Report on the Deliberation Results

November 28, 2019
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Nubeqa Tablets 300 mg
Non-proprietary Name	Darolutamide (JAN*)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	March 5, 2019

Results of Deliberation

In its meeting held on November 25, 2019, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, and the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

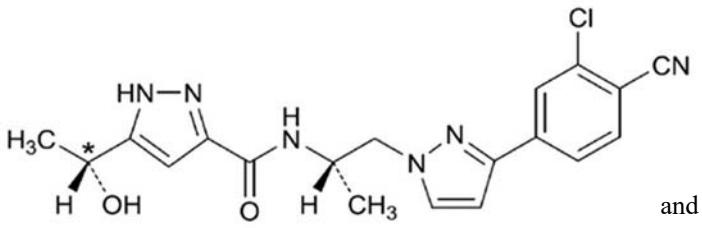
Review Report

November 14, 2019
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Nubeqa Tablets 300 mg
Non-proprietary Name	Darolutamide
Applicant	Bayer Yakuhin, Ltd.
Date of Application	March 5, 2019
Dosage Form/Strength	Tablets: Each tablet contains 300 mg of darolutamide.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



and epimer at C*

Molecular formula: $C_{19}H_{19}ClN_6O_2$
Molecular weight: 398.85
Chemical name: *N*-{(2*S*)-1-[3-(3-Chloro-4-cyanophenyl)-1*H*-pyrazol-1-yl]propan-2-yl}-5-[(1*RS*)-1-hydroxyethyl]-1*H*-pyrazole-3-carboxamide

Items Warranting Special Mention None
Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of non-metastatic castration-resistant prostate cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The development of cardiac disorders should be further investigated.

Indication

Non-metastatic castration-resistant prostate cancer

Dosage and Administration

The usual adult dosage is 600 mg of darolutamide administered orally twice daily, after meals. The dose should be reduced, as appropriate, according to the patient's condition.

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

October 7, 2019

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval	
Brand Name	Nubeqa Tablets 300 mg
Non-proprietary Name	Darolutamide
Applicant	Bayer Yakuhin, Ltd.
Date of Application	March 5, 2019
Dosage Form/Strength	Tablets: Each tablet contains 300 mg of darolutamide.
Proposed Indication	Castration-resistant prostate cancer
Proposed Dosage and Administration	The usual adult dosage is 600 mg of darolutamide administered orally twice daily, after meals.

Table of Contents

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information 2
2. Data Relating to Quality and Outline of the Review Conducted by PMDA.....2
3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA.....5
4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA 11
5. Toxicity and Outline of the Review Conducted by PMDA 21
6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA.....24
7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA.....35
8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA 66
9. Overall Evaluation during Preparation of the Review Report (1).....66

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Upon binding with dihydrotestosterone at the ligand binding domain, the androgen receptor (AR) dimerizes and then translocates to the nucleus, where the homo-dimer binds to the androgen response element of AR target genes, resulting in the increased expression of genes that are associated with cell survival and proliferation (*Cold Spring Harb Perspect Med.* 2017;7: a030452).

Darolutamide is a small-molecule compound that blocks AR-mediated signaling, which was discovered by Orion Corporation Orion Pharma (the US). Darolutamide competitively inhibits (a) androgen binding to the ligand binding domain of AR, (b) nuclear translocation of the transcription factor (i.e., AR), and (c) transcription of the AR target genes, thereby inhibiting AR-mediated signaling and consequently blocking the growth of androgen-dependent tumors.

1.2 Development history etc.

Outside of Japan, Orion Corporation Orion Pharma (the US) initiated a phase I/II study in patients with metastatic castration-resistant prostate cancer (CRPC) (Study 17829) in March 2011. Subsequently, Orion Corporation Orion Pharma and the applicant initiated a global phase III study in patients with non-metastatic CRPC with a prostate-specific antigen (PSA) doubling time of ≤10 months (Study 17712) in September 2014.

In the US and the EU, new drug applications for darolutamide were filed in February and March 2019, respectively, based primarily on the results from Study 17712. In the US, darolutamide was approved in July 2019 for the following indication: "NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC)." The application in the EU is currently under review.

As of August 2019, the US is the only country that has approved darolutamide for the treatment of CRPC.

In Japan, the applicant initiated a phase I study in patients with metastatic CRPC (Study 17719) in February 2015, and began patient enrollment in Study 17712 in [redacted], [redacted].

With the results of Study 17712 serving as pivotal data, the applicant has recently filed a marketing application for darolutamide.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to grayish- or yellowish white powder, with determined physicochemical properties including description, optical rotation, molar absorption coefficient, pH, dissociation constant,

distribution coefficient, density, hygroscopicity, and solubility. A total of 4 crystalline forms of the drug substance ([redacted]), as well as amorphous fractions, have been identified. Among these forms, Crystalline Form [redacted] has been demonstrated to be produced during the manufacturing process at commercial scale and to be stable in stability tests.

The chemical structure of the drug substance has been elucidated by infrared spectroscopy (IR), raman spectroscopy, ultraviolet/visible spectroscopy (UV/VIS), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR), mass spectrometry, and elemental analysis. The drug substance is a mixture of 2 diastereoisomers that differ in the spatial arrangement of 1 of 2 asymmetric carbons.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as starting materials.

A quality by design (QbD) approach has been applied to the following to formulate the quality control strategy (Table 1).

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) through quality risk assessment, etc., and determination of acceptable ranges for manufacturing process parameters

Table 1. Outline of the control strategy for the drug substance

CQA	Control methods
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications

The [redacted] and [redacted] steps for the drug substance have been defined as critical steps, and process control parameters and limits were established for the [redacted] step during the course of the review. The [redacted] and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR and liquid chromatography [LC]), crystal form, purity ([redacted] [inductively coupled plasma atomic emission spectrometry]), related substances (LC), residual solvents and chloroethane (gas chromatography [GC]), loss on drying, residue on ignition, microbial limits, diastereomer ratio (LC), particle size, and assay (LC).

2.1.4 Stability of drug substance

Table 2 shows the main stability tests that have been conducted on the drug substance. A photostability test demonstrated that the drug substance is photostable.

Table 2. Stability testing for the drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 commercial-scale batches	25°C	60%RH	[redacted] polyethylene bag	12 months
Accelerated testing		40°C	75%RH		6 months

Based on the above, a retest period of 12 months was proposed for the drug substance, when stored at room temperature in a double-layer [redacted] polyethylene bag and a shipping container. Long-term testing will be continued up to 60 months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated immediate-release tablet, with each tablet containing 300 mg of the drug substance. It contains the following as excipients: lactose hydrate, anhydrous dibasic calcium phosphate, croscarmellose sodium, povidone, magnesium stearate, and lacquer white.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising mixing, granulation, [redacted], drying, sizing, [redacted] blending [redacted], [redacted] blending [redacted], tableting, film coating, and packaging/labeling steps. A QbD approach was employed for the following to formulate the quality control strategy (Table 3).

- Identification of CQAs
- Identification of CPPs through a failure mode effects analysis, design of experiments, etc., and determination of acceptable ranges for manufacturing process parameters

Table 3. Outline of the quality control strategy for the drug product

CQA	Control methods
[redacted]	Manufacturing method and specifications
[redacted]	Specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications
[redacted]	Specifications
[redacted]	Manufacturing method and specifications
[redacted]	Manufacturing method and specifications

The [redacted] and [redacted] steps are defined as critical process steps, and process control parameters and limits have been defined for the [redacted], [redacted], [redacted], and [redacted] steps.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of content, description, identification (LC and UV/VIS), purity (related substances [LC]), uniformity of dosage units (mass variation test), microbial limits, dissolution (LC), and assay (LC).

2.2.4 Stability of drug product

Table 4 shows the stability tests that have been conducted on the drug product. A photostability test demonstrated that the drug product is photostable.

Table 4. Stability testing for the drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 commercial-scale batches	25°C	60%RH	blister pack (polyvinyl chloride with aluminum foil)	24 months
Accelerated testing		40°C	75%RH		6 months

Based on the above, a shelf life of 36 months was proposed for the drug product when stored in a blister pack of polyvinyl chloride with aluminum foil at room temperature, according to the ICH Q1E guidelines. Long-term testing will be continued up to 36 months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In this section, unless otherwise specified, the dose and concentration of darolutamide are expressed as the total dose and concentration of S,R- and S,S-darolutamide.

3.1 Primary pharmacodynamics

3.1.1 Binding to AR (CTD 4.2.1.1.1)

In a competitive AR binding assay using ^{3}H-mibolerone, a synthetic androgen, the binding affinities to rat AR of darolutamide, its diastereoisomers (S,R- and S,S-darolutamide) and its metabolite, M-1 (keto-darolutamide), and bicalutamide were measured. The inhibition constant (Ki) values (n = 1) of darolutamide, S,R- and S,S-darolutamide, M-1, and bicalutamide were 9.1, 9.3, 18.6, 7.5, and 12.1 nmol/L, respectively.

3.1.2 Inhibition of AR activation (CTD 4.2.1.1.2, 4.2.1.1.4, 4.2.1.1.5, and 4.2.1.1.11)

The inhibition of AR activation by darolutamide, S,R- and S,S-darolutamide, M-1, and bicalutamide was evaluated in human embryonic kidney 293 (HEK293) cells expressing human AR and an androgen-

responsive luciferase (AR-HEK293 cells), by measuring luciferase activity. The IC_{50} values (n = 3-7) of darolutamide, S,R- and S,S-darolutamide, M-1, and bicalutamide in the presence of testosterone were 65 ± 14, 38 ± 21, 51 ± 34, 25 ± 17, and 150 ± 66 nmol/L, respectively.

The inhibition of AR activation by darolutamide, M-1, apalutamide, enzalutamide, and bicalutamide was evaluated in human osteosarcoma-derived U2-OS cells expressing each of 3 AR mutants[1)] and an androgen-responsive luciferase, by measuring luciferase activity. Table 5 shows the IC_{50} values of darolutamide, M-1, apalutamide, enzalutamide, and bicalutamide.

Table 5. Inhibition of AR mutants by darolutamide, M-1, apalutamide, enzalutamide, and bicalutamide

	IC_{50} value (μmol/L)					
	n	W742L	n	F877L	n	T878A
Darolutamide	4	1.1 ± 0.1	3	0.085 ± 0.012	4	2.6 ± 0.9
M-1	4	1.1 ± 0.1	3	0.047 ± 0.015	4	1.4 ± 0.6
Apalutamide	3	>10	3	—	3	1.1 [0.8, 1.7]*
Enzalutamide	3	>10	3	—	3	0.3 [0.2, 0.4]*
Bicalutamide	4	—	NA		4	0.8 ± 0.2

Mean ± SD; n = 3 to 4; —, not determined; NA, not evaluated; *, IC_{50} [95% CI]

3.1.3 Effects on the nuclear translocation of AR (CTD 4.2.1.1.3)

The effects of darolutamide, M-1, and bicalutamide on the testosterone-induced nuclear translocation of AR were evaluated in HS-HEK293[2)] cells by staining AR and nuclei, and determining the nuclear-cytoplasmic ratio of AR immunofluorescence intensity. Darolutamide and M-1 inhibited the testosterone-induced nuclear translocation of AR, whereas bicalutamide failed to block testosterone-induced AR nuclear localization.

3.1.4 Effects on the prostate and seminal vesicles (CTD 4.2.1.1.7)

The inhibition of testosterone-induced increases in prostate and seminal vesicle weights by darolutamide and M-1 was evaluated in immature rats. Darolutamide at 10, 30, or 100 mg/kg/day, or M-1 at 10 or 30 mg/kg/day was orally administered for 6 days to rats that had received a subcutaneous dose of testosterone propionate, and the prostate and seminal vesicles were weighed. All of the darolutamide groups showed a statistically significant inhibitory effect on testosterone-induced increases in prostate and seminal vesicle weights, compared with the control (vehicle[3)]) group (P <0.001, one way analysis of variance).

3.1.5 Inhibition of the proliferation of human prostate cancer-derived cells

3.1.5.1 *In vitro* (CTD 4.2.1.1.6, 4.2.1.1.11)

Inhibition of the proliferation of human prostate cancer-derived VCaP cells by darolutamide, M-1, and bicalutamide was evaluated based on reductase activity in viable cells. Table 6 shows the IC_{50} values

1) Inhibition of AR-mediated signaling induces the following *AR* genetic mutations in patients with CRPC (*Cancer Discov.* 2013;3:1020-29 and *Sci Transl Med.* 2015;7:312re10): W742L, tryptophan 742 replaced by leucine; F877L, phenylalanine 877 replaced by leucine; and, T878A, threonine 878 replaced by alanine.

2) A cell clone of AR-HEK293 that displays an approximate 5-fold overexpression of AR, as compared with AR-HEK293 cells

3) 50% v/v polyethylene glycol 300, 30% v/v propylene glycol, and 20% v/v 5% glucose

(mean ± standard deviation [SD], n = 2-3) of darolutamide, M-1, and bicalutamide, in the presence of mibolerone.

Table 6. Inhibition of the growth of VCaP cells by darolutamide, M-1, and bicalutamide

	n	IC_{50} value (μmol/L)
Darolutamide	3	0.52 ± 0.08
M-1	3	0.66 ± 0.12
Bicalutamide	2	1.36, 1.09

Mean ± SD, individual values for n = 2

Inhibition of the proliferation of VCaP cells by darolutamide, M-1, apalutamide, and enzalutamide was evaluated based on reductase activity in viable cells. The IC_{50} values [95% confidence interval (CI)] (n = 4) of darolutamide, M-1, apalutamide, and enzalutamide were 0.23 [0.19, 0.27], 0.17 [0.14, 0.21], 0.42 [0.37, 0.47], and 0.41 [0.35, 0.48] μmol/L, respectively.

3.1.5.2 *In vivo* (CTD 4.2.1.1.8, 4.2.1.1.10)

The *in vivo* antitumor effect of darolutamide was evaluated in nude mice (6 to 11/group) that had been subcutaneously xenografted with VCaP cells. Starting from 4 weeks after surgical castration, when the tumor volume reached 200 mm^3, darolutamide 50 mg/kg was orally administered once daily or twice daily for 37 days, and the tumor volume was estimated. All of the darolutamide groups showed a statistically significant tumor growth-inhibitory effect, compared with the control (vehicle[3)]) group (Figure 1).

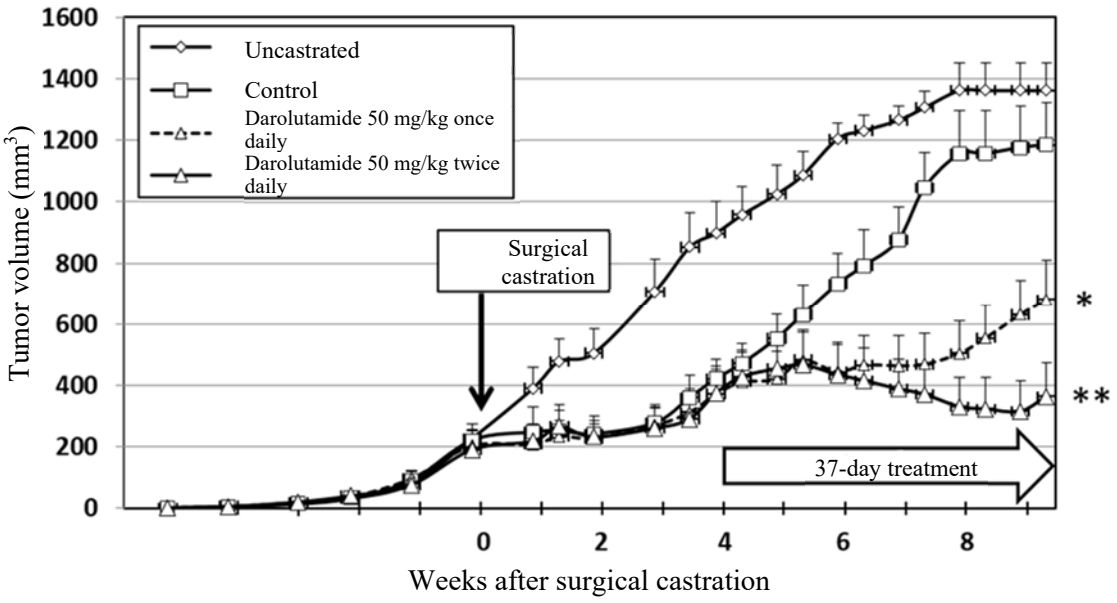


Figure 1. Tumor growth inhibition by darolutamide in nude mice subcutaneously xenografted with VCaP cells

n = 6 to 11; mean ± SD; *, P <0.01 versus the control group; **, P <0.001 versus the control group (repeated measures analysis of variance)

The antitumor effect of darolutamide was evaluated in male nude mice (8/group) that had been subcutaneously xenografted with VCaP cells in the prostate. Starting from approximately 4 weeks after xenografting, darolutamide 50 mg/kg was orally administered twice daily for 21 days, and the tumor volume was estimated. The darolutamide group showed a statistically significant tumor growth-inhibitory effect, compared with the control (vehicle[3)]) group ($P \leq 0.05$, one way analysis of variance).

3.2 Secondary pharmacodynamics

3.2.1 Effects on receptors and enzymes (CTD 4.2.1.2.2, 4.2.1.2.3, and 4.2.1.2.4)

The inhibitory effects of darolutamide, S,R- and S,S-darolutamide, and M-1 against more than 100 receptors and enzymes were evaluated. Darolutamide 10 μmol/L inhibited human progesterone receptor, rat central benzodiazepine receptor, and human serotonin transporter by ≥50%. S,R- and S,S-Darolutamide 5 μmol/L inhibited human serotonin transporter by ≥50%. M-1 10 μmol/L inhibited human progesterone receptor, human serotonin transporter, and human adenosine A3 receptor by ≥50%.

The applicant's explanation about the above results:
The tested concentrations of darolutamide (10 μmol/L), S,R- and S,S-darolutamide (5 μmol/L), and M-1 (10 μmol/L) were higher than the maximum plasma concentration (C_{max}) values of unbound darolutamide, S,S- and S,R-darolutamide, and M-1 (1.16, 2.2, 1.03, and 0.06 μmol/L, respectively)[4)] observed after darolutamide was administered at the clinical recommended dose (600 mg twice daily). Based on these results, as well as other data, the above findings are unlikely to pose any safety concerns regarding the clinical use of darolutamide.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system

The effects of darolutamide on the central nervous system were evaluated in a 4-week repeated dose toxicity study in rats [see Section 5.2]. No darolutamide-related effects were observed.

3.3.2 Effects on the cardiovascular system

3.3.2.1 Effects on hERG potassium current (CTD 4.2.1.3.1 [non-GLP studies])

The effects of darolutamide, S,R- and S,S-darolutamide, and M-1 on the human *ether-a-go-go* related gene (hERG) potassium current were evaluated at 1, 3, 10, and 30 μmol/L in HEK293 cells transfected with hERG. The rate (mean ± SD, n = 4-6) of hERG potassium current inhibition of darolutamide was 6.3 ± 3.5% at 1 μmol/L, 11.8 ± 3.7% at 3 μmol/L, 22.0 ± 2.9% at 10 μmol/L, and 34.5 ± 5.8% at 30 μmol/L. The IC_{50} values of darolutamide, S,R- and S,S-darolutamide, and M-1 were 87.9, 11.5, 30.2, and 8.0 μmol/L, respectively.

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4) Calculated from the C_{max} values of darolutamide, S,S- and S,R-darolutamide, and M-1 (5.80 μg/mL, 865 ng/mL, 5.15 μg/mL, and 11.1 μg/mL, respectively) [see Section 6.1.2.1] and unbound fractions in humans (0.08, 0.08, 0.08, and 0.002, respectively) [see Section 4.2.2] observed on Day 7 of treatment with darolutamide 600 mg, orally administered twice daily in patients with metastatic CRPC in Study 17719

3.3.2.2 Effects on L-type calcium channels (CTD 4.2.1.3.5 [non-GLP studies])

The effects of darolutamide, S,R- and S,S-darolutamide, and M-1 on L-type calcium channels were evaluated at 1, 3, 10, and 30 μmol/L in human neuroblastoma-derived IMR-32 cells. The IC_{50} values (mean ± SD, n = 2-4) of darolutamide, S,R- and S,S-darolutamide, and M-1 were 37.4 ± 3.6, 42.5 ± 4.5, 46.6 ± 4.2, and 22.5 ± 0.3 μmol/L, respectively.

3.3.2.3 Effects on heart rate, blood pressure, and ECG (CTD 4.2.1.3.6 and 4.2.1.3.7)

Single intravenous doses of darolutamide at 3, 10, and 20 mg/kg, or S,S-darolutamide at 1, 3, and 10 mg/kg were administered sequentially to anesthetized dogs (4/group) at an interval of 30 minutes to evaluate the effects of darolutamide on systolic, diastolic, and mean blood pressure, heart rate, body temperature, and electrocardiogram (ECG) parameters (PR, QRS, QT, and QTc intervals). Administration of darolutamide caused a decrease in arterial pressure and a transient increase in mean coronary blood flow at 10 and 20 mg/kg, and a transient increase in cardiac output and a decrease in the QTc interval at 20 mg/kg. Administration of S,S-darolutamide caused transient decreases in arterial blood pressure and mean femoral blood flow at 1 mg/kg, decreases in arterial blood pressure and the QTc interval at 3 and 10 mg/kg, and a transient increase in mean coronary blood flow and atrioventricular block complete at 10 mg/kg.

The applicant's explanation about the above results:

The plasma C_{max} values of unbound darolutamide and S,S-darolutamide (5.7-9.7 μmol/L and 2-9.7 μmol/L, respectively) in dogs when the above findings were observed were higher than the plasma C_{max} values of unbound darolutamide and S,S-darolutamide (1.16 and 1.03 μmol/L, respectively)[4)] observed after darolutamide was administered at the clinical recommended dose (600 mg twice daily). Based on these results, as well as other data, the above findings are unlikely to pose any safety concerns for the clinical use of darolutamide.

3.3.3 Effects on the respiratory system (CTD 4.2.1.3.3)

A single oral dose of darolutamide (suspension)[5)] at 100, 300, or 1,000 mg/kg was administered to rats (5/group) to evaluate the effects of darolutamide on respiratory rate, tidal volume, and minute volume of ventilation. The darolutamide 1,000 mg/kg group showed decreases in tidal volume and respiratory minute volume at 5 and 24 hours post-dose, compared with the control (vehicle)[6)] group and pre-dose.

The applicant's explanation about the above results:

The plasma C_{max} of unbound darolutamide (3 μmol/L) in rats when the above findings were observed was higher than the plasma C_{max} values of unbound darolutamide and S,S-darolutamide (1.16 μmol/L)[4)] observed after darolutamide was administered at the clinical recommended dose (600 mg twice daily). Based on these results, as well as other data, the above findings are unlikely to pose any safety concerns for the clinical use of darolutamide.

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5) Darolutamide was suspended in 0.5% w/v methylcellulose with 0.5% v/v polysorbate 80.
6) 0.5% w/v methylcellulose with 0.5% polysorbate 80

3.3.4 Effects on the gastrointestinal tract (CTD 4.2.1.3.2 and 4.2.1.3.4 [non-GLP studies])

Darolutamide at 30 or 100 mg/kg was administered to rats (7/group) to evaluate the effects of darolutamide on gastric emptying and gastrointestinal motility. Both of the darolutamide groups showed delays in gastric emptying and intestinal movement, compared with the control (vehicle)[3)] group.

Similarly, darolutamide (suspension)[5)] at 30, 100, 300, or 1,000 mg/kg was administered to rats (8/group) to evaluate the effects of darolutamide on gastric emptying and gastrointestinal motility. No effects were seen in any of the groups.

The applicant's explanation about the above results:
For the following reasons, as well as other data, the above findings are unlikely to pose any safety concerns for the clinical use of darolutamide.

- In a 26-week repeated dose toxicity study in rats and a 39-week repeated dose toxicity study in dogs, no gastrointestinal findings were reported [see Section 5.2].
- In clinical studies with darolutamide, the incidence of constipation, an adverse event that is likely to be associated with the above results, did not tend to be higher in the darolutamide group than in the placebo group [see Section 7.3.2].

3.R Outline of the review conducted by PMDA

The above applicant's explanations about the non-clinical pharmacology of darolutamide are acceptable, based on the submitted data and the discussion described in the subsection below.

3.R.1 Mechanism of action and efficacy of darolutamide

The applicant's explanation about the mechanism of action and efficacy of darolutamide in the treatment of prostate cancer:
Prostate cancer is an androgen-dependent tumor, and the proliferation of prostate cancer cells is considered to be accelerated by testosterone, which is produced by multiple testosterone production systems in the body.

Upon binding with dihydrotestosterone formed from testosterone at the ligand binding domain, AR dimerizes and then translocates to the nucleus, where the homo-dimer binds to the androgen response element of the AR target genes, resulting in the increased expression of genes that are associated with cell survival and proliferation (*Cold Spring Harb Perspect Med.* 2017;7: a030452).

