AUC_T$  and a 2.8 fold increase in  $C_{max}$  relative to administration of darolutamide (2 x 300 mg) under fasted conditions.

## 9.6 Drug-Herb Interactions

Avoid concomitant use of St. John's Wort during treatment with NUBEQA, unless there is no therapeutic alternative.

## 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

# 10 CLINICAL PHARMACOLOGY

## 10.1 Mechanism of Action

Darolutamide is an orally administered, non-steroidal androgen receptor (AR) inhibitor with a flexible polar-substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain to retain strong antagonistic activity against the AR.

Darolutamide competitively inhibits androgen binding, androgen receptor nuclear translocation, and AR mediated transcription.

Darolutamide inhibited prostate cancer cell proliferation and resulted in tumor growth inhibition in xenograft animal models of prostate cancer.

## 10.2 Pharmacodynamics

In the ARAMIS study, during the double-blind period, the confirmed prostate-specific antigen (PSA) response rate (defined as a  $\geq 50\%$  reduction from baseline) was 84.0%. The median PSA reduction at 16 weeks from baseline was 87.4% for the darolutamide arm.

In the ARASENS study, patients receiving darolutamide+docetaxel had a PSA response rate (defined as a  $\geq 50\%$  reduction from baseline) of 89.6% at 12 months after randomization.

## Cardiac Electrophysiology

The effect of darolutamide (600 mg twice daily) on the QTc interval was evaluated in a subgroup of 500 patients in the ARAMIS study. No large mean increase in QTc (i.e.,  $>20$  ms) was detected.

### 10.3 Pharmacokinetics

**Table 7: Geometric mean (CV [%]), PK parameters at steady state in study 17712 using the selected Phase III popPK model (Study 18651)**

	<b>Darolutamide (n=388)</b>	<b>Keto-darolutamide (n=388)</b>
$C_{max}$ , µg/L	4786 (30.9)	8475 (35.4)
$t_{max}$ , h	3.64 (4.4)	2.06 (3.3)
$AUC_{(0-12)}$ , µg·h/L	52817 (33.9)	87640 (42.1)
Effective $t_{1/2}$ , h	19.6 (29.7)	20.0 (37.9)

Abbreviations:  $AUC_{(0-12)}$  = area under the plasma concentration time curve from time 0 to 12 hours;  $C_{max}$  = peak concentration; CV% = coefficient of variation; PK = pharmacokinetics; popPK = population pharmacokinetics;  $t_{max}$  = time to peak concentration;  $t_{1/2}$  = half-life.

#### **Absorption:**

Following oral administration of 600 mg (2 tablets of 300 mg), peak plasma concentrations of darolutamide of 4.79 mg/L (coefficient of variation: 30.9%) are usually reached around 4 hours after administration. Following oral administration together with food, steady-state is reached after 2-5 days of repeated twice-daily dosing, with a 2.9-fold accumulation.

The absolute bioavailability following oral administration of a NUBEQA tablet containing 300 mg darolutamide under fasted conditions is approximately 30%. Bioavailability of darolutamide was enhanced by 2.0 to 2.5 fold when administered with food. A similar increase of exposure was observed for the major metabolite keto-darolutamide.

#### **Distribution:**

The apparent volume of distribution of darolutamide after intravenous administration is 119 L. Binding to plasma proteins is 92% for darolutamide and 99.8% for keto-darolutamide. Serum albumin is the main binding protein for darolutamide and keto-darolutamide.

Passage of darolutamide across the blood-brain barrier has not been studied clinically. However, brain exposures to darolutamide in terms of  $AUC_{(0-24)}$  are very low with 4.5% of plasma exposure after single dose in rats and 1.9-3.9% after repeated dose in mice. This indicates low passage of darolutamide across the intact blood-brain barrier in rats and mice and a low likelihood that darolutamide crosses the intact blood-brain barrier in humans to a clinically relevant extent.

#### **Metabolism:**

Following single oral administration of 300 mg C-darolutamide given as an oral solution, keto-darolutamide is the only major metabolite with about 2-fold higher total exposure in plasma compared to darolutamide. Darolutamide and keto-darolutamide together accounted for 87.4% of the C-radioactivity in plasma indicating that all other metabolites are of minor importance. Darolutamide is metabolized primarily by oxidative metabolism mediated mainly by CYP3A4, as well as by direct glucuronidation mediated preferentially by UGT1A9 and UGT1A1.

#### **Elimination:**

The effective half-life of darolutamide and keto-darolutamide in plasma of patients is approximately 20 hours. The clearance of darolutamide following intravenous administration was 116 mL/min (39.7%). Following administration of a radiolabeled oral solution of 300 mg darolutamide, a total of 63.4% of drug related material is excreted in the urine (6.7% unchanged), 32.4% is excreted in the feces (approximately 30% unchanged).



**Linearity / Non-linearity:**

In the dose range of 100 to 700 mg (after single dose and at steady state), the exposure (based on  $C_{max}$  and  $AUC_{0-12}$ ) to darolutamide and the major metabolite keto-darolutamide increases linearly in a nearly dose-related manner. No notable increase in exposure to darolutamide was observed beyond 700 mg twice daily.

**Special Populations and Conditions****Pediatrics:**

Safety and efficacy of NUBEQA have not been studied in children and adolescents below 18 years of age.

**Geriatrics:**

A population pharmacokinetic analysis indicates increased darolutamide exposure with increasing age. Darolutamide  $AUC_{0-12}$  is 1.6-fold greater in patients aged above 85 years compared to patients aged below 65 years. The increase exposure was not associated with increased toxicity.

**Ethnic Origin:**

A population pharmacokinetic analysis indicates a 1.4-fold greater  $AUC_{0-12}$  in Japanese patients. The increased exposure was not associated with increased toxicity.

**Hepatic Insufficiency:**

In a clinical pharmacokinetic study,  $C_{max}$  and  $AUC_{0-48}$  for darolutamide were 1.5 and 1.9-fold higher in non-cancer patients with moderate hepatic impairment (Child-Pugh B) compared to healthy volunteers. There are no data for patients with severe hepatic impairment (Child-Pugh C).

**Renal Insufficiency:**

In a clinical pharmacokinetic study,  $C_{max}$  and  $AUC_{0-48}$  for darolutamide were 1.6 and 2.5-fold higher in non-cancer patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] 15 to 29 mL/min/1.73 m<sup>2</sup>) compared to healthy volunteers.

A population pharmacokinetic analysis indicates a 1.1-, 1.3- and an approximately 1.5-fold higher exposure (AUC) of darolutamide in patients with mild, moderate and severe renal impairment (eGFR 15 to 89 mL/min/1.73 m<sup>2</sup>) compared to patients with normal renal function.

The pharmacokinetics of darolutamide has not been studied in patients with end stage renal disease receiving dialysis (eGFR <15 mL/min/1.73 m<sup>2</sup>).

**11 STORAGE, STABILITY AND DISPOSAL**

Store bottles or blisters at room temperature 15°C to 30°C. Keep out of sight and reach of children.

