Report on the Deliberation Results

February 18, 2019

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

Brand Name	Erleada Tablets 60 mg
Non-proprietary Name	Apalutamide (JAN*)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 28, 2018

Results of Deliberation

In its meeting held on January 30, 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. The re-examination period is 8 years, and the drug product and its drug substance are both classified as powerful drugs.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

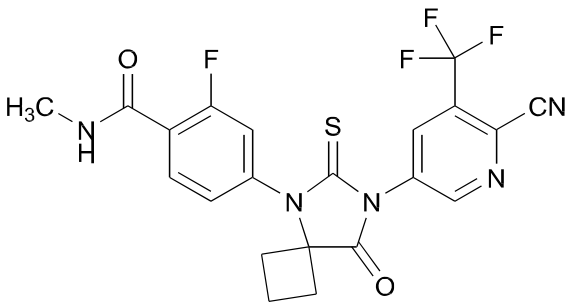
Review Report

January 22, 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	Erleada Tablets 60 mg
Non-proprietary Name	Apalutamide
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 28, 2018
Dosage Form/Strength	Tablets, each containing 60.0 mg of Apalutamide
Application Classification	Prescription drug (1) Drug(s) with a new active ingredient

Chemical Structure



Molecular formula: $C_{21}H_{15}F_4N_5O_2S$

Molecular weight: 477.43

Chemical name: 4-{7-[6-Cyano-5-(trifluoromethyl) pyridin-3-yl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl}-2-fluoro-*N*-methylbenzamide

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 patients with 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 condition. Severe skin disorder and seizure should to be further investigated via post-marketing surveillance.

Indication

Non-metastatic castration-resistant prostate cancer

Dosage and Administration

The usual adult dosage is 240 mg of apalutamide orally administered once daily. The dose may be reduced according to the patient's condition.

Approval Condition

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

Attachment

Review Report (1)

December 3, 2018

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	Erleada Tablets 60 mg
Non-proprietary Name	Apalutamide
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 28, 2018
Dosage Form/Strength	Tablets, each containing 60.0 mg of Apalutamide
Proposed Indication	Castration-resistant prostate cancer

Proposed Dosage and Administration

The usual adult dosage is 240 mg of apalutamide orally administered once daily.

Table of Contents

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

Androgen receptor (AR) forms a homodimer with dihydrotestosterone bound to its ligand binding domain, and the dimer enters the nucleus to bind to the target gene, namely androgen response element (ARE), which enhances the expression of genes related to cell survival and growth (*Cancers.* 2017;9:67-86).

Apalutamide, discovered by the University of California in Los Angeles, the US, is a low molecular weight compound that inhibits AR-mediated signaling. While competitively inhibiting androgen from binding to the ligand binding domain of AR, apalutamide also prevents AR, a transcription factor, from being imported to the nucleus and inhibits AR binding to the transcription factor binding region on deoxyribonucleic acid (DNA) and subsequent transcription of the target gene. Thus, apalutamide inhibits AR-mediated signaling and is thereby expected to suppress androgen-dependent tumor growth.

1.2 Development history etc.

Outside Japan, the applicant initiated a phase I/II study (Study ARN-509-001 [Study 001]) in July 2010 in patients with castration-resistance prostate cancer (CRPC) at high risk for distant metastasis. In September 2013, the applicant further conducted a global phase III study (Study ARN-509-003 [Study 003]) in patients with non-metastatic CRPC, defined by prostate-specific antigen (PSA) doubling time of ≤10 months.

An approval application was submitted in October 2017 in the US and in February 2018 in the EU, with data from Study 003 as the pivotal study data. In the US, apalutamide was approved for the indication described as "ERLEADA is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC)." in February 2018. In the EU, the application is currently under review.

As of October 2018, apalutamide has been approved for the indication of CRPC in 5 countries.

In Japan, a phase I study (Study 56021927PCR1008 [Study 08]) was initiated in July 2014 in patients with metastatic CRPC by the applicant. Patient enrollment in the Study 003 began in [redacted].

The approval application of apalutamide was submitted with pivotal data from Study 003.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white to light yellow powder. The description, melting point, solubility, dissociation constant, and distribution coefficient were determined. Although the drug substance was found in 21 crystal forms including [redacted], it was confirmed that crystal form B ([redacted]) is generated in a commercial production and remains unchanged in stability studies.

The chemical structure of the drug substance was elucidated by mass spectrum, elemental analysis, infrared absorption spectrum (IR), ultraviolet/visible spectrum (UV/VIS), and nuclear magnetic resonance spectrum (NMR) (^{1}H- and ^{13}C-NMR).

2.1.2 Manufacturing process

The drug substance is synthesized from starting materials of [redacted], [redacted], and [redacted].

The quality control strategy was constructed based on the following investigation using the quality-by-design (QbD) approach (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on quality risk assessment and investigation of acceptable ranges for CPPs

Table 1. Summary of control strategy of drug substance

CQA	Control method
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Critical steps identified are [redacted] reaction step and [redacted] step. The process control items and process control values were specified in the [redacted] reaction step. [redacted] is controlled as a critical intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR), purity (related substances [liquid chromatography (LC)] and residual solvents [gas chromatography (GC)]), and assay (LC).

2.1.4 Stability of drug substance

Stability studies of the drug substance are shown in Table 2. The photostability testing showed that the drug substance is photostable.

Table 2. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	Pilot scale: 3 batches	25°C	60%RH	Double-layered low density polyethylene bags with [redacted] + fiber drum	18 months
Accelerated		40°C	75%RH		6 months

Based on the above, a retest period of [redacted] months was proposed for the drug substance in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E guideline, when packaged in the double-layered low density polyethylene bags

with [redacted], which is then placed in a fiber drum, [redacted] or equivalent and stored at room temperature. Long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets, each containing 60 mg of the drug substance. The drug product contains hypromellose acetate succinate, light anhydrous silicic acid, croscarmellose sodium, microcrystalline cellulose, silicified microcrystalline cellulose,[1)] magnesium stearate, and Opadry [redacted] as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through the process consisting of [redacted] preparation, [redacted], [redacted], first-mixing, [redacted], second-mixing, final mixing, tableting, film-coating, and packaging/labeling.

The quality control strategy was constructed based on the following investigation using the QbD approach (Table 3):

- Identification of CQAs
- Identification of material attributes potentially affecting the CPP or CQA of the product by quality risk assessment and design of experiments, and the investigation of acceptable ranges for process parameters

Table 3. Summary of control strategy of drug product

CQA	Control method
Content	Manufacturing process, specifications
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Uniformity of dosage units	Manufacturing process, specifications
Dissolution	Manufacturing process, specifications
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Microbial limit	Manufacturing process

Critical steps identified are steps for [redacted] preparation, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]. Process control items and process control values were specified for the steps for [redacted] and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product include content, description, identification (ultraviolet spectrum and LC), purity (degradation products [LC]), uniformity of dosage units (content uniformity [LC]), dissolution [LC]), [redacted] ([redacted] method), and assay (LC).

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1) [redacted] ([redacted]) was not included in the specifications because the risk assessment conducted according to the ICH Q3D guideline [redacted].

2.2.4 Stability of drug product

Stability studies of the drug product are shown in Table 4. The photostability testing showed that the drug product is photostable.

Table 4. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	Pilot scale: 3 batches	25°C	60%RH	[redacted] blister pack (polyvinyl chloride/ polychlorotrifluoro-ethylene film and aluminum foil)	24 months
Accelerated		40°C	75%RH		6 months
Long-term	Pilot scale: 3 batches	25°C	60%RH	[redacted] blister pack (polyvinyl chloride/ polychlorotrifluoro-ethylene film and aluminum foil)	12 months
Accelerated		40°C	75%RH		6 months

Based on the above, the shelf life of 24 months has been proposed for the drug product based on results from long-term testing in [redacted] blister pack when packaged in the [redacted] blister pack (polyvinyl chloride/polychlorotrifluoro-ethylene film and aluminum foil) and stored at room temperature. Long-term testing with [redacted] and [redacted] blister pack will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

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

2.R.1 Acceptance limit for [redacted]

[redacted] of the drug substance in the drug product was <[redacted]% in the batch analysis and stability studies, but its acceptance limit was specified as <[redacted]% based on the bioequivalence (BE) simulation using a physiologically based pharmacokinetic (PBPK) model. PMDA asked the applicant to explain the appropriateness of the setting.

The applicant's explanation:

The BE simulation was performed using the PBPK model constructed in (a) below between the drug product containing the [redacted] drug substance only and the drug products containing the drug substance with [redacted] ranging from [redacted]% to [redacted]% shown in (b) below. The drug product containing the drug substance with [redacted] of up to [redacted]% was presumed to be biologically equivalent to the drug product containing the [redacted] drug substance only. Based on the result, the acceptance limit for [redacted] of <[redacted]%, the lowest value of [redacted] presumed to be biologically equivalent within the range of [redacted] investigated, is acceptable.

(a) Modeling and validation:

1) The [redacted] ([redacted]) model incorporating the processes related to [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] of the drug (software: GastroPlus version 9.0 [redacted]) was selected.

2) Using the following study data, etc., the model was re-constructed:
   - Results from dissolution tests of drug products with different particle sizes of [redacted], formulations, dosage forms, etc., which were used in clinical

studies (Study 56021927PCR1007 [Study 07], Study 56021927PCR1011 [Study 11], Study 56021927PCR1015 [Study 15], and Study 56021927PCR1017 [Study 17]), using human artificial gastric juice and intestinal juice

- Pharmacokinetics (PK) data from subjects who received the drug product containing [redacted] and [redacted] drug substance (Studies [redacted] and [redacted] respectively)
- Two-step solubility model (a model that allows the estimation of absorption profile of the drug product containing both [redacted] and [redacted] drug substances)

3) Measured values of exposure to apalutamide (C_{max} and AUC_{168h}) in Studies [redacted], [redacted], 11, and 15 were nearly close to the values estimated by the analysis with a re-constructed model as shown below. Change in plasma concentration of apalutamide was also similar.
   - In Study [redacted], (i) measured values and (ii) estimated values were (i) [redacted] μg/mL and [redacted] μg·h/mL and (ii) [redacted] μg/mL and [redacted] μg·h/mL, respectively.
   - In Study [redacted], (i) measured values and (ii) estimated values were (i) [redacted] μg/mL and [redacted] μg·h/mL and (ii) [redacted] μg/mL and [redacted] μg·h/mL, respectively.
   - In Study 11, (i) measured values and (ii) estimated values were (i) 2.42 μg/mL and 120 μg·h/mL and (ii) [redacted] μg/mL and [redacted] μg·h/mL, respectively.
   - In Study 15, (i) measured values and (ii) estimated values were (i) 0.62 μg/mL and 27.9 μg·h/mL and (ii) [redacted] μg/mL and [redacted] μg·h/mL, respectively.

(b) Simulation:

The BE simulation was performed using the PBPK model constructed in (a) above between the drug product containing the [redacted] drug substance only and the drug product containing (i) [redacted]%, (ii) [redacted]%, (iii) [redacted]%, and (iv) [redacted]% of the [redacted] drug substance. The geometric least-squares mean ratios of C_{max} and AUC_{168h} of apalutamide in each drug product relative to the drug product containing the [redacted] drug substance only [90% confidence interval (CI)] were (i) [redacted] [0.8974, 0.9697] and [redacted] [0.9139, 0.9453], (ii) [redacted] [0.8643, 0.9339] and [redacted] [0.8827, 0.9130], (iii) [redacted] [0.8110, 0.8763] and [redacted] [0.8504, 0.8796], and (iv) [redacted] [0.7656, 0.8272] and [redacted] [0.8092, 0.8370]. The ratios for the drug products (i) to (iii) fell within the acceptance criteria for BE (0.80-1.25). Thus, the drug product containing the [redacted] drug substance of up to [redacted]% was presumed to be biologically equivalent to the drug product containing the [redacted] drug substance only.

PMDA accepted the applicant's explanation.

2.R.2 Shelf lie for drug product

The shelf life of the drug product was specified as 24 months based on results from long-term testing up to 24 months, in which the drug product was packaged in [redacted] blister pack, although the product would be marketed in [redacted] blister pack. Because the ICH Q1A guideline instructs that long-term testing and accelerated testing should be conducted using the same packaging form as that for the commercial drug product, PMDA asked the applicant to explain the appropriateness of the shelf life specified for the drug

product in light of the impact of the difference in packaging form (materials, etc.) on the stability of the drug product.

The applicant's explanation:
The difference between these blister pack forms is only that the material of the [redacted] blister pack contains [redacted] but that of [redacted] blister pack does not. Although [redacted] depends on the presence or absence of [redacted], the drug product is stable to [redacted], and thus such difference is considered to have no impact on the stability of the drug product. Furthermore, no clear difference is found in [redacted] rate, [redacted] rate, or [redacted] rate between these blister packs.

Accordingly, the shelf life of 24 months for the drug product is reasonable based on results from long-term testing using [redacted] blister pack.

PMDA's view:
As a rule, the shelf life of the drug product should be determined based on results from long-term testing conducted using the same packaging form as that for the commercial drug production. However, for the following reasons, the shelf life of 24 months is acceptable for the drug product based on results from long-term testing using [redacted] blister pack: (1) the difference in the packaging forms has a limited impact on the stability of the drug product; and (2) long-term testing and accelerated testing using [redacted] blister pack show no changes in any measurement item over time up to 12 and 6 months.

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

In this section, unless otherwise specified, the ethanolate form of apalutamide is used. The dose of apalutamide is expressed as an amount of free base of apalutamide.

3.1 Primary pharmacodynamics

3.1.1 Binding to AR (CTD 4.2.1.1.1)

Binding of apalutamide, enzalutamide, and bicalutamide to AR in LNCaP/AR(cs) cell line[2)] derived from human prostate cancer was investigated by a competitive binding assay to determine the uptake of ^{18}F-labeled 16β-fluoro-5α-dihydrotestosterone (FDHT) as indicator. The 50% inhibitory concentration (IC_{50}) values (mean ± standard error (SE), n = 5) of apalutamide, enzalutamide, and bicalutamide were 16.0 ± 2.1, 21.4 ± 4.4, and 160 ± 29 nmol/L, respectively.

Binding of apalutamide to AR, progesterone receptor (PgR), estrogen receptor-α (ERα), and glucocorticoid receptor (GR) was investigated by a competitive binding assay based on fluorescence polarization used as an indicator. As compared with the binding rate of the positive control[3)] which was defined as 100%, the binding rates of apalutamide to AR, PgR, ERα, and GR were 1.2%, <0.0005%, <0.0005%, and <0.0002%, respectively.