Darolutamide competitively inhibits (a) androgen binding to the ligand binding domain of AR [see Section 3.1.1], (b) nuclear translocation of the transcription factor (i.e., AR) [see Section 3.1.3], and (c) transcription of the AR target genes [see Section 3.1.2], thereby blocking AR-mediated signaling and consequently inhibiting the growth of androgen-dependent tumors.

In view of the fact that darolutamide inhibited the proliferation of human prostate cancer-derived cells [see Section 3.1.5], as well as the above mechanism of action, darolutamide is expected to be effective in the treatment of prostate cancer.

The applicant's explanation about the pharmacological differences between darolutamide and the AR-inhibitory drugs that have been approved for the treatment of prostate cancer in Japan, including apalutamide, enzalutamide, bicalutamide, and flutamide:

- Both darolutamide and all existing drugs bind to AR. Darolutamide, apalutamide, and enzalutamide inhibit the nuclear translocation of AR, whereas bicalutamide has no such inhibitory effect (*Sci Rep.* 2015;5:12007, etc.)
- Bicalutamide has no inhibitory effect on the activation of AR with the W742L mutation,[7)] while apalutamide and enzalutamide have no inhibitory effect on the activation of AR with the F877L mutation.[8)] Darolutamide, on the other hand, inhibits the activation of AR, regardless of the mutant type (including T878A[9)]) [see Section 3.1.2].

PMDA's view:

PMDA accepted the applicant's explanation. However, findings regarding the pharmacological properties of darolutamide, including differences from existing AR-inhibitory drugs, may become useful in selecting eligible patients in clinical practice. Therefore, the pharmacology of darolutamide should continue to be investigated, and new information should be appropriately communicated to healthcare professionals.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

In this section, unless otherwise specified, the dose and concentration of darolutamide are expressed as the total dose and concentration of S,R- and S,S-darolutamide. The non-clinical pharmacokinetics of darolutamide were evaluated in rats, etc. The plasma protein binding, drug metabolizing enzymes, transporters, and other pharmacokinetic properties of darolutamide were investigated using human or animal biomaterials.

4.1 Absorption

4.1.1 Single-dose studies

A single intravenous dose of darolutamide at 10 mg/kg or a single oral dose of ^{14}C-darolutamide at 10 mg/kg was administered to male rats to evaluate the plasma concentrations and pharmacokinetic parameters of darolutamide, S,R- and S,S-darolutamide, and M-1 (keto-darolutamide) (Table 7). The bioavailability of darolutamide after oral administration was >100%. There were no clear differences in pharmacokinetic parameters between S,R- and S,S-darolutamide.

7) A mutation where tryptophan 742 is replaced by leucine, conferring resistance to bicalutamide
8) A mutation where phenylalanine 877 is replaced by leucine, conferring resistance to apalutamide and enzalutamide
9) A mutation where threonine 878 is replaced by alanine, conferring resistance to flutamide

Table 7. Pharmacokinetic parameters of darolutamide, S,R- and S,S-darolutamide, and M-1 (male rats; single intravenous or oral administration)

Dose (Route of administration)	Analyte	C_{max} (μg/mL)	t_{max} (h)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)
10 mg/kg*1 (intravenous)	Darolutamide	18.9 ± 6.45	0.0333 (0.0333, 0.0333)	22.4 ± 6.91	4.05 ± 0.638	0.478 ± 0.136	1.22 ± 0.454
	S,R-darolutamide	10.8 ± 3.72	0.0333 (0.0333, 0.0333)	12.7 ± 4.64	3.99 ± 0.633	0.430 ± 0.139	0.922 ± 0.372
	S,S-darolutamide	8.12 ± 2.74	0.0333 (0.0333, 0.0333)	9.61 ± 2.28	4.09 ± 0.637	0.542 ± 0.127	1.67 ± 0.530
	M-1	7.56 ± 2.83	0.250 (0.0833, 1.00)	22.2 ± 7.03	3.49 ± 0.615	—	—
10 mg/kg*2 (oral)	Darolutamide	5.88	1.00	27.2	3.28	—	—
	S,R-darolutamide	3.75	1.00	14.5	3.29	—	—
	S,S-darolutamide	2.13	1.00	12.7	3.28	—	—
	M-1	3.59	2.00	20.0	3.79	—	—

*1 Median (range) for t_{max}, mean ± SD for other pharmacokinetic parameters, n = 4
*2 Pharmacokinetic parameters were calculated from the mean plasma concentrations of darolutamide, S,R- and S,S-darolutamide, and M-1 at each timepoint (n = 2); —, Not estimated.

4.1.2 Repeated-dose studies

Repeated oral doses of darolutamide at 100, 300, or 1,000 mg/kg were administered to male and female rats once daily for 4 weeks to evaluate the plasma concentrations and pharmacokinetic parameters of darolutamide and M-1 (Table 8). Exposures (C_{max} and AUC_{24h}) to darolutamide and M-1 increased less than dose-proportionally over the dose range tested. The applicant explained that the less than dose-proportional increases in exposures to darolutamide and M-1 may be attributable to the decreased solubility and absorption of darolutamide in the gastrointestinal tract with increasing dose. Exposure to darolutamide tended to be higher in females than in males. The AUC_{24h} ratio of M-1 to darolutamide was lower in females (0.7-1.1[10)]) than in males (1.1-1.4[10)]). The applicant explained that the above sex differences in exposure to darolutamide and the AUC_{24h} ratio of M-1 to darolutamide may be attributable to sex differences in the levels and types of cytochrome P450 (CYP) enzymes expressed in rats (*Drug Metab Rev.* 1998;30:441-98, etc.), given that darolutamide is excreted primarily through metabolism [see Section 4.3.1]. There were no evident increases in exposure to darolutamide or M-1 due to repeated administration.

10) The range of the mean AUC_{24h} ratios, estimated by day of measurement and dose

Table 8. Pharmacokinetic parameters of darolutamide and M-1 (male and female rats; 4-week repeated oral administration)

Day of Measurement (Day)	Dose (mg/kg)	Analyte	n	C_{max} (μg/mL)		t_{max}* (h)		AUC_{24h} (μg·h/mL)	
				Male	Female	Male	Female	Male	Female
1	100	Darolutamide	4	12.4 ± 2.62	10.9 ± 1.22	2.00 (2.00, 2.00)	2.00 (0.500, 2.00)	138 ± 13.5	112 ± 53.0
		M-1	4	12.3 ± 1.74	9.58 ± 1.72	5.00 (2.00, 5.00)	2.00 (0.500, 2.00)	156 ± 27.2	95.4 ± 37.4
	300	Darolutamide	4	14.3 ± 2.46	16.5 ± 1.37	10.0 (5.00, 12.00)	2.00 (2.00, 5.00)	228 ± 41.3	248 ± 27.7
		M-1	4	16.2 ± 2.44	13.4 ± 1.48	8.00 (5.00, 12.0)	2.00 (2.00, 5.00)	243 ± 29.7	183 ± 32.6
	1,000	Darolutamide	4	22.3 ± 3.95	29.9 ± 8.55	6.50 (5.00, 12.0)	10.00 (8.00, 12.0)	373 ± 99.8	514 ± 126
		M-1	4	24.1 ± 6.66	25.2 ± 2.73	6.50 (5.00, 12.0)	8.50 (5.00, 12.0)	409 ± 141	448 ± 70.1
28	100	Darolutamide	4	9.46 ± 0.236	15.5 ± 1.51	2.00 (2.00, 2.00)	3.50 (2.00, 8.00)	88.7 ± 11.8	166 ± 51.4
		M-1	4	11.7 ± 2.26	13.4 ± 0.754	2.00 (2.00, 2.00)	3.50 (2.00, 5.00)	107 ± 24.9	150 ± 46.0
	300	Darolutamide	4	13.0 ± 4.00	18.9 ± 1.61	3.50 (2.00, 5.00)	2.00 (2.00, 2.00)	152 ± 42.1	217 ± 25.7
		M-1	4	17.2 ± 3.96	17.7 ± 3.52	2.00 (2.00, 5.00)	2.00 (2.00, 5.00)	204. ± 57.1	211 ± 37.1
	1,000	Darolutamide	4	14.4 ± 2.50	20.6 ± 4.20	3.50 (2.00, 5.00)	3.50 (2.00, 5.00)	213 ± 62.3	246 ±5 3.8
		M-1	4	19.4 ± 5.15	22.5 ± 9.02	2.00 (2.00, 5.00)	2.00 (2.00, 5.00)	289 ± 91.8	271 ± 128

Mean ± SD; *, Median (range)

4.1.3 *In vitro* membrane permeability

The membrane permeability of darolutamide was evaluated in human colon cancer-derived Caco-2 cells. The apparent permeability coefficient value in the apical to basolateral direction ($P_{app\ A\rightarrow B}$) of darolutamide was 58.0 nm/sec at 5 μmol/L. The applicant explained that darolutamide is highly permeable, given that the $P_{app\ A\rightarrow B}$ of atenolol (100 μmol/L), a known poorly permeable compound, is 2.65 nm/sec, and that of minoxidil (10 μmol/L), a known highly permeable compound, is 65.2 nm/sec.

4.2 Distribution

4.2.1 Tissue distribution

A single oral dose of ^{14}C-darolutamide 100 mg/kg was administered to male albino and pigmented rats to evaluate the tissue distribution of radioactivity using quantitative whole-body autoradiography.

In albino rats, radioactivity was distributed in a wide range of tissues, which peaked by 12 hours post-dose in most tissues. The AUC_{24h} of the radioactivity in urine, the bladder wall, bile, gastric (non-fundus) mucosa, renal cortex, and liver (9,470, 6,760, 1,580, 1,250, 967, and 945 mg Eq·h/kg, respectively) were notably higher than the AUC_{24h} of the radioactivity in blood (412 mg Eq·h/kg). The tissue distribution of the radioactivity in pigmented rats was similar to that in albino rats, except for the skin and uvea/retina. The $t_{1/2}$ values of radioactivity in the skin and uvea/ratina of pigmented rats (203 and 36.3 hours, respectively) were longer than those of albino rats (11.6 and 3.85 hours, respectively). The applicant explained that the results suggest the binding of darolutamide and its metabolites to melanin.

4.2.2 Plasma protein binding

Mouse, rat, dog, or human plasma was incubated with darolutamide (20-5,000 ng/mL) or M-1 (200-10,000 ng/mL) at 37°C for 2 hours, and the plasma protein binding of darolutamide and M-1 was evaluated using equilibrium dialysis. The unbound fractions of darolutamide and M-1 were nearly constant over the concentration ranges tested in mouse, rat, and human plasma. The unbound fractions of darolutamide were from 4.13% to 5.05% in mouse plasma, 5.38 to 5.61% in rat plasma, and 7.02% to 9.75% in human plasma. The unbound fractions of M-1 were from 0.566% to 1.11% in mouse plasma, 0.651% to 0.842% in rat plasma, and 0.182% to 0.214% in human plasma. Meanwhile, the unbound fractions of darolutamide and M-1 in dog plasma tended to increase with increasing concentration, at from 0.710% to 8.35% for darolutamide and 0.285% to 3.40% for M-1. The applicant explained as follows: In view of the above results, as well as the plasma albumin concentration in dogs (530 μmol/L), darolutamide and M-1 are unlikely to be completely saturated with albumin, and are likely to instead bind to α1-acid glycoprotein or other proteins, which are present at lower concentrations in dog plasma.

Human plasma was incubated with S,R-darolutamide (1,000-10,000 ng/mL) or S,S-darolutamide (1,000-10,000 ng/mL) at 37°C for 2 hours, and the plasma protein binding of S,R-darolutamide and S,S-darolutamide was evaluated using equilibrium dialysis. The unbound fractions of S,R-darolutamide and S,S-darolutamide were nearly constant over the concentration ranges tested in human plasma, at from 7.5% to 8.8% and 7.0% to 8.8% respectively.

Human serum albumin (45 mg/mL) or human α1-acid glycoprotein (1 mg/mL) was incubated with darolutamide (20-5,000 ng/mL) or M-1 (200-10,000 ng/mL) at 37°C for 2 hours, and the plasma protein binding of darolutamide and M-1 to human serum albumin and human α1-acid glycoprotein was evaluated using equilibrium dialysis. The unbound fractions of darolutamide were from 13.2% to 15.9% in human serum albumin and 50.6% to 71.0% in human α1-acid glycoprotein. The unbound fractions of M-1 were from 0.291% to 0.361% in human serum albumin and 33.9% to 48.7% in human α1-acid glycoprotein. The applicant explained that darolutamide and M-1 bind mainly to serum albumin in human plasma.

4.2.3 Distribution in blood cells

Mouse, rat, dog, or human blood was incubated with darolutamide (20-1,000 ng/mL) or M-1 (200-10,000 ng/mL) at 37°C for 1 hour, and the distribution of darolutamide and M-1 in blood cells was evaluated based on the blood to plasma radioactivity concentration ratios. The blood to plasma concentration ratios of darolutamide were from 0.562 to 0.575 in mice, 0.639 to 0.673 in rats, 0.466 to 0.510 in dogs, and 0.730 to 0.823 in humans. The blood to plasma concentration ratios of M-1 were from 0.509 to 0.575 in mice, 0.494 to 0.525 in rats, 0.496 to 0.661 in dogs, and 0.495 to 0.514 in humans. The applicant explained that darolutamide is distributed mainly in plasma in all of the animal species tested.

4.2.4 Placental and fetal transfer

Darolutamide is an antitumor drug intended for the treatment of prostate cancer. Therefore, the placental or fetal transfer of darolutamide was not investigated.

4.3 Metabolism

4.3.1 *In vitro*

Mouse, rat, dog, or human hepatocytes were incubated with ^{14}C-darolutamide (5 or 20 μmol/L) at 37°C for 3 hours to identify the metabolites of darolutamide. M-1 was detected predominantly in all of the animal species and humans. Other metabolites observed were M-2 and M-3 (both hydroxylation and glucuronidation), M-4 (hydroxylation and glucuronidation of M-1), M-7 (*O*-glucuronidation), and M-8 (hydroxylation of M-1).

The applicant's explanation:

Based on the following study results (a) and (b), and other findings, it was expected that: (a) darolutamide is metabolized primarily by CYP3A4, and that (b) UGT1A9 and UGT2B10 are responsible for the *O*-glucuronidation and *N*-glucuronidation, respectively, of darolutamide.

- Recombinant human CYP isozymes (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP3A7, CYP4A11, CYP4F2, CYP4F3A, CYP4F3B, CYP4F12, and CYP19) were incubated with ^{14}C-darolutamide (1 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) at 37°C for 1 hour to identify the CYP isozymes participating in the metabolism of darolutamide. The proportion of unchanged darolutamide decreased to 65.6% and 16.4%, respectively, after incubation with CYP1A1 and CYP3A4, while it remained at 86.9% to 100% after incubation with other CYP isozymes, with no clear declines.
- Recombinant human uridine diphosphate glucuronosyl transferase (UGT) isozymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10, UGT2B15, and UGT2B17) were incubated with darolutamide (1 μmol/L) in the presence of uridine diphosphate glucuronic acid (UDPGA) at 37°C for 1 hour to identify the UGT isozymes participating in the glucuronidation of darolutamide. After incubation with UGT1A9, M-7 was predominantly found (formulation concentration of 32.2 nmol/L).[11)] After incubation with UGT2B10, M-15a (*N*-glucuronidation) was predominantly found (formulation concentration of 1.56 nmol/L).

4.3.2 *In vivo*

A single oral dose of ^{14}C-darolutamide at 10 mg/kg was administered to bile duct-uncannulated male rats, and a single intravenous dose of ^{14}C-darolutamide at 2 mg/kg was administered to bile duct-cannulated male rats, to identify the metabolites of darolutamide in plasma, urine, feces, and bile, and the following results were obtained.

11) Total amount of M-7a and M-7b

- The major compounds found in the plasma collected from bile duct-uncannulated male rats at 12 hours post-dose were unchanged darolutamide and M-1 (accounting for 49.9% and 48.6% of the total radioactivity in plasma, respectively).
- The major compounds found in the urine, feces, and bile collected from bile duct-cannulated male rats at 24 hours post-dose were M-24 (dealkylation), unchanged darolutamide, and M-10 (*N*-glucuronidation of M-1), respectively (accounting for 16.1%, 12.6%, and 11.2% of the total administered radioactivity, respectively).

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

The applicant's explanation:

Based on the study results below, darolutamide and its metabolites are expected to be excreted mainly in feces via bile.

- In bile duct-uncannulated male rats, the urinary and fecal excretion rates (relative to the administered radioactivity) for 168 hours after a single oral dose of ^{14}C-darolutamide at 10 mg/kg were 30.4% and 64.2%, respectively.
- In bile duct-cannulated male rats, the urinary, fecal, and biliary excretion rates (relative to the administered radioactivity) for 24 hours after a single intravenous dose of ^{14}C-darolutamide 2 mg/kg were 23.4%, 12.8%, and 52.5%, respectively.

4.4.2 Excretion into milk

Darolutamide is an antitumor drug intended for the treatment of prostate cancer. Therefore, the excretion of darolutamide into milk was not investigated.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation about the pharmacokinetic interactions of darolutamide, S,R- and S,S-darolutamide, and M-1 through the inhibition of metabolizing enzymes:

Based on the following study results, as well as the $C_{max,ss}$ values of darolutamide, S,R- and S,S-darolutamide, and M-1 observed when darolutamide was administered according to the proposed dosage and administration (14.5, 2.2, 12.9, and 27.9 μmol/L, respectively[12)]), darolutamide, S,R- and S,S-darolutamide, and M-1 are unlikely to cause pharmacokinetic interactions through the inhibition of any CYP or UGT isozyme in humans.

- Human liver microsomes were incubated with darolutamide (0.03-100 μmol/L) or M-1 (0.03-100 μmol/L) in the presence of substrates for CYP isozymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A)[13)] and NADPH to evaluate the inhibitory

12) The $C_{max, ss}$ values observed when darolutamide 600 mg was orally administered twice daily in a Japanese phase I study (Study 17719)

13) The tested substrates for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 were phenacetin, coumarin, bupropion, paclitaxel, diclofenac, *S*-mephenytoin, bufuralol, and chlorzoxazone, respectively. The tested substrates for CYP3A were midazolam and testosterone.

effects of darolutamide and M-1 on each CYP isozyme. Darolutamide inhibited the metabolism of the substrates for CYP2C9, CYP2C19, and CYP2D6 with IC_{50} values of 30.3, 64.1, and 81.9 μmol/L, respectively. M-1 inhibited the metabolism of the substrates for CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, with IC_{50} values of 54.2, 48.6, 9.6, 39.5, and 51.9 μmol/L, respectively. Neither darolutamide nor M-1 displayed evident inhibitory effects on the metabolism of the substrates for the other CYP isozymes tested.

- Human liver microsomes and recombinant human CYP2J2 were incubated with S,R- or S,S-darolutamide (1.56-50 μmol/L for both) in the presence of substrates for CYP isozymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, and CYP3A[14)] and NADPH to evaluate the inhibitory effects of S,R- and S,S-darolutamide on each CYP isozyme. S,R-darolutamide inhibited the metabolism of the substrates for CYP2C8, CYP2C9, and CYP2C19 with IC_{50} values of 36.2, 22.6, and 46.7 μmol/L, respectively. S,S-darolutamide inhibited the metabolism of the substrates for CYP2C8 and CYP2D6 with IC_{50} values of 46.3 and 40.2 μmol/L, respectively. S,R- or S,S-darolutamide did not display evident inhibitory effects on the metabolism of the substrates for the other CYP isozymes tested.
- Human liver microsomes were incubated with S,R- or S,S-darolutamide (0.1-100 μmol/L for both), or M-1 (0.05-50 μmol/L) in the presence of substrates for UGT isozymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7)[15)] and UDPGA to evaluate the inhibitory effects of S,R- and S,S-darolutamide and M-1 on each UGT isozyme. S,R-darolutamide inhibited the metabolism of the substrates for UGT1A1 and UGT1A9 with IC_{50} values of 26.5 and 12.5 μmol/L, respectively. S,S-darolutamide and M-1 inhibited the metabolism of the substrate for UGT1A1, with IC_{50} values of 31.7 and 6.41 μmol/L, respectively. S,R- or S,S-darolutamide, or M-1 did not display evident inhibitory effects on the metabolism of the substrates for the other UGT isozymes tested.

4.5.2 Enzyme induction

The applicant's explanation about the pharmacokinetic interactions of darolutamide, S,R- and S,S-darolutamide, and M-1 through the induction of metabolizing enzymes:

Based on the following study results, as well as the $C_{max,ss}$ values of darolutamide, S,R- and S,S-darolutamide, and M-1 observed when darolutamide was administered according to the proposed dosage and administration (5,799, 865, 5,150, and 11,100 ng/mL respectively),[12)] darolutamide, S,R- and S,S-darolutamide, and M-1 are unlikely to cause pharmacokinetic interactions through the induction of CYP1A2 or CYP2B6 in humans. However, darolutamide, S,R- and S,S-darolutamide, and M-1 are likely to cause pharmacokinetic interactions through the induction of CYP3A4.

- Primary human hepatocytes were incubated with darolutamide, S,R- and S,S-darolutamide, and M-1 (5-10,000 mg/mL) for 3 days to determine the mRNA expression of CYP isozymes (CYP1A2, CYP2B6, and CYP3A4). Darolutamide, S,R- and S,S-darolutamide, and M-1 increased the mRNA

14) The tested substrates for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP2J2 were phenacetin, coumarin, bupropion, amodiaquine, diclofenac, *S*-mephenytoin, dextromethorphan, chlorzoxazone, and ebastine, respectively. The tested substrates for CYP3A were midazolam and testosterone.

15) The tested substrates for UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 were estradiol, trifluoperazine, serotonin, propofol, and 3'-azido-3'-deoxythymidine, respectively.

expression of CYP3A4. The inhibition of CYP3A4 mRNA expression by darolutamide, S,R- and S,S-darolutamide, and M-1 was up to 24%, 24%, 32%, and 23%, respectively, of that by rifampicin (10,000 ng/mL), a positive control. The half maximal effective concentration (EC_{50}) values for the induction of CYP3A4 mRNA expression by darolutamide, S,R- and S,S-darolutamide, and M-1 were from 1,472 to 4,035, 1,112 to 11,056, 1,025 to 8,417, and 1,071 to 4,160 ng/mL, respectively. Similarly, the maximum fold induction (E_{max}) values were from 3.3 to 10.0, 2.7 to 20.3, 2.6 to 21.7, and 4.0 to 9.7, respectively. Darolutamide, S,R- or S,S-darolutamide, or M-1 did not display evident inhibitory effects on the mRNA expression of either CYP1A2 or CYP2B6.

4.5.3 Transporters

The applicant's explanation about the pharmacokinetic interactions of darolutamide and M-1 through transporters:

Based on the following study results and other available data, darolutamide and M-1 were demonstrated not to be a substrate for organic anion transporting polypeptide (OATP) 1B1, OATP1B3, or organic cation transporter (OCT) 1, but to be substrates for p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Given the absolute bioavailability (98.9%) of darolutamide following administration of the oral liquid formulation in humans [see Section 6.2.1.2] and other available data, however, the contribution of P-gp to the gastrointestinal absorption of darolutamide is expected to be limited. Therefore, darolutamide is unlikely to cause pharmacokinetic interactions, when administered concomitantly with P-gp inhibitors in humans.

- The P-gp- or BCRP-mediated transport of darolutamide (2 μmol/L) was investigated in Caco-2 cells, and Caco-2 cells with a lower expression of human P-gp or BCRP. The efflux ratio of darolutamide was 98 in Caco-2 cells, 3.6 in Caco-2 cells with lower P-gp expression, and 36 in Caco-2 cells with lower BCRP expression.
- P-gp- or BCRP-mediated transport of M-1 (1 μmol/L) was investigated in canine kidney-derived MDCK cells expressing human P-gp or BCRP. The efflux ratios of M-1 without and with a P-gp inhibitor (valspodar, 1 μmol/L) were 69.3 and 1.14, respectively, while those without and with a BCRP inhibitor (Ko143, 0.5 μmol/L) were 13.5 and 1.89, respectively.
- The OATP1B1- or OATP1B3-mediated intracellular uptake of darolutamide (0.5-10 μmol/L) and M-1 (1-10 μmol/L) was investigated in HEK293 cells expressing human OATP1B1 or OATP1B3. The ratios of the uptake of darolutamide and M-1[16)] were ≤2, over the concentration ranges tested.
- The OCT1-mediated intracellular uptake of ^{14}C-darolutamide (1-10 μmol/L) and ^{14}C-M-1 (1-10 μmol/L) was investigated in HEK293 cells expressing human OCT1. The ratios of the uptake of ^{14}C-darolutamide and ^{14}C-M-1 uptake into transporter-expressing cells to that into non-expressing cells[16)] were ≤1.2, over the concentration ranges tested.