Keep the bottle tightly closed after first opening. Once the bottle is opened the medicinal product has shown to be stable for 3 months.

**12 SPECIAL HANDLING INSTRUCTIONS**

There are no special handling requirements for this product.

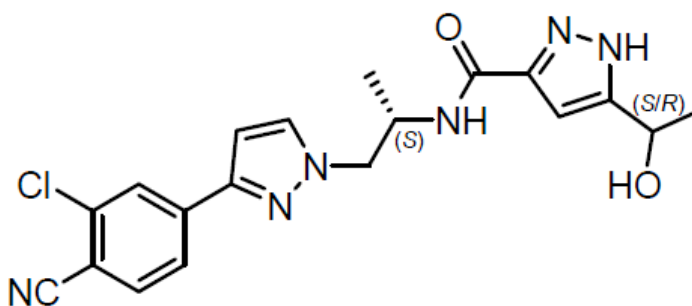
## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

<b>Proper/Common name:</b>	darolutamide
<b>Chemical name:</b>	N-((2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide
<b>Molecular formula and molecular mass:</b>	C <sub>19</sub> H <sub>19</sub> Cl N <sub>6</sub> O <sub>2</sub> 398.85 g/mol

#### Structural formula:



#### Physicochemical properties:

Darolutamide is a white to greyish- or yellowish-white powder. Darolutamide milled drug substance is practically insoluble in water. Using the method described in the Ph. Eur. a saturated solution in water gives a pH-value of 6.4. The pKa value was found to be  $11.75 \pm 0.06$ . The aqueous solubility of darolutamide milled drug substance is practically not dependent on pH. Theoretically, darolutamide milled drug substance has another pKa under pH 2, but experimental solubility results show only slight effect within pH 1.0 – 6.8.

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

#### Non-Metastatic Castration Resistant Prostate Cancer (nmCRPC) (ARAMIS)

The efficacy and safety of NUBEQA was assessed in a randomized, double-blind, placebo-controlled multi-centre phase III study (ARAMIS) in patients with nmCRPC with a prostate-specific antigen doubling time (PSADT) of  $\leq 10$  months (considered to be at high risk of developing metastatic disease). In total, 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA orally twice daily (n=955) or matching placebo (n=554). Randomization was stratified by PSADT ( $\leq 6$  months or  $> 6$  months) and use of osteoclast-targeted therapy at study entry (yes or no).

All patients received a gonadotropin-releasing hormone (GnRH) analog concurrently or had a bilateral orchiectomy. Patients with presence of pelvic lymph nodes < 2 cm in short axis below the aortic bifurcation were allowed to enter the study. Absence or presence of metastasis was assessed by independent central radiological review. Included in these analyses were 89 patients that were retrospectively identified with metastases at baseline.

The following patient demographics and disease characteristics were balanced between treatment arms (see [Table 8](#)). The median age was 74 years (range 48-95) and 9% of patients were 85 years of age or older. The racial distribution was 79% White, 13% Asian and 3% Black. A majority of patients had a Gleason score of 7 or higher at diagnosis (73%). The median PSADT was 4.5 months. Nine percent (9%) of patients had prior orchiectomy, 25% of patients had prior prostatectomy and 50% of patients had at least one prior radiotherapy. Seventy-three percent (73%) of patients received prior treatment with an anti-androgen (bicalutamide or flutamide). All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 (69% and 31%, respectively) at study entry.

Treatment with NUBEQA continued until radiographic disease progression as assessed by conventional imaging (CT, MRI, Tc99m bone scan) by blinded central review, unacceptable toxicity or withdrawal.

The primary efficacy endpoint was metastasis free survival (MFS) which was defined as the time from randomization to confirmed evidence of distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Distant metastasis was defined as new bone or soft tissue lesions or enlarged lymph nodes above the aortic bifurcation. Secondary endpoints, evaluated in a hierarchical order, were overall survival (OS), time to pain progression, and time to initiation of first cytotoxic chemotherapy for prostate cancer.

**Table 8: Demographic and baseline cancer characteristics (ARAMIS)**

	<b>NUBEQA N = 955</b>	<b>Placebo N = 554</b>
<b>Age: years, median (range)</b>	74.0 (48-95)	74.0 (50-92)
<b>Age group (years), n (%)</b>		
<65	113 (11.8%)	84 (15.2%)
65-74	373 (39.1%)	216 (39.0%)
75-84	384 (40.2%)	209 (37.7%)
≥85	85 (8.9%)	45 (8.1%)
<b>Race, n (%)</b>		
White	760 (79.6%)	434 (78.3%)
Asian	122 (12.8%)	71 (12.8%)
Black or African American	28 (2.9%)	24 (4.3%)
Missing	36 (3.8%)	19 (3.4%)
Other	9 (0.9%)	6 (1.1%)
<b>Geographical region, n (%)</b>		
North America	108 (11.3%)	76 (13.7%)
Asia Pacific	119 (12.5%)	67 (12.1%)
Rest of the World	728 (76.2%)	411 (74.2%)
<b>PSA central laboratory: ng/mL, median (range)</b>	9.030 (0.31-858.30)	9.670 (1.46-885.21)
<b>Categories, n (%)</b>		
≤10 ng/mL	508 (53.2%)	285 (51.4%)

	<b>NUBEQA N = 955</b>	<b>Placebo N = 554</b>
>10 to ≤20 ng/mL	215 (22.5%)	122 (22.0%)
>20 ng/mL	232 (24.3%)	147 (26.5%)
<b>Baseline value of PSADT, n (%)</b>		
≤6 months	669 (70.1%)	371 (67.0%)
>6 months	286 (29.9%)	183 (33.0%)
<b>PSADT (months); median (range)</b>	4.389 (0.744-10.991)	4.650 (0.662-13.194)
<b>ECOG PS, n (%)</b>		
0	650 (68.1%)	391 (70.6%)
1	305 (31.9%)	163 (29.4%)
<b>Gleason score at diagnosis (factor1+factor2), n (%)</b>		
Missing	27 (2.8%)	17 (3.1%)
<7	217 (22.7%)	142 (25.6%)
≥7	711 (74.5%)	395 (71.3%)
<b>Baseline presence of regional pathological lymph nodes by central imaging review, n (%)<sup>a,b</sup></b>		
No	855 (89.5%)	488 (88.1%)
Yes	100 (10.5%)	66 (11.9%)
<b>Time since initial diagnosis to start of study treatment (months) median (range)</b>	86.15 (2.6 – 337.5)	84.23 (0.5 – 344.7)
<b>Baseline osteoclast-targeted therapy, Yes, n (%)</b>	36 (3.8%)	28 (5.1%)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time.

a pathological lymph nodes were defined according to RECIST criteria as having the short axis ≥15mm as measured by CT scan. The protocol allowed presence at baseline of lymph nodes with short axis of <2cm below the aortic bifurcation

b Baseline values are observed at Screening Visit

The median treatment duration at the time of the primary analysis for NUBEQA-treated patients was 14.8 months compared to 11.0 months for placebo-treated patients. The median treatment duration at the time of the final analysis for NUBEQA-treated patients was 25.8 months (combined double blind + open-label) compared to 11.6 months for placebo-treated patients.