2) Human prostate cancer-derived cell line expressing wild-type AR in which T877A mutant (threonine at the position of 877 replaced by alanine) AR is endogenously expressed
3) Positive controls used for binding to AR, PgR, ERα, and GR were RU59063, progesterone, estradiol, and dexamethasone, respectively.

3.1.2 Inhibitory effect against AR binding to the target genes (CTD 4.2.1.1.1, 4.2.1.1.5, and 4.2.1.1.6)

Inhibitory effects of apalutamide, enzalutamide, and bicalutamide against AR binding to the enhancer region of the target genes (*PSA* and *transmembrane protease serine 2* [*TMPRSS2*] genes) were investigated in LNCaP/AR(cs) cell line by a chromatin immunoprecipitation (ChIP) method. In the presence of R1881, a synthetic androgen, apalutamide, enzalutamide, and bicalutamide inhibited AR binding to the target genes.

Effects of apalutamide, enzalutamide, and bicalutamide on the transcription of the target genes were investigated in human hepatocellular carcinoma-derived HepG2 cell line expressing virion protein 16 (VP16)-AR fusion protein and AR-driven luciferase, using the luciferase activity as an indicator. In the presence of R1881, apalutamide, enzalutamide, and bicalutamide inhibited the transcription of the target genes.

Inhibitory effects of apalutamide, enzalutamide, and bicalutamide against AR activation were investigated in human prostate cancer-derived LNCaP/AR-Luc cell line[4)] expressing AR-driven luciferase, using the luciferase activity as an indicator. In the presence of R1881, apalutamide, enzalutamide, and bicalutamide inhibited AR activation.

Inhibitory effects of apalutamide and apalutamide metabolites, namely, M1, M2, M3, and M4, against the transcription of the target genes were investigated in HepG2 cell line expressing VP16-AR fusion protein and AR-driven luciferase, using the luciferase activity as an indicator. Table 5 shows IC_{50} values of apalutamide, M1, M2, M3, and M4.

Table 5. AR-mediated inhibitory effects of apalutamide, M1, M2, M3, and M4 against the transcription of target genes

	n	IC_{50} value
Apalutamide	107	0.11 ± 0.005
M1	2	3.872, 2.475
M2	2	4.3264, 3.7037
M3	7	0.3 ± 0.13
M4	2	13.784, 25.296

Mean ± SE, Individual values in the case of n = 2

3.1.3 Apoptosis induction (CTD 4.2.1.1.1)

To castrated severe combined immunodeficient (SCID) mice subcutaneously implanted with LNCaP/AR(cs) cell line (n = 9-10/group), apalutamide 10 mg/kg was orally administered QD for 28 days, and apoptosis induction of apalutamide was investigated in tumor tissue after the last dose by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining. Apalutamide induced apoptosis.

4) LNCaP cell line expressing wild-type AR in which the luciferase gene is expressed under AR-dependent probasin promoter regulation

3.1.4 Growth inhibition against human prostate cancer-derived cell line

3.1.4.1 *In vitro* (CTD 4.2.1.1.1)

Growth inhibition of apalutamide, enzalutamide, and bicalutamide was investigated in human prostate cancer-derived VCaP cell line, using ATP as an indicator of viable cells. In the presence of R1881, apalutamide, enzalutamide, and bicalutamide inhibited cell growth.

3.1.4.2 *In vivo* (CTD 4.2.1.1.2, 4.2.1.1.3, and 4.2.1.1.4)

In castrated SCID mice subcutaneously implanted with LNCaP/AR(cs) cell line (n = 7-8/group), tumor-growth inhibitory effect of apalutamide and enzalutamide was investigated. After the tumor volume reached 292.5 mm^3, apalutamide or enzalutamide 1 or 10 mg/kg was orally administered QD for 28 days to calculate the tumor volume. As compared with the control (vehicle[5)]), apalutamide 10 mg/kg and enzalutamide 10 mg/kg inhibited tumor growth statistically significantly ($P < 0.05$, Dunnett's multiple comparison test).

In castrated SCID mice subcutaneously implanted with LNCaP/AR(cs) cell line (n = 10 or 20/group), tumor-growth inhibitory effect of apalutamide and enzalutamide was investigated. After the tumor volume reached 150 mm^3, apalutamide or enzalutamide 30 or 100 mg/kg was orally administered QD for 29 days to calculate the tumor volume. As compared with the control (vehicle[5)]), apalutamide and enzalutamide at any concentration inhibited tumor growth statistically significantly ($P < 0.05$, Dunnett's multiple comparison test).

In castrated SCID mice subcutaneously implanted with LNCaP/AR(cs) cell line (n = 8/group), tumor-growth inhibitory effect of apalutamide and enzalutamide was investigated. After the tumor volume reached 150 mm^3, apalutamide or enzalutamide 10 or 30 mg/kg was orally administered QD for 42 days to calculate the tumor volume. As compared with the control (vehicle[5)]), apalutamide and enzalutamide at any concentration inhibited tumor growth statistically significantly (Figure 1).

5) A solution of 18% polyethylene glycol (PEG) 400, 1% Tween 80, 1% Povidone, and 15% Vitamin E-D-α-tocopherol polyethylene glycol succinate conjugate (TPGS) in 20 mmol/L citric acid buffer containing 0.5% carboxymethyl cellulose (CMC) (pH 4.0)

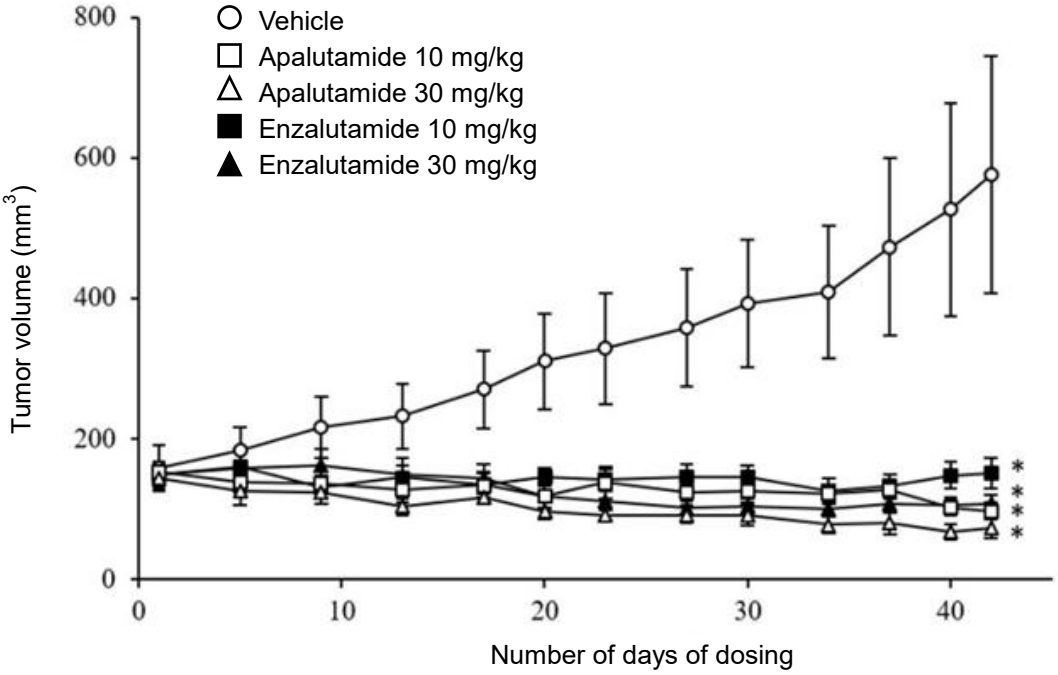

Figure 1. Tumor growth inhibitory effect of apalutamide and enzalutamide in castrated SCID mice subcutaneously implanted with LNCaP/AR(cs) cell line

n = 8; Mean ± SE; * $P < 0.05$ vs. the control (vehicle) group (Dunnett's multiple comparison test)

3.2 Secondary pharmacodynamics

3.2.1 Effects on various receptors, ion channels, and transporters (CTD 4.2.1.2.1, 4.2.1.2.2, 4.2.1.2.3, 4.2.1.2.4, and 4.2.1.2.5)

Inhibitory effects of apalutamide 10 μmol/L against 55 types of receptors, ion channels, and transporters were investigated. Apalutamide only inhibited ligand binding to γ-aminobutyric acid $(GABA)_A$ receptor by ≥50%.

Inhibitory effects of apalutamide, M1, M2, M3, and M4 against GABA-gated chloride channel were investigated. The IC_{50} values (n = 1) of apalutamide, M2, M3, and M4 were 3.0, 19, 3.2, and 25 μmol/L, respectively. M1 inhibited ligand binding by 10% as compared with the control (20 μmol/L picrotoxin).

The applicant explained that appropriate caution against convulsion be given to healthcare professionals via the package insert, in relation to the inhibitory effect of apalutamide on the above GABA-gated chloride channel, based on the following observations:

- A relationship between the inhibitory effect on GABA-gated chloride channel and convulsion was reported (*Neurobehav Toxicol.* 1980;2:117-24, *J Toxicol Clin Toxicol.* 2004;42:955-63, *Toxicol Appl Pharmacol.* 1989;100:1-8).

- In the 28-day repeated-dose toxicity study in dogs, tremor and convulsion were observed in the apalutamide 25 mg/kg/day group [see Section 5.2].

- Convulsion occurred also in the clinical studies of apalutamide [see Section 7.R.3.5].

3.3 Safety pharmacology

3.3.1 Effects on central nervous system (CTD 4.2.1.3.1)

Apalutamide was orally administered to rats (n = 10-15/group) at 50, 150, and 250 mg/kg QD for 28 days to investigate clinical signs and effects on behavior by a functional observation battery. Death occurred in the apalutamide 150 and 250 mg/kg groups. Piloerection, abnormal respiration, hypothermia, dehydration, and decreased activity were observed in the apalutamide 250 mg/kg group.

The applicant explained that the above outcomes were unlikely to raise the safety issues in the clinical use of apalutamide for the following reasons, etc.:

- In a 26-week repeated-dose toxicity study in rats, no apalutamide-related death occurred [see Section 5.2].

- C_{max} (2.27 μg/mL) of unbound apalutamide in plasma in rats orally receiving apalutamide 150 mg/kg QD was 7.1 fold C_{max} (0.318 μg/mL)[6)] of unbound apalutamide in human plasma at the recommended clinical dose (240 mg/day).

3.3.2 Effects on cardiovascular system

3.3.2.1 Effects on hERG potassium current (CTD 4.2.1.3.2)

The effect of apalutamide[7)] on human *ether-a-go-go* related gene (hERG) potassium current was investigated at 0.407, 1.33, 4.52, and 14.4 μmol/L in Chinese hamster ovary (CHO)-K1 cell line transfected with hERG. As compared with the control (0.3% [v/v] dimethyl sulfoxide [DMSO]-containing Tyrode's solution[8)]), apalutamide inhibited hERG potassium current at 1.33, 4.52, and 14.4 μmol/L statistically significantly ($P < 0.05$, unpaired t test), and the IC_{50} value was 6.17 μmol/L.

3.3.2.2 Effects on action potential (CTD 4.2.1.3.3)

Effects of apalutamide[7)] and M3 on myocardial action potential (action potential duration at 60% repolarization [APD_{60}], action potential duration at 90% repolarization [APD_{90}], action potential amplitude, resting membrane potential, and maximum rate of depolarization [V_{max}]) were investigated at 3, 10, and 30 μmol/L using ventricular Purkinje fibers isolated from dogs. As compared with the control (0.3% [v/v] DMSO-containing Tyrode's solution[9)]), apalutamide reduced action potential amplitude at 3 and 10 μmol/L statistically significantly ($P < 0.05$, Dunnett's multiple comparison test).

3.3.2.3 Effects on heart rate, blood pressure, and electrocardiogram (CTD 4.2.1.3.4)

A single dose of apalutamide was orally administered at 10, 20, and 40 mg/kg to dogs (n = 6) ≥13 days apart in an escalating manner to investigate effects of apalutamide on systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, body temperature, and electrocardiogram (PR, QRS, QT, QT corrected for heart rate [QTcR], QT corrected with Bazzet formula [QTcB], QT interval

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6) Calculated from C_{max} (7.57 μg/mL) [see Section 6.2.1.2] on Day 22 of Cycle 1 in Japanese patients with metastatic CRPC orally receiving apalutamide 240 mg QD in Study 08 and unbound fraction (0.042) in humans [see Section 4.2.2].

7) The non-ethanolate form of apalutamide was used.

8) A solution containing 140 mmol/L sodium chloride, 4.0 mmol/L potassium chloride, 2.5 mmol/L calcium chloride, 1.0 mmol/L magnesium chloride, 10 mmol/L D-(+)-glucose, and 5.0 mmol/L HEPES (pH 7.4)

9) A solution containing 131 mmol/L sodium chloride, 4.0 mmol/L potassium chloride, 2.0 mmol/L calcium chloride, 0.5 mmol/L magnesium chloride, 18.0 mmol/L sodium bicarbonate, 1.8 mmol/L sodium dihydrogen phosphate, and 5.5 mmol/L glucose

corrected with Fridericia approach [QTcF], and QT corrected with Van de Water formula [QTcV]). No effects of apalutamide were observed.

3.3.3 Effects on respiratory system (CTD 4.2.1.3.5)

A single dose of apalutamide was orally administered at 25, 50 and 100 mg/kg to rats (n = 6/group) to investigate the effects on the respiratory rate, tidal volume, and minute ventilation. Apalutamide at any dose slightly decreased respiratory rate from baseline at 8 and 12 hours post-dose. Apalutamide 50 and 100 mg/kg decreased minute ventilation by 9% to 14% from baseline.

The applicant explained that the above changes were unlikely to pose a safety issue in the clinical use of apalutamide, because these changes returned to normal in any apalutamide group within 72 hours post-dose and there were only slight changes in the minute ventilation.

3.R Outline of the review conducted by PMDA

Based on the submitted data and review in the following section, PMDA concluded that the applicant's explanation about non-clinical pharmacological changes of apalutamide is acceptable.

3.R.1 Mechanism of action of apalutamide and its efficacy

The applicant's explanation about the action mechanism of apalutamide and its efficacy:
Prostate cancer is an androgen-dependent tumor. The growth of tumor cell is considered to be stimulated by testosterone produced by multiple testosterone production systems in the body.