Given the following study results, as well as the $C_{max,ss}$ values of darolutamide and M-1 (14.5 and 27.9 μmol/L, respectively)[12)] and the estimated gastrointestinal concentrations (up to 270 μmol/L) of

16) The ratios of the uptake of darolutamide and M-1 into transporter-expressing cells to that into transporter non-expressing cells

darolutamide administered with the proposed dosage and administration, darolutamide is unlikely to cause pharmacokinetic interactions through the inhibition of OAT1, OATP2B1, OCT1, OCT2, NTCP, BSEP, or MRP2. Similarly, M-1 is unlikely to cause pharmacokinetic interactions through the inhibition of OAT1, OAT3, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, NTCP, P-gp, BCRP, BSEP, MRP2, MATE1, or MATE2-K. Darolutamide is likely to cause pharmacokinetic interactions through the inhibition of P-gp, BCRP, MATE1, MATE2-K, OAT3, OATP1B1, or OATP1B3 in humans.

- The inhibitory effects of darolutamide (0.1-60 μmol/L)[17] on the transport of substrates[18] for various transporters through P-gp, BCRP, BSEP, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, or NTCP were investigated in Caco-2 cells, HEK293 cells expressing human MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, or NTCP, and sandwich-cultured human hepatocytes expressing human BSEP. Darolutamide inhibited the transport of substrates for P-gp, BCRP, MATE1, MATE2-K, OAT3, OATP1B1, and OATP1B3 with IC_{50} values of 16.4, 1.33, 32.3, 9.5, 4.5, 3.8, and 5.0 μmol/L, respectively. Darolutamide had no evident inhibitory effects on the transport of the substrates for BSEP, MRP2, OAT1, OATP2B1, OCT1, OCT2, or NTCP.
- The inhibitory effects of M-1 (0.2-50 μmol/L)[19] on the transport of substrates[17] for transporters through P-gp, BCRP, BSEP, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, or NTCP were investigated in MDCK cells expressing human P-gp or BCRP, HEK293 cells expressing human MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, or NTCP, and sandwich-cultured human hepatocytes expressing human BSEP. M-1 inhibited the transport of the substrates for P-gp, BCRP, MATE2-K, OATP1B1, and OATP1B3 with IC_{50} values of 2.6, 0.6, 2.9, 3.0, and 14.2 μmol/L, respectively. M-1 had no evident inhibitory effects on the transport of the substrates for BSEP, MATE1, MRP2, OAT1, OAT3, OATP2B1, OCT1, OCT2, and NTCP.

4.R Outline of the review conducted by PMDA

Based on the submitted data and the discussions in the following subsections, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics of darolutamide was acceptable.

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17) The tested concentrations of darolutamide were 0.25 to 60 μmol/L for P-gp, BCRP, and OAT3; 5 and 50 μmol/L for MRP2, OATP2B1, OAT1, OCT1, OCT2, and NTCP; 0.206 to 50 μmol/L for MATE1 and MATE2-K; and, 0.2 to 50 μmol/L for OATP1B1 and OATP1B3.

18) The tested substrates for P-gp, BCRP, BSEP, MRP2, OAT1, OAT3, OCT1, and OCT2 were digoxin (10 μmol/L), cladribine (10 μmol/L), taurocholic acid (5 μmol/L), 5(6)-carboxy-2',7'-dichlorofluorescein (5 μmol/L), *p*-aminohippuric acid (10 μmol/L), furosemide (5 μmol/L), ^{3}H-1-methyl-4-phenylpyridinium iodide (10 μmol/L), and 1-methyl-4-phenylpyridinium iodide (5 μmol/L), respectively. The tested substrate for MATE1 and MATE2-K was metformin (50 μmol/L), that for OATP1B1 and OATP1B3 was pravastatin (5 μmol/L), and that for OATP2B1 and NTCP was ^{3}H-estrone sulfate (2 and 5 μmol/L).

19) The tested concentrations of M-1 were 0.0412 to 10 μmol/L for P-gp and BCRP, 1 to 300 μmol/L for BSEP, 1 to 10 μmol/L for MRP2, MATE1, OATP2B1, OCT1, and NTCP, 0.313 to 10 μmol/L for MATE2-K, and 0.2 to 2 μmol/L for OAT1, OAT3, and OCT2.

4.R.1 Tissue distribution

The study results suggested that darolutamide or its metabolites bind to melanin [see Section 4.2.1]. PMDA asked the applicant to explain the safety of darolutamide in melanin-containing tissues.

The applicant's explanation:

In view of the following study outcomes and other data, the distribution of darolutamide and its metabolites in melanin-containing tissues is unlikely to pose a safety concern for its clinical use.

- The results of a 39-week repeated dose toxicity study in dogs provided no toxicity findings in melanin-containing tissues such as skin and eyes [see Section 5.2].
- The incidence of skin- or eye-related adverse events in Japanese patients enrolled in a global phase III study (Study 17712) did not clearly differ between the darolutamide group (12.9% [8 of 62 patients]) and the placebo group (18.2% [6 of 33 patients]).

PMDA accepted the applicant's explanation.

4.R.2 Pharmacokinetic interactions

The following *in vitro* data suggested that darolutamide may cause pharmacokinetic interactions through some metabolizing enzymes or transporters in humans.

- UGT1A9 is mainly responsible for the glucuronidation of darolutamide [see Section 4.3.1].
- Darolutamide inhibits MATE1, MATE2-K, and OAT3 [see Section 4.5.3].
- Darolutamide and M-1 are substrates for BCRP [see Section 4.5.3].

The applicant's explanation about the pharmacokinetic interactions between darolutamide or M-1, and the above metabolizing enzymes or transporters:

- In a global phase III study (Study 17712), a Japanese phase I study (Study 17719), a foreign phase I study (Study 17830), a foreign phase I/II study (Study 17829), and a foreign phase II study (Study 18035), darolutamide administered in combination with a substrate for MATE1, MATE2-K, or OAT3, or a UGT or BCRP inhibitor caused no particular safety concerns. Based on these study results, as well as other data, coadministration with the above substrates or inhibitors is unlikely to pose a safety concern for the clinical use of darolutamide.
- In a global phase III study (Study 17712), the efficacy of darolutamide did not clearly differ between patients treated with darolutamide alone and those treated with darolutamide in combination with a UGT inhibitor. Therefore, coadministration with UGT inhibitors is unlikely to pose a safety concern for the clinical use of darolutamide.

PMDA's view:

PMDA accepted the applicant's explanation in general. However, information on the pharmacokinetic interactions of darolutamide through UGT1A9, MATE1, MATE2-K, OAT3, and BCRP is important for the proper use of darolutamide. Therefore, relevant information should continue to be collected, and any beneficial information should be appropriately communicated to healthcare professionals.

The following findings are detailed in Section "6.2.2 Drug-drug interaction studies."

- CYP3A4 is mainly responsible for the metabolism of darolutamide [see Section 4.3.1].
- Darolutamide, S,R- and S,S-darolutamide, and M-1 induce CYP3A4 [see Section 4.5.2].
- Darolutamide inhibits P-gp, BCRP, OATP1B1, and OATP1B3 [see Section 4.5.3].

5. Toxicity and Outline of the Review Conducted by PMDA

Darolutamide used in the studies described in this section was a mixture of its 2 diastereomers, S,S- and S,R-darolutamide, in equal proportions.

In *in vivo* studies, unless otherwise specified, darolutamide was suspended in a vehicle composed of 0.5% (w/v) methylcellulose with 0.5% (v/v) polysorbate 80 for administration.

5.1 Single-dose toxicity

No single dose toxicity study was conducted for darolutamide. However, the acute toxicity of darolutamide was evaluated based on the results of a 3-day repeated oral dose study in male rats, and 3-day and 7-day repeated oral dose studies, respectively, in female and male dogs (Table 9).

Table 9. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male rats (Wister) 3-day repeated doses	Oral	500, 1,000, 2,000[a)] (once daily)	2,000: transiently decreased weight gain	>2,000	4.2.3.2.1 (for reference)
Male dogs (beagle) 3-day repeated doses	Oral	50, 200, 400, 800, 1,000 (once daily)	No toxic changes	>1,000	4.2.3.2.6 (for reference)
Female dogs (beagle) 3-day repeated doses	Oral	200, 400 (twice daily) 200, 400, 800, 1,000 (once daily)	No toxic changes	>1,000	4.2.3.2.7 (for reference)

a) 0.5% methylcellulose was used as the vehicle.

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies were conducted in rats (4 and 26 weeks) and dogs (4, 13, and 39 weeks) (Table 10). The major toxicological target organs were the male reproductive organs, both in rats and dogs. In addition, decreased body weight, which was considered to be attributable to the antianabolic effect of darolutamide, was also found. In (a) a 26-week repeated oral dose toxicity study in rats and (b) a 39-week repeated oral dose toxicity study in dogs, exposure to darolutamide (C_{max} and $AUC_{0\text{-}24h}$) at the no observed adverse effect level (NOAEL) ((a) 1,000 mg/kg/day and (b) 400 mg/kg/day) in male animals was (a) 8.48 µg/mL and 135 µg·h/mL, and (b)12.1 µg/mL and 206 µg·h/mL, which were (a) 2.5- and 2.3-fold, and (b) 3.6- and 3.6-fold higher than the clinical exposure.[20)]

[20)] The C_{max} and $AUC_{0\text{-}24h}$ values in healthy adults receiving repeated oral doses of darolutamide 600 mg twice daily were 3.33 µg/mL and 57.6 µg·h/mL, respectively.

Table 10. Repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Wister)	Oral	4 weeks (once daily)	0, 100, 300, 1,000	≥100: Decreased food consumption and decreased body weight gain (males), decreased prostate and epididymis weights, and increased thymus weight (males), small epididymis, decreased secretion in the prostate and seminal vesicle, and delayed atrophy of the thymus (males) 1,000: Salivary hypersecretion	1,000	4.2.3.2.4
Male and female rats (Wister)	Oral	26 weeks (twice daily) + 4 weeks of recovery	0, 100, 300, 1,000	≥100: Decreased body weight gain accompanied by a tendency toward decreased food consumption (males), decreased prostate, epididymis, and testis weights, small epididymis, prostate and testis atrophy, narrow epididymal duct, mammary gland atrophy, and anterior pituitary vacuolation (males) The findings were reversible.	1,000	4.2.3.2.5
Male dogs (beagle)	Oral	4 weeks (once daily)	0, 50, 200, 800	≥50: Decreased body weight, decreased prostate and epididymis weights, prostate atrophy, and epididymal hypospermia and epididymis epithelial vacuolation ≥200: Decreased food consumption	800	4.2.3.2.8
Male and female dogs (beagle)	Oral	13 weeks (twice daily) + 4 weeks of recovery	0, 50, 150, 400	≥50: Decreased prostate and epididymis weights, prostate atrophy, narrow epididymal duct, and epididymis epithelial vacuolation and epididymis atrophy 400: White feces, decreased body weight gain (females), decreased relative kidney weight (males) The findings were reversible.	400	4.2.3.2.9
Male and female dogs (beagle)	Oral	39 weeks (twice daily) + 8 weeks of recovery	0, 50, 150, 400	Electively euthanized[a)]: 400 (1 of 4 females) ≥50: Decreased body weight gain (males), decreased prostate and epididymis weights, increased testis weight, decreased absolute spleen weight (males), prostate atrophy, narrow epididymal duct and epididymal hypospermia, and epididymis epithelial atrophy ≥150: Decreased red blood cell parameters (males), sperm retention in the seminiferous tubules 400: Seminiferous tubular dilation and degeneration/atrophy The findings were reversible.	400	4.2.3.2.10

a) Due to dosing error

5.3 Genotoxicity

The genotoxicity study of darolutamide consisted of 2 *in vitro* studies: a bacterial reverse mutation assay and a chromosomal aberration assay in cultured mammalian cells, and 2 *in vivo* studies: rodent micronucleus and comet assays (Table 11). Darolutamide tested positive (at ≥200 µg/mL without metabolic activation or at ≥240 µg/mL with metabolic activation) in the chromosomal aberration assay in cultured mammalian cells, but negative in the rodent micronucleus and comet assays. These study results indicated that darolutamide is unlikely to be genotoxic in the body.

Table 11. Genotoxicity studies

Type of study		Test system	Metabolic activation (Treatment)	Concentration (µg/plate or µg/mL) or dose (mg/kg/day)	Test result	Attached document CTD
in vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100, TA102	S9−/+	0,[a] 3, 10, 33, 100, 333, 1,000, 2,500, 5,000	Negative	4.2.3.3.1.1
	Chromosomal aberration assay in cultured mammalian cells	Human peripheral blood lymphocytes	S9−/+ (−, 4 and 22 hours; +, 4 hours)	S9− (4 hours)(a): 0,[a] 130.6, 228.6, 400 S9− (4 hours)(b): 0,[a] 100, 200, 225, 250, 275, 300, 325, 350, 375 S9− (22 hours): 0,[a] 24.4, 42.6, 74.6 S9+ (4 hours)(a): 0,[a] 74.6, 130.6, 228.6 S9+ (4 hours)(b): 0,[a] 100, 200, 250 S9+ (4 hours)(c): 0,[a] 200, 240, 260, 340	Positive	4.2.3.3.1.2
in vivo	Rodent micronucleus assay	Male rats (Wister) Bone marrow		0,[b] 100, 500, 1,000 (Once daily for 3 days, oral)	Negative	4.2.3.3.2.1
	Rodent comet assay	Male rats (Wister) Liver, duodenum		0,[b] 100, 500, 1,000 (Once daily for 3 days, oral)	Negative	4.2.3.3.2.1

a) The vehicle (DMSO) only; b) The vehicle (100% Labrasol) only

5.4 Carcinogenicity

Darolutamide is an antineoplastic agent intended to treat advanced cancer. Therefore, no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

Darolutamide is an antineoplastic agent intended to treat advanced cancer. Therefore, no studies were conducted to evaluate the effects of darolutamide on fertility and early embryonic development to implantation, pre- and postnatal development, including maternal function, or embryo-fetal development.

However, the possibility that darolutamide affects male fertility or embryo-fetal development cannot be ruled out, for the following and other reasons.

- In a repeated dose toxicity studies in rats and dogs [see Section 5.2], atrophic changes in the male reproductive organs were found in both species.

- The pharmacology of darolutamide suggests that exposure to darolutamide of pregnant women or women who may be pregnant may cause harm to the fetus.

5.6 Local tolerance

The local irritant effect of darolutamide administered orally was evaluated as part of the general toxicity studies in rats and dogs [see Sections 5.1 and 5.2]. The study results showed no findings suggestive of the local irritant effect of darolutamide on the gastrointestinal tract.

5.7 Other toxicity studies

5.7.1 Photosafety

An *in vitro* 3T3-neutral red uptake (NRU) phototoxicity assay was conducted on darolutamide. The result showed that darolutamide is not phototoxic (Table 12).

Table 12. Phototoxicity study

Test method	Dose (mg/L)	Main findings	Attached document CTD
3T3-NRU assay	0,[a)] 1.78-100	No photo-inducible cytotoxicity	4.2.3.7.7.1

a) The vehicle (1% DMSO/Dulbecco's phosphate buffered saline supplemented with Ca^{2+} and Mg^{2+} ions) only

5.R Outline of the review conducted by PMDA

The applicant's explanation about the toxicity of darolutamide is acceptable, based on the submitted data.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

In this section, unless otherwise specified, the dose and concentration of darolutamide are expressed as the total dose and concentration of S,R- and S,S-darolutamide.

6.1 Summary of biopharmaceutic studies and associated analytical methods

The available oral formulations of darolutamide are oral liquid, capsules, uncoated tablets, and blue film coating (FC) tablets. In addition to these oral formulations, an injectable formulation was used for evaluation of the pharmacokinetics and other aspects of darolutamide (Table 13). The proposed commercial formulation of darolutamide is white FC tablets (each tablet contains 300 mg of darolutamide). The white FC tablets were demonstrated to be bioequivalent to the blue FC tablets, based on the results of a dissolution study conducted according to the Guidelines for Bioequivalence Testing of Oral Solid Dosage Forms with Formulation Modifications (Notification No. 67 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau [PMSB/ELD], Ministry of Health and Welfare [MHLW], dated February 14, 2000; partially revised by Notification No. 0229-(10) of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau [PFSB/ELD], MHLW, dated February 29, 2012).

Table 13. Formulations used in clinical studies

Formulation	Study
^{14}C-darolutamide-containing injectable formulation	Foreign phase I study (Study 17831)
^{14}C-darolutamide-containing oral liquid formulation	Foreign phase I study (Study 17831)
Capsules (100 mg)	Foreign phase I study (Study 17830), foreign phase I/II study (Study 17829), foreign phase II study (Study 18035)
Uncoated tablets (300 mg)*	Foreign phase I study (Study 17830)
Blue FC tablets (300 mg)	Japanese phase I study (Study 17719), global phase III study (Study 17712), foreign phase I studies (Studies 17721, 17723, 17726. 17830, 17831, and 18860), foreign phase II study (Study 18035)

* Uncoated tablets A and B, with different particle size distributions of the drug substance (median particle diameter: 63 and 574 μm, respectively) were used.

6.1.1 Assay

S,R- and S,S-Darolutamide, and M-1 (keto-darolutamide) in human plasma were quantitatively determined using a liquid chromatography/tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantitation of 5 ng/mL[21)] for all of the compounds.

6.1.2 Japanese clinical study

6.1.2.1 Japanese phase I study (CTD 5.3.3.2.2 and 5.3.3.2.3: Study 17719, February 2015 to December 2017)

An open-label, uncontrolled study was conducted in 9 patients with metastatic CRPC (all were included in the pharmacokinetic analysis) to evaluate food effects on the pharmacokinetics and other aspects of darolutamide (blue FC tablets). Darolutamide was administered according to the following dosage regimens, and the plasma concentrations of darolutamide, S,R- and S,S-darolutamide, and M-1 were determined. A washout period of ≤2 days was placed between the treatment periods.

Single dose period: A single oral dose of darolutamide 300 or 600 mg was administered under fasting conditions,[22)] and after 3 days, a single oral dose of darolutamide 300 or 600 mg was administered after a standard Japanese meal.[23)]

Repeated dose period: Darolutamide 300 or 600 mg was orally administered twice daily, within 30 minutes after a standard Japanese meal.[23)]

Table 14 shows the pharmacokinetic parameters of darolutamide and M-1. The geometric mean ratios [90% CIs] of C_{max} and AUC_{last} following the administration of darolutamide 600 mg under fed conditions, to those under fasted conditions were 2.78 [2.00, 3.88] and 2.53 [1.99, 3.21], respectively. The accumulation rates[24)] of darolutamide and M-1, when darolutamide 600 mg was orally administered twice daily, were 2.34 and 2.49, respectively. The ratio of the AUC_{last} of S,S-darolutamide after a single

21) An assay with a lower limit of quantitation of 10 ng/mL for M-1 was used for plasma samples from Studies 17721, 17723, 17726, and 18860.
22) Patients received a single oral dose of darolutamide after fasting for ≥10 hours (overnight), and refrained from eating for ≥4 hours post-dose.
23) Approximately a total of 500 kcal, in which fat accounted for approximately 22% (*Nutrients.* 2018;10:1551)
24) Ratios of AUC_{12h} on Day 7 of twice-daily repeated doses to that after a single dose

oral dose of darolutamide 600 mg administered under fed conditions to that of S,R-darolutamide was 8.5.

Table 14. Pharmacokinetic parameters of darolutamide and M-1

Day of Measurement	Fed/fasted	Dose (mg)	Analyte	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{12h} (μg·h/mL)	AUC_{last} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)
After a single dose	Fasted	300	Darolutamide	3	1.05 (92.9)	3.05 (2.95, 4.97)	8.08 (84.8)	15.7 (69.6)	18.8, 31.1	14.9, 15.5
			M-1	3	1.29 (36.5)	4.97 (2.95, 5.12)	10.30 (51.0)	19.9 (51.6)	22.7 (49.9)	16.2 (15.8)
		600	Darolutamide	6	1.26 (41.3)	4.85 (3.05, 4.92)	10.8 (38.9)	22.0 (41.4)	19.0*2 (34.8)	10.1*2 (21.2)
			M-1	6	1.77 (59.2)	2.88 (1.47, 7.80)	15.7 (53.0)	31.5 (59.4)	31.5*3 (71.4)	11.1*3 (38.5)
	Fed	300	Darolutamide	3	2.59 (7.57)	4.92 (2.98, 8.00)	20.4 (15.3)	39.0 (20.1)	38.6, 53.7	13.2, 16.6
			M-1	3	3.58 (79.7)	4.92 (2.98, 5.00)	27.4 (87.6)	51.6 (85.8)	52.8, 120	11.9, 14.2
		600	Darolutamide	6	3.50 (12.1)	6.29 (4.93, 7.90)	25.1 (15.3)	55.6 (24.0)	63.5*2 (28.9)	14.1*2 (36.7)
			M-1	6	5.84 (31.8)	6.29 (4.93, 7.90)	41.8 (38.9)	89.2 (50.0)	96.5 (54.7)	12.4 (24.7)
Day 7 of repeated dose period	Fed	300	Darolutamide	3	4.60 (10.3)	4.98 (3.00, 8.10)	44.4 (18.2)	41.4 (17.4)	—	—
			M-1	3	6.72 (54.6)	4.98 (3.00, 8.10)	62.0 (62.2)	58.1 (59.6)	—	—
		600	Darolutamide	6	5.80 (22.0)	5.48 (2.87, 10.9)	58.7 (26.9)	54.3 (25.6)	—	—
			M-1	6	11.1 (47.2)	4.89 (2.87, 7.93)	104 (48.8)	97.1 (48.3)	—	—

Geometric mean (geometric CV [%]) (individual values for n = 2); —, Not estimated; *1, Median (range); *2, n = 4; *3, n = 5

In the Japanese phase I study (Study 17719) and a foreign phase I study (Study 17830) [see Section 6.1.3.2], the C_{max} and AUC of darolutamide administered under fed conditions were higher than those under fasted conditions. The applicant explained as follows: Given the solubility of darolutamide in artificial intestinal fluids, which simulated human intestinal fluids in fasted and fed states (30 and 108 μg/mL, respectively), it is likely that food intake increased the solubility of darolutamide, and the increased absorption of darolutamide in the gastrointestinal tract resulted in the increased exposure to darolutamide.

6.1.3 Foreign clinical studies

6.1.3.1 Foreign phase I study (CTD 5.3.1.1.2: Part 1 of Study 17831, March to May 2015)

An open-label, uncontrolled study was conducted in 6 healthy adults (all were included in the pharmacokinetic analysis) to evaluate the absolute bioavailability of darolutamide (blue FC tablets). A single oral dose of darolutamide 300 mg was administered, and after 2 hours and 45 minutes, an intravenous dose of ^{14}C-darolutamide 100 μg was administered over a period of 15 minutes.

The geometric mean absolute bioavailability (geometric coefficient of variation [CV] [%]) calculated from the AUC_{inf} values of darolutamide was 0.299 (19.4).

6.1.3.2 Foreign phase I study (CTD 5.3.1.1.1: Study 17830, March 2013 to April 2017)

A 3-period, crossover study was conducted in 30 patients with chemotherapy-naïve, metastatic CRPC (29 were included in the pharmacokinetic analysis) to evaluate food effects on the pharmacokinetics of darolutamide (uncoated tablets A and B), and to determine the relative bioavailability between the capsules, and uncoated tablets A and B. A single oral dose of darolutamide 600 mg was administered under fasted conditions[22)] or within 30 minutes after a high-fat meal.[25)] A washout period of ≥7 days was placed between treatment periods. Since the uncoated tablets were used only in Study 17830, the results regarding the relative bioavailability between the capsules and the uncoated tablets are not described in this review report.

The geometric mean ratios [90% CIs] of the C_{max} and AUC_{48h} of darolutamide administered as uncoated tablets A under fed conditions, to those under fasted conditions were 2.13 [1.82, 2.50] and 2.56 [2.19, 3.00], respectively. The geometric mean ratios [95% CIs] of the C_{max} and AUC_{48h} of darolutamide administered as uncoated tablets B under fed conditions, to those under fasted conditions were 1.81 [1.57, 2.10] and 2.01 [1.71, 2.36], respectively. The geometric mean ratios [90% CIs] of the C_{max} and AUC_{48h} of darolutamide administered as uncoated A to those as uncoated B were 1.06 [0.931, 1.22] and 1.01 [0.869, 1.18], respectively. Based on these results, the applicant explained that the difference in the particle size of the drug substance does not evidently affect exposure to darolutamide.

6.1.4 Effects of gastric pH on the pharmacokinetics of darolutamide

The applicant's explanation:

Given the fact that the solubility of darolutamide was nearly constant (14-23 μg/mL) over the pH range from 1.0 to 6.8, the pharmacokinetics of darolutamide is unlikely to be affected by increases in gastric pH due to low gastric acidity or the administration of proton pump inhibitors, etc.