At the primary analysis, treatment with NUBEQA resulted in a statistically significant improvement in MFS compared to placebo (median MFS 40.4 vs. 18.4 months) with a p-value of <0.000001 and a hazard ratio (HR) of 0.413 (see [Table 9](#) and [Figure 1](#)).

**Table 9: Efficacy Results from the ARAMIS study**

Efficacy parameter <sup>a</sup>	Number (%) of patients with events		Median (95% CI)		Hazard Ratio <sup>c,d</sup> (95% Confidence Interval [CI]) p-value (two-sided)
	NUBEQA (N=955)	Placebo (N=554)	NUBEQA (N=955)	Placebo (N=554)	
Metastasis free survival <sup>e</sup>	221 (23.1%)	216 (39.0%)	40.4 months (34.3, NR)	18.4 months (15.5, 22.3)	0.413 (0.341, 0.500) <0.000001
Overall survival	148 (15.5%)	106 <sup>b</sup> (19.1%)	NR (56.1, NR)	NR <sup>b</sup> (46.9, NR)	0.685 (0.533, 0.881) 0.003048
Time to pain progression <sup>e,f</sup>	251 (26.3%)	178 (32.1%)	40.3 months (33.2, 41.2)	25.4 months (19.1, 29.6)	0.647 (0.533, 0.785) 0.000008
Time to initiation of first cytotoxic chemotherapy <sup>e</sup>	127 (13.3%)	98 <sup>b</sup> (17.7%)	NR (NR, NR)	NR <sup>b</sup> (NR, NR)	0.579 (0.444, 0.755) 0.000044

a Analyses were performed in the full analysis set.

b including 170 patients who crossed over to open-label NUBEQA.

c Hazard ratio < 1 favors NUBEQA.

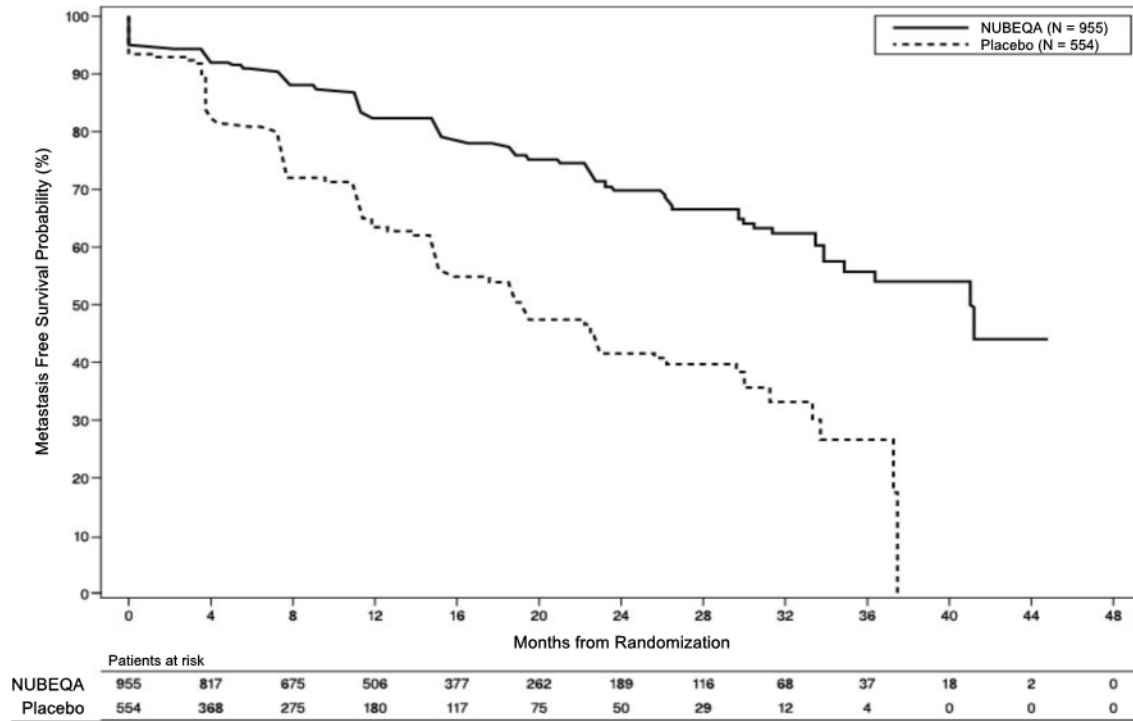
d P-value is based on a log-rank test stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no).

e MFS and time to pain progression endpoints were performed at the time of primary analysis and time to initiation of first cytotoxic chemotherapy was performed at the time of final OS analysis.

f Patient reported outcome as evaluated by Brief Pain Inventory-Short Form questionnaire.