AR forms a homodimer when dihydrotestosterone is bound to its ligand binding domain, and enters the nucleus to bind to the target gene, i.e., ARE, thereby enhancing the expression of genes related to cell survival and growth (*Cancers.* 2017;9:67-86).

Apalutamide competitively inhibits androgen's binding to the ligand binding domain of AR [see Section 3.1.1], and also inhibits nuclear import of AR that is a transcription factor (*Sci Rep.* 2015;5:12007-18), resulting in the inhibition of AR binding to the transcription factor binding region on DNA and the subsequent transcription of the target gene [see Section 3.1.2]. By inhibiting AR-mediated signaling, apalutamide is expected to suppress androgen-dependent tumor growth.

Based on the above mechanism and observed its inhibitory effect on the growth of human prostate cancer-derived cell line [see Section 3.1.4], apalutamide has promising efficacy against prostate cancer.

The applicant's explanation about differences in pharmacological attributes between apalutamide and drugs approved for the indication of prostate cancer in Japan, namely, enzalutamide, bicalutamide, or flutamide, with the inhibitory effect on AR:
All these drugs target AR as with apalutamide. Apalutamide, however, differs with respect that it does not bind to any other hormone receptors (HRs) than AR [see Section 3.1.1] while enzalutamide and bicalutamide bind to PgR as well ("Review Report of Xtandi Capsules 40 mg dated January 15, 2014," *Mol Cancer Ther.* 2013;12:621-31). In addition, apalutamide inhibits nuclear import of AR, while

bicalutamide and flutamide do not (*Sci Rep.* 2015;5:12007-18, *J Steroid Biochem Mol Biol.* 2007;107:1-14).

PMDA's view:
The applicant's explanation is acceptable. Meanwhile, the findings on pharmacological attributes of apalutamide including differences between apalutamide and enzalutamide are potentially useful information in selecting appropriate patients in the clinical use of apalutamide. The applicant should continue the investigation and communicate new findings once available, to healthcare professionals appropriately.

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

The PK of apalutamide in animals was investigated in mice, rats, and dogs. Plasma protein binding, drug-metabolizing enzymes, and transporter, etc. of apalutamide were investigated in human or animal biological samples.

4.1 Absorption

4.1.1 Single-dose studies

A single dose of apalutamide was administered intravenously at 3 mg/kg or orally at 10 mg/kg to male mice, and plasma apalutamide concentrations were determined (Table 6). The bioavailability (BA) of oral apalutamide 10 mg/kg was 93.3%.

Table 6. PK parameters of apalutamide (male mice, single intravenous or oral administration)

Dose (route of administration)	C_{max} (μg/mL)	t_{max} (h)	AUC_{inf} (μg•h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)
3 mg/kg (intravenous)	-	-	37.7	19.5	1.33	2.10
10 mg/kg (oral)	3.51	1.0	118	17.8	-	-

PK parameters were calculated from mean plasma apalutamide concentrations (n = 3) at measurement timepoints; -, Not calculated.

4.1.2 Repeated-dose studies

Apalutamide was orally administered QD at 20, 50, or 100 mg/kg for 10 days to male and female mice, and plasma concentrations of apalutamide and M3 (*N*-desmethyl apalutamide) were determined (Table 7). There were no clear sex differences in the PK parameters of apalutamide. In the dose range investigated, C_{max} and AUC_{24h} of apalutamide on Day 1 and those of M3 on Days 1 and 10 increased in an almost dose-proportional manner, but C_{max} and AUC_{24h} of apalutamide on Day 10 showed less than dose-proportional increase. The applicant explained that the difference in the dose-proportionality was considered attributable to the autoinduction of metabolic enzymes.

Table 7. PK parameters of apalutamide and M3 (male and female mice, 10-day repeated oral administration)

Day of measurement (Day)	Dose (mg/kg)	Analyte	C_{max} (μg/mL)		t_{max} (h)		AUC_{24h} (μg•h/mL)	
			Male	Female	Male	Female	Male	Female
1	20	Apalutamide	5.04	5.85	7	7	102	109
		M3	0.674	0.658	24	24	7.97	7.74
	50	Apalutamide	13.5	11.8	7	7	256	244
		M3	2.09	1.56	24	24	23.6	19.6
	100	Apalutamide	23.1	27.5	7	3	491	503
		M3	7.39	3.91	24	24	72.6	42.9
10	20	Apalutamide	6.75	11.1	7	7	113	170
		M3	1.62	1.24	7	7	35.7	28.8
	50	Apalutamide	11.6	15.1	3	7	136	228
		M3	4.06	3.78	3	7	84.9	71.6
	100	Apalutamide	13.9	-	3	-	140	-
		M3	7.58	-	7	-	127	-

PK parameters were calculated from mean plasma concentrations of apalutamide and M3 (n = 2 or 3) at measurement timepoints; -, Not calculated.

Apalutamide was orally administered QD at 25, 50, or 100 mg/kg for 13 weeks to male rats, and plasma concentrations of apalutamide, M3, and M4 (amide hydrolysis) were determined (Table 8). In the dose range investigated, C_{max} and AUC_{24h} of apalutamide on Days 1 and 91 and those of M3 on Day 1, and those of M4 on Days 1 and 91 increased in an almost dose-proportional manner, but C_{max} and AUC_{24h} of M3 on Day 91 showed a more than dose-proportional increase. The applicant explained that the difference in the dose-proportionality may have been attributable to inter-individual variability of plasma M3 concentration, etc. C_{max} and AUC_{24h} of apalutamide, M3, and M4 on Day 91 were higher than those on Day 1.

Table 8. PK parameters of apalutamide, M3, and M4 (male rats, 13-week repeated oral administration)

Day of measurement (Day)	Dose (mg/kg)	Analyte	C_{max} (μg/mL)	t_{max} (h)	AUC_{24h} (μg•h/mL)
1	25	Apalutamide	4.12	8.00	67.9
		M3	0.152	12.0	2.37
		M4	0.315	8.00	6.37
	50	Apalutamide	7.49	12.0	128
		M3	0.252	12.0	4.07
		M4	0.629	6.00	11.7
	100	Apalutamide	15.5	12.0	272
		M3	0.554	12.0	9.68
		M4	1.79	24.0	28.4
91	25	Apalutamide	7.48	12.0	136
		M3	0.200	12.0	3.86
		M4	0.482	24.0	10.5
	50	Apalutamide	11.9	8.00	240
		M3	0.413	12.0	8.57
		M4	0.962	12.0	21.6
	100	Apalutamide	30.1	8.00	521
		M3	1.49	8.00	28.5
		M4	2.48	8.00	52.4

PK parameters were calculated from mean plasma concentrations of apalutamide, M3, and M4 (n = 2 or 3) at measurement timepoints

Apalutamide was orally administered QD at 2.5, 5, or 10 mg/kg for 13 weeks to male dogs, and plasma concentrations of apalutamide, M3, and M4 were determined (Table 9). Within the dose range investigated, C_{max} and AUC_{24h} of apalutamide, M3, and M4 increased in an almost dose-proportional manner. C_{max} and AUC_{24h} of apalutamide, M3, and M4 on Day 91 were higher than those on Day 1.

Table 9. PK parameters of apalutamide, M3, and M4 (male dogs, 13-week repeated oral administration)

Day of measurement (Day)	Dose (mg/kg)	n	Analyte	C_{max} (μg/mL)	t_{max} (h)	AUC_{24h} (μg•h/mL)
1	2.5	5	Apalutamide	0.558 ± 0.294	5 ± 4	10.6 ± 5.84
			M3	0.127 ± 0.0787	24 ± 0	1.51 ± 0.956
			M4	0.0223 ± 0.0135	21 ± 6*	0.310 ± 0.192
	5	7	Apalutamide	1.56 ± 0.274	7 ± 4	31.9 ± 7.27
			M3	0.459 ± 0.212	24 ± 0	5.77 ± 2.56
			M4	0.0818 ± 0.0289	22 ± 6	1.18 ± 0.375
	10	8	Apalutamide	2.85 ± 0.469	7 ± 8	56.2 ± 10.1
			M3	0.588 ± 0.251	21 ± 6	8.01 ± 3.81
			M4	0.134 ± 0.0354	18 ± 6	2.32 ± 0.732
91	2.5	5	Apalutamide	3.78 ± 0.907	4 ± 3	84.2 ± 21.9
			M3	2.55 ± 0.270	1 ± 1	57.4 ± 6.23
			M4	0.469 ± 0.103	3 ± 5	7.44 ± 0.906
	5	8	Apalutamide	10.3 ± 4.92	5 ± 8	202 ± 57.4
			M3	4.63 ± 0.881	3 ± 4	100 ± 18.3
			M4	1.22 ± 0.349	1 ± 1	17.9 ± 5.63
	10	8	Apalutamide	19.6 ± 3.14	5 ± 8	419 ± 58.8
			M3	8.93 ± 1.64	9 ± 10	196 ± 32.0
			M4	2.85 ± 0.812	2 ± 2	45.6 ± 12.6

Arithmetic mean ± standard deviation (SD); * n = 4

4.1.3 *In vitro* membrane permeability

Membrane permeability of apalutamide was investigated using human colon cancer-derived Caco-2 cell line. Apparent permeability in apical to basolateral direction ($P_{app\ A \rightarrow B}$) of apalutamide 5 μmol/L was 42.3×10^{-6} cm/sec. The applicant explained that apalutamide was considered to have high membrane permeability given that the $P_{app\ A \rightarrow B}$ of 10 μmol/L of propranolol, which is highly membrane permeable, was 17.3×10^{-6} cm/second.

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ^{14}C-labeled apalutamide (^{14}C-apalutamide) was orally administered at 50 mg/kg to male albino rats and pigmented rats, and the tissue distribution of radioactivity was investigated by quantitative whole-body autoradiography.

In the albino rats, radioactivity was widely distributed in tissues, and the radioactivity concentration peaked by 12 hours post-dose in most tissues. The maximum tissue radioactivity concentrations in the abdominal fat, liver, brown fat, renal cortex, Harderian gland, adrenal cortex, pancreas, and renal medulla (190, 107, 88.2, 66.4, 61.0, 54.2, 45.6, and 45.2 μg Eq./g, respectively) except for the gastrointestinal tract tissue were remarkably higher than the maximum plasma radioactivity concentration (11.8 μg Eq./g). The radioactivity concentrations in most tissues at 168 hours post-dose were below the lower limit of quantitation (0.209 μg Eq./g).

The tissue distribution of radioactivity in pigmented rats was similar to that in albino rats. The radioactivity concentrations in all the tissues except for non-pigmented skin and pigmented skin at 504 hours post-dose were below the lower limit of quantitation (0.209 μg Eq./g). The radioactivity concentration in the non-pigmented skin was comparable to that in the pigmented skin. Given these, the

applicant explained that apalutamide and its metabolites were considered to have low affinity for melanin.

4.2.2 Plasma protein binding

Apalutamide (10 μg/mL) and M3 (10 μg/mL) were incubated with plasma specimens from mice, rats, rabbits, dogs, or humans at 37°C for 15 minutes, and plasma protein binding of apalutamide and M3 was investigated using ultracentrifugation. The plasma protein unbound fractions of (a) apalutamide and (b) M3 in specimens from mice, rats, rabbits, dogs, and humans were (a) 8.21%, 7.16%, 11.4%, 6.30%, and 4.18%, and (b) 9.44%, 8.55%, 13.2%, 8.24%, and 5.11%, respectively.

Apalutamide (10 μg/mL) and M3 (10 μg/mL) were incubated with human serum albumin (43 mg/mL) or human α1-acid glycoprotein (0.7 mg/mL) at 37°C for 15 minutes, and binding of apalutamide and M3 to human serum albumin or human α 1-acid glycoprotein was investigated using ultracentrifugation. The unbound fractions of (a) apalutamide and (b) M3 in human serum albumin and human α1-acid glycoprotein were (a) 6.42% and 77.8% as well as (b) 6.76% and 82.0%, respectively. Accordingly, the applicant explained that apalutamide and M3 were considered to mainly bind to serum albumin.

4.2.3 Distribution in blood cells

^{14}C-apalutamide (10 μg/mL) and ^{14}C-labeled M3 (*N*-desmethyl apalutamide) (^{14}C-M3) (10 μg/mL) were incubated with blood specimens from mice, rats, rabbits, dogs, or humans at 37°C for 15 minutes, and the distribution of apalutamide and M3 in blood cells was investigated. The blood/plasma radioactivity concentration ratio of (a) apalutamide and (b) M3 in specimens from mice, rats, rabbits, dogs, and humans were (a) 0.83, 0.86, 0.96, 0.85, and 0.79, and (b) 0.89, 0.92, 0.97, 0.86, and 0.78, respectively. Accordingly, the applicant explained that apalutamide was considered to be mainly distributed in plasma of any animal species.

4.2.4 Placental transfer and fetal transfer

Because apalutamide is an antineoplastic agent intended for treatment of prostate cancer, its placental or fetal transfer was not investigated.

4.3 Metabolism

4.3.1 *In vitro*

Apalutamide (30 μmol/L) was incubated with liver microsomes from rats, dogs, or humans at 37°C for 6 hours to investigate metabolites of apalutamide. In liver microsomes from any animal species and humans, M1 (amide form), M2 (oxidative desulfurized form), M3, and M4 were detected.

The applicant's explanation about enzymes involved in metabolism of apalutamide and M3 in humans: Based on results below, the metabolism of apalutamide in humans is considered to be mediated mainly by cytochrome P-450 (CYP) 2C8 and carboxylesterase and partially by CYP3A. The pharmacokinetic interactions of apalutamide with CYP2C8 inhibitors or inducer and CYP3A inhibitors and inducer are described in Sections "6.2.3.1 Study for drug interactions with itraconazole or gemfibrozil" and "6.R.2 Pharmacokinetic interactions mediated by CYP3A and CYP2C8."

- Apalutamide (1 or 5 μmol/L) was incubated with human hepatocytes in the presence or absence of a non-selective inhibitor of CYP (1-aminobenzotriazole), CYP2C8 inhibitors (gemfibrozil and gemfibrozil glucuronide in combination), [10)] and CYP3A inhibitors (itraconazole and troleandomycin) at 37°C for 16 hours. The formation of (a) M3 and (b) M4 was inhibited in the presence of non-selective inhibitor of CYP, CYP2C8 inhibitors, and CYP3A inhibitors by (a) 98%, 55%, 17%, and 23%, and (b) 18%, 4.8%, 11%, and 0%,[11)] respectively.