6.2 Clinical pharmacology

The pharmacokinetics of darolutamide, administered alone and in combination with itraconazole or rifampicin, were evaluated in healthy adults and patients with cancer. In addition, the effects of darolutamide on the pharmacokinetics of midazolam, rosuvastatin, and dabigatran etexilate (DABE) were also evaluated.

6.2.1 Foreign clinical studies

6.2.1.1 Foreign phase I/II study (CTD 5.3.3.2.1: Phase I part of Study 17829, March 2011 to July 2013)

An open-label, uncontrolled study was conducted in 24 patients with metastatic CRPC (all were included in the pharmacokinetic analysis) to evaluate the pharmacokinetics and other aspects of darolutamide. Darolutamide 100 to 900 mg was orally administered twice daily under fed conditions, and the plasma concentrations and pharmacokinetic parameters of darolutamide and M-1 were determined.

[25)] Approximately a total of 800 to 1,000 kcal, in which fat accounted for approximately 50%

Table 15 shows the pharmacokinetic parameters of darolutamide and M-1. The C_{max} and AUC_{last} of darolutamide and M-1 were non-linear over the dose range tested. The applicant explained that the non-linearity of the parameters may be attributable to saturation of the absorption of darolutamide with increasing dose. The C_{max} and AUC_{last} of darolutamide and M-1 on Day 7 were higher than those on Day 1.

Table 15. Pharmacokinetic parameters of darolutamide and M-1

Dose (mg)	Day of Measurement (Day)	Analyte	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{last} (μg·h/mL)
100	1	Darolutamide	4	0.437 (18.4)	3.00 (1.0, 5.0)	3.05 (22.8)
		M-1	4	0.691 (24.1)	3.00 (1.0, 5.0)	4.70 (36.7)
	7	Darolutamide	3	1.00 (17.5)	4.00 (1.0, 4.0)	6.36 (12.1)
		M-1	3	1.78 (35.8)	4.00 (1.5, 4.0)	11.1 (43.4)
200	1	Darolutamide	7	0.732 (35.6)	3.00 (1.5, 3.0)	5.59 (39.4)
		M-1	7	1.14 (27.8)	1.52 (1.5, 5.0)	8.26 (29.2)
	7	Darolutamide	7	1.62 (43.3)	2.03 (0.5, 4.0)	10.0 (44.6)*2
		M-1	7	2.47 (13.2)	2.03 (1.0, 6.0)	15.3 (18.6)*2
300	1	Darolutamide	3	1.07 (27.1)	3.00 (1.5, 3.2)	7.38 (27.5)
		M-1	3	1.61 (12.7)	3.00 (1.5, 3.2)	11.0 (16.6)
	7	Darolutamide	3	2.02 (14.4)	4.00 (4.0, 4.0)	14.1 (15.8)
		M-1	3	3.68 (49.0)	4.00 (1.5, 4.0)	23.2 (47.5)
500	1	Darolutamide	4	1.53 (27.2)	5.08 (5.0, 8.0)	12.7 (25.2)
		M-1	4	2.66 (5.31)	5.04 (3.0, 8.0)	21.6 (13.1)
	7	Darolutamide	3	2.37 (16.7)	4.00 (0.8, 6.0)	14.4 (28.0)
		M-1	3	4.50 (32.8)	4.00 (2.0, 4.0)	28.2 (47.6)
700	1	Darolutamide	3	1.87 (24.8)	3.00 (3.0, 5.0)	16.4 (32.2)
		M-1	3	3.23 (25.1)	3.00 (3.0, 5.0)	27.6 (27.8)
	7	Darolutamide	3	4.35 (27.5)	4.00 (4.0, 4.1)	30.9 (29.0)
		M-1	3	9.17 (23.9)	4.00 (4.0, 4.1)	62.1 (27.8)
900	1	Darolutamide	3	1.79 (17.7)	5.00 (3.0, 6.0)	15.4 (20.3)
		M-1	3	4.15 (60.2)	5.00 (5.0, 6.0)	35.0 (66.9)
	7	Darolutamide	3	4.20 (15.4)	4.00 (1.5, 6.0)	28.6 (16.9)
		M-1	3	9.04 (36.1)	4.00 (1.5, 4.0)	61.8 (36.5)

Geometric mean (geometric CV [%]); *1, Median (range); *2, n = 6

6.2.1.2 Foreign phase I study (CTD 5.3.1.1-2: Part 2 of Study 17831, March to May 2015)

An open-label, uncontrolled study was conducted in 6 healthy adults (all were included in the pharmacokinetic analysis) to evaluate the mass balance and other aspects of darolutamide. A single oral dose of ^{14}C-darolutamide 300 mg was administered, and radioactivity concentrations in the blood, plasma, urine, and feces were determined.

The ratio of the blood radioactivity concentration to the plasma radioactivity concentration was nearly constant (0.646-0.669) from 1 hour to 24 hours post-dose. The geometric mean absolute bioavailability (geometric CV [%]) of darolutamide (^{14}C-darolutamide-containing oral liquid formulation) was 0.989 (21.3).[26)] In plasma, unchanged darolutamide and M-1 were predominantly detected (accounting for 28.6% and 58.8%, respectively, of the AUC_{inf} of the total radioactivity in plasma). The applicant explained that darolutamide and its metabolites are primarily distributed in plasma.

26) Calculated from the AUC_{inf} value observed after a single intravenous dose of ^{14}C-darolutamide 100 μg administered over 15 minutes in part 1 of Study 17831 [see Section 6.1.2.1].

The urinary and fecal excretion rates (percent excretion of the administered radioactivity) of radioactivity during 168 hours post-dose were 63.4% and 32.4%, respectively. In the urine collected during 168 hours post-dose, M-7 (*O*-glucuronidation) was the primary metabolite (accounting for 25.5% of the administered radioactivity), while unchanged darolutamide (accounting for 6.7% of the administered radioactivity) was also found. In the feces collected during 168 hours post-dose, unchanged darolutamide was found predominantly (accounting for 30.3% of the administered radioactivity), and the primary metabolites were M-1 and M-28 (carboxylation) (accounting for 0.6% and 1.0%, respectively, of the administered radioactivity).

6.2.2 Drug interaction studies

6.2.2.1 Drug interaction study with rosuvastatin (CTD 5.3.3.4.1, Study 17723, February to May 2016)

An open-label, uncontrolled study was conducted in 30 healthy adults (29 were included in the pharmacokinetic analysis) to evaluate the effects of darolutamide on the pharmacokinetics of rosuvastatin (a substrate for BCRP, OATP1B1, and OATP1B3). The study drugs were administered according to the following dosage regimens, and a washout period of ≥6 days was placed between the treatment periods.

Period 1: A single oral dose of rosuvastatin 5 mg was administered under fed conditions on Day 1.
Period 2: Darolutamide 600 mg was administered as a single oral dose under fed conditions on Day 1, and as repeated oral doses twice daily under fed conditions on Days 4 to 8, while a single oral dose of rosuvastatin 5 mg was administered under fed conditions on Day 8.

The geometric mean ratios [90% CIs] of the C_{max} and AUC_{24h} of rosuvastatin administered in combination with darolutamide to those of rosuvastatin administered alone were 5.01 [4.48, 5.61] and 5.19 [4.76, 5.66], respectively. The applicant explained that darolutamide may increase exposure to a substrate for BCRP, OATP1B1, or OATP1B3, and that this will be properly communicated to healthcare professionals.

6.2.2.2 Drug interaction study with itraconazole and rifampicin (CTD 5.3.3.4.2: Study 17726, February to May 2017)

An open-label, uncontrolled study was conducted in 15 healthy adults (all were included in the pharmacokinetic analysis) to evaluate the effects of itraconazole (a potent CYP3A inhibitor) and rifampicin (a potent CYP3A inducer) on the pharmacokinetics of darolutamide. The study drugs were administered according to the following dosage regimens. A washout period of ≥4 days was placed between Period 1 and Period 2, and a washout period of ≥7 days was placed between Period 2 and Period 3.

Period 1: A single oral dose of darolutamide 600 mg was administered under fed conditions on Day 1.

Period 2: Itraconazole 200 mg was orally administered twice daily under fed conditions on Day 1, and once daily under fed conditions on Days 2 to 7, while a single oral dose of darolutamide 600 mg was administered under fed conditions on Day 5.

Period 3: Rifampicin 600 mg was orally administered once daily under fasted conditions on Days 1 to 10, while a single oral dose of darolutamide 600 mg was administered under fed conditions on Day 8.

The geometric mean ratios [90% CIs] of the C_{max} and AUC_{72h} of darolutamide administered in combination with itraconazole, to those of darolutamide administered alone were 1.36 [1.27, 1.47] and 1.75 [1.59, 1.93], respectively. The geometric mean ratios [90% CIs] of the C_{max} and AUC_{72h} of darolutamide administered in combination with rifampicin, to those of darolutamide administered alone were 0.476 [0.442, 0.513] and 0.282 [0.256, 0.311], respectively.

The applicant's explanation about coadministration of darolutamide and (a) CYP3A inhibitors or (b) CYP3A4 inducers, based on the above results:

(a) Given the exposure[27)] to darolutamide observed in a global phase III study (Study 17712) which demonstrated the tolerable safety profile of darolutamide [see Section 7.R.3] and other data, the increase in exposure to darolutamide due to coadministration with a potent CYP3A inhibitor is unlikely to pose a safety concern, and no cautionary statement regarding coadministration with CYP3A inhibitors will be necessary.

(b) The AUC of darolutamide was decreased by 72% by coadministration with a potent CYP3A4 inducer, and was expected to be decreased by up to 58%[28)] by coadministration with a moderate CYP3A4 inducer. Based on these AUC decreases, as well as the data from a global phase III study (Study 17712), the steady-state AUC_{12h} (median) of S,S-darolutamide was estimated via a population pharmacokinetic (PPK) analysis [see Section 6.2.5]. The estimated steady-state AUC_{12h} (median) of S,S-darolutamide was <15,000 ng·h/mL when darolutamide was administered with a potent CYP3A4 inducer, and 18,000 ng·h/mL when darolutamide was administered with a moderate CYP3A4 inducer. In view of these results, and the relationship between the exposure and efficacy of darolutamide [see Section 6.2.6.1], the decrease in exposure to darolutamide accompanying coadministration with a potent CYP3A4 inducer may reduce the efficacy of darolutamide; therefore, a cautionary statement regarding coadministration of darolutamide with a potent CYP3A4 inducer will be necessary. Meanwhile, the decrease in exposure to darolutamide accompanying coadministration with a moderate CYP3A4 inducer is unlikely to clearly affect the

27) The PPK analysis [see Section 6.2.5] provided a geometric mean (range) steady-state AUC_{12h} of darolutamide of 52,817 (15,771, 143,791) ng·h/mL.

28) Calculated based on the decrease in the AUC_{72h} (72%) of darolutamide administered in combination with a potent CYP3A4 inducer, according to the following categorization of CYP3A4 inducers: Potent CYP3A4 inducers are drugs that decrease the AUC of a substrate for CYP3A4 to ≤20%, while moderate CYP3A4 inducers are drugs that decrease the AUC of a substrate for CYP3A4 to >20% and ≤50% (Notification No. 0723-(4) of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau [PSEHB], dated July 23, 2018).

efficacy of darolutamide; therefore, no cautionary statement regarding coadministration with a moderate CYP3A4 inducer will be necessary.

6.2.2.3 Drug interaction study with midazolam and DABE (CTD 5.3.3.4.3: Study 18860, August to October 2017)

An open-label, uncontrolled study was conducted in 15 healthy adults (13 were included in the pharmacokinetic analysis) to evaluate the effects of darolutamide on the pharmacokinetics of midazolam (a substrate for CYP3A) and DABE (a substrate for P-gp). The study drugs were administered according to the following dosage regimens, and a washout period of ≥4 days was placed between the treatment periods.

Period 1: Single oral doses of midazolam 1 mg and DABE 75 mg were administered under fed conditions on Day 1.

Period 2: Darolutamide 600 mg was orally administered twice daily under fed conditions on Days 1 to 11, while a single oral dose of DABE 75 mg was administered under fasted conditions[24)] on Day 3, and single oral doses of DABE 75 mg and midazolam 1 mg were administered under fed conditions on Day 9.

Table 16 shows the geometric mean ratios [90% CIs] of the C_{max} and AUC_{inf} of midazolam and DABE (conjugate and unconjugate combined) administered in combination with darolutamide, to those of midazolam and DABE administered alone. Coadministration with darolutamide caused a limited decrease in exposure to midazolam, and no increase in exposure to DABE (conjugate and unconjugate combined). Based on these results and other data, the applicant explained that no cautionary statement regarding coadministration with a substrate for CYP3A or P-gp will be necessary.

Table 16. Effects of darolutamide on the pharmacokinetics of midazolam and DABE (conjugate and unconjugate combined)

Analyte	Fed/fasted	Geometric mean ratio [90% CI]	
		C_{max}	AUC_{inf}
Midazolam	Fed	0.678 [0.594, 0.774]	0.714 [0.616, 0.827]
DABE (conjugate and unconjugate combined)	Fasted	0.885 [0.689, 1.14]	0.787 [0.626, 0.990]
	Fed	0.827 [0.644, 1.06]	0.878 [0.698, 1.10]

6.2.3 Foreign phase I study to evaluate the effects of hepatic or renal impairment on the pharmacokinetics of darolutamide (CTD 5.3.3.3-1: Study 17721, September 2016 to April 2017)

An open-label, uncontrolled study was conducted in 10 healthy adults (all were included in the pharmacokinetic analysis), 9 patients with moderate hepatic impairment (Child-Pugh class B) (all were included in the pharmacokinetic analysis), and 10 patients with severe[29)] renal impairment (all were included in the pharmacokinetic analysis) to evaluate the effects of hepatic or renal impairment on the pharmacokinetics of darolutamide. A single oral dose of darolutamide 600 mg was administered under

[29)] Estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2 and ≤29 mL/min/1.73 m^2

fed conditions, and the plasma concentrations and pharmacokinetic parameters of darolutamide were determined.

The geometric mean ratios [90% CIs] of the C_{max} and AUC_{48h} of darolutamide in (a) patients with moderate hepatic impairment and (b) patients with severe renal impairment, to those in healthy adults were (a) 1.46 [1.09, 1.96] and 1.85 [1.37, 2.51], and (b) 1.59 [1.23, 2.06] and 2.47 [1.83, 3.34]. In view of the exposure[27)] to darolutamide observed in a global phase III study (Study 17712) which demonstrated the tolerable safety profile of darolutamide [see Section 7.R.3] and other findings, the applicant explained that the increase in exposure to darolutamide in patients with severe renal impairment is unlikely to pose a safety concern for its clinical use; therefore, no dose adjustment will be necessary for patients with renal impairment.

The administration of darolutamide to patients with hepatic impairment is described in Section "6.R.2 Administration of darolutamide to patients with hepatic impairment."

6.2.4 Relationship between exposure and change in QT/QTc interval

The relationship between plasma darolutamide concentration and the difference from placebo in the change from baseline in the QT interval corrected by Fridericia's formula (ΔΔQTcF) was analyzed using a linear mixed effects model, based on the data from 500 patients (323 in the darolutamide group, 177 in the placebo group) who had evaluable plasma darolutamide concentration data at the ECG recording points in a global phase III study (Study 17712). The analysis results showed no clear relationship between plasma darolutamide concentration and ΔΔQTcF.

Based on the above results and other data, the applicant explained that darolutamide administered according to the proposed dosage and administration is unlikely to prolong the QT/QTc interval.

6.2.5 PPK analysis

A PPK analysis was performed (NONMEM, version 7.3) using a non-linear mixed effect model, based on the pharmacokinetic data (388 patients, 1,794 timepoints) for darolutamide, S,R- and S,S-darolutamide, and M-1 collected in a global phase III study (Study 17712). The pharmacokinetics of darolutamide, S,R- and S,S-darolutamide, and M-1 were described by a 1-compartment model with first-order absorption and first-order elimination.

The factors assessed as potential covariates for (a) CL and (b) the rate of reconversion from M-1 to S,R- or S,S-darolutamide (RR) in the PPK analysis were body weight, age, height, race, geographic region (Japan vs. rest of the world), eGFR, hepatic function,[30)] renal function,[31)] serum creatinine, serum

30) Categorized according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria
31) Categorized based on eGFR

albumin, total protein, total bilirubin, AST, ALT, concomitant medications[32] (yes vs. no), and drug product batch.

Among these factors, (a) age, serum creatinine, and geographical region (Japan vs. rest of world) were identified as significant covariates for CL, and (b) AST was identified as a significant covariate for RR; however, the effects of the covariates on the exposures (steady-state AUC_{12h}) to darolutamide, S,R- and S,S-darolutamide, and M-1 were limited. The applicant explained that none of these covariates are likely to have clinically relevant effects on the pharmacokinetics of darolutamide, S,R- and S,S-darolutamide, or M-1.

6.2.6 Relationship between exposure and efficacy or safety

6.2.6.1 Relationship between exposure and efficacy

The following investigations were conducted to evaluate the relationship between exposure and efficacy.

- Based on the data from a foreign phase I/II study (Study 17829), a foreign phase I study (Study 17830), and a global phase III study (Study 17712), the relationship between the exposure[33] (steady-state AUC_{12h}) to S,S-darolutamide, as estimated by a PPK analysis [see Section 6.2.5], and the maximum percent change from baseline in the PSA level was evaluated. The result indicated that the PSA level declined rapidly from baseline, and the maximum percent change from baseline in the PSA level reached a plateau at an exposure to S,S-darolutamide of approximately 15,000 ng·h/mL.
- Based on the data from a global phase III study (Study 17712), patients in the darolutamide group were divided into quartile groups based on exposure (steady-state AUC_{12h}) to S,S-darolutamide as estimated by a PPK analysis [see Section 6.2.5] to estimate metastasis-free survival (MFS) in each quartile group using the Kaplan-Meier method. The results showed no clear relationship between exposure to S,S-darolutamide and MFS.

6.2.6.2 Relationship between exposure and safety

Based on the data from a global phase III study (Study 17712), the relationship between exposure (steady-state AUC_{12h}) to S,S-darolutamide, as estimated by a PPK analysis [see Section 6.2.5] and the incidences of adverse events (fatigue, asthenia, lack of motivation, feeling strange, dermatitis, erythema, rash [including maculopathy, papule, and pustule], and pain in extremity) was evaluated. The result showed no clear relationship between exposure to S,S-darolutamide and the incidences of adverse events

6.2.7 Pharmacokinetic differences between Japanese and non-Japanese populations

The applicant's explanation:

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[32] BCRP inhibitors, CYP3A inducers and inhibitors, P-gp inducers and inhibitors, proton pump inhibitors, or UGT1A9 inhibitors

[33] In a model defined by EC_{50} and E_{max}, exposure to S,S-darolutamide was shown to be most closely associated with the maximum percent change from baseline in the PSA level among exposure to darolutamide, S,R- and S,S-darolutamide, or M-1.

In view of the following findings and other data, there are no clinically relevant differences in the pharmacokinetics of darolutamide between Japanese and non-Japanese patients.

- In a Japanese phase I study (Study 17719) [see Section 6.1.3.1] and a foreign phase I study (Study 17830) [see Section 6.1.2.2], the C_{max} and AUC_{inf} (geometric means [geometric CVs]) of darolutamide administered as a single oral dose of 600 mg under fed conditions tended to be higher in Japanese patients (3,500 ng/mL [12.1%] and 63,500 ng·h/mL [28.9%], respectively) than in non-Japanese patients (2,270 ng/mL [25.0%] and 42,600 ng·h/mL [33.8%], respectively].[34)] However, darolutamide was demonstrated to have a tolerable safety profile in the Japanese subpopulation of a global phase III study (Study 17712) [see Section 7.R.3].
- In a global phase III study (Study 17712), the trough plasma concentration (geometric means [geometric CVs]) of darolutamide administered as repeated oral doses of 600 mg under fed conditions tended to be higher in Japanese patients (4,637 ng/mL [54.7%]) than in non-Japanese patients (3,081 ng/mL [80.5%]). However, there were no clear differences in the safety profile of darolutamide between Japanese and non-Japanese patients [see Section 7.R.3].

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the applicant's explanation about the clinical pharmacology, etc. of darolutamide is acceptable, except for the discussion described in Section "6.R.2 Administration of darolutamide to patients with hepatic impairment."

6.R.1 Food effects

The applicant's explanation about the dosing timing of darolutamide:

The results of a foreign phase I study (Study 17830) and a Japanese phase I study (Study 17719) showed that exposure to darolutamide was increased by food intake [see Sections 6.1.2.2 and 6.1.3.1]. Based on this finding and other data, darolutamide was to be administered "after meals" in the subsequent clinical studies including a global phase III study (Study 17712), and these studies demonstrated the clinical benefit of darolutamide. Accordingly, the proposed dosage and administration recommended dosing darolutamide after meals.

PMDA's view:

PMDA accepted the applicant's explanation. The dosage and administration of darolutamide should be described after taking the efficacy and safety results from clinical studies into consideration [see Section 7.R.5].

6.R.2 Administration of darolutamide to patients with hepatic impairment

The applicant's explanation about administration of darolutamide to patients with hepatic impairment:

In a foreign phase I study (Study 17721), exposure to darolutamide increased in patients with moderate hepatic impairment, compared with healthy adults [see Section 6.2.3]. However, given the exposure to

34) Calculated using the pooled data from patients receiving uncoated tablets A and those receiving uncoated tablets B

darolutamide[27] observed in a global phase III study which demonstrated the tolerable safety profile of darolutamide (Study 17712) and other findings, the increase in exposure to darolutamide in patients with moderate hepatic impairment is unlikely to pose a safety concern for its clinical use. Therefore, no dose adjustment is necessary for patients with mild or moderate hepatic impairment. On the other hand, administration of darolutamide to patients with severe hepatic impairment cannot be recommended, as darolutamide has never been administered to such patients in clinical studies.

PMDA's view:
PMDA accepted the applicant's explanation about administration of darolutamide to patients with mild or moderate hepatic impairment. In view of the fact that darolutamide is excreted primarily through hepatic metabolism [see Section 6.2.1.2], as well as the above explanation of the applicant, PMDA concluded that the administration of darolutamide to patients with severe hepatic impairment cannot be recommended, and that this should be communicated to healthcare professionals through the package insert.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of result data from the following 9 clinical studies: 1 Japanese phase I study, 1 global phase III study, 5 foreign phase I studies, 1 foreign phase I/II study, and 1 foreign phase II study (Table 17). The applicant also submitted the results of a foreign phase I study as reference data (Table 17).

Table 17. Summary of clinical efficacy and safety studies

Data category	Geographical location	Study identity	Phase	Study population	Number of patients enrolled	Dosing regimen	Main endpoints
Evaluation data	Japan	17719	I	Patients with metastatic CRPC	9	(a) Single dose period: In combination with ADT, darolutamide 300 or 600 mg administered as a single oral dose under fasted conditions, followed by a 3-day washout, and then darolutamide 300 or 600 mg administered as a single oral dose under fed conditions (b) Repeated dose period: In combination with ADT, darolutamide 300 or 600 mg orally, administered twice daily under fed conditions	PK Safety Tolerability
	Global	17712	III	Patients with non-metastatic CRPC with a PSA doubling time of ≤10 months	1,509 (a) 955 (b) 554	In combination with ADT: (a) Darolutamide 600 mg orally administered twice daily under fed conditions (b) Placebo orally administered twice daily under fed conditions	Efficacy Safety
	Foreign	17721	I	Healthy adults, and patients with renal impairment or hepatic impairment	29	Darolutamide 600 mg administered as a single oral dose under fed conditions	PK Safety Tolerability
		17723	I	Healthy adults	30	Rosuvastatin 5 mg administered as a single oral dose under fed conditions, followed by a washout of ≥6 days, and then darolutamide 600 mg administered once daily on Day 1 and twice daily on Days 4-8, under fed conditions, with rosuvastatin 5 mg administered as a single oral dose on Day 8	PK Safety

Data category	Geographical location	Study identity	Phase	Study population	Number of patients enrolled	Dosing regimen	Main endpoints
		17726	I	Healthy adults	15	(a) Period 1: Darolutamide 600 mg administered as a single oral dose under fed conditions (b) Period 2: Itraconazole 200 mg orally administered twice daily on Day 1 and once daily on Days 2-7, under fed conditions, with darolutamide 600 mg administered as a single oral dose under fed conditions on Day 5 (c) Period 3: Rifampicin 600 mg administered once daily under fasted conditions on Days 1-10, with darolutamide 600 mg administered as a single oral dose under fed conditions on Day 8	PK Safety Tolerability
		17830	I	Patients with chemotherapy-naïve, metastatic CRPC	30	In combination with ADT, darolutamide (capsules, uncoated tablets A and B) 600 mg administered as a single oral dose under fasted or fed conditions, in a crossover fashion, followed by a washout of ≥7 days, and then darolutamide (capsules) 600 mg orally administered twice daily under fed conditions	PK Safety Tolerability
		18860	I	Healthy adults	15	Midazolam 1 mg and DABE 75 mg administered as single doses under fed conditions, followed by a washout of ≥4 days, and then darolutamide 600 mg orally administered twice daily under fed conditions on Days 1-11, with DABE 75 mg orally administered once daily on Days 3 and 9, and midazolam 1 mg orally administered once daily on Day 9	PK Safety Tolerability
		17829	I/II	Patients with metastatic CRPC	Phase I part 24 Phase II part 110	Phase I part In combination with ADT, darolutamide 100, 200, 300, 500, 700, or 900 mg orally administered twice daily under fed conditions Phase II part In combination with ADT, darolutamide 100, 200, or 700 mg orally administered twice daily under fed conditions	PK Efficacy Safety Tolerability
		18035	II	Patients with metastatic CRPC	76*	In combination with ADT, darolutamide 100, 200, 300, 500, 700, or 900 mg orally administered twice daily under fed conditions	Efficacy Safety Tolerability
Reference data	Foreign	17831	I	Healthy adults	12 (a) 6 (b) 6	(a) Darolutamide (tablets) 300 mg administered as a single oral dose, followed by ^{14}C-darolutamide 100 μg administered as a single intravenous dose (b) ^{14}C-Darolutamide (oral liquid formulation) 300 mg administered as a single oral dose	PK Safety Tolerability

* Patients who completed the Phase I and Phase II parts of Study 17829 were enrolled.