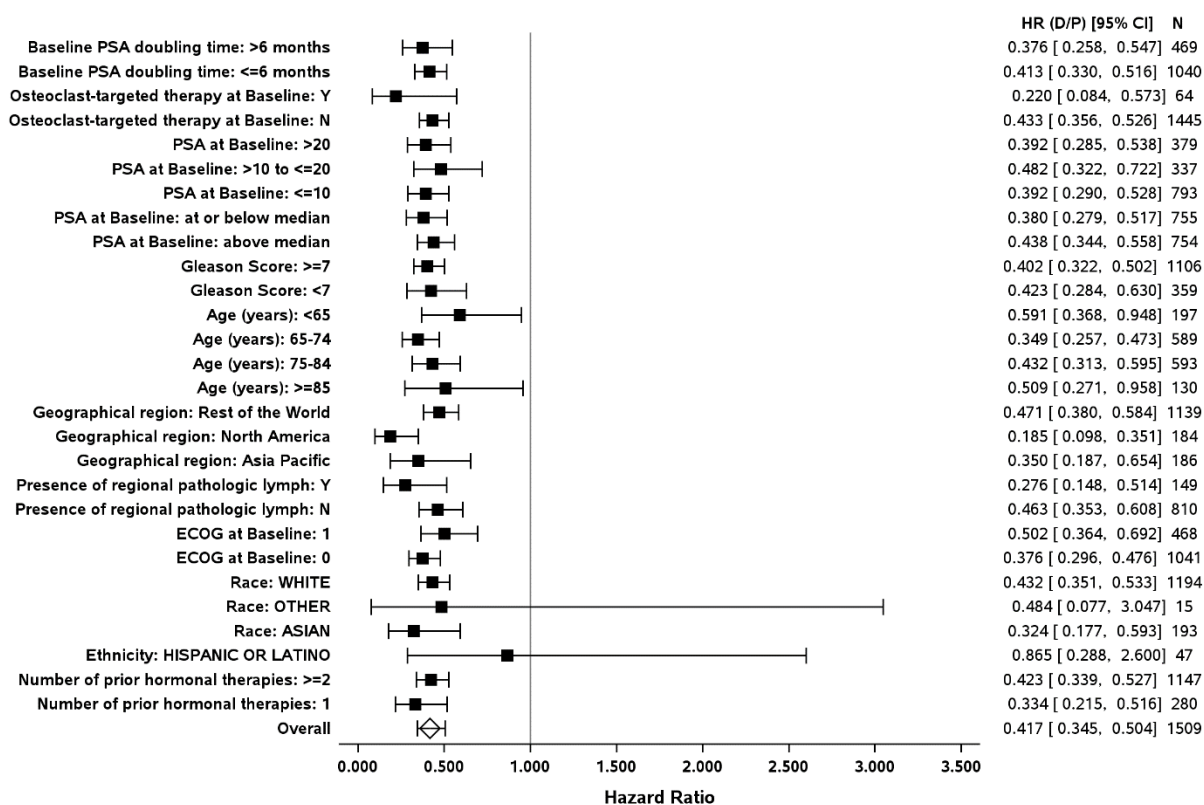
NR not reached

**Figure 1: Kaplan Meier curves of Metastasis Free Survival (ARAMIS)**



MFS results were consistent across patient subgroups (see [Figure 2](#)) regardless of PSADT, prior use of bone-targeting agents or loco-regional disease. Additional subgroups with consistent MFS results included PSA at baseline, Gleason score at diagnosis, age, geographical region, ECOG PS at baseline, race, and number of prior hormonal therapies.

**Figure 2: Forest plot of subgroup analysis: Metastasis Free Survival (ARAMIS)**



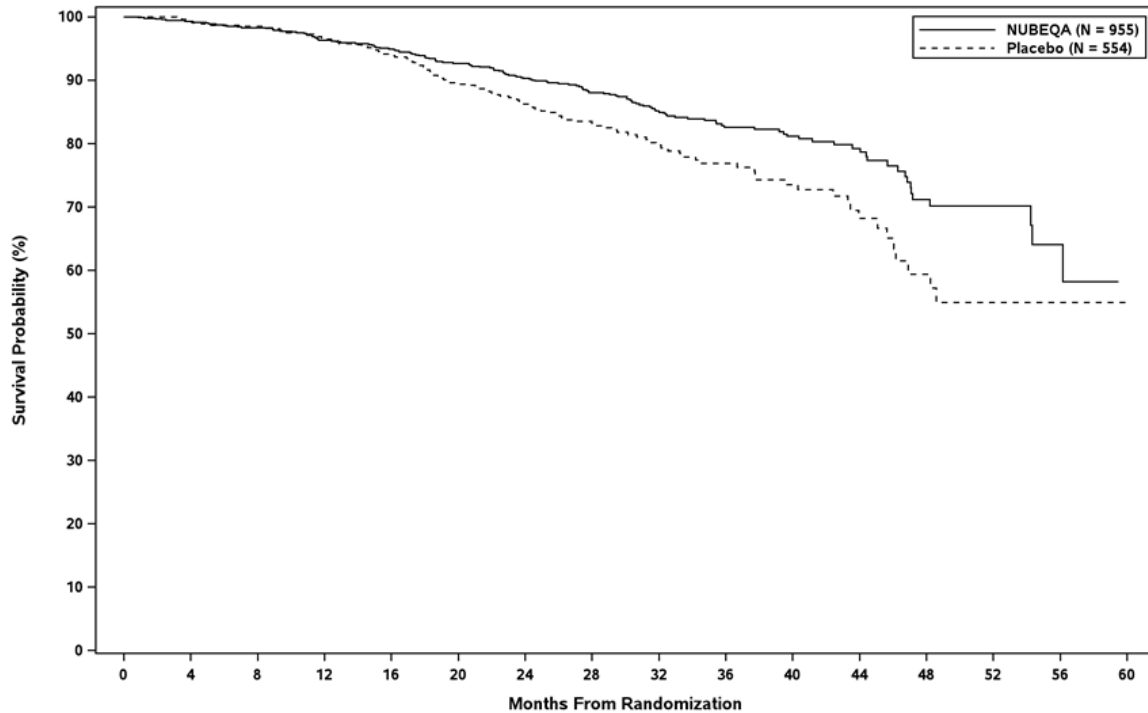
A Hazard ratio < 1 indicates superiority of Darolutamide over Placebo.  
Hazard ratio and CI were obtained from univariate analysis using Cox regression (unstratified).

The final analysis of OS was event-driven conducted after 254 OS events had occurred, 14 months after the primary analysis of MFS. After the primary analysis of MFS, all patients receiving placebo at time of database cut-off were offered treatment with open-label NUBEQA (cross-over option) once the study was unblinded. Among the 554 patients randomized to placebo, 170 (31%) crossed over to receive NUBEQA treatment. The OS analysis was not adjusted for confounding effects of cross-over.

For patients who crossed over from placebo to NUBEQA after study unblinding, the median treatment duration was 11.0 months.

At the protocol-specified final OS analysis, treatment with NUBEQA resulted in a statistically significant improvement in OS compared to placebo (HR=0.685, p=0.003048, median was not reached in either arm (see [Table 9](#) and [Figure 3](#)). The treatment effect for overall survival favored NUBEQA in pre-specified subgroups, including patients with PSA doubling time less than or equal to 6 months and greater than 6 months, presence or absence of lymph node involvement at baseline, and ECOG performance status of 0 or 1.

**Figure 3: Kaplan-Meier curves of Overall Survival (ARAMIS)**



	Patients at Risk															
	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
NUBEQA	955	932	908	863	816	771	680	549	425	293	214	129	69	37	12	0
Placebo	554	530	497	460	432	394	333	261	182	130	93	54	28	16	4	0

Treatment with NUBEQA also resulted in statistically significant delays in time to pain progression (median 40.3 vs. 25.4 months, HR=0.647, p=0.000008), and time to initiation of first cytotoxic chemotherapy (HR=0.579, p=0.000044) compared to placebo (see [Table 9](#)).



## Metastatic Castration-Sensitive Prostate Cancer (mCSPC) (ARASENS)

ARASENS was a randomized, multi-centre, double-blind, placebo-controlled phase III study in 1306 patients with mCSPC. Patients were randomized (1:1) to receive 600 mg darolutamide orally twice daily (n=651) or matching placebo (n=655), in combination with 75 mg/m<sup>2</sup> of docetaxel once every 3 weeks for 6 cycles. Treatment with NUBEQA or placebo continued until symptomatic progressive disease, change of antineoplastic therapy, or unacceptable toxicity. All patients received a gonadotropin-releasing hormone (GnRH) analog concurrently or had a bilateral orchiectomy. 87.6% and 85.5% of patients received full 6 cycles of docetaxel and 1.5% and 2.0% of patients did not receive docetaxel, in NUBEQA+docetaxel and placebo+docetaxel arm, respectively.

Presence of metastasis was assessed by independent central radiological review. Patients with regional lymph node involvement only (M0) were excluded from the study.

Randomization was stratified by extent of disease (non-regional lymph nodes metastases only (M1a), bone metastases with or without lymph node metastases (M1b), or visceral metastases with or without lymph node metastases or with or without bone metastases (M1c)), and by alkaline phosphatase level (< or ≥ upper limit of normal) at study entry.