- Apalutamide (1 or 5 μmol/L) was incubated with human hepatocytes in the presence or absence of a carboxyesterase inhibitor (bis-nitrophenyl phosphate) at 37°C for 16 hours. The formation of M3 and M4 was inhibited in the presence of the carboxyesterase inhibitor by 42% and 98%,[11)] respectively.

The following results indicate that metabolism from M3 to M4 is considered to be mediated by carboxyesterase.

- M3 (1 μmol/L) was incubated with human hepatocytes in the presence of (a) non-selective inhibitor of CYP (1-aminobenzotriazole), (b) carboxyesterase inhibitor (bis-nitrophenyl phosphate) and (c) the non-selective inhibitor of CYP and carboxyesterase inhibitor at 37°C for 16 hours. The formation of M4 was inhibited in the presence of the (a) non-selective inhibitor of CYP, (b) carboxyesterase inhibitor, and (c) non-selective inhibitor of CYP and carboxyesterase inhibitor by (a) 22%, (b) 100%, and (c) 100%, respectively.

4.3.2 *In vivo*

A single dose of ^{14}C-apalutamide was orally administered at 50 mg/kg to non-bile duct-cannulated and bile duct-cannulated male rats and metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained:

- In plasma collected from non-bile duct-cannulated male rats at 24 hours post-dose, mainly unchanged apalutamide and M4 were detected and accounted for 53% and 15% of the total radioactivity in plasma.

- In urine collected from non-bile duct-cannulated male rats until 48 hours post-dose, mainly M4 was detected and accounted for 26% of the administered radioactivity.

- In feces collected from non-bile duct-cannulated male rats until 48 hours post-dose, mainly M4 was detected and accounted for 26% of the administered radioactivity.

- In bile collected from bile duct-cannulated male rats until 48 hours post-dose, mainly unchanged apalutamide, M4, and M9 (cysteine condensate) were detected and accounted for 10%, 22%, and 4%, respectively, of the administered radioactivity.

[10)] For the first 4 hours of the incubation, gemfibrozil and gemfibrozil glucuronide were used as inhibitors, and for the remaining time of the incubation, gemfibrozil was used.

[11)] Mean obtained by treatment with apalutamide at 1 and 5 μmol/L

A single dose of ^{14}C-apalutamide was orally administered at 10 mg/kg to male dogs, and metabolites in plasma, urine, and feces were investigated. The following results were obtained:

- In plasma collected from male dogs at 528 hours post-dose, mainly unchanged apalutamide, M3, and M4 were detected and accounted for 41%, 51%, and 4%, respectively, of the total radioactivity in plasma.

- In urine collected from male dogs until 360 hours post-dose, mainly M4 was detected and accounted for 16% of the administered radioactivity.

- In feces collected from male dogs until 360 hours post-dose, mainly M4 was detected and accounted for 19% of the administered radioactivity.

4.4 Excretion

4.4.1 Excretion into urine, feces, and bile

Based on results below, the applicant explained that apalutamide is excreted mainly into feces through bile in rats and equally into urine and feces in dogs:

- In non-bile duct-cannulated male rats which orally received a single dose of ^{14}C-apalutamide 50 mg/kg, 34.2% and 58.2%, respectively, of the administered radioactivity were excreted into urine and feces until 168 hours post-dose.

- In bile duct-cannulated male rats which orally received a single dose of ^{14}C-apalutamide 50 mg/kg, 29.7%, 11.2%, and 50.0%, respectively, of the administered radioactivity were excreted into urine, feces, and bile until 72 hours post-dose.

- In male dogs which orally received a single dose of ^{14}C-apalutamide at 10 mg/kg, 41.8% and 40.2%, respectively, of the administered radioactivity were excreted into urine and feces until 360 hours post-dose.

4.4.2 Excretion into milk

Because apalutamide is an antineoplastic agent intended for the treatment of prostate cancer, its excretion into milk was not investigated.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation about pharmacokinetic interactions mediated by the inhibition of metabolic enzymes by apalutamide and M3:

In light of the investigation results below and C_{max} of apalutamide and M3 (15.9 and 15.3 μmol/L)[12)] at steady state in subjects who received apalutamide according to the proposed dosage and administration, the pharmacokinetic interactions mediated by the inhibition of CYP1A2, CYP2A6, CYP2D6, and CYP2E1 by apalutamide and M3 are unlikely to occur in the clinical use of apalutamide. On the other

12) C_{max} on Day 22 of Cycle 1 in Japanese patients with metastatic CRPC orally receiving apalutamide 240 mg QD in Study 08

hand, the pharmacokinetic interactions mediated by the inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A by apalutamide and M3 may possibly occur.

- Substrates[13)] of CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) were incubated with human liver microsomes in the presence of apalutamide (0.075-75 μmol/L) and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) to investigate the inhibitory effect of apalutamide against the metabolism of the CYP substrates. Apalutamide inhibited the metabolism of substrates of CYP2B6, CYP2C8, CYP2C9,[14)] CYP2C19, and CYP3A,[15)] with the IC_{50} values of 36, 18, 56, 67, and 54 μmol/L, respectively. On the other hand, apalutamide did not clearly inhibit the metabolism of other CYP substrates investigated.

- Substrates[13)] of CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) were incubated with human liver microsomes in the presence of M3 (0.075-75 μmol/L) and NADPH to investigate the inhibitory effect of M3 against metabolisms of the CYP substrates. M3 inhibited the metabolism of substrates of (a) CYP2B6, (b) CYP2C8, (c) CYP2C9, (d) CYP2C19, and (e) CYP3A[15)] with the IC_{50} values of (a) 49, (b) 47, (c) 49 and 38, (d) 75, and (e) 69 μmol/L, respectively. On the other hand, M3 did not clearly inhibit the metabolism of other CYP substrates investigated.

- Substrates[16)] of CYP isoforms (CYP1A, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) were incubated with human liver microsomes in the presence of apalutamide (0.1-25 μmol/L) or M3 (0.1-25 μmol/L) and NADPH to investigate the inhibitory effect of apalutamide or M3 against the metabolism of CYP substrates. Apalutamide inhibited the metabolism of substrate of CYP2C8 with the IC_{50} value of 13.9 μmol/L. On the other hand, M3 did not clearly inhibit the metabolism of substrate of CYP2C8. Neither apalutamide nor M3 clearly inhibited the metabolism of other CYP substrates investigated.

- Substrates[17)] of CYP isoforms (1A, 2C9, 2C19, 2D6, and 3A) were incubated with human liver microsomes in the presence of apalutamide (25 μmol/L) or M3 (25 μmol/L) and NADPH to investigate time-dependent inhibitory effect of apalutamide or M3 against the metabolism of the CYP substrates. Neither apalutamide nor M3 clearly inhibited the metabolism of any CYP substrates in a time-dependent manner.

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13) Phenacetin, coumarin, bupropion, amodiaquine, S-mephenytoin, dextromethorphan, and chlorzoxazone were used as substrates of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, and CYP2E1, respectively; tolbutamide and diclofenac were used as substrates of CYP2C9; and testosterone, midazolam, and nifedipine were used as substrates of CYP3A.

14) Diclofenac was used as a substrate.

15) Testosterone was used as a substrate.

16) Ethoxyresorufin, paclitaxel, tolbutamide, S-mephenytoin, and dextromethorphan were used as substrates of CYP1A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, respectively; and testosterone and midazolam were used as substrates of CYP3A.

17) Ethoxyresorufin, diclofenac, S-mephenytoin, dextromethorphan, and midazolam were used as substrates of CYP1A, CYP2C9, CYP2C19, CYP2D6, and CYP3A, respectively.

4.5.2 Enzyme induction

The applicant's explanation about the pharmacokinetic interactions mediated by metabolic enzyme induction of apalutamide and M3:

In light of the investigation results below and C_{max} of apalutamide and M3 (15.9 and 15.3 μmol/L)[12] at steady state in subjects who received apalutamide according to the proposed dosage and administration, the pharmacokinetic interactions mediated by CYP1A2 induction of apalutamide and M3 are unlikely to occur in the clinical use of apalutamide. On the other hand, the pharmacokinetic interactions mediated by CYP2B6 and CYP3A induction of apalutamide and M3 may possibly occur.

- Human hepatocytes were incubated in the presence of apalutamide (3-30 μmol/L) for 2 days, and enzyme activity of CYP isoforms (CYP1A2, CYP2B6, and CYP3A) were determined. Apalutamide induced CYP2B6 and CYP3A enzyme activities. The CYP2B6 and CYP3A enzyme activities induced by apalutamide at (a) 10 and (b) 30 μmol/L were (a) 61% to 76% and (b) 82% to 117%, and (a) 85% to 123% and (b) 91% to 137%, respectively, of those induced by the respective positive controls.[18] On the other hand, apalutamide did not clearly increase the CYP1A2 enzyme activity.

- Human hepatocytes were incubated in the presence of M3 (3-30 μmol/L) for 2 days, and enzyme activity of CYP isoforms (CYP1A2, CYP2B6 and CYP3A) were determined. M3 induced CYP2B6 and CYP3A enzyme activities. The CYP2B6 and CYP3A enzyme activities induced by M3 at (a) 10 and (b) 30 μmol/L were (a) 17% to 66% and (b) 30% to 88%, and (a) 57% to 65% and (b) 65% to 72%, respectively, of those induced by the respective positive controls.[18] On the other hand, M3 did not clearly increase the CYP1A2 enzyme activity.

- Human hepatocytes were incubated in the presence of apalutamide (3-50 μmol/L) or M3 (3-50 μmol/L[19]) for 2 days, and the messenger ribonucleic acid (mRNA) expression level of CYP1A2 was determined. Neither apalutamide nor M3 clearly increased the mRNA level of CYP1A2.

4.5.3 Transporters

The applicant's explanation about the pharmacokinetic interactions mediated by transporters of apalutamide:

The investigation results below suggested that apalutamide and M3 were substrates of P-glycoprotein (P-gp) but not substrates of breast cancer resistant protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, or OATP1B3. In light of the absolute BA of apalutamide in humans (approximately 100%, see Section 6.1.2.1), however, the clinical use of apalutamide with a P-gp inhibitor is unlikely to cause pharmacokinetic interactions.

- P-gp-mediated transport of ^{14}C-apalutamide ([a] 1 and [b] 5 μmol/L) and ^{14}C-M3 ([c] 1 and [d] 5 μmol/L) was investigated using porcine kidney-derived LLC-PK1 cell line expressing human P-gp. The ratios of apparent permeability in basolateral to apical direction ($P_{app\ B\rightarrow A}$) to $P_{app\ A\rightarrow B}$ in the

[18] Phenobarbital (1 mmol/L) and rifampicin (10 μmol/L) were used as positive controls of CYP2B6 and CYP3A.

[19] Non-cytotoxic concentration ranges (3-30 μmol/L for hepatocytes from 2 donors and 3-50 μmol/L for hepatocytes from 1 donor) were used for the evaluation.

absence or presence of the P-gp inhibitor (GF120918 1 μmol/L) were (a) 1.58 and 0.59, (b) 1.32 and 0.56, (c) 1.97 and 0.57 as well as (d) 1.56 and 0.56, respectively.

- BCRP-mediated transport of ^{14}C-apalutamide (1 and 5 μmol/L) and ^{14}C-M3 (1 and 5 μmol/L) was investigated using canine kidney-derived MDCKII cell line expressing human BCRP. The BCRP inhibitor (KO143 1 μmol/L) did not clearly inhibit transport of ^{14}C-apalutamide or ^{14}C-M3.

- Intracellular uptake of ^{14}C-apalutamide (1 and 5 μmol/L) and ^{14}C-M3 (1 and 5 μmol/L) was investigated using human embryonic kidney-derived HEK293 cell line expressing human OATP1B1 or OATP1B3. The OATP1B1 and OATP1B3 inhibitor (rifampicin 25 μmol/L) did not clearly inhibit the intracellular uptake of ^{14}C-apalutamide or ^{14}C-M3.

In light of the investigation results below and C_{max} of apalutamide and M3 (15.9 and 15.3 μmol/L)[12)] at steady state in subjects who received apalutamide according to the proposed dosage and administration, the pharmacokinetic interactions mediated by the inhibition of OATP1B1, OATP1B3, organic anion transporter (OAT) 1 and multidrug and toxin extrusion (MATE) 2-K by apalutamide and M3 or the inhibition of OAT3 and organic cation transporter (OCT) 2 by apalutamide are unlikely to occur in the clinical use of apalutamide. On the other hand, the pharmacokinetic interactions mediated by the inhibition of MATE1 by apalutamide and M3 or the inhibition of OAT3 and OCT2 by M3 may possibly occur.

In light of the simulated apalutamide concentration (2,011 μmol/L) in the gastrointestinal tract in subjects who received apalutamide according to the proposed dosage and administration, the pharmacokinetic interactions of apalutamide with P-gp and BCRP substrates may possibly occur in the gastrointestinal tract in the clinical use of apalutamide. In light of the absolute BA of apalutamide (approximately 100%, see Section 6.1.2.1), on the other hand, M3 is hardly formed in the process of gastrointestinal absorption, and thus the clinical use of apalutamide is unlikely to cause a pharmacokinetic interaction of M3 with P-gp and BCRP substrates in the gastrointestinal tract.

- The inhibitory effect of apalutamide (0.3-30 μmol/L) and M3 (0.3-30 μmol/L) against P-gp-mediated transport of ^{3}H-digoxin (0.03 μmol/L) was investigated using LLC-PK1 cell line expressing human P-gp. Apalutamide (30 μmol/L) and M3 (30 μmol/L) inhibited P-gp-mediated transport of ^{3}H-digoxin by 56% and 42%, respectively.

- The inhibitory effect of apalutamide (0.3-30 μmol/L) and M3 (0.3-30 μmol/L) against BCRP-mediated transport of ^{3}H-topotecan (1 μmol/L) was investigated using MDCKII cell line expressing human BCRP. Apalutamide (30 μmol/L) and M3 (30 μmol/L) inhibited BCRP-mediated transport of ^{3}H-topotecan by 45% and 33%, respectively.