A summary of the clinical studies is presented below.

Common adverse events other than deaths reported in the studies are detailed in Section "7.3 Adverse events reported in the clinical studies." Clinical pharmacokinetic data are detailed in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Clinical pharmacology studies

The results of the following 5 clinical pharmacology studies in healthy adults, patients with renal impairment or hepatic impairment, and chemotherapy-naïve patients with metastatic CRPC were submitted [see Section 6.2]. One patient died during the study treatment period (1 of 30 patients in Study

17830). The cause of the death was disease progression, for which a causal relationship to darolutamide was denied.

7.1.1.1 Foreign phase I study (CTD 5.3.3.3.1: Study 17721, September 2016 to April 2017)

7.1.1.2 Foreign phase I study (CTD 5.3.3.4.1: Study 17723, February to May 2016)

7.1.1.3 Foreign phase I study (CTD 5.3.3.4.2: Study 17726, February to May 2017)

7.1.1.4 Foreign phase I study (CTD 5.3.1.1.1: Study 17830, March 2013 to April 2017)

7.1.1.5 Foreign phase I study (CTD 5.3.3.4.3: Study 18860, August to October 2017)

7.1.2 Japanese clinical study

7.1.2.1 Japanese phase I study (CTD 5.3.3.2.2 and 5.3.3.2.3: Study 17719, February 2015 to December 2017)

An open-label, uncontrolled study was conducted at 1 study site in Japan to evaluate the safety, tolerability, and other aspects of darolutamide administered in combination with ADT in patients with metastatic CRPC[35] (target sample size, 9 patients).

In the single dose period, patients received a single oral dose of darolutamide 300 or 600 mg under fasted and fed conditions at an interval of 3 days. In the repeated dose period, patients received repeated oral doses of darolutamide 300 or 600 mg twice daily under fed conditions on Days 1 to 84. If the continuation of treatment with darolutamide was possible at the discretion of the investigator or subinvestigator after the repeated dose period was completed, treatment with darolutamide 300 or 600 mg twice daily was continued until disease progression or a withdrawal criterion was met.

All 9 patients enrolled (3 in the 300 mg cohort and 6 in the 600 mg cohort) were treated with darolutamide and included in the safety analysis set.

During the dose limiting toxicity (DLT) assessment period defined as 28 days after the start of the repeated dose period, no DLTs occurred.

For safety, no patients died during the study treatment period or within 30 days after the last dose of darolutamide.

[35] Patients with CRPC were enrolled in the study, if the serum testosterone level was <50 ng/dL, the PSA level was ≥2.0 ng/mL, and a PSA rise was documented on 3 consecutive occasions at least 1 week apart.

7.1.3 Global clinical study

7.1.3.1 Global phase III study (CTD 5.3.5.1.1: Study 17712, ongoing since September 2014 [data cutoff on September 3, 2018])

A double-blind, randomized, comparative study was conducted at 409 study sites in 36 countries/regions including Japan to compare the efficacy and safety of darolutamide administered in combination with ADT with those of placebo in patients with non-metastatic CRPC[35)] with a PSA doubling time of ≤10 months[36)] (target sample size, 1,500 patients).

Patients received repeated oral doses of darolutamide 600 mg or placebo twice daily under fed conditions. The treatment was continued until disease progression or a withdrawal criterion was met.

All 1,509 enrolled and randomized patients (955 in the darolutamide group and 554 in the placebo group, including 62 and 33 Japanese patients, respectively) were included in the full analysis set (FAS). The efficacy analysis set was the FAS population. Of these 1,509 patients, 1 in the darolutamide group did not receive the study drug, and the remaining 1,508 (954 in the darolutamide group and 554 in the placebo group, including 62 and 33 Japanese patients, respectively) were included in the safety analysis set.

The primary endpoint was MFS,[37)] as assessed centrally based on Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1. At the start of the study, the primary analysis aiming at demonstrating the superiority of darolutamide in MFS over placebo was planned, when a total of 572 MFS events had occurred. However, the results of a phase II study[38)] with enzalutamide, a drug which inhibited AR-mediated signaling, like darolutamide, and other findings suggested that the prolongation of MFS by darolutamide would be longer than initially anticipated; therefore, the primary analysis was to be conducted when 385 MFS events had occurred (Protocol amendment ver. 4, dated February 26, 2018).

Table 18 presents the efficacy results based on the primary MFS analysis (data cutoff on September 3, 2018), while Figure 2 presents the Kaplan-Meier curves for MFS. The results demonstrated the superiority of darolutamide in MFS over placebo.

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36) Patients with CRPC were enrolled in the study, if they had at least 3 PSA measurements during ADT, and the estimated PSA doubling time was ≤10 months.

37) Defined as the time to the date of the first documentation of metastasis or death from any cause, whichever occurs first. In this study, an imaging assessment at baseline for determining eligibility for enrollment in the study and an imaging assessment for evaluating efficacy were performed by independent assessors, and some of the patients enrolled in the study were found to have had baseline metastases at the imaging assessment for efficacy. Patients who were later found to have baseline metastases, but had been enrolled were to be handled as having an MFS event at the date of randomization in the US, or to be censored at the date of randomization in other countries/regions in the primary analysis (Statistical analysis plan amendment ver. 4.2, dated September 20, 2018). When the clinical study report was prepared, however, such patients were to be handled as having an MFS event at the date of randomization in all of the countries/regions.

38) A phase II study that compared the efficacy and safety of enzalutamide with those of bicalutamide in patients with CRPC (*J Clin Oncol*. 2016;34:2098-106)

Table 18. Primary MFS analysis (central assessment, FAS, data cutoff on September 3, 2018)

	Darolutamide	Placebo
N	955	554
Number of events (%)	221 (23.1)	216 (39.0)
Median [95% CI] (months)	40.37 [34.33, —]	18.43 [15.51, 22.34]
Hazard ratio [95% CI][*1]	0.413 [0.341, 0.500]	
P-value (2-sided)[*2]	<0.000001	

—, Not evaluable; *1, Cox regression stratified by PSA doubling time (≤6 months vs. >6 months) and use of bone resorption inhibitor (yes vs. no); *2, Log-rank test stratified by PSA doubling time (≤6 months vs. >6 months) and use of bone resorption inhibitor (yes vs. no) with a 2-sided significance level of 0.05

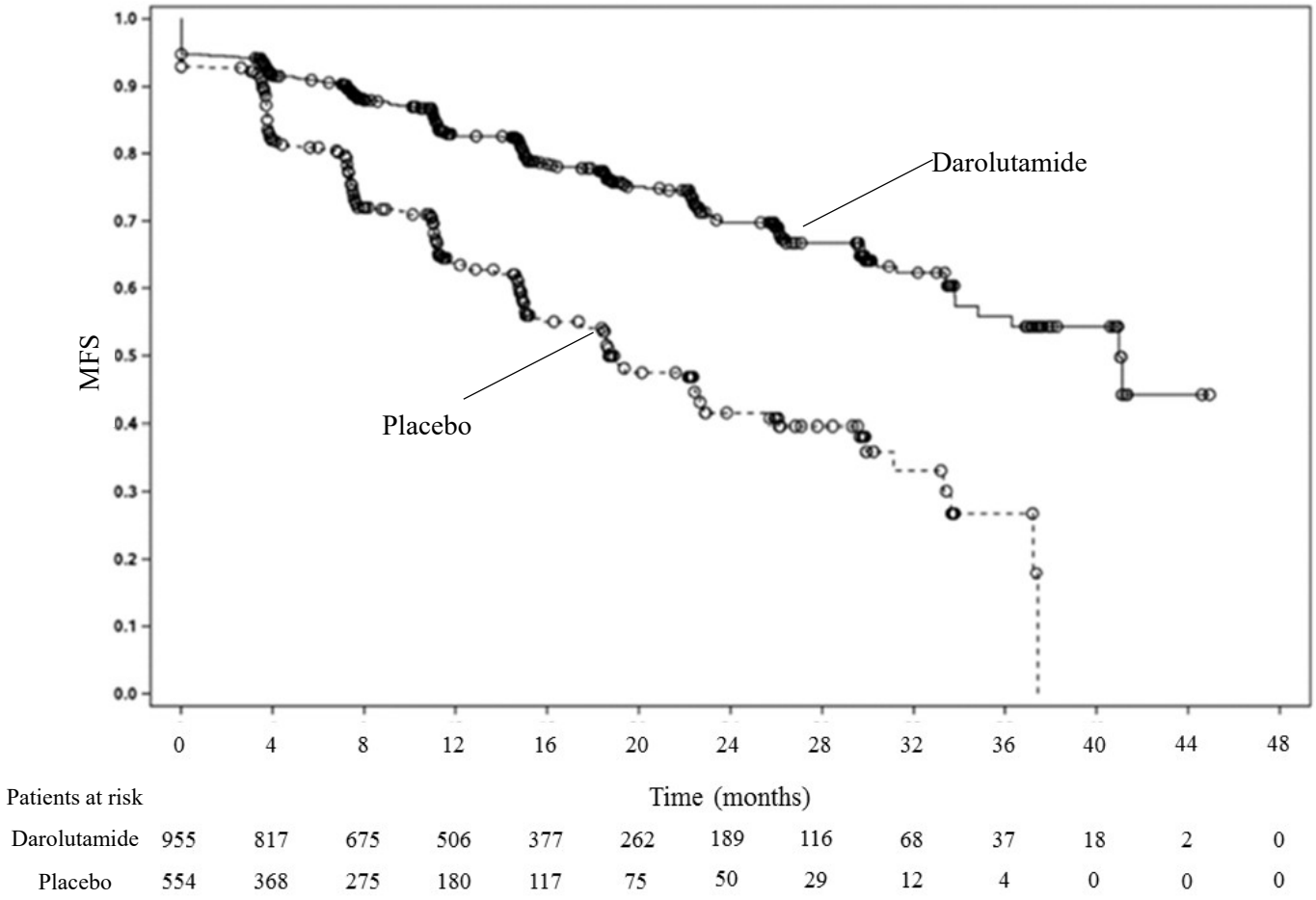

Figure 2. Kaplan-Meier curves for the primary MFS analysis (central assessment, FAS, data cutoff on September 3, 2018)

The safety analysis revealed deaths, during the treatment period or within 30 days after the last dose, of 35 of 954 patients (3.7%, including 1 of 62 Japanese patients) in the darolutamide group and 18 of 554 patients (3.2%) in the placebo group. The causes of deaths other than disease progression (2 patients in the darolutamide group and 1 patient in the placebo group) in the darolutamide group were cardiac failure and death (unknown cause) in 3 patients each, cardiac arrest, general physical health deterioration, and pulmonary embolism in 2 patients each, acute myocardial infarction, alcohol poisoning, angina pectoris, aortic dissection, cardiac disorder, cardiac failure acute, coronary artery disease, diarrhoea, dyspnoea, endocarditis, heart injury, influenza, ischaemic stroke, lung infection, meningitis bacterial, multiple injuries, pancreatic carcinoma, pneumonia, small intestinal perforation, sudden cardiac death,

and sudden death in 1 patient each; while those in the placebo group were cardiac arrest and cardiac failure in 3 patients each, acute respiratory failure in 2 patients, and cellulitis gangrenous, cerebral ischaemia, cerebrovascular accident, circulatory collapse, death, haemorrhage intracranial, hypertensive heart disease, ischaemic stroke, and myocardial infarction in 1 patient each. A causal relationship to the study drug could not be ruled out for the small intestinal perforation in 1 patient in the darolutamide group, and the haemorrhage intracranial and myocardial infarction in 1 patient each in the placebo group. (A cause of death in the Japanese patient in the darolutamide group was influenza for which a causal relationship to the study drug was denied.)

7.1.4 Foreign clinical studies

7.1.4.1 Foreign phase I/II study (CTD 5.3.3.2.1: Study 17829, March 2011 to July 2013)

An open-label, uncontrolled study was conducted at 23 study sites outside of Japan to evaluate the safety, tolerability, and other aspects of darolutamide administered in combination with ADT in patients with metastatic[39] CRPC[40] (target sample size: 24 patients in the phase I part, 105 patients in the phase II part).

In the phase I part, patients received repeated oral doses of darolutamide 100, 200, 300, 500, 700, or 900 mg twice daily under fed conditions on Days 1 to 84. In the phase II part, patients received repeated oral doses of darolutamide 100, 200, or 700 mg[41] twice daily under fed conditions on Days 1 to 84.

In the phase I part, all 24 enrolled patients (4 in the 100 mg cohort, 7 in the 200 mg cohort, 3 in the 300 mg cohort, 4 in the 500 mg cohort, 3 in the 700 mg cohort, and 3 in the 900 mg cohort) were treated with darolutamide and included in the safety analysis set. In the phase II part, a total of 112 patients were enrolled (38 in the 100 mg cohort, 38 in the 200 mg cohort, and 36 in the 700 mg cohort). Of these 112 patients, 2 (1 in the 200 mg cohort and 1 in the 700 mg cohort) did not receive the study drug, and the remaining 110 were included in the intention-to-treat (ITT) population and used for the safety analyses. Of the 110 patients in the ITT population, 96 were included in the per protocol set, excluding 14 (4 in the 100 mg cohort, 5 in the 200 mg cohort, and 5 in the 700 mg cohort) who had major protocol deviations. The efficacy analysis set was the per protocol set.

In the phase I part, the DLT assessment period was defined as 28 days after the start of darolutamide therapy, during which no DLTs occurred in any cohort, and no maximal tolerated dose (MTD) was reached.

In the phase II part, the primary endpoint was the percent change in PSA at Week 12. A PSA response was defined as a ≥50% decline in PSA from baseline to Week 12, and PSA response data were

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[39] Patients were defined as having a metastasis, if they had at least one of the following conditions: (a) A PSA rise of >2.0 ng/mL was demonstrated on ≥2 consecutive occasions at least 1 week apart or a new soft tissue lesion appeared, (b) a measurable disease defined by RECIST ver. 1.1 was present, or (c) ≥2 bone lesions were demonstrated by bone scan.

[40] Patients with CRPC who had a serum testosterone level of <50 ng/dL within 14 days prior to enrollment were enrolled.

[41] The doses to be administered in the phase II part were determined based on the results from the phase I part.

summarized by dose and the history of chemotherapy or CYP17-inhibitor (e.g., abiraterone acetate) therapy.

Table 19 shows the efficacy results based on the PSA response rate at Week 12, which was the primary endpoint in the phase II part.

Table 19. Primary PSA response rate analysis (per protocol set, data cutoff on July 9, 2013)

	Chemotherapy-naïve and CYP17 inhibitor-naïve			Chemotherapy-treated and CYP17 inhibitor-naïve			CYP17 inhibitor-treated		
	100 mg cohort	200 mg cohort	700 mg cohort	100 mg cohort	200 mg cohort	700 mg cohort	100 mg cohort	200 mg cohort	700 mg cohort
N	10	8	6	9	8	10	15	16	14
Number of events	4	4	5	3	0	3	0	3	1
PSA response rate [60% CI (2-sided)] (%)*	40.0 [27.0, 53.0]	50.0 [35.1, 64.9]	83.3 [70.5, 96.1]	33.3 [20.1, 46.6]	0 [0, 0]	30.0 [17.8, 42.2]	0 [0, 0]	18.8 [10.5, 27.0]	7.1 [1.3, 12.9]

* The threshold PSA response rate was 55%.

The safety analysis revealed deaths, during the treatment period or within 28 days after the last dose, of 1 of 24 patients (4.2%) (200 mg cohort) in the phase I part and 3 of 110 patients (2.7%) (2 in the 100 mg cohort and 1 in the 700 mg cohort) in the phase II part. The causes of all 4 deaths were disease progression, for which a causal relationship to darolutamide was denied.

7.1.4.2 Foreign phase II study (CTD 5.3.5.2.1: Study 18035, June 2011 to October 2015)

An open-label, uncontrolled study was conducted at 17 study sites outside of Japan to evaluate the long-term safety, tolerability, and other aspects of darolutamide administered in combination with ADT in patients with CRPC who had completed the 84-day darolutamide therapy without experiencing serious adverse events or disease progression in Study 17829 [see Section 7.1.4.1] (target sample size, 130 patients).

Patients received repeated oral doses of darolutamide at the dose which had been administered at Week 12 in Study 17829 (100, 200, 300, 500, 700, or 900 mg), twice daily under fed conditions. The treatment was continued until disease progression or a withdrawal criterion was met.

All 76 patients (25 in the 100 mg cohort, 25 in the 200 mg cohort, 3 in the 300 mg cohort, 2 in the 500 mg cohort, 18 in the 700 mg cohort, and 3 in the 900 mg cohort) enrolled into the study were treated with darolutamide and included in the safety analysis set.

The safety analysis revealed deaths, during the treatment period or within 28 days after the last dose, of 1 of 25 patients (4.0%) in the 100 mg cohort. The cause of the death was disease progression, for which the causal relationship to darolutamide was denied.

7.2. Reference data

7.2.1 Clinical pharmacology study

In the following clinical pharmacology study in healthy adults, no deaths were reported during the study treatment period.

7.2.1.1 Foreign phase I study (CTD 5.3.1.1.2: Study 17831, March to May 2015)

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA selected the data to be used for the review, as follows:

The global phase III study in patients with non-metastatic CRPC with a PSA doubling time of ≤10 months (Study 17712) was important in evaluating the efficacy and safety of darolutamide; therefore, the efficacy and safety of darolutamide were to be evaluated primarily based on the submitted results from the study. Efficacy in Japanese patients was to be evaluated from the viewpoint of the consistency between the entire study population and the Japanese subpopulation of Study 17712 according to "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007), "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice, dated September 5, 2012), "Guidelines on General Principles for Planning and Design of Multi-Regional Clinical Trials" (PSEHB/PED Notification No. 0612-1, dated June 12, 2018), and other relevant regulations.

7.R.2 Efficacy

Based on the discussion presented below, PMDA concluded that the efficacy of darolutamide had been demonstrated in patients with non-metastatic CRPC with a PSA doubling time of ≤10 months.

7.R.2.1 Control group selection

The applicant's explanation about the selection of placebo as the control in Study 17712:

When Study 17712 was being planned, no standard therapy had been established for patients with non-metastatic CRPC, although ADT was cited as a treatment option in the National Comprehensive Cancer Network Clinical Practice Guidelines (NCCN guidelines) (v.2.2014) or any other guidelines. Study 17712 was designed to evaluate the efficacy and safety of darolutamide administered in combination with ADT in the treatment of non-metastatic CRPC. Therefore, placebo was selected as the control.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the appropriateness of selecting MFS as the primary endpoint in Study 17712:

For the following reasons, MFS with (a) documentation of metastasis or (b) death counted as an event was selected as the primary endpoint in Study 17712.

- In patients with non-metastatic CRPC, the presence of metastases is a higher risk factor of death than the progression of local lesions or regional lymph nodes (*J Clin Oncol. 2016*;34:1652-9).
- Metastases can cause pain and complications, requiring additional treatments in patients with CRPC. Therefore, the prolongation of MFS is of clinical significance (*U.S. Food and Drug Administration, Summary Minutes of the Oncologic Drugs Advisory Committee Meeting*, February 8, 2012)

The prolongation of MFS is clinically significant in the target patient population of Study 17712, because it can lead to the maintenance of patient physical functions and quality of life. Thus, the selection of MFS as the primary endpoint in Study 17712 is appropriate.

PMDA's view:
As patients with non-metastatic CRPC receive treatments to prolong their survival, OS would be the appropriate primary endpoint for Study 17712. However, the above explanation of the applicant that the prolongation of MFS has a certain level of clinical significance in the target patient population of Study 17712 is understandable. PMDA concluded that evaluating the efficacy of darolutamide based on the results of the primary endpoint of MFS, while also confirming the results for OS, is acceptable.

7.R.2.3 Efficacy evaluation results

The results from Study 17712 demonstrated the superiority of darolutamide over placebo in the primary endpoint of MFS as assessed centrally [see Section 7.1.3.1].
Table 20 and Figure 3 present the results of the sensitivity analysis for MFS with baseline metastases censored at the date of randomization and the Kaplan-Meier curves for the MFS in Study 17712, respectively.

Table 20. Sensitivity analysis for MFS with baseline metastases censored at the date of randomization (Central assessment, FAS, data cutoff on September 3, 2018)

	Darolutamide	Placebo
N	955	554
Number of events (%)	171 (17.9)	177 (31.9)
Median [95% CI] (months)	40.51 [35.78, —]	22.08 [18.83, 25.76]
Hazard ratio [95% CI]*1	0.356 [0.287, 0.441]	
P-value (2-sided)*2	<0.000001	

—, Not evaluable; *1, Cox regression stratified by PSA doubling time (≤6 months vs. >6 months) and use of bone resorption inhibitor (yes vs. no); *2, Log-rank test stratified by PSA doubling time (≤6 months vs. >6 months) and use of bone resorption inhibitor (yes vs. no)

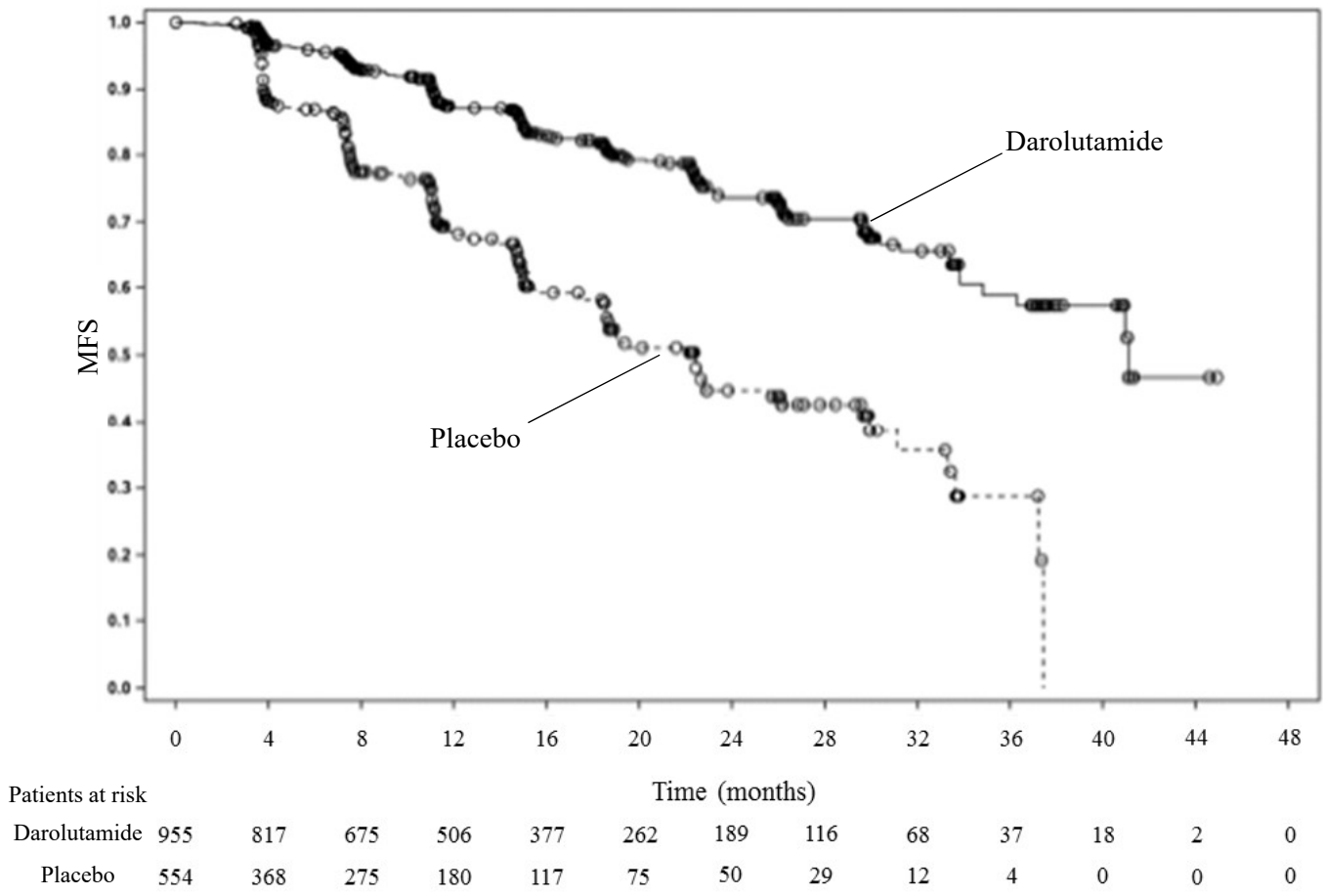

Figure 3. Kaplan-Meier curves for sensitivity analysis for MFS with baseline metastases censored at the date of randomization (Central assessment, FAS, data cutoff on September 3, 2018)

In Study 17712, if the primary MFS analysis demonstrated a statistically significant difference between the darolutamide group and the placebo group, hypothesis tests were to be conducted for secondary endpoints in the following hierarchical order: OS, time to pain progression, time to initiation of first cytotoxic chemotherapy, and time to first symptomatic skeletal events. Further, an interim OS analysis with the aim of efficacy evaluation was to be performed at the time of the primary MFS analysis. A rho-family spending function (rho = 10) was used to control the probability of a type I error associated with the interim analysis (EAST Version 6.4).