The following patient demographics and disease characteristics were balanced between treatment arms (see [Table 10](#)). The median age was 67 years (range 41-89) and 17% of patients were 75 years of age or older. The racial distribution was 52% White, 36% Asian and 4% Black. A majority of patients had a Gleason score of 8 or higher at diagnosis (78%). Seventy one percent (71%) of patients had an ECOG PS score of 0 and 29% of patients had an ECOG PS score of 1. There were 86% of patients with de novo (initial diagnosis with metastases) and 13% with recurrent disease (initial diagnosis with localized disease, recurred with metastases). At study entry, 3% of patients were M1a, 79.5% were M1b and 17.5% were M1c; alkaline phosphatase was <ULN in 45% of patients and ≥ ULN in 55% of patients; median PSA level at baseline was 30.3 µg/L and 24.2 µg/L for NUBEQA+docetaxel vs placebo+docetaxel arm, respectively. Patients with a medical history of seizure were allowed to enter the study (4 patients (0.6%) in the NUBEQA+docetaxel arm and 2 patients (0.3%) in the placebo+docetaxel arm).

**Table 10: Demographics and baseline characteristics (FAS) (ARASENS)**

	<b>NUBEQA+ docetaxel arm N=651</b>	<b>Placebo+ docetaxel arm N=654<sup>a</sup></b>
<b>Age (years)</b>		
Mean (StD)	66.7 (7.9)	67.0 (7.8)
Median (Min, Max)	67.0 (41, 89)	67.0 (42, 86)
<b>Age group (years), n (%)</b>		
<65	243 (37.3%)	234 (35.8%)
65–74	303 (46.5%)	306 (46.8%)
75–84	102 (15.7%)	110 (16.8%)
≥85	3 (0.5%)	4 (0.6%)
<b>Race, n (%)</b>		
White	345 (53.0%)	333 (50.9%)
Black or African American	26 (4.0%)	28 (4.3%)
Asian	230 (35.3%)	245 (37.5%)
Other <sup>b</sup>	7 (1.1%)	2 (0.3%)
Not reported	43 (6.6%)	46 (7.0%)

	<b>NUBEQA+ docetaxel arm N=651</b>	<b>Placebo+ docetaxel arm N=654<sup>a</sup></b>
<b>Ethnicity, n (%)</b>		
Hispanic or Latino	40 (6.1%)	49 (7.5%)
Not Hispanic or Latino	561 (86.2%)	557 (85.2%)
Not reported	50 (7.7%)	48 (7.3%)
<b>Geographical region, n (%)</b>		
North America	125 (19.2%)	119 (18.2%)
Asia Pacific	229 (35.2%)	244 (37.3%)
Rest of the World	297 (45.6%)	291 (44.5%)
<b>Body mass index group (kg/m<sup>2</sup>), n (%)</b>		
<20	45 (6.9%)	34 (5.2%)
20 – <25	254 (39.0%)	248 (37.9%)
25 – <30	240 (36.9%)	254 (38.8%)
≥30	108 (16.6%)	116 (17.7%)
Missing	4 (0.6%)	2 (0.3%)
<b>Renal function - eGFR at baseline (mL/min)<sup>e</sup></b>		
Normal	375 (57.6%)	365 (55.8%)
Mild impairment	236 (36.3%)	235 (35.9%)
Moderate impairment	39 (6.0%)	53 (8.1%)
Severe impairment <sup>d</sup>	1 (0.2%)	0
Missing	0	1 (0.2%)
<b>Hepatic function at baseline<sup>e</sup></b>		
Normal	597 (91.7%)	593 (90.7%)
Mild impairment	49 (7.5%)	52 (8.0%)
Moderate impairment	2 (0.3%)	0
Missing	3 (0.5%)	9 (1.4%)
<b>Extent of metastatic disease at study entry (eCRF), n (%)</b>		
M1a: Non-regional lymph nodes only	23 (3.5%)	16 (2.4%)
M1b: Bone with or without lymph nodes	517 (79.4%)	520 (79.5%)
M1c: Visceral with or without lymph nodes or bone	111 (17.1%)	118 (18.0%)
<b>ALP at baseline (central laboratory<sup>f</sup>; eCRF) (U/L), n (%)</b>		
ALP < ULN	290 (44.5%)	291 (44.5%)
ALP ≥ ULN	361 (55.5%)	363 (55.5%)
<b>Stage of prostate cancer at initial diagnosis</b>		
<b>TNM classification<sup>g</sup>, n (%)</b>		
Stage I	12 (1.8%)	10 (1.5%)
Stage IIA	18 (2.8%)	10 (1.5%)
Stage IIB	15 (2.3%)	10 (1.5%)
Stage III	36 (5.5%)	38 (5.8%)
Stage IV	563 (86.5%)	580 (88.7%)
Stage IV, M0	5 (0.8%)	14 (2.1%)
Stage IV, M1	558 (85.7%)	566 (86.5%)
Missing	7 (1.1%)	6 (0.9%)
<b>Gleason score at initial diagnosis of prostate cancer, n (%)</b>		
<8	122 (18.7%)	118 (18.0%)
≥8	505 (77.6%)	516 (78.9%)
Missing	24 (3.7%)	20 (3.1%)

	<b>NUBEQA+ docetaxel arm N=651</b>	<b>Placebo+ docetaxel arm N=654<sup>a</sup></b>
<b>PSA at baseline (central laboratory) (ng/mL)</b>		
n	651	653
Mean (StD)	248.47 (714.08)	204.71 (742.54)
Median (Min, Max)	30.30 (0.0, 9219.0)	24.20 (0.0, 11947.0)
Missing	0	1
<b>ECOG Performance Status, n (%)</b>		
0	466 (71.6%)	462 (70.6%)
1	185 (28.4%)	190 (29.1%)
Missing	0	2 (0.3%)
<b>Testosterone at baseline (central laboratory) (ng/mL)</b>		
<0.5	339 (52.1%)	353 (54.0%)
≥0.5	309 (47.5%)	296 (45.3%)
Missing	3 (0.5%)	5 (0.8%)

Abbreviations: AJCC=American Joint Committee on Cancer; ALP=Alkaline phosphatase; AST=Aspartate aminotransferase; eCRF=Electronic case report form; eGFR=Estimated glomerular filtration rate; FAS=Full analysis set; Max=Maximum; Min=Minimum; N=Total number of patients (100%); n=Number of patients with event; PSA=Prostate-specific antigen; StD=Standard deviation; TNM=Tumor, Node, Metastasis; U/L=Unit per litre; ULN=Upper limit of normal

- a One patient in the placebo arm was excluded from all analyses
- b Race 'Other' includes "American Indian or Alaska Native", "Native Hawaiian or other Pacific Islander", and "Multiple"
- c Renal function: normal: eGFR ≥90 mL/min; mild impairment: 60 ≤ eGFR <90 mL/min; moderate impairment: 30 ≤ eGFR <60 mL/min; severe impairment: 15 ≤ eGFR <30 mL/min
- d One patient with severe renal impairment at baseline was eligible based on a serum creatinine level below ≤2.0 x ULN.
- e Hepatic function: normal: Total bilirubin and AST ≤ ULN; mild impairment: Total bilirubin and AST >ULN to 1.5x ULN or Total bilirubin ≤ ULN and AST >ULN; moderate impairment: Total bilirubin >1.5 to 3x ULN, any AST
- f For 2 patients (one in the NUBEQA+docetaxel arm and the other in the placebo+docetaxel arm), central laboratory ALP values were not available at baseline and the local laboratory ALP values were selected as baseline instead.
- g According to AJCC 7th edition, Stage IV could be M1 or M0 disease. For the purpose of this analysis, the Stage IV M0 group was defined as the time interval of >3 months between initial diagnosis and initial diagnosis of metastases.