- The inhibitory effect of (a) apalutamide (0.3-30 μmol/L) and (b) M3 (0.3-30 μmol/L) against OATP1B1 or OATP1B3-mediated transport of ^{3}H-estradiol-17β-glucuronide (1 μmol/L) was investigated using HEK293 cell line expressing human OATP1B1 or OATP1B3. (a) Apalutamide (30

μmol/L) and (b) M3 (30 μmol/L) inhibited OATP1B1 and OATP1B3-mediated transports of ^{3}H-estradiol-17β-glucuronide by (a) 33% and 52%, and (b) 42% and 38%, respectively.

- The inhibitory effect of apalutamide (0.5-50 μmol/L) and M3 (0.5-50 μmol/L) against OAT1 or OCT2-mediated transport of the corresponding transporter's substrates[20] was investigated using CHO cell line expressing human OAT1 or OCT2. Apalutamide and M3 inhibited OCT2-mediated transport with the IC_{50} values of 27.2 and 4.8 μmol/L, respectively. Neither apalutamide nor M3 clearly inhibited OAT1-mediated transport.

- The inhibitory effect of apalutamide (0.5-50 μmol/L) and M3 (0.5-50 μmol/L) against OAT3 or MATE1 or MATE2-K-mediated transport of the corresponding transporter's substrates[21] was investigated using MDCKII cell line expressing human OAT3, MATE1, or MATE2-K. Apalutamide inhibited OAT3, MATE1, and MATE2-K-mediated transport with the IC_{50} values of 12.0, 13.8, and 37.9 μmol/L, respectively. M3 inhibited OAT3 and MATE1-mediated transport with the IC_{50} values of 7.6 and 17.6 μmol/L, respectively. On the other hand, M3 did not clearly inhibit MATE2-K-mediated transport.

4.R Outline of the review conducted by PMDA

Based on the submitted data and review in the following section, PMDA concluded that the applicant's explanation about non-clinical pharmacokinetics of apalutamide is acceptable.

4.R.1 Pharmacokinetic interactions

In vitro study results suggested that the clinical use of apalutamide would give rise to a pharmacokinetic interaction mediated by the inhibition or induction of metabolic enzymes and transporters presented below.

- The inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, and MATE1 by apalutamide and M3, the inhibition of P-gp and BCRP by apalutamide, and the inhibition of OAT3 and OCT2 by M3 [see Sections 4.5.1 and 4.5.3]

- CYP2B6 and CYP3A induction by apalutamide and M3 [see Section 4.5.2]

The applicant's explanation:

The pharmacokinetic interactions of apalutamide and M3 with substrates of the above metabolic enzymes and transporters were investigated in the Japanese phase I study (Study 08), global phase III study (Study 003), foreign phase Ib study (Study 56021927PCR1019 [Study 19]), and foreign phase I/II study (Study 001). The results identified patients receiving apalutamide concomitantly with the substrates of CYP2B6 and CYP2C8, OAT3, OCT2, and MATE1. Because no particular safety concerns were observed in these patients, the clinical use of apalutamide in combination with these substrates is unlikely to raise safety issues.

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20) ^{14}C-p-aminohippuric acid (5 μmol/L) was used as OAT1 substrate and ^{14}C-metformin (10 μmol/L) was used as OCT2 substrate.

21) ^{3}H-estrone-3-sulfate (1 μmol/L) was used as OAT3 substrate. ^{14}C-tetraethyl ammonium bromide (40 μmol/L) was used as MATE1 and MATE2K substrates.

PMDA's view:
The applicant's explanation is largely acceptable. However, the information about the pharmacokinetic interactions of apalutamide mediated by CYP2B6, OAT3, OCT2, and MATE1 is important to ensure the proper use of apalutamide, and the applicant should continue collecting the relevant information. Once available, useful information should be provided to healthcare professionals appropriately.

The pharmacokinetic interactions of apalutamide with substrates of CYP2C8, CYP2C9, CYP2C19, CYP3A, P-gp, and BCRP are discussed in Section "6.2.3.2 Study for concomitant use with substrates of various CYP enzymes and transporters."

5. Toxicity and Outline of the Review Conducted by PMDA

In this section, unless otherwise specified, the ethanolate form of apalutamide was used. The dose of apalutamide is expressed as an amount of free base of apalutamide.

In *in vivo* studies, unless otherwise specified, a fatty emulsion containing Acconon MC8-2, Capmul MCM, polyethylene glycol (PEG) 400, and Vitamin E-D-α-tocopherol polyethylene glycol succinate conjugate (TPGS) at 10:45:30:15 (w/w) was used as a vehicle.

5.1 Single-dose toxicity

Although no single-dose toxicity studies were conducted, acute toxicity of apalutamide was evaluated based on results after the first dose in a micronucleus assay in rodents, 28-day repeated-dose toxicity study in female rats, safety pharmacology study in dogs and 10-day repeated-dose toxicity study in mice (Table 10).

Table 10. Single-dose toxicity study

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male rats (Sprague Dawley)	Oral	0,[a)] 500, 1000, 2000	No toxic changes	>2000	4.2.3.3.2.1
Female rats (Sprague Dawley)	Oral	0,[a)] 50, 100, 150, 250	No toxic changes	>250	Reference 4.2.3.2.5
Male and female dogs (beagle)	Oral	0,[a)] 10, 20, 40	40: Vomiting, watery stool 20: White gum and auricle, cold limbs ≥10: Salivation	>40	4.2.1.3.4
Male and female mice (CD-1)	Oral	0,[a)] 20, 50, 100, 500	Death: 500 (3/12 males, 6/12 females) 500: Tremor, convulsion, hypotonia, decreased activity	500	Reference 4.2.3.4.2.1

a) Only vehicle was administered.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in male rats (28 days, 13 and 26 weeks) and male dogs (28 days, 13 and 39 weeks) (Table 11). Major toxicological target organs were male genitalia in both rats and dogs, and increased cholesterol value and decreased body weight were also observed. Decreased erythroid parameter values and increases in platelet and white blood cell counts were observed in rats.

In (a) 26-week repeated-dose toxicity study in male rats and (b) 39-week repeated-dose toxicity study in male dogs, exposure (C_{max} and AUC_{24h}) to apalutamide at the no observed adverse effect level (NOAEL) ([a] 25 mg/kg/day and [b] <2.5 mg/kg/day) were (a) 7.20 μg/mL and 135 μg·h/mL and (b) 3.82 μg/mL and 86.6 μg·h/mL (at the dose of 2.5 mg/kg/day), respectively, which were (a) 1.0 and 1.1 fold and (b) 0.5 and 0.7 fold, respectively, the clinical exposure.[22)]

[22)] C_{max} and AUC_{24h} on Day 22 of Cycle 1 in Japanese patients with metastatic CRPC orally receiving apalutamide 240 mg QD in Study 08 were 7.57 μg/mL and 122 μg·h/mL, respectively [see Section 6.2.1.2].

Table 11. Repeated-dose toxicity

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male rats (Sprague Dawley)	Oral	28 days (QD) + Recovery 14 days	0,[a] 0,[b] 50, 150, 250	Death or moribund sacrifice: 150[c] (2/5 animals in the recovery group), 250 (10/10 animals in the main study group, 5/5 animals in the recovery group) 250: Decreased body weight, piloerection, decreased activity, abnormal respiration 150: Decreased erythrocyte parameters; increases in reticulocyte count, platelet count, and white blood cell count; prolonged APTT and prothrombin time; increases in cholesterol, GGT, total protein, albumin, globulin, urea nitrogen, creatinine, calcium, and phosphorus; increased weights of pituitary gland, liver, and thyroid; hypertrophy of the anterior pituitary gland, hepatocyte, and follicle epithelium in the thyroid; enhanced extramedullary hematopoiesis in the spleen; hyperplasia of hematopoietic cells in the femoral bone marrow; feminization of the mammary gland; decreased sperm count in the epididymis; atrophy of the prostate gland and seminal vesicle; hyperplasia of testicular interstitial cells; degeneration of seminiferous tubular epithelium ≥50: Decreased weights of epididymis, prostate gland, and seminal vesicle; decreased weight of salivary gland; increased weight of adrenal gland; and hypertrophy of the adrenal cortex Reversibility: reversible[d]	150	4.2.3.2.2
Male rats (Sprague Dawley)	Oral	13 weeks (QD) + Recovery 30 days	0,[a] 25, 50,[c] 100	Moribund sacrifice[f]: 50 (1/15 animals in the main study group), 100 (1/15 animals in the main study group) 100: Decreased body weight, increased weight of the testis, increased MCH, bone marrow hyperplasia ≥50: Increased MCV, atrophy of the epididymis, increased weights of spleen and adrenal gland, adrenal cortex hypertrophy, enhanced extramedullary hematopoiesis in the splenic red pulp ≥25: Decreased erythrocyte parameters; increases in reticulocyte count, RDW, platelet count, fibrinogen, and white blood cell count; increases in cholesterol, HDL, LDL, total protein, albumin, globulin, creatinine, and ALP; decreased weights of the prostate gland and epididymis; increased weights of the pituitary gland, thymus, and liver; atrophy of the prostate gland and seminal vesicle; testicular interstitial cell hyperplasia; feminization of the mammary gland; anterior pituitary gland hypertrophy; increased CYP1A activity Reversibility: reversible[g]	100	4.2.3.2.3
Male rats (Sprague Dawley)	Oral	26 weeks (QD)	0,[a] 25, 75, 150	Death or moribund sacrifice[f]: 75 (3/20 animals) 150: Increased thymus weight ≥75: Decreased body weight; increases in MCH and MCV; increases in total protein, albumin, and globulin; increased weights of the liver and spleen; reduced or enlarged testis size; testicular interstitial cell adenoma; hepatocyte hypertrophy ≥25: Decreased erythrocyte parameters; increases in reticulocyte count, RDW, platelet count, fibrinogen, and white blood cell count; increases in cholesterol, creatinine, urea nitrogen, and ALP; decreased weights of the epididymis, prostate gland, and seminal vesicle; increased weights of the pituitary gland and adrenal gland; atrophy of the prostate gland, seminal vesicle, and epididymis; degeneration of the testis; hyperplasia of testicular interstitial cells; feminization of the mammary gland; hypertrophy of the anterior pituitary gland and adrenal cortex; bone marrow hyperplasia	25	4.2.3.2.4

Male dogs (beagle)	Oral	28 days (QD) + Recovery 28 days	0,[a] 5, 10, 25[h]	Euthanasia: 25 (3/5 animals in the main study group) 25: Convulsion, tremor, decreased activity, reduced body weight gain, apoptosis of the epididymis, vascular and perivascular inflammation in the heart ≥10: Decreased weight of the testis, atrophy of the epididymis ≥5: Increased cholesterol,[i] decreased weights of the prostate gland and epididymis; partial adenoid formation of the prostate gland (atrophy finding), decreased spermatogenesis and aspermatogenesis in the testis Reversibility: reversible[j]	10	4.2.3.2.8
Male dogs (beagle)	Oral	13 weeks (QD) + Recovery 60 days	0,[a] 2.5, 5, 10	10: Decreased body weight, decreased testis weight ≥2.5: Increases in cholesterol and HDL; decreased testosterone concentration; decreased weights of the prostate gland and epididymis; prostate gland atrophy; epididymis atrophy and decreased sperm count; degeneration of seminiferous tubules in the testis and decreased sperm count; anterior pituitary gland hypertrophy[k]; increased CYP2B activity Reversibility: reversible[l]	5	4.2.3.2.10
Male dogs (beagle)	Oral	39 weeks (QD)	0,[a] 2.5, 5, 10	≥5: Increased ALP ≥2.5: Decreased body weight; increased cholesterol; decreased weights of the prostate gland, epididymis, and kidney; atrophy of the prostate gland and epididymis; degeneration and atrophy of seminiferous tubules; testicular interstitial cell hypertrophy; hyperplasia of the bile duct and oval cells in the liver	<2.5	4.2.3.2.11

a) Only vehicle was administered. b) Reverse osmosis water was administered. c) No deaths occurred in the 150 mg/kg/day group in the 26-week repeated-dose toxicity study in male rats, and the change may have been due to possible aspiration of the viscous vehicle but is not attributable to apalutamide. d) The changes in the bone marrow, testis and epididymis were irreversible. e) JNJ-61177584 and JNJ-61232574, degradation products of apalutamide, were added at 2%. f) None of these are attributable to apalutamide. g) The decreased weights of epididymis and prostate gland and cellular hypertrophy of the anterior pituitary gland were irreversible. h) The treatment was discontinued on Day 8. i) It was not observed in the 25 mg/kg/day group. j) Decreased weights of the epididymis and testis, increased prostate gland weight, decreased sperm count and azoospermic in the epididymis, decreased spermatogenesis and aspermatogenesis in the testis were irreversible. k) It was observed at the 2.5 and 10 mg/kg/day groups. l) The decreased body weight, decreased food consumption, increased prostate gland weight, and decreased weight of the epididymis were irreversible.

5.3 Genotoxicity

Genotoxicity studies of apalutamide and its metabolites, i.e., M3, and M4, were conducted. *In vitro* studies were a bacterial reverse mutation assay and chromosomal aberration assay in mammalian cells; and *in vivo* studies included micronucleus assay in rodents and comet assay in rat liver (Table 12). Results from all the studies of apalutamide and M3 were negative. M4 tested slightly positive in the chromosomal aberration assay with mammalian cells but negative in the comet assay with rat liver. M4 was thus considered unlikely to pose genotoxicity *in vivo*.

Table 12. Genotoxicity studies

Study type		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Result	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames) for apalutamide and M3	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2 *uvrA*	S9−/+	0,[a] 15.8,[b] 50, 158, 500, 1581, 5000	Negative	4.2.3.3.1.1
	Bacterial reverse mutation assay (Ames) for M4	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2 *uvrA*	S9−/+	0,[a] 1.6, 5, 16, 50, 160, 500, 1600, 5000	Negative	4.2.3.3.1.2
	Chromosomal aberration assay with mammalian cells for apalutamide and M3	Human peripheral lymphocytes	S9−/+ (−, 4 and 21 hours) (+, 4 hours)	0,[a] 32,[b] 64, 128, 256[d]	Negative	4.2.3.3.1.3
	Chromosomal aberration assay with mammalian cells for M4	Human peripheral lymphocytes	S9−/+ (−, 3 and 24 hours) (+, 3 hours)	0,[a] 120, 172, 245, 500	245: Slightly positive following 24-hour treatment (S9:−)	4.2.3.3.1.4
In vivo	Micronucleus assay in rodents for apalutamide and M3	Male rat (Sprague Dawley) bone marrow		0,[c] 500, 1000, 2000 (single dose/oral)	Negative	4.2.3.3.2.1
	Comet assay of M4	Male rat (Sprague Dawley) hepatocyte		0,[c] 50, 100, 150 (QD, 2 days/oral)	Negative	4.2.3.3.2.3

a) Only vehicle (DMSO) was added. b) For M3 only. c) Only vehicle was administered. d) For treatment of M3 without S9, the maximum dose was 128 μg/mL.