The results of the interim OS analysis (data cutoff on September 3, 2018) and the Kaplan-Meier curves for OS are presented in Table 21 and Figure 4, respectively.

Table 21. Interim OS analysis (FAS, data cutoff on September 3, 2018)

	Darolutamide	Placebo
N	955	554
Number of events (%)	78 (8.2)	58 (10.5)
Median [95% CI] (months)	— [44.45, —]	— [—, —]
Hazard ratio [95% CI][*1]	0.706 [0.501, 0.994]	
P-value (2-sided)[*2]	0.045210	

—, Not evaluable; *1, Cox regression stratified by PSA doubling time (≤6 months vs. >6 months) and use of bone resorption inhibitor (yes vs. no); *2, Log-rank test stratified by PSA doubling time (≤6 months vs. >6 months) and use of bone resorption inhibitor (yes vs. no) with a 2-sided significance level of 0.0005

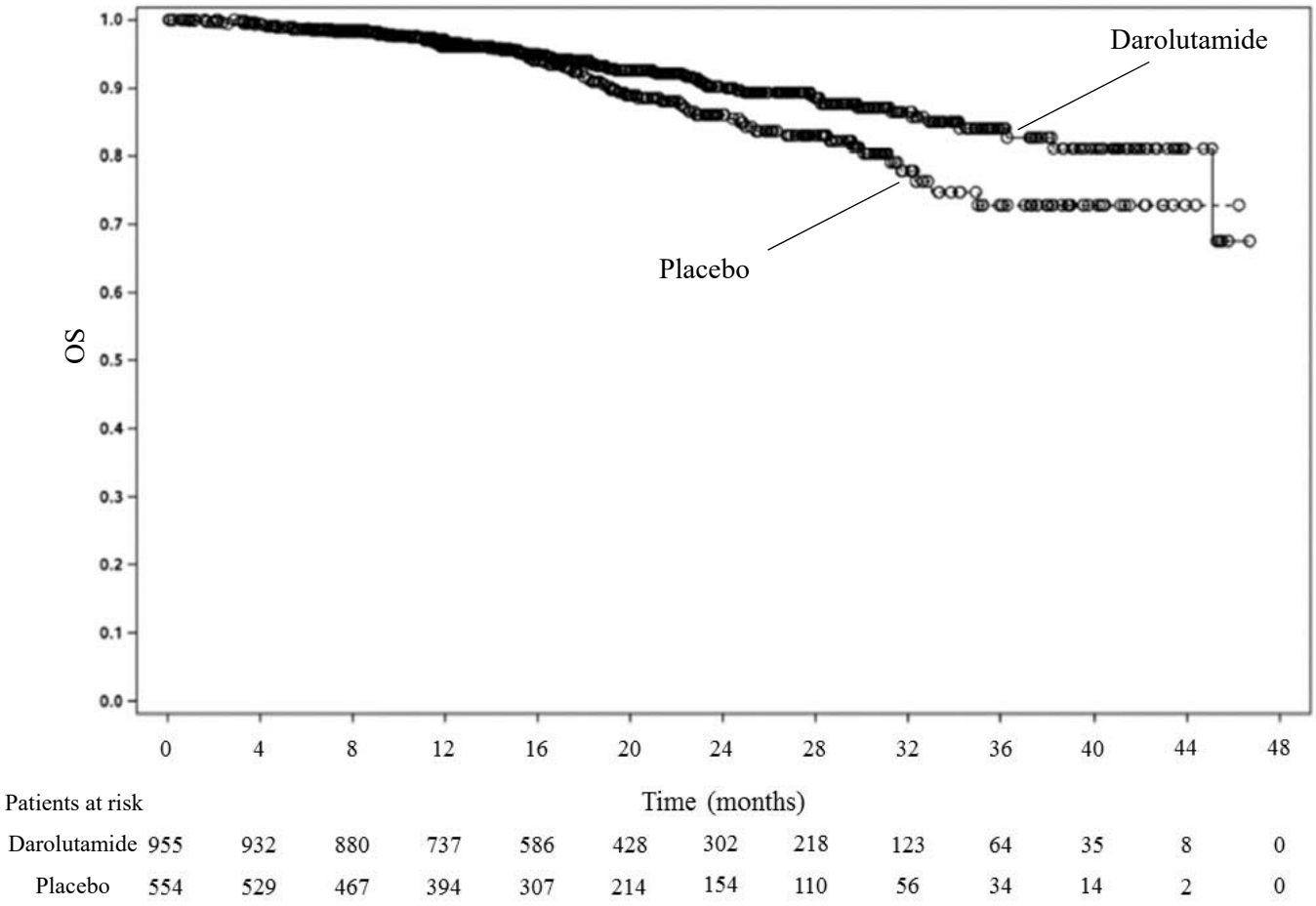

Figure 4. Kaplan-Meier curves for the interim OS analysis (FAS, data cutoff on September 3, 2018)

The results of the MFS[42)] analysis and the Kaplan-Meier curves for MFS in the Japanese subpopulation of Study 17712 are presented in Table 22 and Figure 5, respectively.

42) Baseline metastases were handled as events occurring on the day of randomization.

Table 22. Analysis for MFS with event at randomization for Japanese patients with baseline metastasis (Central assessment, FAS, September 3, 2018)

	Darolutamide	Placebo
N	62	33
Number of events (%)	9 (14.5)	11 (33.3)
Median [95% CI] (months)	— [—, —]	18.20 [14.52, —]
Hazard ratio [95% CI]*1	0.278 [0.110, 0.698]	
P-value (2-sided)*2	0.003469	

—, Not evaluable; *1, Non-stratified Cox regression; *2, Non-stratified log-rank test

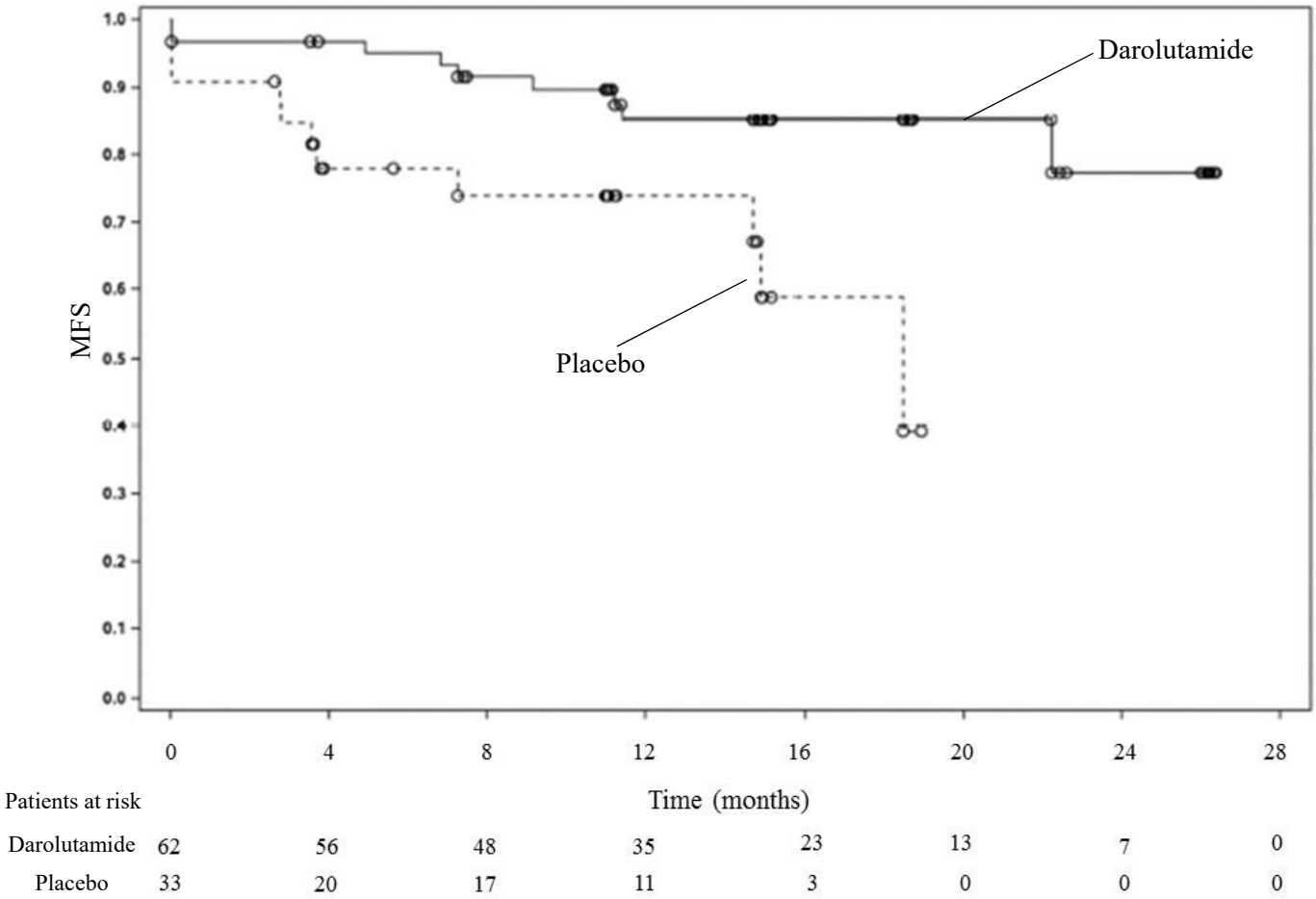

Figure 5. Kaplan-Meier curves for the primary analysis for MFS with event at randomization for Japanese patients with baseline metastasis (Central assessment, FAS, data cutoff on September 3, 2018)

PMDA's view:

PMDA concluded that darolutamide had been demonstrated to be effective in the target patient population of Study 17712 for the following and other reasons.

- The applicant's explanation that the prolongation of MFS, which was the primary endpoint in Study 17712, has a certain level of clinical significance in the treatment of non-metastatic CRPC is understandable. Further, the results of Study 17712 demonstrated that darolutamide is superior in MFS over placebo, and the magnitude of the effect of darolutamide is clinically meaningful.
- The results of a sensitivity analysis for MFS with baseline metastases censored at the baseline did not clearly differ from those of the primary MFS analysis.

- The secondary endpoint of OS did not tend to be shorter in the darolutamide group than in the placebo group.
- The Japanese subpopulation of Study 17712 and the number of MFS events occurring in the Japanese subpopulation were not sufficient to precisely evaluate the efficacy of darolutamide in Japanese patients. However, the results from the Japanese subpopulation did not tend to clearly differ from those from the entire study population.

7.R.3 Safety [For adverse events, see Section "7.3 Adverse events reported in the clinical studies."]

PMDA's view:

According to the discussions in the subsections, darolutamide therapy in patients with non-metastatic CRPC particularly requires attention regarding the development of cardiac disorders, and patients should be closely monitored for the development of cardiac disorders during darolutamide therapy.

At the same time, darolutamide, despite these attention calling adverse events, is tolerable in patients with non-metastatic CRPC, as long as they are followed up by physicians with sufficient knowledge and experience in cancer pharmacotherapy, through the monitoring and management of adverse events, drug interruption or discontinuation, dose reduction, and other appropriate measures.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of darolutamide in patients with non-metastatic CRPC based on the safety data from Study 17712:

Table 23 presents a summary of the safety data from Study 17712.

Table 23. Safety summary (Study 17712, safety analysis set)

	n (%)	
	Entire study population	
	Darolutamide N = 954	Placebo N = 554
All adverse events	794 (83.2)	426 (76.9)
Grade ≥3 adverse events	273 (28.6)	126 (22.7)
Adverse events leading to death	37 (3.9)	18 (3.2)
Serious adverse events	237 (24.8)	111 (20.0)
Adverse event leading to drug discontinuation	85 (8.9)	48 (8.7)
Adverse events leading to drug interruption	119 (12.5)	49 (8.8)
Adverse events leading to dose reduction	46 (4.8)	9 (1.6)

Adverse events of any grade reported with a ≥1% higher incidence in the darolutamide group than in the placebo group were fatigue (12.1% [115 patients] in the darolutamide group, 8.7% [48 patients] in the placebo group), diarrhoea (6.9% [66 patients], 5.6% [31 patients]), hypertension (6.6% [63 patients], 5.2% [29 patients]), pain in extremity (5.8% [55 patients], 3.2% [18 patients]), anaemia (5.6% [53 patients], 4.5% [25 patients]), hot flush (5.2% [50 patients], 4.2% [23 patients]), oedema peripheral (4.1% [39 patients], 3.1% [17 patients]), pollakiuria (4.0% [38 patients], 2.9% [16 patients]), headache (3.9% [37 patients], 2.5% [14 patients]), musculoskeletal pain (3.9% [37 patients], 2.0% [11 patients]),

dizziness (3.7% [35 patients], 2.5% [14 patients]), weight decreased (3.6% [34 patients], 2.2% [12 patients]), cough (3.0% [29 patients], 2.0% [11 patients]), influenza (2.8% [27 patients], 1.6% [9 patients]), upper respiratory tract infection (2.6% [25 patients], 1.6% [9 patients]), and pyrexia (2.0% [19 patients], 0.9% [5 patients]). There were no adverse events leading to death, adverse events leading to drug discontinuation, drug interruption, or dose reduction, Grade ≥3 adverse events, or serious adverse events reported with a ≥1% higher incidence in the darolutamide group than in the placebo group.

PMDA's view:
Although some adverse events were reported more frequently in the darolutamide group than in the placebo group in Study 17712, most of these adverse events were Grade ≤2 and manageable with symptomatic therapies or other measures. Therefore, darolutamide is tolerable in patients with non-metastatic CRPC, as long as patients are followed up by physicians with sufficient knowledge and experience in cancer pharmacotherapy through the monitoring and management of adverse events, drug interruption or discontinuation, dose reduction, and other appropriate measures.

7.R.3.2 Safety differences between Japanese and non-Japanese patients

The applicant's explanation about the differences in the safety of darolutamide between Japanese patients and non-Japanese patients:
Table 24 shows a summary of the safety data from Japanese and non-Japanese patients receiving darolutamide in Study 17712.

Table 24. Safety summary (Study 17712, the darolutamide group)

	n (%)	
	Japanese N = 62	Non-Japanese N = 892
All adverse events	53 (85.5)	741 (83.1)
Grade ≥3 adverse events	18 (29.0)	255 (28.6)
Adverse events leading to death	1 (1.6)	36 (4.0)
Serious adverse events	20 (32.3)	217 (24.3)
Adverse event leading to drug discontinuation	5 (8.1)	80 (9.0)
Adverse events leading to drug interruption	9 (14.5)	110 (12.3)
Adverse events leading to dose reduction	8 (12.9)	38 (4.3)

In the darolutamide group of Study 17712, adverse events of any grade reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were nasopharyngitis (19.4% [12 patients] in Japanese patients, 2.7% [24 patients] in non-Japanese patients), constipation (12.9% [8 patients], 5.8% [52 patients]), fall (12.9% [8 patients], 3.1% [28 patients]), decreased appetite (11.3% [7 patients], 2.4% [21 patients]), upper respiratory tract infection (8.1% [5 patients], 2.2% [20 patients]), rash (6.5% [4 patients], 1.5% [13 patients]), and hepatic function abnormal(6.5% [4 patients], 0%). Grade ≥3 adverse events reported with a ≥2% higher incidence in Japanese patients than in non-Japanese patients were hydronephrosis (3.2% [2 patients], 0.6% [5 patients]) and bladder neoplasm (3.2% [2 patients], 0.1% [1 patient]). Serious adverse events reported with a ≥2% higher incidence in Japanese patients than in non-Japanese patients were angina pectoris (3.2% [2 patients], 0.2% [2 patients]), decreased appetite (3.2% [2 patients], 0.2% [2 patients]), and bladder neoplasm (3.2% [2 patients], 0.1% [1 patient]). The

adverse event that led to drug interruption with a ≥2% higher incidence in Japanese patients than in non-Japanese patients was decreased appetite (3.2% [2 patients], 0.2% [2 patients]). Similarly, the adverse event that led to dose reduction with a ≥2% higher incidence in Japanese patients than in non-Japanese patients was decreased appetite (3.2% [2 patients], 0%). There were no adverse events leading to death or adverse events leading to drug discontinuation, with a ≥2% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:
Although the small number of Japanese patients treated with darolutamide for non-metastatic CRPC in Study 17712 precludes a rigorous comparison of the safety of darolutamide between Japanese and non-Japanese patients, neither the incidence of adverse events leading to death nor that of Grade ≥3 adverse events tended to be clearly higher in Japanese patients than in non-Japanese patients. Therefore, darolutamide is also tolerable in Japanese patients with non-metastatic CRPC, as long as appropriate measures, such as drug interruption or discontinuation, and dose reduction, are taken.

In the following sections, PMDA reviews the safety of darolutamide, focusing on the adverse events that were reported as serious cases for which a causal relationship to darolutamide could not be ruled out in Study 17712.

7.R.3.3 Cardiac disorders

The applicant's explanation about cardiac disorders associated with darolutamide therapy:
As cardiac disorders, events categorized into the following Medical Dictionary for Regulatory Activities (MedDRA) High Level Group Terms (HLGTs) were summarized: "cardiac arrhythmias," "coronary artery disorders," and "heart failures."

Table 25 shows the incidence of cardiac disorders in Study 17712.

Table 25. Cardiac disorders with a ≥1% incidence in either treatment group (Study 17712)

PT (MedDRA ver.21.0)	n (%)			
	Darolutamide N = 954		Placebo N = 554	
	All grades	Grade ≥3	All grades	Grade ≥3
Cardiac disorders	101 (10.6)	40 (4.2)	35 (6.3)	9 (1.6)
Atrial fibrillation	22 (2.3)	6 (0.6)	8 (1.4)	2 (0.4)
Arrhythmia	14 (1.5)	2 (0.2)	3 (0.5)	0
Cardiac failure	13 (1.4)	5 (0.5)	5 (0.9)	3 (0.5)
Angina pectoris	12 (1.3)	3 (0.3)	4 (0.7)	0
Coronary artery disease	10 (1.0)	6 (0.6)	1 (0.2)	0
Bradycardia	10 (1.0)	1 (0.1)	1 (0.2)	1 (0.2)

In Study 17712, cardiac disorders led to death in 7 of 954 patients (0.7% [cardiac failure in 3 patients, and acute myocardial infarction, angina pectoris, coronary artery disease, and cardiac failure acute in 1 patient each]) in the darolutamide group and 4 of 554 patients (0.7% [cardiac failure in 3 patients and myocardial infarction in 1 patient]) in the placebo group. A causal relationship to the study drug could

not be ruled out in 1 of 554 patients (myocardial infarction) in the placebo group. Serious cardiac disorders were reported in 44 of 954 patients (4.6% [atrial fibrillation and cardiac failure in 8 patients each, acute myocardial infarction in 5 patients, angina pectoris and myocardial infarction in 4 patients each, arrhythmia, atrioventricular block second degree, bradycardia, sinus node dysfunction, coronary artery disease, and coronary artery stenosis in 2 patients each, and atrioventricular block, atrioventricular block complete, conduction disorder, coronary artery occlusion, cardiac failure acute, and cardiac failure congestive in 1 patient each; including patients reporting ≥2 events]) in the darolutamide group and 14 of 554 patients (2.5% [cardiac failure in 4 patients, atrial fibrillation in 3 patients, angina pectoris and myocardial infarction in 2 patients each, and angina unstable, coronary artery disease, myocardial ischaemia, and bradycardia in 1 patient each]) in the placebo group. A causal relationship to the study drug could not be ruled out in 2 of 954 patients (conduction disorder and atrioventricular block complete in 1 patient each) in the darolutamide group and 1 of 554 patients (myocardial infarction) in the placebo group. Cardiac disorders led to drug discontinuation in 8 of 954 patients (0.8% [cardiac failure in 4 patients, and angina pectoris, coronary artery disease, myocardial infarction, and cardiac failure acute in 1 patient each]) in the darolutamide group and 5 of 554 patients (0.9% [cardiac failure in 4 patients and myocardial infarction in 1 patient]) in the placebo group. Cardiac disorders led to drug interruption in 13 of 954 patients (1.4% [atrial fibrillation in 4 patients, arrhythmia, bradycardia, conduction disorder, sinus node dysfunction, tachycardia, acute myocardial infarction, angina pectoris, coronary artery disease, coronary artery stenosis, myocardial infarction, and myocardial ischaemia in 1 patient each, including patients reporting ≥2 events]) in the darolutamide group and 4 of 554 patients (0.7% [cardiac failure in 2 patients, and atrial fibrillation, acute coronary syndrome, and myocardial infarction in 1 patient each, including patients reporting ≥2 events]) in the placebo group. Cardiac disorders led to dose reduction in 2 of 954 patients (0.2% [atrial fibrillation and tachycardia in 1 patient each]) in the darolutamide group.

The median (range) time to the first onset of cardiac disorders was 228.5 (1-1,197) days in the darolutamide group and 212.0 (1-808) days in the placebo group.

Table 26 presents a list of patients experiencing serious cardiac disorders (that are causally related to darolutamide) in all of the clinical studies submitted for the current application.

Table 26. Patients experiencing serious cardiac disorders (that are causally related to darolutamide)

Study	Age	Race	PT (MedDRA ver.21.0)	Grade	Time of onset (Day)	Duration (Day)	Darolutamide	Outcome
17712	69	Non-Japanese	Conduction disorder	3	37	4	Interrupted	Resolved
	68	Non-Japanese	Atrioventricular block complete	3	16	3	Continued	Resolved

In Study 17712, the incidence of cardiac disorders tended to be higher in the darolutamide group than in the placebo group. However, given that the treatment duration was longer in the darolutamide group than in the placebo group, and that the proportion of patients with a history of cardiac disorders was

higher in the darolutamide group (46.1%) than in the placebo group (40.3%), no particular measures or cautions will be necessary regarding the development of cardiac disorders.

PMDA's view:
In Study 17712, serious cardiac disorders for which a causal relationship to darolutamide could not be ruled out were reported in the darolutamide group. Further, the intended patient population of darolutamide includes many patients with hypertension or other chronic diseases, who would be at risk of cardiac disorders. In view of these facts and other reasons, patients receiving darolutamide should be carefully monitored for the development of cardiac disorders. Therefore, to communicate proper information to healthcare professionals, the package insert should include a caution to take appropriate measures, including monitoring cardiac disorder-related symptoms (e.g., arrhythmia and cardiac failure) and conducting cardiac function tests as needed, and should state the incidence of cardiac disorders in the clinical studies and actions to be taken for cardiac disorders.

7.R.3.4 Others

In view of the mechanism of action of darolutamide, and the reported incidences of adverse events that require attention with drugs, like ADT and darolutamide, that inhibit AR-mediated signaling (e.g., apalutamide, enzalutamide), it is expected that (a) hypertension, (b) seizure, and (c) fracture may occur when darolutamide is administered in combination with ADT. PMDA asked the applicant to explain the incidences of the above adverse events (a) to (c).

The applicant's explanation:
(a) Hypertension
As hypertension events, events categorized into the following MedDRA preferred terms (PTs) were summarized: "blood pressure ambulatory increased," "blood pressure diastolic increased," "blood pressure increased," "blood pressure systolic increased," "diastolic hypertension," "essential hypertension," "hypertension," "labile hypertension," "mean arterial pressure increased," "systolic hypertension," and "withdrawal hypertension."