Note: Data collection for race and ethnicity was not allowed in some countries (eg, France) due to local regulations.

The primary efficacy endpoint was overall survival (OS). Secondary endpoints, evaluated in a hierarchical order, included time to castration-resistant prostate cancer, time to pain progression, symptomatic skeletal event free survival (SSE-FS), time to first symptomatic skeletal event (SSE), and time to initiation of subsequent antineoplastic therapy.

A statistically significant improvement in OS with a 32.5% reduction in risk of death was observed in the NUBEQA+docetaxel arm compared to the placebo+docetaxel arm (see [Table 11](#) and [Figure 4](#)). OS results were consistent across all patient subgroups, including stratification subgroups (extent of disease and alkaline phosphatase level) (see [Figure 5](#)). Of the patients who entered active or survival follow-up, 56.8% in the darolutamide +docetaxel arm and 75.6% in the placebo+docetaxel arm received subsequent life-prolonging therapy after stopping study treatment.

The following secondary efficacy endpoints showed a statistically significant advantage in favor of NUBEQA+docetaxel: time to castration-resistant prostate cancer, time to pain progression, time to first symptomatic skeletal event, time to initiation of subsequent antineoplastic chemotherapy, and longer symptomatic skeletal event free survival time (see [Table 11](#)). For the time to castration-resistant prostate cancer endpoint, although PSA progression represented the majority of events in both treatment arms, the proportion of radiological progression events in the absence

of PSA progression was higher in the darolutamide+docetaxel arm (see [7 WARNINGS AND PRECAUTIONS](#)).

Pain progression was assessed using the Patient-Reported Outcome (PRO) Brief Pain Inventory-Short Form (BPI-SF). A statistically significant delay in time to pain progression was observed for patients treated in the NUBEQA+docetaxel arm compared to placebo+docetaxel arm.

**Table 11: Efficacy Results from the ARASENS study**

Efficacy parameter	Number (%) of patients with events		Median in months (95% CI)		Hazard Ratio <sup>b</sup> (95% Confidence Interval [CI]) p-value (one-sided) <sup>c</sup>
	NUBEQA+ docetaxel (N=651)	Placebo+ docetaxel (N=654) <sup>a</sup>	NUBEQA+ docetaxel (N=651)	Placebo+ docetaxel (N=654) <sup>a</sup>	
<b>Primary Endpoint</b>					
Overall survival	229 (35.2%)	304 (46.5%)	NR (NR, NR)	48.9 (44.4, NR)	0.675 (0.568, 0.801) <0.0001
<b>Key Secondary Endpoints</b>					
Time to CRPC <sup>d</sup>	225 (34.6%)	391 (59.8%)	NR (NR, NR)	19.1 (16.5, 21.8)	0.357 (0.302, 0.421) <0.0001
Time to pain progression <sup>e</sup>	222 (34.1%)	248 (37.9%)	NR (30.5, NR)	27.5 (22.0, 36.1)	0.792 (0.660, 0.950) 0.0058
Symptomatic skeletal event free survival (SSE-FS) <sup>f</sup>	257 (39.5%)	329 (50.3%)	51.2 (47.2, NR)	39.7 (36.0, 42.3)	0.609 (0.516, 0.718) <0.0001
Time to first symptomatic skeletal event (SSE) <sup>g</sup>	95 (14.6%)	108 (16.5%)	NR (NR, NR)	NR (NR, NR)	0.712 (0.539, 0.940) 0.0081
Time to initiation of subsequent antineoplastic therapy	219 (33.6%)	395 (60.4%)	NR (NR, NR)	25.3 (23.1, 28.8)	0.388 (0.328, 0.458) <0.0001

a One patient in the placebo arm was excluded from all analyses

b Hazard ratio < 1 favors NUBEQA

c Based on stratified log-rank test

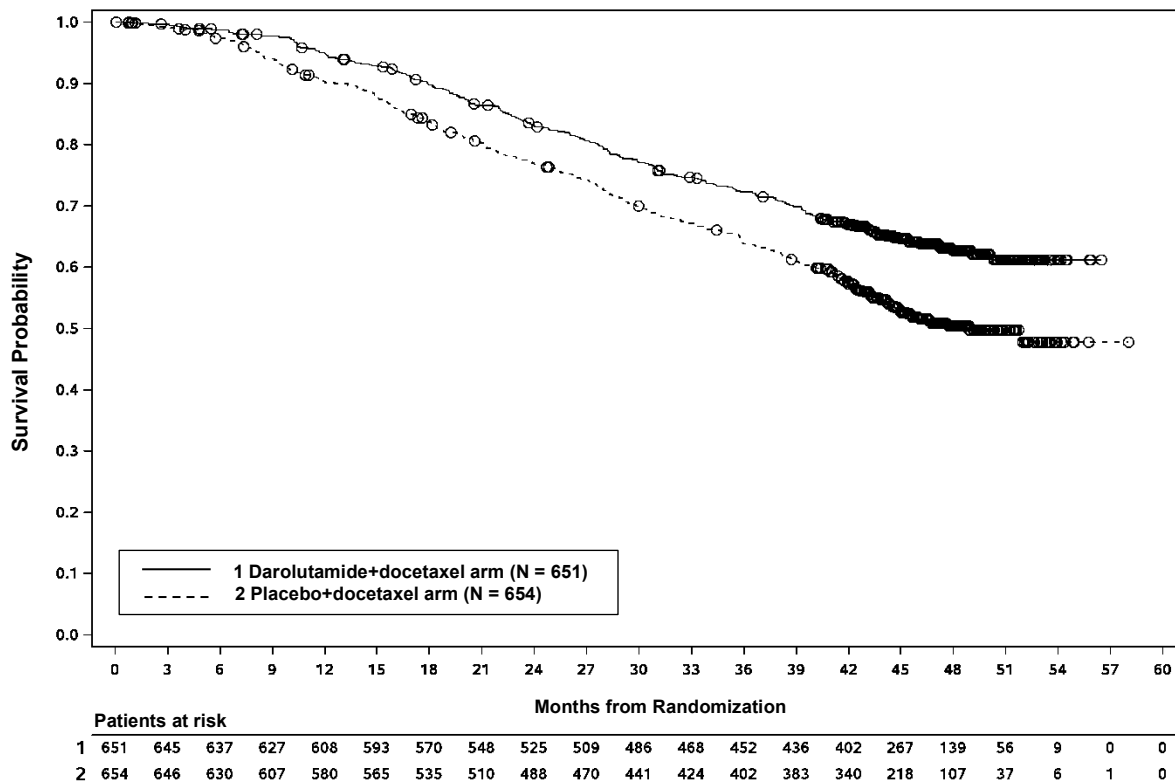
d Time to CRPC defined as time from randomization to first occurrence of: PSA progression (≥25% increase and an absolute increase of 2 ng/mL or more from nadir), radiological progression by soft tissue and visceral lesions according to RECIST version 1.1, or radiological progression by bone lesions.