5.4 Carcinogenicity

Because apalutamide is an antineoplastic agent intended for the treatment of advanced cancer, no carcinogenicity studies were conducted.

5.5 Reproductive and developmental toxicity

Because apalutamide is an antineoplastic agent intended for the treatment of prostate cancer, no study was conducted to investigate the effect of apalutamide on pre- and postnatal development, including maternal function or embryo-fetal development.

A study of fertility and early embryonic development to implantation was conducted in male rats (Table 13). Male rats treated with oral apalutamide QD for 4 weeks were mated with untreated female rats. In the 150 mg/kg/day group, the copulation index and fertility index decreased, and the preimplantation embryonic loss increased in pregnant rats. The applicant explained that the decreased fertility index and increased preimplantation embryonic loss were changes attributable to the decreased sperm count and sperm motility because apalutamide and its metabolites were not suggested to be genotoxic [see Section 5.3].

C_{max} and AUC_{24h} (7.20 μg/mL and 135 μg·h/mL in the 26-week repeated-dose toxicity study in male rats) representing the exposure to apalutamide in male rats at the NOAEL (25 mg/kg/day) were, respectively, 1.0 and 1.1 fold those of clinical exposure.[22)]

Table 13. Reproductive and developmental toxicity

Study type	Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male Rat (Sprague Dawley)	Oral	4 weeks (QD)	0,[a] 25, 150	Death[b]: 25 (1/32 animals), 150 (1/32 animals) [4-week-treatment and necropsy group) 150: Decreased sperm motility ≥25: Decreased sperm count in the epididymis, small coagulating gland, seminal vesicle, and prostate gland, decreased weight of the epididymis [Mating group][c] Mating after 4-week treatment: 150: Decreased mating index and fertility index, increased preimplantation embryonic loss[d] 8-week drug-free and mating: No effects	25	4.2.3.5.1.1

a) Only vehicle was administered. b) Neither death was considered related to apalutamide. c) Male rats which had received apalutamide for 4 weeks were mated with untreated female rats. After the 8-week drug-free period, these male rats were mated with untreated female rats. d) (count of corpora lutea – count of implantation sites)/count of corpora lutea × 100

5.6 Local tolerance

The local tolerance of oral apalutamide was assessed as a part of general toxicity studies in rats and dogs [see Sections 5.1 and 5.2]. In these studies, no findings suggesting the local irritant effects were found.

5.7 Other studies

5.7.1 Toxicity of impurities

Repeated-dose toxicity studies of Impurity A, Impurity B, and Impurity C were conducted in rats, and safety was confirmed (Table 14).

Table 14. General toxicity studies of impurities

Test system	Route of administration	Treatment period	Dose[a] (mg/kg/day)	Major findings	Attached document CTD
Male Rat (Sprague Dawley) Impurity A	Oral	1 month (QD)	0,[b] 25, 25 (spiked with the impurity at 1.2%), 150/100,[c] 150/100 (spiked with the impurity at 1.2%)	No clear differences were observed in toxicity between the impurity-added group and no-additional-impurity group.	4.2.3.7.6.1
Male Rat (Sprague Dawley) Impurity B	Oral	1 month (QD)	0,[b] 25, 25 (spiked with the impurity at 0.56%), 100, 100 (spiked with the impurity at 0.56%)	No clear differences were observed in toxicity between the impurity-added group and no-additional-impurity group.	4.2.3.7.6.2
Male Rat (Sprague Dawley) Impurity C	Oral	1 month (QD)	0,[b] 25, 25 (spiked with the impurity at 0.65%), 100, 100 (spiked with the impurity at 0.65%)	No clear differences were observed in toxicity between the impurity-added group and no-additional-impurity group.	4.2.3.7.6.3

a) In studies of Impurity A and Impurity C, the non-ethanolate form of apalutamide was used. b) Only vehicle was administered. c) The treatment was temporarily discontinued because of deteriorated general condition and resumed at the decreased dose of 100 mg/kg/day on Day 5.

5.7.2 Photosafety

Phototoxicity testing of apalutamide and M3 was conducted using the 3T3 neutral red uptake (3T3-NRU) method. Both were shown to have no phototoxicity (Table 15).

Table 15. Photosafety testing

Method	Dose (mg/L)	Major findings	Attached document CTD
3T3-NRU method	10.6 (apalutamide), 10.0 (M3)	None	4.2.3.7.7.1

5.7.3 Toxicity of synthetic starting material and intermediate

The synthetic starting material and intermediate of apalutamide were subjected to an *in silico* or bacterial reverse mutation test in accordance with ICH M7 guideline, and were shown to be non-mutagenic.

5.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the applicant's explanation about the toxicity of apalutamide is acceptable.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Apalutamide is available as oral formulations including soft capsule, hard capsule, uncoated tablet, and film coating (FC) tablet. To investigate the PK of apalutamide, these dosage forms and injection were used (Table 16). The proposed commercial formulation is FC tablet.

Table 16. Dosage forms used in clinical studies

Formulation	Study
Injection	Foreign phase I (Study 006)
Soft capsule (30 mg)	Japanese phase I (Study 08), global phase III (Study 003), foreign phase I (Studies 006, 07, 11, and 12), foreign phase Ib (Study 10), foreign phase I/II (Study 001)
Hard capsule (400 μg)	Foreign phase I (Study 006)
Uncoated tablet (60 and 120 mg)	Foreign phase I (Study 07)
FC tablet (60 mg)	Japanese phase I (Studies 08 and 21), global phase III (Study 003), foreign phase I (Studies 11, 15, 17, 18, and 20), foreign phase Ib (Studies 10 and 19), foreign phase I/II (Study 001)

6.1.1 Assay

Concentrations of apalutamide and M3 (*N*-desmethyl apalutamide) in human plasma were determined by liquid chromatography/tandem mass chromatography (LC-MS/MS). Lower limits of quantitation are shown in Table 17.

Table 17. Lower limit of quantitation for analytical procedures used in clinical studies

Analyte	Lower limit of quantitation (μg/mL)	Study
Apalutamide	5	Study 21
	5 or 25	Studies 15 and 17
	20 or 25	Study 001
	25	Studies 08, 003, 006, 07, 11, 12, 18, 20, 10, and 19
M3	5	Study 21
	5 or 25	Studies 15 and 17
	25	Studies 08, 003, 006, 07, 11, 12, 18, 20, 10, 19, and 001

6.1.2 Foreign clinical studies

6.1.2.1 Foreign phase I study (CTD 5.3.1.1.1, PART A of Study ARN-509-006 [Study 006], March to May 2013)

An open-label study was conducted in 6 healthy adults (6 subjects included in the PK analysis) to investigate the absolute BA. Approximately 2 hours after a single oral dose of apalutamide (soft capsule) 240 mg, a single intravenous dose of ^{14}C-apalutamide 100 μg was administered.

The geometric mean (range) of absolute BA calculated from AUC_{inf} of apalutamide was 1.11 (1.08, 1.13).

6.1.2.2 Foreign phase I study (CTD 5.3.1.2.2, Study 11, June to November 2014)

An open-label, randomized study was conducted in 30 healthy adults (30 subjects included in the PK analysis) to investigate the effect of dosage forms on the PK of apalutamide. A single dose of apalutamide 240 mg was orally administered in soft capsules or FC tablets in the fasted state[23)] to investigate plasma apalutamide concentrations. The geometric mean ratios [90% CI] of C_{max} and AUC_{last} of apalutamide FC tablet to those of soft capsule were 0.90 [0.79, 1.03] and 1.08 [0.95, 1.23], respectively.

Another open-label, randomized study was conducted in 30 healthy adults (30 subjects included in the PK analysis) to investigate the food effect on the PK of apalutamide (FC tablet). A single dose of apalutamide 240 mg was orally administered in the fasted state[23)] or after a high-fat meal (a total of approximately 900 to 1000 kcal, including approximately 500 to 600 kcal from fat) to investigate plasma apalutamide concentrations. The median t_{max} of apalutamide administered in the fasted state and after a high-fat meal was 3.03 and 5.05 hours, respectively. The geometric mean ratios [90% CI] of C_{max} and AUC_{last} of apalutamide administered after a high-fat meal to those of apalutamide administered in the fasted state were 0.84 [0.75, 0.94] and 0.97 [0.86, 1.09], respectively.

The applicant's explanation about the food effect on the PK of apalutamide based on the above results:
The high-fat meal prolonged the gastric emptying time, potentially leading to delay in t_{max} and decrease in C_{max}. In light of the coefficient of variation for the C_{max} (15.7% and 20.2%, respectively, after the fasting dose and the high-fat meal dose), however, the decreased C_{max} after non-fasting dose of apalutamide is considered unlikely to pose a problem in its clinical use, and thus no meal condition needs to be specified in the dosage regimen [see Section 7.R.5].

6.1.3 Effect of gastric pH on the PK of apalutamide

The applicant's explanation:
Increased gastric pH in response to a concomitant proton pump inhibitor, etc. is considered unlikely to affect the PK of apalutamide, in light of the solubility of apalutamide, which is <0.01 mg/mL[24)] at physiological pH and almost remains unchanged irrespective of pH.

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23) Subjects received the drug after fasting for ≥10 hours and continued fasting for ≥4 hours.

24) Determined using solutions of hydrochloric acid (0.1 and 0.01 mol/L); citric acid-sodium hydroxide-hydrochloric acid buffer solution (pH 2); citric acid-sodium hydroxide buffer solution (pH 5); phosphate buffer solution (pH 7); water; boric acid-sodium hydroxide-potassium chloride buffer solution (pH 9), phosphate-sodium hydroxide buffer solution (pH 12), and sodium hydroxide (0.1 mol/L). In the phosphate-sodium hydroxide buffer solution (pH 12) and sodium hydroxide (0.1 mol/L), no results were obtained owing to the degradation of apalutamide.

6.2 Clinical pharmacology

The PK profiles of apalutamide in healthy adults and patients with cancer were determined after apalutamide was administered alone or concomitantly with itraconazole or gemfibrozil. In addition, effects of apalutamide on the PK of midazolam, pioglitazone, S-warfarin, omeprazole, fexofenadine, or rosuvastatin were investigated.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.3.1.1, Study 56021927PCR1021 [Study 21], October to December 2016)

An open-label, randomized study was conducted in 18 healthy adults (18 subjects included in the PK analysis) to investigate the PK of apalutamide. A single dose of apalutamide 60, 120, or 240 mg was orally administered to investigate plasma concentrations of apalutamide and M3.

Table 18 shows the PK parameters of apalutamide and M3. C_{max} and AUC_{inf} of apalutamide and M3 increased in an almost dose-proportional manner in the dose range investigated.

Table 18. PK parameters of apalutamide and M3

Dose (mg)	Analyte	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{inf} (μg•h/mL)	$t_{1/2}$ (h)
60	Apalutamide	6	0.870 ± 0.192	2.50 (1.50, 4.00)	63.9 ± 13.1	138 ± 62.0
	M3	6	0.112 ± 0.0396	156 (120, 336)	52.3 ± 8.81	169 ± 70.2
120	Apalutamide	6	1.73 ± 0.285	1.75 (1.00, 3.00)	147 ± 36.7	169 ± 54.0
	M3	6	0.175 ± 0.0481	324 (144, 504)	105 ± 5.67	220 ± 77.3
240	Apalutamide	6	3.12 ± 0.745	3.50 (2.00, 5.00)	227 ± 26.6*2	130 ± 36.9*2
	M3	6	0.385 ± 0.102	156 (120, 336)	206 ± 34.9*2	167 ± 32.4*2

Arithmetic mean ± SD; *1 Median (range), *2 n = 5

6.2.1.2 Japanese phase I study (CTD 5.3.5.2.2, Study 08, ongoing since July 2014 [data cutoff on [redacted], [redacted]])

An open-label study was conducted in 6 patients with metastatic CRPC (6 patients included in the PK analysis) to investigate the PK of apalutamide (soft capsule). Each treatment cycle consisted of 28 days. A single dose of apalutamide 240 mg was orally administered 7 days before start of Cycle 1, and QD oral administration was started on Day 1 of Cycle 1. In this study, plasma concentrations of apalutamide and M3 were determined.

Table 19 shows the PK parameters of apalutamide and M3. The accumulation index for apalutamide[25)] (arithmetic mean) was 3.55. The applicant explained that a steady state would be reached at Week 4 because the plasma trough concentration of apalutamide almost remained unchanged at Week 4 and later.

25) Ratio of AUC_{24h} on Day 22 of Cycle 1 to that on Day −7 of Cycle 1

Table 19. PK parameters of apalutamide and M3

Dose (mg)	Analyte	Day of measurement	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{24h} (μg•h/mL)	AUC_{last} (μg•h/mL)
240	Apalutamide	Day−7 of Cycle 1	5	3.88 ± 0.793	1.58 (1.00, 2.05)	33.6 ± 4.78	116 ± 14.1
	M3			0.366 ± 0.0751	168 (95.5, 168)	2.69 ± 0.307	45.4 ± 8.59
	Apalutamide	Day 22 of Cycle 1	6	7.57 ± 1.19	1.44 (0.950, 4.00)	122 ± 17.5	-
	M3			7.11 ± 0.551	3.68 (0, 23.8)	150 ± 15.6	-

Arithmetic mean ± SD; * Median (range); -, Not calculated

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I/II study (CTD 5.3.5.2.1-1, phase I part of Study 001, ongoing since July 2010 [data cutoff on December 31, 2014])

An open-label study was conducted in 30 patients with metastatic CRPC (30 patients included in the PK analysis) to investigate the PK of apalutamide (soft capsule). Each treatment cycle consisted of 28 days. A single dose of apalutamide 30 to 480 mg was orally administered 7 days before start of Cycle 1, and QD or BID[26] oral administration was started on Day 1 of Cycle 1. In this study, plasma concentrations of apalutamide and M3 were determined.

Tables 20 and 21 show the PK parameters of apalutamide and M3, respectively. In the dose range investigated, C_{max} and AUC_{24h} of apalutamide on Day −7 and Day 22 of Cycle 1 increased in an almost dose-proportional manner.[27] The accumulation indices[25] (arithmetic mean) of apalutamide and M3 in the 240 mg group were 5.70 and 106, respectively. The applicant explained that the steady state would be reached at Week 4 to 5 because the plasma trough concentration of apalutamide almost remained unchanged at Week 4 to 5 and later.