Table 27 shows the incidence of hypertension events in Study 17712.

Table 27. Incidence of hypertension events (Study 17712)

PT (MedDRA ver.21.0)	n (%)			
	Darolutamide N = 954		Placebo N = 554	
	All grades	Grade ≥3	All grades	Grade ≥3
Hypertension events	70 (7.3)	32 (3.4)	33 (6.0)	13 (2.3)
Hypertension	63 (6.6)	30 (3.1)	29 (5.2)	12 (2.2)
Blood pressure increased	4 (0.4)	1 (0.1)	3 (0.5)	0
Essential hypertension	3 (0.3)	1 (0.1)	0	0
Blood pressure systolic increased	0	0	1 (0.2)	1 (0.2)

No patients died from hypertension events in Study 17712. Serious hypertension events were reported in 1 of 954 patients (0.1% [hypertension in 1 patient]) in the darolutamide group and 0 patients in the placebo group. A causal relationship to the study drug was denied for the serious hypertension event in the darolutamide group. Hypertension events led to drug discontinuation in 0 patients in the darolutamide group and 2 of 554 patients (0.4% [hypertension in 2 patients]) in the placebo group. Hypertension events led to drug interruption in 6 of 954 patients (0.6% [hypertension in 6 patients]) in the darolutamide group and 0 patients in the placebo group. Hypertension events led to dose reduction in 3 of 954 patients (0.3% [hypertension in 3 patients]) in the darolutamide group and 1 of 554 patients (0.2% [hypertension in 1 patient]) in the placebo group.

The median (range) time to the first onset of hypertension events was 221.0 (1-940) days in the darolutamide group.

Table 28 presents a list of patients experiencing serious hypertension events during darolutamide therapy in all of the clinical studies submitted for the current application.

Table 28. Patients experiencing serious hypertension events

Study	Age	Race	PT (MedDRA ver.21.0)	Grade	Time of onset (Day)	Duration (Day)	Darolutamide	Causal relationship to darolutamide	Outcome
17712	73	Non-Japanese	Hypertension	1	192	3	Continued	No	Resolved

(b) Seizure

As seizure events, events categorized into the following MedDRA PTs were summarized: “Partial seizures,” “petit mal epilepsy,” “seizure,” “atonic seizures,” “atypical benign partial epilepsy,” “automatism epileptic,” “autonomic seizure,” “change in seizure presentation,” “clonic convulsion,” “convulsions local,” “convulsive threshold lowered,” “drug withdrawal convulsions,” “epilepsy,” “epileptic aura,” “focal dyscognitive seizures,” “frontal lobe epilepsy,” “generalised non-convulsive epilepsy,” “generalised tonic-clonic seizure,” “idiopathic generalised epilepsy,” “idiopathic partial epilepsy,” “myoclonic epilepsy,” “myoclonic epilepsy and ragged-red fibres,” “partial seizures with secondary generalisation,” “seizure cluster,” “simple partial seizures,” “status epilepticus,” “temporal lobe epilepsy,” “tonic clonic movements,” “tonic convulsion,” “tonic posturing,” and “uncinate fits.”

Table 29 shows the incidence of seizure events in Study 17712.

Table 29. Incidence of seizure events (Study 17712)

PT (MedDRA ver.21.0)	n (%)			
	Darolutamide N = 954		Placebo N = 554	
	All grades	Grade ≥3	All grades	Grade ≥3
Seizure events	2 (0.2)	0	1 (0.2)	0
Seizure	1 (0.1)	0	1 (0.2)	0
Partial seizures	1 (0.1)	0	0	0

In Study 17712, no seizure events led to death, or led to drug discontinuation, drug interruption, or dose reduction. Serious seizure events were reported in 2 of 954 patients (0.2% [partial seizures and seizure in 1 patient each]) in the darolutamide group and 0 patients in the placebo group. A causal relationship to darolutamide was denied for both of these seizure events.

The median (range) time to the first onset of seizure events was 359.5 (262-457) days in the darolutamide group.

Table 30 provides a list of patients experiencing serious seizure events during darolutamide therapy in all of the clinical studies submitted for the current application.

Table 30. Patients experiencing serious seizure events

Study	Age	Race	PT (MedDRA ver.21.0)	Grade	Time of onset (Day)	Duration (Day)	Darolutamide	Causal relationship to darolutamide	Outcome
17712	79	Non-Japanese	Seizure	2	457	26*	Continued	No	Not resolved
	62	Non-Japanese	Partial seizures	1	262	3	Continued	No	Resolved

* Died on Day 482

(c) Fracture

As fracture events, events categorized into the following MedDRA High Level Terms (HLTs) were summarized: “fractures and dislocations NEC,” “limb fractures and dislocations,” “pelvic fractures and dislocations,” “skull fractures, facial bone fractures, and dislocations,” “spinal fractures and dislocations,” and “thoracic cage fractures and dislocations.”

Table 31 shows the incidence of fracture events in Study 17712.

Table 31. Fracture events reported by ≥2 patients in either treatment group (Study 17712)

PT (MedDRA ver.21.0)	n (%)			
	Darolutamide N = 954		Placebo N = 554	
	All grades	Grade ≥3	All grades	Grade ≥3
Fracture events	40 (4.2)	9 (0.9)	20 (3.6)	5 (0.9)
Rib fracture	11 (1.2)	0	8 (1.4)	0
Traumatic fracture	4 (0.4)	1 (0.1)	2 (0.4)	0
Hand fracture	4 (0.4)	0	1 (0.2)	1 (0.2)
Femoral neck fracture	2 (0.2)	2 (0.2)	0	0
Femur fracture	2 (0.2)	1 (0.1)	1 (0.2)	1 (0.2)
Fracture	2 (0.2)	1 (0.1)	1 (0.2)	0
Ankle fracture	2 (0.2)	1 (0.1)	0	0
Patella fracture	2 (0.2)	1 (0.1)	0	0
Spinal compression fracture	2 (0.2)	0	1 (0.2)	0
Radius fracture	2 (0.2)	0	0	0
Wrist fracture	2 (0.2)	0	0	0
Foot fracture	1 (0.1)	0	2 (0.4)	1 (0.2)
Facial bones fracture	0	0	2 (0.4)	1 (0.2)

In Study 17712, no fracture events led to death or led to dose reduction. Serious fracture events were reported in 8 of 954 patients (0.8% [femoral neck fracture and femur fracture in 2 patients each, and ankle fracture, fibula fracture, fracture, patella fracture, and skull fracture in 1 patient each]) in the darolutamide group and 6 of 554 patients (1.1% [facial bones fracture, femur fracture, foot fracture, fracture, hand fracture, and hip fracture in 1 patient each]) in the placebo group. A causal relationship to the study drug was denied for all of these events. Fracture events led to drug discontinuation in 0 patients in the darolutamide group and 1 of 554 patients ([0.2% facial bones fracture in 1 patient]) in the placebo group. Fracture events led to drug interruption in 1 of 954 patients (0.1% [femur fracture in 1 patient]) in the darolutamide group and 1 of 554 patients (0.2% [hand fracture in 1 patient]) in the placebo group.

The median (range) time to the first onset of fracture events was 292.5 (9-782) days in the darolutamide group.

Table 32 presents a list of patients experiencing serious fracture events during darolutamide therapy in all of the clinical studies submitted for the current application.

Table 32. Patients experiencing serious fracture events

Study	Age	Race	PT (MedDRA ver.21.0)	Grade	Time of onset (Day)	Duration (Day)	Darolutamide	Causal relationship to darolutamide	Outcome
17712	63	Non-Japanese	Fibula fracture	3	649	13	Continued	No	Resolved
			Patella fracture	3	649	13	Continued	No	Resolved
	88	Non-Japanese	Ankle fracture	3	348	7	Continued	No	Resolved
	73	Non-Japanese	Femur fracture	3	198	22	Continued	No	Resolved
	71	Non-Japanese	Femur fracture	2	485	28	Interrupted	No	Resolved
	82	Non-Japanese	Femoral neck fracture	3	663	45	Continued	No	Resolved
			Femoral neck fracture	1	708	—	Continued	No	Not resolved
	73	Non-Japanese	Femoral neck fracture	3	12	11	Continued	No	Not resolved
			Femoral neck fracture	1	23	96	Continued	No	Resolved
	65	Non-Japanese	Skull fracture	3	404	13	Continued	No	Resolved
	84	Japanese	Fracture	3	602	1	Continued	No	Not resolved
			Fracture	3	603	—	Continued	No	Not resolved
17829	73	Non-Japanese	Facial bones fracture	2	211	—	Continued	No	Resolved
	82	Non-Japanese	Hand fracture	3	26	32	Continued	No	Resolved
	73	Non-Japanese	Cervical vertebral fracture	3	215	—	Continued	No	Not resolved
			Rib fracture	1	215	—	Continued	No	Not resolved

PMDA's view:

As above, the adverse events (a) to (c) were reported by some patients in clinical studies. However, due to the limited number of patients experiencing these events and the fact that a causal relationship to darolutamide was denied, the currently available data are not sufficient to draw a concrete conclusion regarding the relationship between the development of such adverse events and darolutamide therapy. Therefore, the applicant should collect relevant data in the post-marketing setting and appropriately communicate new findings to healthcare professionals.

7.R.4 Clinical positioning and indication

The proposed indication was "castration-resistant prostate cancer." The proposed "Precautions Concerning Indication" was described as follows:

- Eligible patients must be selected by physicians with full knowledge of the information in the "Clinical Studies" section, and sufficient understanding of the efficacy and safety of darolutamide.

Based on the reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety," and the discussions in the subsections below, PMDA concluded that the indication of darolutamide should be "non-metastatic castration-resistant prostate cancer," and that the following statement should be presented in the "Precautions Concerning Indication" section.

- Eligible patients must be selected by physicians with full knowledge of the information in the "Clinical Studies" section, and sufficient understanding of the efficacy and safety of darolutamide.

7.R.4.1 Clinical positioning and indication of darolutamide

In representative clinical practice guidelines or representative textbooks for clinical oncology in and outside Japan, there are no descriptions of darolutamide therapy.

The applicant's explanation about the intended patient population and indication of darolutamide:
When Study 17712 was planned, given the following available reports, patients with CRPC with a PSA doubling time of ≤10 months were defined as patients at a greater risk for metastatic disease in the study. Based on this definition, Study 17712 enrolled patients with non-metastatic CRPC with a PSA doubling time of ≤10 months, and the study succeeded in demonstrating the clinical benefit of darolutamide in these patients. Therefore, administration of darolutamide to patients with non-metastatic CRPC with a PSA doubling time of ≤10 months can be recommended.

- In patients with non-metastatic CRPC, a shorter PSA doubling time was suggested to be associated with shorter bone metastasis-free survival and shorter OS (*J Clin Oncol.* 2005;23:2918-25).
- In a clinical study of denosumab in patients with non-metastatic CRPC, patients with a PSA doubling time of ≤10 months were defined as those at high risk for metastatic disease, and the prolongation of bone metastasis-free survival by denosumab was evaluated in these high-risk patients (*Lancet.* 2012;379:39-46).

There have been no study results demonstrating the clinical benefit of darolutamide in patients with non-metastatic CRPC with a PSA doubling time of >10 months, who were excluded from Study 17712. However, the use of darolutamide in such patients is acceptable for the following and other reasons.

- Approximately 40% of CRPC patients with a PSA doubling time of >18.8 months were reported to have metastases within 3 years (*J Clin Oncol.* 2005;23:2918-25); thus, even patients with CRPC with a PSA doubling time of >10 months are expected to be at risk for metastases.
- Strictly, 3 PSA measurements are needed to estimate a PSA doubling time. However, the disease may progress, and metastases may develop during these 3 measurements, and patients may miss the opportunity to be treated with darolutamide.

At present, no supporting clinical data are available for the clinical benefit of darolutamide in patients with metastatic CRPC. However, a foreign phase I/II study in patients with metastatic CRPC (Study 17829) showed a certain level of PSA response rate in patients treated with darolutamide [see Section 7.1.4.1]. In view of this result and other findings, administration of darolutamide to patients with metastatic CRPC is acceptable.

As above, the indication does not need to specify any target PSA doubling time or the absence of metastases; however, the selection criteria used in Study 17712 should be described in the "Clinical Studies" section of the package insert. Accordingly, the proposed indication was "castration-resistant

prostate cancer" and the following statement was included in the proposed "Precautions Concerning Indication" section.

- Eligible patients must be selected by physicians with full knowledge of the information in the "Clinical Studies" section, and sufficient understanding of the efficacy and safety of darolutamide.

Since there are no clinical study data on the efficacy or safety of darolutamide, in comparison with apalutamide or enzalutamide in the treatment of non-metastatic CRPC, the choice of drug to be prioritized is currently unknown and should be made on a patient-by-patient basis according to patient condition, with a good understanding of the mechanism of action and other aspects of each drug.

PMDA's view:
Taking into consideration that darolutamide will be administered by physicians with sufficient knowledge and experience in cancer pharmacotherapy, the applicant's explanation that the indication of darolutamide does not need to specify any target PSA doubling time is acceptable. However, in view of the fact that Study 17712, a clinical study that demonstrated the clinical benefit of darolutamide, employed MFS as the primary endpoint and enrolled patients with non-metastatic CRPC, the absence of metastases is important information for selecting eligible patients for darolutamide therapy, and this should be clearly described in the "Indication" section.

Based on the above, the fact that the target patient population of Study 17712 were patients with non-metastatic CRPC with a PSA doubling time of ≤10 months should be included in the "Clinical Studies" section of the package insert. Accordingly, the indication should be "non-metastatic castration-resistant prostate cancer," and the following statement should be included in the "Precautions Concerning Indication" section.

- Eligible patients must be selected by physicians with full knowledge of the information in the "Clinical Studies" section, and sufficient understanding of the efficacy and safety of darolutamide.

7.R.5 Dosage and administration

The proposed dosage and administration was "The usual adult dosage is 600 mg of darolutamide administered orally twice daily, after meals," and the following statements were included in the proposed "Precautions Concerning Dosage and Administration" section.

- The efficacy and safety of darolutamide, when used without surgical or medical castration, have not been established.
- If a patient experiences a Grade ≥3 or intolerable adverse drug reaction, darolutamide therapy must be interrupted or the dose must be reduced to 300 mg twice daily (dose reduction to below 300 mg twice daily is not recommended), until the symptoms improve. The dose may then be increased to the usual dose.

Based on the reviews in Sections "7.R.2 Efficacy" and "7 R.3 Safety," and the subsections below, the dosage and administration should be modified as follows: "The usual adult dosage is 600 mg of

darolutamide administered orally twice daily, after meals. The dose should be reduced, as appropriate, according to the patient's condition." At the same time, the following statements should be included in the "Precautions Concerning Dosage and Administration" section.

- The efficacy and safety of darolutamide, when used without surgical or medical castration, have not been established.
- If a patient experiences a Grade ≥3 or intolerable adverse drug reaction, darolutamide therapy must be interrupted or the dose must be reduced to 300 mg twice daily, until the symptoms improve to Grade ≤2. The dose may then be increased to the usual dose.

7 R.5.1 Dosage and administration of darolutamide

The applicant's explanation about the rationale for the proposed dosage and administration:

Study 17712 was conducted using a dosage regimen that was selected based on the following study results and other available findings, and the results of the study demonstrated the clinical benefit of darolutamide in the treatment of non-metastatic CRPC. Therefore, the proposed dosage and administration was set based on the dosage regimen used in Study 17712.

- The result of the phase I part of Study 17829 demonstrated the tolerability of darolutamide administered at doses of 100, 200, 300, 500, 700, or 900 mg twice daily under fed conditions in combination with ADT.
- When darolutamide was administered as repeated oral doses twice daily in the phase I part of Study 17829, the plasma darolutamide concentration on Day 7 increased dose-dependently over the dose range from 100 mg to 700 mg, but did not increase for doses between 700 mg and 900 mg.
- In the phase II part of Study 17829, darolutamide 700 mg administered twice daily under fed conditions in combination with ADT provided a certain level of PSA response rate [see Section 7.1.4.1].
- The results of Study 17830[43)] suggested that the efficacy of darolutamide 600 mg administered twice daily under fed conditions would be comparable to that of darolutamide 700 mg twice daily under fed conditions.
- In Studies 17719 and 17830, exposure to darolutamide was affected by the timing of dosing in relation to food intake; in particular, exposure to darolutamide administered under fed conditions was approximately 2.5-fold higher than that under fasted conditions.

Currently, there are no available data regarding the efficacy or safety of darolutamide administered without ADT (surgical or medial castration). Therefore, this should be described in the "Precautions Concerning Dosage and Administration" section.

PMDA's view:

43) In the extension part, 25 of 30 patients (83.3%) who received darolutamide 600 mg twice daily showed a ≥50% decrease in serum PSA from baseline to Month 3.

PMDA accepted the applicant's explanation, and concluded that the proposed dosage and administration should be modified as follows: "The usual adult dosage is 600 mg of darolutamide administered orally twice daily, after meals. The dose should be reduced, as appropriate, according to the patient's condition."

7.R.5.2 Dosage adjustment of darolutamide

The applicant's explanation about the criteria for drug interruption, dose reduction, and drug discontinuation:

Study 17712 employed specific criteria for drug interruption, dose reduction, and drug discontinuation, and demonstrated the clinical benefit of darolutamide by following the criteria. Therefore, dosage adjustment criteria based on the criteria used in Study 17712 will be included in the "Precautions Concerning Dosage and Administration" section. On the other hand, Study 17712 actually identified no adverse events for which the incidences increased dose-dependently, and no adverse events requiring drug interruption, dose reduction, or drug discontinuation. The description was therefore modified as follows:

- If a patient experiences a Grade ≥3 or intolerable adverse drug reaction, darolutamide therapy must be interrupted or the dose must be reduced to 300 mg twice daily (dose reduction to below 300 mg twice daily is not recommended), until the symptoms improve. The dose may then be increased to the usual dose.

PMDA's view:

PMDA accepted the applicant's explanation, and the statement regarding dosage adjustment in the proposed "Precautions Concerning Dosage and Administration" section was modified as shown below.

- If a patient experiences a Grade ≥3 or intolerable adverse drug reaction, darolutamide therapy must be interrupted or the dose must be reduced to 300 mg twice daily, until the symptoms improve to Grade ≤2. The dose may then be increased to the usual dose.

7.R.6 Post-marketing investigations

The applicant's explanation:

In view of the following study outcomes, there are no identified safety concerns in the current application, and it is not necessary to conduct post-marketing surveillance aiming at evaluating the safety and other aspects of darolutamide in patients treated with darolutamide for CRPC immediately after approval of the current application.

- In Study 17712, some adverse events were reported more frequently in the darolutamide group than in the placebo group; however, most of these adverse events were Grade ≤2 and manageable with symptomatic treatments or other measures [see Section 7.R.3].
- Study 17712 identified no safety concerns specific to Japanese patients.

PMDA's view:

Based on the results of the review in Section "7.R.3 Safety" in addition to the fact that only limited safety information is available from Japanese patients treated with darolutamide for CRPC, post-marketing surveillance involving cardiac disorders as the safety specification should be conducted in Japanese patients with CRPC to evaluate the relationship between darolutamide and cardiac disorders, as well as other issues in the post-marketing setting.

7.3 Adverse events reported in clinical studies

Among the clinical study results submitted for safety evaluation, deaths are presented in Sections "7.1 Evaluation data" and "7.2 Reference data," while major adverse events other than death are detailed below.

7.3.1 Japanese phase I study (Study 17719)

Adverse events were reported in 3 of 3 patients (100%) in the 300 mg group and 6 of 6 patients (100%) in the 600 mg group. Adverse events for which a causal relationship to darolutamide could not be ruled out were reported in 2 of 3 patients (66.7%) in the 300 mg group and 2 of 6 patients (33.3%) in the 600 mg group. Adverse events reported with a ≥30% incidence in the 300 mg group were nausea, decreased appetite, and insomnia in 2 patients (66.7%) each, and enterocolitis, vomiting, pyrexia, hyperglycaemia, musculoskeletal pain, headache, and urinary retention in 1 patient (33.3%) each; while those in the 600 mg group were anaemia in 3 patients (50%) and nausea, vomiting, malaise, pyrexia, fall, lipase increased, and decreased appetite in 2 patients (33.3%) each.

Serious adverse events were reported in 2 of 3 patients (66.7%) in the 300 mg group and 1 of 6 patients (16.7%) in the 600 mg group. Reported serious adverse events were enterocolitis and nausea in 1 patient (33.3%) each in the 300 mg group, and malaise in 1 patient (33.3%) in the 600 mg group. A causal relationship to darolutamide could not be ruled out for the nausea in the 300 mg group.

The adverse event that led to drug discontinuation was nausea in 1 of 3 patients (33.3%) in the 300 mg group, for which a causal relationship to darolutamide could not be ruled out.

7.3.2 Global phase III study (Study 17712)

Adverse events were reported in 794 of 954 patients (83.2%) in the darolutamide group and 426 of 554 patients (76.9%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 258 of 954 patients (27.0%) in the darolutamide group and 110 of 554 patients (19.9%) in the placebo group. Adverse events reported with a ≥5% incidence in either treatment group are shown in Table 33.

Table 33. Adverse events with a ≥5% incidence in either treatment group

SOC PT (MedDRA ver.21.0)	n (%) Darolutamide N = 954		 Placebo N = 554	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	794 (83.2)	273 (28.6)	426 (76.9)	126 (22.7)
Blood and lymphatic system disorders				
Anaemia	53 (5.6)	8 (0.8)	25 (4.5)	2 (0.4)
General disorders and administration site conditions				
Fatigue	115 (12.1)	4 (0.4)	48 (8.7)	5 (0.9)
Gastrointestinal disorders				
Constipation	60 (6.3)	0	34 (6.1)	0
Diarrhoea	66 (6.9)	1 (0.1)	31 (5.6)	1 (0.2)
Nausea	48 (5.0)	2 (0.2)	32 (5.8)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	77 (8.1)	3 (0.3)	51 (9.2)	2 (0.4)
Back pain	84 (8.8)	4 (0.4)	50 (9.0)	1 (0.2)
Pain in extremity	55 (5.8)	0	18 (3.2)	1 (0.2)
Infections and infestations				
Urinary tract infection	47 (5.8)	6 (0.6)	28 (5.1)	3 (0.5)
Renal and urinary disorders				
Urinary retention	33 (3.5)	15 (1.6)	36 (6.5)	11 (2.0)
Vascular disorders				
Hot flush	50 (5.2)	0	23 (4.2)	0
Hypertension	63 (6.6)	30 (3.1)	29 (5.2)	12 (2.2)

Serious adverse events were reported in 237 of 954 patients (24.8%) in the darolutamide group and 111 of 554 patients (20.0%) in the placebo group. Serious adverse events reported by ≥4 patients in the darolutamide group were urinary retention in 15 patients (1.6%), pneumonia in 13 patients (1.4%), haematuria in 10 patients (1.0%), atrial fibrillation and cardiac failure in 8 patients (0.8%) each, urinary tract infection in 7 patients (0.7%), urinary tract obstruction in 6 patients (0.6%), acute myocardial infarction, ischaemic stroke, and pulmonary embolism in 5 patients (0.5%) each, and acute kidney injury, angina pectoris, death, decreased appetite, dyspnoea, general physical health deterioration, intestinal obstruction, and myocardial infarction in 4 patients (0.4%) each; while those in the placebo group were urinary retention in 18 patients (3.2%), pneumonia and haematuria in 6 patients (1.1%) each, and cardiac failure and renal failure in 4 patients (0.7%) each. A causal relationship to the study drug could not be ruled out for the urinary retention and pulmonary embolism in 1 patient each in the darolutamide group, and the urinary retention in 1 patient in the placebo group.

Adverse events led to drug discontinuation in 85 of 954 patients (8.9%) in the darolutamide group and 48 of 554 patients (8.7%) in the placebo group. Such adverse events reported by ≥2 patients in the darolutamide group were cardiac failure and death in 4 patients (0.4%) each, and abdominal pain, blood creatinine increased, cardiac arrest, cerebral infarction, diarrhoea, general physical health deterioration, ischaemic stroke, pancreatic carcinoma, pneumonia, and pulmonary embolism in 2 patients (0.2%) each; while those in the placebo group were cardiac failure in 4 patients (0.7%), and cardiac arrest, ischaemic stroke, acute respiratory failure, cerebrovascular accident, and hypertension in 2 patients (0.4%) each. A causal relationship to the study drug could not be ruled out for the blood creatinine increased in 2

patients and diarrhoea in 1 patient in the darolutamide group, and the hypertension in 1 patient in the placebo group.

7.3.3 Foreign phase I study (Study 17721)

Adverse events were reported in 1 of 10 patients with severe renal impairment (10.0%) and 2 of 10 healthy adults (20.0%). A causal relationship to darolutamide was denied for all of these events. The reported adverse event was headache in 1 patient with severe renal impairment (10.0%) and headache in 2 healthy adults (20.0%).