e Evaluated by BPI-SF and initiation of short- or long-acting opioid for pain for ≥7 consecutive days. Analysis included patients who received subsequent anti-cancer therapies.

f SSE-FS defined as time from randomization to first occurrence of an SSE or death from any cause. SSE defined as first occurrence of: external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, spinal cord compression, or tumor-related orthopedic surgical intervention. The number of deaths in this analysis was 162 for the NUBEQA+docetaxel arm and 221 for the docetaxel+placebo arm. Analysis included patients who received subsequent anti-cancer therapies.

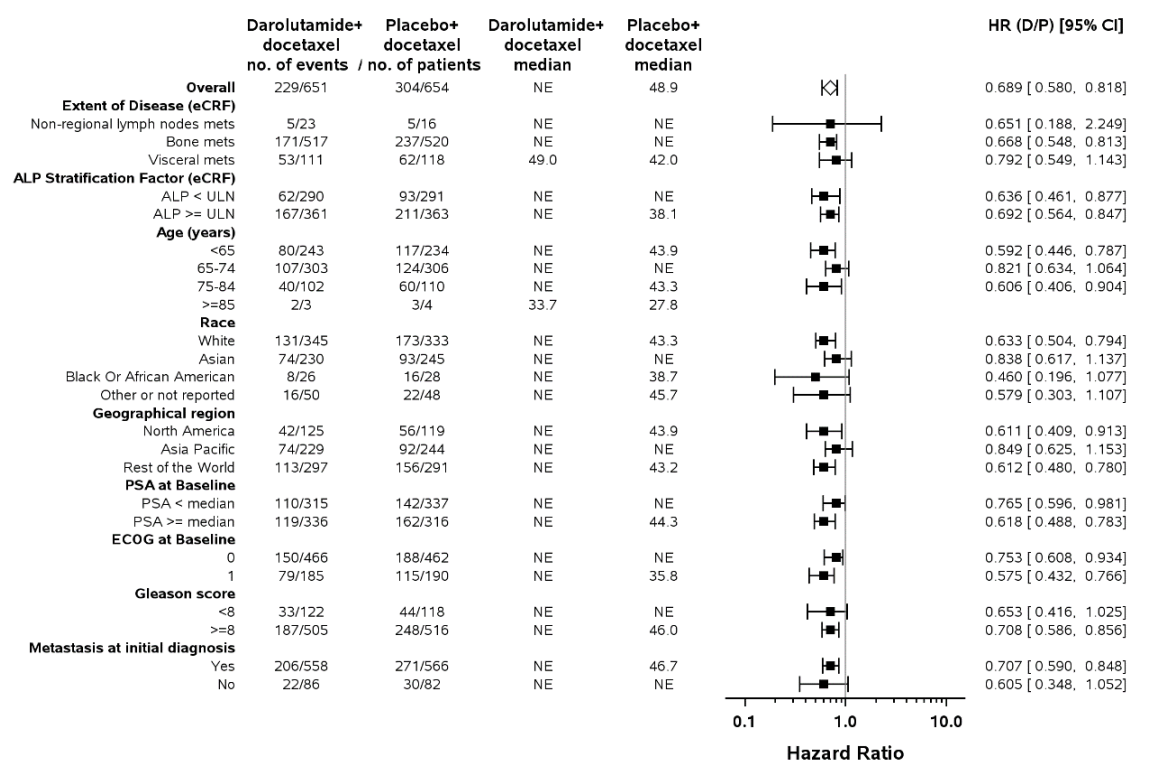
g Time to first SSE defined as time from randomization to first occurrence of an SSE. Analysis included patients who received subsequent anti-cancer therapies.  
 CRPC=castration-resistant prostate cancer  
 NR=not reached

**Figure 4: Kaplan-Meier curves of Overall Survival: mCSPC population (ARASENS)<sup>1</sup>**



<sup>1</sup> OS rate at 36 months was 72.3% (95% CI, 68.8 to 75.8) in the NUBEQA+docetaxel arm versus 63.8% (95% CI, 60.1 to 67.6) in the placebo+docetaxel arm. OS rate at 48 months was 62.7% (95% CI, 58.7 to 66.7) in the NUBEQA+docetaxel arm versus 50.4% (95% CI, 46.3 to 54.6) in the placebo+docetaxel arm.

**Figure 5: Forest plot of subgroup analysis results of overall survival (ARASENS)**



A hazard ratio <1 favours the darolutamide+docetaxel arm over the placebo+docetaxel arm.

Hazard ratios and CIs were obtained from univariate analysis using Cox regression (unstratified). Medians were computed using Kaplan-Meier estimates.

No HR was calculated if <10 total events were observed within the subgroups across the treatment arms.

Extent of disease classification: non-regional lymph node metastases=M1a; bone metastases=M1b; visceral metastases=M1c

## 15 MICROBIOLOGY

Not applicable.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology

In repeated dose toxicity studies in rats and dogs, the main findings were changes in the male reproductive organs (decreases in organ weight with atrophy of the prostate and epididymides). Additional changes to reproductive tissues included minimal increase in vacuolation of the pituitary gland, atrophy in seminal vesicles and mammary glands in rats as well as testicular hypospermia, seminiferous tubule dilatation and degeneration in dogs. These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison). Changes in the male reproductive organs in both species were consistent with the pharmacological activity of darolutamide and reversed or partially resolved after 4- to 8-week recovery periods. In addition, a slight decrease of body weight gain in the highest dose group in male rats (2x500 mg/kg/d) after 26-weeks and male dogs (2x200 mg/kg/d) after 39 weeks was observed. In male and female dogs decreases of small magnitude in mean red blood cell parameters (red blood cell, hemoglobin, packed cell volume) within or close to the background control range were seen at the highest dose during 39-weeks treatment.

### **Carcinogenicity**

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been performed.

### **Genotoxicity**

Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay. Additionally, darolutamide did not induce genotoxicity in the *in vivo* combined bone marrow rat micronucleus assay or the Comet assay in the liver and duodenum of the rat. However, clastogenicity was observed in the *in vitro* chromosome aberration assay in human lymphocytes.

### **Reproductive and Developmental Toxicology**

Studies on reproductive toxicity have not been performed. However, in repeated dose toxicity studies in rats and dogs, atrophy and hypospermia in the male reproductive system were observed, which is consistent with the pharmacological activity of darolutamide. These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison).