[26] In the apalutamide 300, 390, and 480 mg groups, apalutamide was administered at 150, 195, and 240 mg BID except for on Days −7 and 22 of Cycle 1.

[27] The linearity on Day 22 of Cycle 1 was analyzed using the power model, etc.

Table 20. PK parameters of apalutamide

Dose (mg)	Day of measurement	n	C_{max} (μg/mL)	t_{max}[*1] (h)	AUC_{24h} (μg•h/mL)	AUC_{inf} (μg•h/mL)	$t_{1/2}$ (h)
30	Day −7 of Cycle 1	3	0.268 ± 0.128	3.0 (1.0, 4.0)	2.58 ± 1.13	20.8 ± 1.99	205 ± 89.1
	Day 22 of Cycle 1	3	0.841 ± 0.136	0.5 (0.5, 1.0)	14.7 ± 2.01	-	85.8 ± 9.27
60	Day −7 of Cycle 1	3	0.665 ± 0.104	1.0 (1.0, 1.5)	4.76 ± 0.741	50.9 ± 24.8	242 ± 136
	Day 22 of Cycle 1	3	1.60 ± 0.176	1.0 (1.0, 4.0)	29.7 ± 6.40	-	107, 128[*2]
90	Day −7 of Cycle 1	3	1.14 ± 0.361	1.0 (1.0, 1.5)	6.94 ± 1.51	43.0 ± 1.16	135 ± 44.6
	Day 22 of Cycle 1	3	2.53 ± 0.176	1.0 (0.5, 2.0)	38.3 ± 3.75	-	93.2 ± 82.9
120	Day −7 of Cycle 1	3	1.31 ± 0.237	1.0 (1.0, 1.5)	9.09 ± 2.82	214 ± 170	486 ± 499
	Day 22 of Cycle 1	3	3.30 ± 0.542	2.0 (2.0, 24.0)	59.4 ± 10.8	-	55.7, 71.9[*2]
180	Day −7 of Cycle 1	3	2.48 ± 1.39	1.0 (1.0, 6.0)	20.1 ± 8.68	162 ± 21.1	206 ± 123
	Day 22 of Cycle 1	3	5.98 ± 1.24	1.0 (1.0, 1.0)	93.7 ± 27.2	-	81.3 ± 45.7
240	Day −7 of Cycle 1	3	2.97 ± 0.414	1.0 (1.0, 3.0)	21.9 ± 2.66	231 ± 93.2	218 ± 128
	Day 22 of Cycle 1	3	7.55 ± 1.15	1.5 (1.0, 8.0)	127 ± 36.3	-	100, 112[*2]
300	Day −7 of Cycle 1	6	2.89 ± 0.547	1.5 (1.0, 4.0)	30.5 ± 8.26	251 ± 58.5	173 ± 68.0
	Day 22 of Cycle 1	5	7.08 ± 2.19	2.0 (1.0, 24.0)	134 ± 37.3	-	2270 ± 4340[*3]
390	Day −7 of Cycle 1	3	3.79 ± 1.01	1.5 (1.0, 2.0)	28.3 ± 4.02	285 ± 87.7	213 ± 44.6
	Day 22 of Cycle 1	3	8.91 ± 0.995	1.0 (0.5, 1.5)	140 ± 22.0	-	47.7 ± 21.9
480	Day −7 of Cycle 1	3	3.56 ± 0.759	1.5 (1.0, 1.5)	35.5 ± 1.53	351 ± 154	205 ± 163
	Day 22 of Cycle 1	3	11.2 ± 0.473	1.5 (0.5, 1.5)	202 ± 9.70	-	153 ± 111

Arithmetic mean ± SD (individual values for n = 2); *[1] Median (range); *[2] n = 2; *[3] n = 4; -: Not calculated

Table 21. PK parameters of M3

Dose (mg)	Day of measurement	n	C_{max} (μg/mL)	t_{max}[*1] (h)	AUC_{24h} (μg•h/mL)	$t_{1/2}$ (h)
240	Day−7 of Cycle 1	3	0.197 ± 0.0695	168.0 (168.0, 168.0)	1.16 ± 0.264	-
	Day 22 of Cycle 1	3	5.30 ± 0.889	6.0 (4.0, 8.0)	119 ± 19.4	3240[*2]
300	Day−7 of Cycle 1	6	0.361 ± 0.116	168.0 (96.0, 168.0)	1.82 ± 0.840	-
	Day 22 of Cycle 1	5	7.52 ± 1.37	8.0 (0.0, 24.0)	172 ± 30.2	-
390	Day−7 of Cycle 1	3	0.395 ± 0.220	168.0 (168.0, 168.0)	2.04 ± 0.781	-
	Day 22 of Cycle 1	3	7.17 ± 1.82	1.0 (0.0, 8.0)	148 ± 33.1	268, 579[*3]
480	Day−7 of Cycle 1	3	0.232 ± 0.0117	168.0 (96.0, 168.0)	1.40 ± 0.357	-
	Day 22 of Cycle 1	3	8.53 ± 0.521	0.0 (0.0, 24.0)	181 ± 2.25	159[*2]

Arithmetic mean ± SD (individual values for n = 1 or 2); *[1] Median (range); *[2] n = 1; *[3] n = 2; -: Not calculated

6.2.2.2 Foreign phase I study (CTD 5.3.1.1.1, PART B of Study 006, March to May 2013)

An open-label study was conducted in 6 healthy adults (6 subjects included in the PK analysis) to investigate mass balance of apalutamide. A single dose of apalutamide (soft capsule) was orally administered at 240 mg with 400 μg of ^{14}C-apalutamide to investigate radioactivity concentrations in plasma, urine, and feces.

The applicant explained that the blood/plasma ratios of the radioactivity concentration were 0.91 to 0.98 until 168 hours post-dose, indicating similar distribution of apalutamide and its metabolites in plasma and blood cells. In addition, unchanged apalutamide, M3, and M4 (amide hydrolysis) were mainly detected in plasma samples collected until 71 days post-dose (accounting for 42%, 41%, and 2.7%, respectively, of the total plasma radioactivity).

Until 71 days post-dose, 64.6% and 24.3% of the administered radioactivity were excreted into urine and feces, respectively. In addition, in urine and feces until 71 days post-dose, M4 was mainly detected (accounting for 31.12% and 2.38%, respectively, of the administered radioactivity). Furthermore, 1.20% and 2.73% of the administered radioactivity were excreted into urine until 71 days post-dose as unchanged apalutamide and M3, respectively. Based on the above, the applicant explained that apalutamide was considered to be mainly eliminated by metabolism, and renal excretion would hardly contribute to the elimination.

6.2.3 Drug-drug interaction studies

6.2.3.1 Study for drug interactions with itraconazole or gemfibrozil (CTD 5.3.3.4.1, Study 56021927PCR1012 [Study 12], September to December 2014)

An open-label, randomized study was conducted in 45 healthy adults (15 subjects per group included in the PK analysis) to investigate effects of itraconazole (strong CYP3A inhibitor) and gemfibrozil (strong CYP2C8 inhibitor) on the PK of apalutamide, M3, and unbound active ingredient.[28)] Dosage regimens are as follows:

Group 1: A single oral dose of apalutamide 240 mg

Group 2: Oral dose of itraconazole 200 mg QD from Days1 to 32, and a single oral dose of apalutamide 240 mg on Day 4

Group 3: Oral dose of gemfibrozil 600 mg BID from Days 1 to 32, and a single oral dose of apalutamide 240 mg on Day 4

The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of (a) apalutamide, (b) M3, and (c) unbound active ingredient in concomitant use with itraconazole to those of apalutamide alone were (a) 0.78 [0.71, 0.86] and 1.01 [0.90, 1.14], (b) 0.85 [0.71, 1.02] and 1.12 [1.02, 1.23], and (c) 0.78 [0.71, 0.87] and 1.04 [0.94, 1.14], respectively. In addition, the geometric mean ratios [90% CI[of C_{max} and AUC_{inf} of (a) apalutamide, (b) M3, and (c) unbound active ingredient in concomitant use with gemfibrozil to those of apalutamide alone were (a) 0.79 [0.72, 0.87] and 1.68 [1.49, 1.88], (b) 0.55 [0.46, 0.66] and 0.85 [0.77, 0.94], and (c) 0.79 [0.71, 0.87] and 1.45 [1.31, 1.60], respectively.

[28)] The result of the unbound active ingredient was determined from the sum of the plasma protein unbound apalutamide concentration plus one third of the plasma protein unbound M3 concentration in consideration that the pharmacological activity of M3 is approximately one third of that of apalutamide [see Section 3.1.2].

6.2.3.2 Study for concomitant use with substrates of various CYP isoforms and transporters (CTD 5.3.3.4.2, Study 56021927PCR1020 [Study 20], March to November 2016)

An open-label study was conducted in 23 patients with CRPC (21 patients included in the PK analysis) to investigate effects of apalutamide on the PK of substrates of various CYP isoforms and transporters. In each 28-day cycle, patients orally received midazolam (CYP3A substrate) 2 mg, warfarin (CYP2C9 substrate) 10 mg, omeprazole (CYP2C19 substrate) 40 mg, and fexofenadine (P-gp substrate) 30 mg on Days 1 and 43, pioglitazone (CYP2C8 substrate) 15 mg on Days 8 and 50, rosuvastatin (BCRP and OATP1B1 substrate) 10 mg on Days 9 and 51, and oral apalutamide 240 mg QD from Day 15. To alleviate the anticoagulation effect of warfarin, 10 mg of vitamin K was concomitantly administered.

Table 22 shows the geometric mean ratios of C_{max} and AUC_{last} of the substrates of various CYP isoforms and transporters in concomitant use with apalutamide to each substrate alone. No clear difference was observed between exposure to pioglitazone with and without apalutamide, but the concomitant use of apalutamide decreased the exposures to midazolam, S-warfarin, omeprazole, fexofenadine, and rosuvastatin. Accordingly, the applicant explained that caution should be used against concomitant use with any substrate of CYP3A, CYP2C9, CYP2C19, P-gp, BCRP, and OATP1B1.

Table 22. Effects of apalutamide on PK of various CYP substrates

Analyte	n	With/without apalutamide	
		C_{max}	AUC_{last}
Midazolam (CYP3A substrate)	21	0.23 [0.18, 0.30]	0.08 [0.06, 0.11]
Pioglitazone (CYP2C8 substrate)	20	0.91 [0.80, 1.03]	0.82 [0.75, 0.91]
S-warfarin (CYP2C9 substrate)	21	0.84 [0.77, 0.91]	0.54 [0.50, 0.58]
Omeprazole (CYP2C19 substrate)	20	0.33 [0.24, 0.44]	0.15 [0.11, 0.22]
Fexofenadine (P-gp substrate)	21	0.93 [0.80, 1.08]	0.70 [0.61, 0.80]
Rosuvastatin (BCRP and OATP1B1 substrate)	20	0.99 [0.83, 1.19]	0.59 [0.50, 0.69]

Geometric mean ratio [90% CI]

6.2.4 Foreign phase I study for the effect of hepatic impairment on the PK of apalutamide (CTD 5.3.3.3.1, Study 56021927PCR1018 [Study 18], August 2015 to February 2017)

An open-label study was conducted in 8 healthy adults (8 subjects included in the PK analysis), 8 patients with mild (Child-Pugh Class A) hepatic impairment, and 8 patients with moderate (Child-Pugh Class B) hepatic impairment (a total of 16, all included in the PK analysis) to investigate the effect of hepatic impairment on the PK of apalutamide. A single dose of apalutamide was orally administered at 240 mg to investigate plasma concentrations of apalutamide and M3.

Table 23 shows the PK parameters of apalutamide and M3. No clear differences were observed in C_{max} or AUC_{inf} of apalutamide and M3 between healthy adults and patients with mild hepatic impairment. Furthermore, no clear differences were observed in C_{max} or AUC_{inf} of apalutamide between healthy adults and patients with moderate hepatic impairment, but the C_{max} and AUC_{inf} of M3 in these patients were, respectively, 27% and 19% lower than those in healthy adults.

Table 23. PK parameters of apalutamide and M3 by severity of hepatic impairment

Analyte	Severity of hepatic impairment	n	C_{max} (μg/mL)	AUC_{inf} (μg•h/mL)	Geometric mean ratio [90% CI] (patients with hepatic impairment/healthy adults)	
					C_{max}	AUC_{inf}
Bound + unbound forms						
Apalutamide	Normal	8	1.91	200	-	-
	Mild	8	1.94	189	1.02 [0.77, 1.34]	0.95 [0.76, 1.18]
	Moderate	8	1.99	226	1.04 [0.74, 1.47]	1.13 [0.82, 1.57]
M3	Normal	8	0.271	177	-	-
	Mild	8	0.267	171	0.99 [0.73, 1.34]	0.96 [0.84, 1.11]
	Moderate	8	0.199	144*	0.73 [0.50, 1.07]	0.81 [0.65, 1.01]
Unbound form						
Apalutamide	Normal	8	0.0889	9.30	-	-
	Mild	8	0.0896	8.71	1.01 [0.74, 1.38]	0.94 [0.71, 1.23]
	Moderate	8	0.0893	10.2	1.00 [0.68, 1.49]	1.09 [0.79, 1.51]
M3	Normal	7	0.0150	9.47	-	-
	Mild	8	0.0138	8.79	0.92 [0.64, 1.31]	0.93 [0.77, 1.12]
	Moderate	8	0.0101	7.32*	0.67 [0.45, 1.01]	0.77 [0.57, 1.05]

Geometric mean; Bound form, plasma protein-bound form of apalutamide or M3; Unbound form, plasma protein unbound apalutamide or M3;
* n = 7; -, Not calculated

6.2.5 Use of apalutamide in patients with renal impairment

The applicant's explanation:

The dose of apalutamide need not be adjusted for patients with renal impairment in light of the following observations:

- Renal excretion of apalutamide is suggested to contribute insignificantly to its elimination [see Section 6.2.2.2].

- In the apalutamide group in Study 003, the incidences of (a) all adverse events and (b) Grade ≥3 adverse events in patients with normal renal function[29] (n = 377), patients with mild renal impairment (n = 280), and patients with moderate or severe renal impairment (n = 141[30]) were (a) 96.0%, 97.1%, and 96.5%, and (b) 43.0%, 47.5%, and 46.8%, respectively, showing that the incidences in patients with mild renal impairment and in patients with moderate or severe renal impairment were not clearly different from the incidences in patients with normal renal function.