There were no serious adverse events or adverse events that led to drug discontinuation.

7.3.4 Foreign phase I study (Study 17723)

Adverse events were reported in 15 of 30 patients (50.0%) during the darolutamide monotherapy period and 8 of 30 patients (26.7%) during the darolutamide + rosuvastatin combination therapy period. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 12 of 30 patients (40.0%) during the darolutamide monotherapy period and 3 of 30 patients (10.0%) during the combination therapy period. Adverse events reported with a ≥5% incidence during the darolutamide monotherapy period were headache in 7 patients (23.3%), fatigue in 4 patients (13.3%), and dyspepsia, nausea, lipase increased, and dizziness in 2 patients (6.7%) each; while those during the combination therapy period were medical device site pruritus and dizziness in 2 patients (6.7%) each.

There were no serious adverse events or adverse events that led to drug discontinuation.

7.3.5 Foreign phase I study (Study 17726)

Adverse events were reported in 2 of 15 patients (13.3%) during the darolutamide monotherapy period, 5 of 15 patients (33.3%) during the darolutamide + itraconazole combination therapy period, and 6 of 15 patients (40.0%) during the darolutamide + rifampicin combination therapy period. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 0 patients during the darolutamide monotherapy period, 1 of 15 patients (6.7%) during the darolutamide + itraconazole period, and 4 of 15 patients (26.7%) during the darolutamide + rifampicin period. Reported adverse events were blood creatine phosphokinase increased, muscle spasms, and throat irritation in 1 patient (6.7%) each during the darolutamide monotherapy period; medical device site pruritus in 2 patients (13.3%), and blood creatine phosphokinase increased, headache, and throat irritation in 1 patient (6.7%) each during the darolutamide + itraconazole period; and headache in 5 patients (33.3%), and nausea, feeling cold, and malaise in 1 patient (6.7%) each during the darolutamide + rifampicin period.

There were no serious adverse events or adverse events that led to drug discontinuation.

7.3.6 Foreign phase I study (Study 17830)

Adverse events were reported in 23 of 30 patients (76.7%). Adverse events for which a causal relationship to darolutamide could not be ruled out were reported in 6 of 30 patients (20.0%). Adverse events reported with a ≥10% incidence were abdominal pain, diarrhoea, fatigue, and nausea in 4 patients (13.3%) each, and prostate cancer, cough, back pain, bone pain, and dysuria in 3 patients (10.0%) each.

Serious adverse events were reported in 11 of 30 patients (36.7%). Serious adverse events reported by ≥2 patients were prostate cancer in 3 patients (10.0%) and back pain in 2 patients (6.7%). A causal relationship to darolutamide was denied for all of these events.

Adverse events led to discontinuation of darolutamide in 4 of 30 patients (13.3%), including respiratory failure, lung adenocarcinoma, prostate cancer, and neuroendocrine carcinoma in 1 patient (3.3%) each. A causal relationship to darolutamide was denied for all these events.

7.3.7 Foreign phase I study (Study 18860)

Adverse events were reported in 5 of 15 patients (33.3%) during the darolutamide monotherapy period, 6 of 15 patients (40.0%) during the darolutamide + DABE combination therapy period, and 7 of 15 patients (46.7%) during the darolutamide + midazolam + DABE combination therapy period. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 4 of 30 patients (26.7%) during the darolutamide monotherapy period, 6 of 15 patients (40.0%) during the darolutamide + DABE combination therapy period, and 5 of 15 patients (33.3%) during the darolutamide + midazolam + DABE combination therapy period. Adverse events reported with a ≥10% incidence were diarrhoea in 2 patients (13.3%) during the darolutamide monotherapy period, fatigue in 3 patients (20.0%) and aphasia in 2 patients (13.3%) during the darolutamide + DABE combination therapy period, and fatigue in 3 patients (20.0%) during the darolutamide + midazolam + DABE combination therapy period.

There were no serious adverse events.

Adverse events led to drug discontinuation in 1 of 15 patients (6.7%) during the darolutamide + midazolam + DABE combination therapy period. The adverse events that led to drug discontinuation were dizziness, nausea, and vomiting in 1 patient (6.7%) each. A causal relationship to the study drug could not be ruled out for all of these events.

7.3.8 Foreign phase I/II study (Study 17829)

Adverse events were reported in 37 of 42 patients (88.1%) in the 100 mg cohort, 40 of 44 patients (90.9%) in the 200 mg cohort, 2 of 3 patients (66.7%) in the 300 mg cohort, 4 of 4 patients (100%) in the 500 mg cohort, 32 of 38 patients (84.2%) in the 700 mg cohort, and 2 of 3 patients (66.7%) in the 900 mg cohort. Adverse events for which a causal relationship to darolutamide could not be ruled out were reported in 10 of 42 patients (23.8%) in the 100 mg cohort, 13 of 44 patients (29.5%) in the 200

mg cohort, 1 of 3 patients (33.3%) in the 300 mg cohort, 1 of 4 patients (25.0%) in the 500 mg cohort, 11 of 38 patients (28.9%) in the 700 mg cohort, and 2 of 3 patients (66.7%) in the 900 mg cohort. Adverse events reported with a ≥10% incidence were fatigue in 7 patients (16.7%), constipation in 6 patients (14.3%), and nausea and back pain in 5 patients (11.9%) each in the 100 mg cohort, fatigue in 9 patients (20.5%), constipation and back pain in 7 patients (15.9%) each, diarrhoea and pain in 5 patients (11.4%) each in the 200 mg cohort, diarrhoea, flatulence, viral infection, hypertension, abdominal distension, and presyncope in 1 patient (33.3%) each in the 300 mg cohort, nausea, fatigue, cough, dyspnoea, abdominal pain, erythema, headache, bone pain, laceration, pyrexia, urinary incontinence, bronchitis, hand fracture, muscle injury, cardiac murmur, hyperkalaemia, and sciatica in 1 patient (25.0%) each in the 500 mg cohort, fatigue in 6 patients (15.8%), oedema peripheral, weight decreased, and decreased appetite in 5 patients (13.2%) each, and pain, back pain, and pain in extremity in 4 patients (10.5%) each in the 700 mg cohort, and diarrhoea in 2 patients (66.7%), and constipation, nausea, fatigue and hot flush, flatulence, headache, nasopharyngitis, dizziness, epistaxis, oral herpes, and sunburn in 1 patient (33.3%) each in the 900 mg cohort.

Serious adverse events were reported in 2 of 42 patients (4.8%) in the 100 mg cohort, 5 of 44 patients (11.4%) in the 200 mg cohort, 0 patients in the 300 mg cohort, 1 of 4 patients (25.0%) in the 500 mg cohort, 5 of 38 patients (13.2%) in the 700 mg cohort, and 0 patients in the 900 mg cohort. Reported serious adverse events were bacteraemia and liver tumour in 1 patient (2.4%) each in the 100 mg cohort, back pain, anaemia, cardiac failure, colitis ulcerative, fatigue, general physical health deterioration, diverticulitis, staphylococcal infection, prostate cancer, cerebral ischaemia, dyspnoea, and lymphoedema in 1 patient (2.3%) each in the 200 mg cohort, hand fracture, laceration, and muscle injury in 1 patient (25.0%) each in the 500 mg cohort, and back pain, pneumonia, bone pain, metastases to meninges, and urinary retention in 1 patient (2.6%) each in the 700 mg cohort. A causal relationship to darolutamide was denied for all of these events.

Adverse events led to discontinuation of darolutamide in 1 of 42 patients (2.4%) in the 100 mg cohort, 0 patients in the 200 mg cohort, 0 patients in the 300 mg cohort, 1 of 4 patients (25.0%) in the 500 mg cohort, 0 patients in the 700 mg cohort, and 0 patients in the 900 mg cohort. The adverse events that led to discontinuation of darolutamide were cauda equina syndrome in 1 patient (2.4%) in the 100 mg cohort and bone pain in 1 patient (25.0%) in the 500 mg cohort. A causal relationship to darolutamide was denied for both of these events.

7.3.9 Foreign phase II study (Study 18035)

Adverse events were reported in all patients (100%) in each dose cohort (100 mg, 200 mg, 300 mg, 500 mg, 700 mg, and 900 mg). Adverse events for which a causal relationship to darolutamide could not be ruled out were reported in 10 of 25 patients (40.0%) in the 100 mg cohort, 10 of 25 patients (40.0%) in the 200 mg cohort, 1 of 3 patients (33.3%) in the 300 mg cohort, 2 of 2 patients (100%) in the 500 mg cohort, 8 of 18 patients (44.4%) in the 700 mg cohort, and 2 of 3 patients (66.7%) in the 900 mg cohort. Adverse events reported with a ≥15% incidence in each dose cohort were as follows: arthralgia in 9

patients (36.0%), pain in 8 patients (32.0%), constipation in 5 patients (20.0%), and diarrhoea, asthenia, oedema peripheral, decreased appetite, back pain, haematuria, and dyspnoea in 4 patients (16.0%) each in the 100 mg cohort; back pain in 9 patients (36.0%), fatigue and decreased appetite in 6 patients (24.0%), constipation and nausea in 5 patients (20.0%) each, and asthenia, insomnia, and arthralgia in 4 patients (16.0%) each in the 200 mg cohort; diarrhoea, arthralgia, and back pain in 2 patients (66.7%) each, and abdominal distension, flatus, nausea, fatigue, pain, peripheral swelling, muscle spasms, dizziness, rash, hypertension, lymphoedema, dysuria, spinal pain, paraesthesia, erythema, viral infection, deep vein thrombosis, ocular hyperaemia, haemorrhoidal haemorrhage, hypersensitivity, dupuytren's contracture, joint stiffness, rectal adenocarcinoma, presyncope, urinary tract inflammation, and nail discolouration in 1 patient (33.3%) each in the 300 mg cohort; fatigue, pain, nasopharyngitis, muscular weakness, urinary incontinence, gynaecomastia, cough, dyspnoea, erythema, sciatica, bronchitis, cheilitis, rhinitis, cardiac murmur, hyporeflexia, and aortic arteriosclerosis in 1 patient (50.0%) each in the 500 mg cohort; fatigue in 9 patients (50.0%), back pain in 7 patients (38.9%), oedema peripheral in 6 patients (33.3%), and nausea, vomiting, pain, arthralgia, muscular weakness, urinary incontinence, and hypertension in 3 patients (16.7%) each in the 700 mg cohort; and diarrhoea, fatigue, and nasopharyngitis in 2 patients (66.7%), and constipation, flatus, nausea, vomiting, urinary tract infection, arthralgia, back pain, pain in extremity, dizziness, headache, gynaecomastia, epistaxis, rash, hot flush, lymphoedema, spinal pain, rectal haemorrhage, oral herpes, foot fracture, sunburn, sleep disorder, and erythema in 1 patient (33.3%) each in the 900 mg cohort.

Serious adverse events were reported in 5 of 8 patients (32.0%) in the 100 mg cohort, 4 of 25 patients (16.0%) in the 200 mg cohort, 2 of 3 patients (66.7%) in the 300 mg cohort, 0 patients in the 500 mg cohort, 5 of 18 patients (27.8%) in the 700 mg cohort, and 0 patients in the 900 mg cohort. Serious adverse events reported by ≥2 patients in each dose cohort were acute kidney failure in 2 patients (8.0%) in the 100 mg cohort and back pain in 2 patients (11.1%) in the 700 mg cohort. A causal relationship to darolutamide was denied for both of these events.

Adverse events led to discontinuation of darolutamide in 1 of 25 patients (4.0%) in the 100 mg cohort, 1 of 25 patients (4.0%) in the 200 mg cohort, 1 of 3 patients (33.3%) in the 300 mg cohort, 0 patients in the 500 mg cohort, 0 patients in the 700 mg cohort, and 0 patients in the 900 mg cohort, including prostate cancer in the 100 mg cohort, fatigue in the 200 mg cohort, and rectal adenocarcinoma in the 300 mg cohort. A causal relationship to darolutamide could not be ruled out for the fatigue in the 200 mg cohort.

7.3.10 Foreign phase I study (Study 17831)

Adverse events were reported in 2 of 6 patients (33.3%) during Part 1 and 1 of 6 patients (16.7%) during Part 2. Adverse events for which a causal relationship to darolutamide could not be ruled out were reported in 1 of 6 patients (16.7%) during Part 1 and 1 of 6 patients (16.7%) during Part 2. Reported adverse events were atrial flutter and somnolence in 1 patient (16.7%) each during Part 1, and lymphadenopathy and diarrhoea in 1 patient (16.7%) each during Part 2.

A serious adverse event, atrial flutter, was reported in 1 of 6 patients (16.7%) during Part 1. A causal relationship to darolutamide was denied for the event.

No adverse events led to discontinuation of darolutamide.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that darolutamide has efficacy in the treatment of non-metastatic CRPC, and that darolutamide has acceptable safety in view of its benefits. Darolutamide is a drug with a new active ingredient, which is expected to competitively inhibit (a) androgen binding to the ligand binding domain of AR, (b) nuclear translocation of the transcription factor (i.e., AR), and (c) transcription of AR target genes, thereby blocking AR-mediated signaling and consequently blocking the growth of androgen-dependent tumors. Darolutamide provides a new therapeutic option for patients with non-metastatic CRPC, which is of clinical significance. The indication, post-marketing investigations, etc. of darolutamide should be further evaluated.

PMDA has concluded that darolutamide may be approved if darolutamide is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 13, 2019

Product Submitted for Approval	
Brand Name	Nubeqa Tablets 300 mg
Non-proprietary Name	Darolutamide
Applicant	Bayer Yakuhin, Ltd.
Date of Application	March 5, 2019

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of its review described in Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that the efficacy of darolutamide has been demonstrated by the results of a global phase III study (Study 17712) involving patients with non-metastatic castration-resistant prostate cancer (CRPC)[44] with a prostate specific antigen (PSA) doubling time of ≤10 months,[45] showing the superiority of darolutamide in the primary endpoint of metastasis-free survival (MFS) over placebo, as well as by other data.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

1.2 Safety

As a result of its review described in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that darolutamide therapy in patients with non-metastatic CRPC requires particular attention to the development of cardiac disorders.

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44) Patients with CRPC were enrolled in the study, if the serum testosterone level was <50 ng/dL, the PSA level was ≥2.0 ng/mL, and a PSA rise was documented on 3 consecutive occasions at least 1 week apart.

45) Patients with CRPC were enrolled in the study, if they had at least 3 PSA measurements during ADT, and the estimated PSA doubling time was ≤10 months.

At the same time, PMDA has concluded that darolutamide, despite these attention requiring adverse events, is tolerable in patients with non-metastatic CRPC, as long as they are followed up by physicians with sufficient knowledge and experience in cancer pharmacotherapy, through monitoring and management of adverse events, drug interruption or discontinuation, dose reduction, and other appropriate measures.

After the Review Report (1) had been prepared, serious cases of intestinal lung disease (ILD), including fatal cases, were reported in patients treated with apalutamide, an approved AR-inhibitory drug like darolutamide, and the marketing authorization holder released "Recommendations on the Proper Use of Erleada Tablets 60 mg - risk of intestinal lung disease-" (dated October 2019). Based on this information, PMDA asked the applicant to explain the incidence of ILD in patients treated with darolutamide.

The applicant's explanation:
In Study 17712, ILD events were reported in 6 of 954 patients (0.6% [pneumonitis and pulmonary fibrosis in 3 patients each]), but a causal relationship to darolutamide was denied by investigators for all the events. Among the ILD events, the pneumonitis in 1 patient was Grade ≥3, and none of the events were serious or required the discontinuation of darolutamide therapy. There were no ILD events in the placebo group.

PMDA's view:
Based on the small number of patients experiencing ILD during darolutamide therapy, and the fact that a causal relationship to darolutamide was denied by investigators for all of the ILD events, including Grade ≥3 events, that were reported in Study 17712, it is difficult to definitely determine the relationship between darolutamide therapy and the development of ILD based on the available data. However, given that ILD events were reported only in the darolutamide group, and not in the placebo group in Study 17712, and that patients treated with an AR-inhibitory drug, like darolutamide have been reported to experience fatal ILD events for which a causal relationship to the drug cannot be ruled out, as well as other findings, the applicant should appropriately caution healthcare professionals through the package insert, etc. to carefully monitor patients receiving darolutamide for the development of ILD-related symptoms, and to perform a chest X-ray or other proper measures. Further, the applicant should continue to actively collect information on the development of ILD in the post-marketing setting, and appropriately communicate new findings to healthcare professionals.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

Based on the above, PMDA instructed the applicant to appropriately address the above issues. The applicant agreed.

1.3 Clinical positioning and indication

As a result of its review described in Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the indication of darolutamide should be "non-metastatic castration-resistant prostate cancer," along with a statement of the fact that the target patient population of Study 17712 was patients with non-metastatic CRPC with a PSA doubling time of ≤10 months in the "Clinical Studies" section of the package insert, and presentation of the following cautionary statement in the "Precautions Concerning Indication" section.

Precautions Concerning Indication

- Eligible patients must be selected by physicians with full knowledge of the information in the "Clinical Studies" section, and sufficient understanding of the efficacy and safety of darolutamide.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

Based on the above, PMDA instructed the applicant to define the "Indication" and "Precautions Concerning Indication" sections as described above. The applicant agreed.

1.4 Dosage and administration

As a result of its review described in Section "7.R.5 Dosage and Administration" of the Review Report (1), PMDA has concluded that the "Dosage and Administration" section should be described as "The usual adult dosage is 600 mg of darolutamide administered orally twice daily, after meals. The dose should be reduced, as appropriate, according to the patient's condition," along with presentation of the following statement in the "Precautions Concerning Dosage and Administration" section.

Precautions Concerning Dosage and Administration

- The efficacy and safety of darolutamide, when used without surgical or medical castration, have not been established.
- If a patient experiences a Grade ≥3 or intolerable adverse drug reaction, darolutamide therapy must be interrupted or the dose must be reduced to 300 mg twice daily, until the symptoms improve to Grade ≤2. The dose may then be increased to the usual dose.

At the Expert Discussion, the expert advisors generally supported the above PMDA conclusion, while the following comment was raised.

- In Study 17712, the following criteria for drug interruption, dose reduction, and drug discontinuation were set: "If a patient experiences a Grade ≥3 or intolerable adverse drug reaction, darolutamide therapy must be interrupted until the symptoms improve. The therapy may then be resumed, with the dose reduced to 300 mg twice daily." Despite such adverse events reported in Study 17712, no information is available regarding the safety of darolutamide therapy continued at reduced doses, without interruption. Therefore, the criteria for drug interruption, dose reduction,

and drug discontinuation to be included in the "Precautions Concerning Dosage and Administration" section should be based on the criteria employed in Study 17712.

PMDA's view:
Based on the above comment from the expert advisors, PMDA has concluded that the criteria for drug interruption, dose interruption, and drug discontinuation to be included in the "Precautions Concerning Dosage and Administration" section should be based on the criteria employed in Study 17712, and that the following statement should be included in the "Precautions Concerning Dosage and Administration" section.

Precautions Concerning Dosage and Administration

- The efficacy and safety of darolutamide, when used without surgical or medical castration, have not been established.
- If a patient experiences a Grade ≥3 or intolerable adverse drug reaction, darolutamide therapy must be interrupted until the symptoms improve. Afterwards, consider resumption of the therapy with the dose reduced to 300 mg twice daily. The dose may be increased to the usual dose, according to the patient's condition.

Based on the above, PMDA instructed the applicant to define the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as described above. The applicant agreed.

1.5 Risk management plan (draft)

In view of the discussion presented in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA has concluded that post-marketing surveillance involving cardiac disorders as the safety specification should be conducted in patients treated with darolutamide for non-metastatic CRPC.

At the Expert Discussion, the expert advisors supported PMDA's conclusion.

Based on the above, PMDA instructed the applicant to plan post-marketing surveillance involving cardiac disorders as the safety specification in patients treated with darolutamide for non-metastatic CRPC. The applicant responded as follows:

- The safety specification will be cardiac disorders.
- The planned sample size will be 150, in view of the incidence of cardiac disorders in Study 17712.
- The observation period will be ≥36 months, in view of the duration of treatment with darolutamide in Study 17712, etc.

PMDA accepted the applicant's response.

In view of the discussions above, discussions in Section "7.R.3 Safety" of Review Report (1), and discussions in Section "1.2 Safety" of Review Report (2), PMDA has concluded that the risk

management plan (draft) for darolutamide should include the safety specification presented in Table 34, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Tables 35 and 36.

Table 34. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	• Cardiac disorders • ILD	None
Efficacy specification		
None		

Table 35. Summary of additional pharmacovigilance activities, survey/study on efficacy, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Survey/study on efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey • Post-marketing clinical study (extension study of Study 17712)	None	• Disseminate data gathered during early post-marketing phase vigilance

Table 36. Outline of the specified use-results survey (draft)

Objective	To evaluate the incidence of cardiac disorders in clinical practice
Survey method	Central registration system
Population	Patients treated with darolutamide for non-metastatic CRPC
Observation period	≥36 months
Planned sample size	150 patients
Main survey items	Safety specification: cardiac disorders Other main survey items: patient characteristics (e.g., age, Eastern Cooperative Oncology Group performance status [ECOG-PS], prior treatments for the primary disease, medical history, complications), exposure to darolutamide, concomitant drugs/therapies, and other relevant items

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of the document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The clinical studies were generally performed in accordance with GCP. PMDA thus concluded that there were no obstacles to conducting its regulatory review based on the application documents submitted. At the same time, the inspection revealed the following finding at some of the study sites used by the applicant, despite its minor impact on the overall assessment of the studies. The heads of the study sites were notified of the issue.

Issue to be improved

Study sites

- Protocol deviations (entry errors for stratified factors)

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as follows, with the approval condition shown below, provided that the necessary precautionary statements are included in the package insert, and information on the proper use of the product is properly disseminated after the market launch, and provided that the product is properly used under the supervision of physicians with sufficient knowledge and experience in cancer pharmacotherapy at medical institutions capable of emergency response. The product is a drug with a new active ingredient; accordingly, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug substance and its drug product are both classified as powerful drugs.

Indication

Non-metastatic castration-resistant prostate cancer

Dosage and Administration

The usual adult dosage is 600 mg of darolutamide administered orally twice daily, after meals. The dose should be reduced, as appropriate, according to the patient's condition.

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

Contraindication

Patients with a history of hypersensitivity to any component of darolutamide

Precautions Concerning Indication

Eligible patients must be selected by physicians with full knowledge of the information in the "Clinical Studies" section, and sufficient understanding of the efficacy and safety of darolutamide.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of darolutamide, when used without surgical or medical castration, have not been established.
2. If a patient experiences a Grade ≥3 or intolerable adverse drug reaction, darolutamide therapy must be interrupted until the symptoms improve. Afterwards, consider resumption of the therapy with the dose reduced to 300 mg twice daily. The dose may be increased to the usual dose, according to the patient's condition.

Appendix

List of Abbreviations

ADT	androgen deprivation therapy (surgical or medical castration)
ALT	alanine aminotransferase
application	marketing application
AR	androgen receptor
ARE	androgen response element
AST	aspartate aminotransferase
BA	bioavailability
BCRP	breast cancer resistance protein
BSEP	bile salt export pump
CI	confidence interval
$C_{max,ss}$	maximum plasma concentration at steady state
CPP	critical process parameter
CQA	critical quality attribute
CRPC	castration-resistant prostate cancer
CYP	cytochrome P450
^{14}C-darolutamide	^{14}C-labeled darolutamide
DABE	dabigatran etexilate
darolutamide	darolutamide
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
efflux ratio	the ratio of the permeability coefficient in the secretory direction to that in the absorptive direction
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FC	film coating
GC	gas chromatography
hERG	human *ether-a-go-go* related gene
HLGT	high level group term
HLT	high level term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E guidelines	"Evaluation of stability data" (PFSB/ELD Notification No. 0603004, dated June 3, 2003)
ILD	interstitial lung disease
IR	infrared absorption spectrum
LC	liquid chromatography
LC-MS/MS	liquid chromatography/tandem mass spectrometry
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MFS	metastasis-free survival
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Prostate Cancer
NMR	nuclear magnetic resonance spectrum
NTCP	sodium taurocholate cotransporting polypeptide

OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability coefficient value in the apical to basolateral direction
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PSA	prostate-specific antigen
PT	preferred term
QbD	quality by design
QT	QT interval
QTc	corrected QT interval
ΔΔQTcF	difference from placebo in the change from baseline in the QT interval, corrected by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RR	rate of reconversion from M-1 to S,R- or S,S-darolutamide
SOC	system organ class
S,R-darolutamide	S,R-diastereomer of darolutamide
S,S-darolutamide	S,S-diastereomer of darolutamide
3T3-NRU	3T3 neutral red uptake phototoxicity test
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
UV/VIS	ultraviolet/visible spectrum