## **PATIENT MEDICATION INFORMATION**

### **READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrNUBEQA®**

#### **darolutamide tablets**

Read this carefully before you start taking **NUBEQA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NUBEQA**.

Your cancer may be treated with NUBEQA in combination with another medication called docetaxel. In this case, read the consumer information leaflet for docetaxel as well as this one.

#### **What is NUBEQA used for?**

NUBEQA is used in adults to treat prostate cancer that:

- has not spread to other parts of the body, and no longer responds to a medicine or surgery that lowers testosterone, or
- has spread to other parts of the body (metastatic) and still responds to a medicine or surgery that lowers testosterone. For these patients, NUBEQA is used with another drug called docetaxel.

NUBEQA has not been studied in patients with low risk of the cancer spreading to other parts of the body. Talk to your healthcare professional if you have any questions about this.

#### **How does NUBEQA work?**

NUBEQA contains darolutamide. Darolutamide works by blocking the activity of androgens (like testosterone). This will slow the spread of your prostate cancer and the start of disease symptoms.

#### **What are the ingredients in NUBEQA?**

Medicinal ingredients: darolutamide

Non-medicinal ingredients: calcium hydrogen phosphate, croscarmellose sodium, hypromellose 15 cP, lactose monohydrate, macrogol 3350, magnesium stearate, povidone K 30, titanium dioxide

#### **NUBEQA comes in the following dosage forms:**

Tablet (film-coated): 300 mg

#### **Do not use NUBEQA if:**

- you are allergic to darolutamide or any of the other ingredients in this medicine.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NUBEQA. Talk about any health conditions or problems you may have, including if you:**

- have high blood pressure, diabetes, or high levels of fat in your blood (dyslipidemia).
- have a history of seizures.
- suffer from a lactose intolerance. This is because NUBEQA contains lactose.
- have or have had liver or kidney problems.
- have a partner who is pregnant or may become pregnant. NUBEQA may harm your unborn baby or may make your partner lose the baby. Men who are sexually active with



a pregnant woman must use a condom during and for 3 months after the last dose. If your sexual partner may become pregnant, highly effective birth control must be used during and for 3 months after treatment. Talk with your healthcare professional if you have questions about birth control. If your sexual partner becomes pregnant while you are taking NUBEQA, tell your healthcare professional right away.

**Other warnings you should know about:**

**Liver Problems:** Taking NUBEQA may affect your liver. Tell your doctor right away if you notice any of the following changes:

- abdominal discomfort or loss of appetite
- feeling sick (nausea) or vomiting
- yellowing of the skin or eyes
- darkening of the urine

**Fertility:**

- NUBEQA may affect your ability to have a child. Talk to your doctor if this is a concern for you.
- Do NOT donate sperm while taking NUBEQA and for 3 months after stopping NUBEQA.

**Women, pregnancy and breast-feeding:**

- NUBEQA is NOT for use in women.
- NUBEQA is NOT to be used in women who are or may become pregnant. NUBEQA can harm the unborn baby or make a woman lose the baby.
- NUBEQA is NOT to be used in women who are breast-feeding. This is because it may get into breast milk and harm the baby.

**Children and adolescents:**

- NUBEQA is NOT for use in patients under the age of 18 years.

**Check-ups and testing:**

You will have regular visits with your healthcare professional during treatment with NUBEQA to monitor your health. They may:

- Check for signs and symptoms of heart problems
- Do blood tests to check your liver health

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with NUBEQA:**

- rifampicin – used to treat bacterial infections
- carbamazepine, phenobarbital – used to treat epilepsy
- St. John's Wort (*hypericum perforatum*) – a herbal product used mainly to treat depression
- rosuvastatin, fluvastatin, and atorvastatin – used to treat high cholesterol
- methotrexate – used to treat severe joint inflammation, severe cases of the skin disease psoriasis, and cancers
- sulfasalazine – used to treat inflammatory bowel disease
- itraconazole – used to treat fungal infections

**How to take NUBEQA:**

- Always take exactly as your healthcare professional tells you. Check with your doctor or pharmacist if you are not sure.

- Take your prescribed dose twice a day with food (a snack or meal) at about the same time each day.
- Do NOT stop taking NUBEQA without talking to your doctor first.
- Swallow the tablets whole.
- Your doctor may also prescribe a gonadotropin-releasing hormone (GnRH) analog therapy while you are taking NUBEQA, unless you have had surgical castration. This is a surgery to remove your testicles in order to lower the amount of testosterone in your body.
- You may also receive docetaxel. Your healthcare professional will tell you how and when you will get it.

**Usual dose:**

**Usual daily adult dose:**

**1200 mg (600 mg twice daily):** Take two 300 mg tablets (600 mg) by mouth twice a day. This is a total daily dose of 1200 mg.

Your doctor may reduce your NUBEQA dose if needed.

**Reduced daily adult dose:**

**600 mg (300 mg twice daily):** Take one 300 mg tablet by mouth twice a day. This is a total daily dose of 600 mg.

**Overdose:**

If you think you, or a person you are caring for, have taken too much NUBEQA, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you are late in taking NUBEQA, take it as soon as you remember before the next scheduled dose. Do NOT take a double dose to make up for the missed dose.

**What are possible side effects from using NUBEQA?**

These are not all the possible side effects you may feel when taking NUBEQA. Some of these side effects may occur when taking NUBEQA or when taking NUBEQA with docetaxel. If you experience any side effects not listed here, contact your healthcare professional.

- fatigue (tiredness)
- rash
- pain in arms and legs or joints
- bone fracture
- constipation
- weight gain
- decreased appetite
- high blood pressure

NUBEQA may cause abnormal blood test results. This includes abnormal blood cell counts, blood sugar, calcium and liver enzymes. Your healthcare professional will decide when to perform blood tests and will interpret the results.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>VERY COMMON</b>			
<b>Hemorrhage</b> (bleeding): nose bleeds, blood in urine, dark tarry stool or bright red blood in your stool		✓	
<b>COMMON</b>			
<b>Cardiac problems</b> (including heart attack, heart disease and heart failure): pressure or pain in your chest or arms that may spread to neck, jaw or back, chest pain or discomfort or shortness of breath at rest or with activity, changes in heart rate, dizziness or lightheadedness, nausea			✓
<b>UNCOMMON</b>			
<b>Seizure</b> (convulsion): uncontrollable shaking with or without loss of consciousness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

### **Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

- Store bottles or blisters at room temperature (15°C to 30°C).
- Do NOT use this medicine after the expiry date stated on the product labels.
- Keep the bottle tightly closed after you first open it.
- Do NOT throw away any medicines away in the garbage, down the sink or in the toilet. Ask your pharmacist how to throw away expired or unused NUBEQA. These measures will help protect the environment.
- **Keep out of sight and reach of children.**

**If you want more information about NUBEQA:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website <http://www.bayer.ca> or by calling Bayer Medical Information at 1-800-265-7382 or emailing [canada.medinfo@bayer.com](mailto:canada.medinfo@bayer.com).

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