6.2.6 Relationship of exposure with changes in QT/QTc interval

Based on results from a foreign phase Ib study (Study 19), a relationship of plasma apalutamide concentration with a change in QTcF from baseline (ΔQTcF) was investigated using a linear mixed-effects model. In patients who orally received apalutamide 240 mg QD, ΔQTcF [90% CI] (ms) at $C_{max,ss}$ (5.95 μg/mL) of apalutamide was estimated to be 13.81 [9.77, 17.85].

Based on the above, the applicant explained that the oral administration of apalutamide 240 mg QD could prolong QT/QTc interval.

[29] Normal renal function, CrCL ≥90 mL/min; mild renal impairment, CrCL ≥60 mL/min and <90 mL/min; moderate renal impairment, CrCL ≥30 mL/min and <60 mL/min; and severe renal impairment, CrCL <30 mL/min

[30] Although 137 and 4 patients were found to have moderate and severe renal impairment, respectively, these patients were pooled into a subgroup of 141 patients for the analysis.

6.2.7 PPK analysis

A population pharmacokinetic (PPK) analysis (NONMEM Version 7.1.0 or subsequent versions) was performed using a non-linear mixed effect model on the PK data of (a) apalutamide and (b) M3 (covering [a] 8579 sampling points in 1092 subjects and [b] 7944 sampling points in 1092 subjects) from Japanese clinical studies (Studies 08 and 21), global study (Study 003), and foreign clinical studies (Studies 11, 18, 19, and 001). The PK data of (a) apalutamide and (b) M3 were described using (a) a two-compartment model with first-order absorption after a lag-time and (b) a two-compartment model.

In this analysis, an absorption rate constant (K_a) for each formulation was applied to modeling. Covariates for K_a, apparent volume of distribution of central compartment of apalutamide (V_c/F), CL_{tot}/F, apparent peripheral volume of distribution of apalutamide (V_p/F), apparent inter-compartmental clearance of apalutamide (Q/F), apparent volume of distribution of central compartment of M3 (V_{cm}/F), apparent clearance of M3 (CL_m/F), apparent volume of distribution of peripheral compartment of M3 (V_{pm}/F), apparent inter-compartmental clearance of M3 (Q_m/F), and relative bioavailability (F) investigated were age, body weight, race, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, serum albumin, total protein, estimated glomerular filtration rate (eGFR), health status (healthy adults or CRPC patients), Eastern Cooperative Oncology Group performance status (ECOG PS), and concomitant use with a CYP2C8 inducer or CYP3A inducer. Selected significant covariates were (i) body weight, serum albumin, and health status (healthy adults or CRPC patients) for F, (ii) body weight for V_p/F, and (iii) health status (healthy adults or CRPC patients) for Q_m/F.

The applicant's explanation about results from the above analysis:

- The K_a value for soft capsule was estimated to be 14.9% lower than that for FC tablet. This is considered attributable to the estimation of Ka values for the soft capsule and Fc tablet based on the dataset mostly comprising data from Study 003, which had limited sampling points for plasma apalutamide concentration.

- Because post-hoc estimated $C_{max,ss}$ and $AUC_{24h,ss}$ of apalutamide and M3 showed potentially limited effects of body weight and serum albumin on these parameters, these covariate values are considered unlikely to have clinically relevant effects on the PK of apalutamide and M3.

- The F of apalutamide and Q_m/F of M3 in healthy adults were estimated to be 27%[31)] higher and 35.5% lower than those in patients with CRPC. Causes for these differences are unknown.

6.2.8 Association between exposure and efficacy or safety

Association between exposure to apalutamide or M3 estimated by the PPK analysis on data from Study 003 [see Section 6.2.7] with efficacy or safety were investigated.

[31)] Values corrected for differences in body weight and albumin

6.2.8.1 Association between exposure and efficacy

The metastasis-free survivals (MFSs) in the placebo, apalutamide, and M3 groups were estimated using the Kaplan-Meier plots in which the exposure ($AUC_{24h,ss}$) to apalutamide and M3 were categorized by quartiles.[32)] No clear relationship of exposure to apalutamide or M3 with MFS was observed.

6.2.8.2 Association between exposure and safety

Relationships of exposure ($AUC_{24h,ss}$) to apalutamide and M3 with development of fatigue, fall, skin eruption, weight decreased, and arthralgia[33)] were investigated using univariate and multivariate logistic regression models. In patients in the apalutamide group, exposure ($AUC_{24h,ss}$) to apalutamide and M3 were found positively correlated to the occurrence of skin eruption and weight decreased.

6.2.9 Difference in PK between Japanese and non-Japanese patients

The applicant's explanation:

No clear differences were observed in exposure (C_{max} and AUC_{24h}) to apalutamide after the oral administration of 240 mg as a single dose or QD between the Japanese phase I study (Study 08) [see Section 6.2.1.2] and the phase I part of a foreign phase I/II study (Study 001) [see Section 6.2.2.1]. Thus, there was no difference in the PK of apalutamide between Japanese and non-Japanese patients.

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the clinical pharmacology findings of apalutamide is acceptable, except for that in the following subsections.

6.R.1 Use of apalutamide in patients with hepatic impairment

The applicant's explanation about the use of apalutamide in patients with hepatic impairment:

The foreign phase I study (Study 18) shows that mild or moderate hepatic impairment does not have any clear effect on the PK of apalutamide [see Section 6.2.4]. Thus, the dose of apalutamide needs not be adjusted for patients with mild or moderate hepatic impairment. Meanwhile, apalutamide has not been used in patients with severe hepatic impairment, and the "Pharmacokinetics" section of the package insert will note that the pharmacokinetics of apalutamide in this patient population remains unknown.

PMDA's view:

PMDA accepted the applicant's explanation about the use of apalutamide in patients with mild or moderate hepatic impairment. Furthermore, careful use of apalutamide in should be advised for patients with severe hepatic impairment via the package insert, given that apalutamide is mainly eliminated through hepatic metabolism [see Section 6.2.2.2].

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32) Medians (range) of $AUC_{24h,ss}$ (μg·h/mL) of (a) apalutamide and (b) M3 in each category divided by quartiles were (a) 78.1 (0, 89.5), 98.8 (89.7, 107.4), 116.1 (107.4, 124.2), and 143.5 (124.2, 279.8), and (b) 114.2 (0, 151.3), 139.0 (90.8, 176.8), 155.2 (107.5, 186.8), and 172.4 (116.4, 299.2), respectively.

33) The adverse events analyzed were selected from events for which a causal relationship to apalutamide could not be ruled out in Study 003 taking account of the incidence (>10%), severity (Grade ≥3), and clinical significance.

6.R.2 Pharmacokinetic interactions mediated by CYP3A and CYP2C8

The applicant's explanation about the concomitant use of apalutamide with a CYP3A or CYP2C8 inhibitor and CYP3A or CYP2C8 inducer:

The *In vitro* studies indicated that CYP3A and CYP2C8 contribute to the metabolism of apalutamide and that apalutamide and M3 inhibit CYP3A and CYP2C8 and induce CYP3A [see Sections 4.3.1, 4.5.1, and 4.5.2]. A PBPK model analysis was performed to investigate the effect of multiple doses of apalutamide on the involvement of CYP3A and CYP2C8 in the metabolism of apalutamide. In addition, another PBPK model analysis was performed to investigate effects of concomitant ketoconazole (strong CYP3A inhibitor), gemfibrozil (strong CYP2C8 inhibitor), and rifampicin (strong CYP3A inducer and moderate CYP2C8 inducer) on steady-state PK of apalutamide, M3, and unbound active ingredient.[28)]

Simcyp version 16.1, software widely used for the investigations of pharmacokinetic interactions, was applied to the PBPK model analyses. The first-order model was selected for the absorption of apalutamide and the full PBPK model was selected for the distribution of apalutamide and M3. Based on the results from the foreign phase I study (Study 12) [see Section 6.2.3.1], contributions of CYP3A and CYP2C8 to the metabolism of a single dose of apalutamide were 13% and 58%, respectively. Based on results from the *in vitro* studies [see Sections 4.5.1 and 4.5.2] and from the foreign phase I study (Study 20) [see Section 6.2.3.2], parameters relevant to CYP3A and CYP2C8 inhibition or induction by apalutamide and M3 were identified. Physiological parameters and chemical compound parameters for ketoconazole, gemfibrozil, and rifampicin were selected based on publications (*J Antimicrob Chemother.* 1988;21:633-5, *Clin Pharmacol Ther.* 2005;77:404-14, etc.).

The following observations justify the use of the PBPK model for the investigations of pharmacokinetic interaction of apalutamide and M3 mediated by CYP3A and CYP2C8:

- For the exposure (geometric mean C_{max} and AUC_{24h}) to (a) apalutamide and (b) M3 in subjects receiving oral apalutamide 240 mg QD, the observed values ([a] 7.55 µg/mL and 127 µg·h/mL, [b] 5.30 µg/mL and 119 µg·h/mL) in the foreign phase I study (Study 001) were almost in agreement with the simulated values ([a] 7.00 µg/mL and 117 µg·h/mL, [b]5.68 µg/mL and 135 µg·h/mL) in the above PBPK model analysis. Plasma concentrations of apalutamide and M3 also showed the same tendency.

- For the geometric mean ratios[34)] of C_{max} and AUC_{inf} of apalutamide in its concomitant use with itraconazole to those of apalutamide alone, the observed values (0.78 and 1.01) in the foreign phase I study (Study 12) were almost in agreement with the simulated values (1.01 and 1.14) in the above PBPK model analysis.

- For the geometric mean ratios[35)] of C_{max} and AUC_{inf} of apalutamide in its concomitant use with gemfibrozil to those of apalutamide alone, the observed values (0.79 and 1.68) in the foreign phase

34) The observed and simulated geometric mean ratio of C_{max} of M3 were 0.85 and 0.83, respectively. The observed geometric mean ratio of AUC_{inf} of M3 was 1.12, but the simulated value was not calculated.

35) The observed and simulated geometric mean ratio of C_{max} of M3 were 0.55 and 0.39, respectively. For the geometric mean ratio of AUC_{inf} of M3, the observed value was 0.85, but the simulated value was not calculated.

I study (Study 12) were almost in agreement with the simulated values (1.01 and 1.88) in the above PBPK model analysis.

- For the geometric mean ratios of C_{max} and AUC_{inf} of (a) midazolam and (b) pioglitazone in concomitant use with apalutamide to those of midazolam or pioglitazone alone, the observed values ([a] 0.23 and 0.08, [b] 0.91 and 0.82) in the foreign phase I study (Study 20) were almost in agreement with the simulated values ([a] 0.13 and 0.09, [b] 0.96 and 0.87) in the above PBPK model analysis.

The above PBPK model analyses indicated the following results:

- The contribution of CYP3A and CYP2C8 to the metabolism of (a) a single dose and (b) multiple doses (steady state) of apalutamide were (a) 13% and 58% and (b) 37% and 40%, respectively.

- After multiple doses of apalutamide 240 mg at steady state,[36] the geometric mean ratios of C_{max} and $AUC_{24h,ss}$ of (a) apalutamide, (b) M3, and (c) unbound active ingredient following doses with concomitant ketoconazole (400 mg QD) to those of apalutamide alone were (a) 1.38 and 1.51, (b) 0.76 and 0.75, and (c) 1.23 and 1.28, respectively.

- After multiple doses of apalutamide 240 mg at steady state,[37] the geometric mean ratios of C_{max} and $AUC_{24h,ss}$ of (a) apalutamide, (b) M3, and (c) unbound active ingredient following doses with concomitant gemfibrozil (600 mg BID) to those of apalutamide alone were (a) 1.32 and 1.44, (b) 0.87 and 0.87, and (c) 1.19 and 1.23, respectively.

- After multiple doses of apalutamide 240 mg at steady state,[38] the geometric mean ratios of C_{max} and $AUC_{24h,ss}$ of (a) apalutamide, (b) M3, and (c) unbound active ingredient following apalutamide with concomitant rifampicin (600 mg QD) to those of apalutamide alone were (a) 0.75 and 0.66, (b) 1.10 and 1.10, and (c) 0.85 and 0.81, respectively.

The applicant's explanation about the concomitant use with CYP3A and CYP2C8 inhibitors or CYP3A and CYP2C8 inducers based on the results from the foreign phase I study (Study 12) and simulation results from the above PBPK model analyses:

- Based on the results from the foreign phase I study (Study 12) and the above simulation results for ketoconazole and gemfibrozil, healthcare professionals should be advised that the dose of apalutamide be reduced according to the tolerability of the patient when a strong CYP3A or CYP2C8 inhibitors are concomitantly administered.

- On the other hand, the above simulation results for ketoconazole and gemfibrozil indicate that the geometric mean ratio of $AUC_{24h,ss}$ of unbound active ingredient[28] when apalutamide is administered concomitantly with moderate or mild (a) CYP3A and (b) CYP2C8 inhibitors to that when

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36) Because ketoconazole is mainly metabolized by CYP3A (*Int J Mol Sci.* 2017;18:621), it was evaluated on the assumption without the CYP3A induction of apalutamide.

37) Because gemfibrozil is mainly metabolized by UGT2B7 and CYP2C9 (*Drug Metabol Drug Interact.* 2003;19:161-76, etc.), it was evaluated on the assumption without the CYP3A induction potentially leading to UGT induction and CYP2C9 induction of apalutamide.

38) Rifampicin is metabolized by esterase and CYP3A (*Eur J Pharm Sci.* 2014;56:1-15), but it also induces CYP3A. The CYP3A induction of apalutamide was considered unlikely to affect the metabolism, and thus the evaluation was performed on the assumption without the concerned CYP3A induction.

apalutamide is administered alone are predicted to be not greater than (a) 1.28 and (b) 1.23. Therefore, cautionary advice is not necessary on the concomitant use with moderate or mild CYP3A and CYP2C8 inhibitors.

- Based on the above simulation results for rifampicin, $AUC_{24h,ss}$ of apalutamide is predicted to be decreased by up to 34% when administered concomitantly with a strong CYP3A inducer or moderate CYP2C8 inducer. However, the exposure was not correlated to MFS in Study 003 [see Section 6.2.8.1], and cautionary advice is not necessary on the concomitant use with CYP3A and CYP2C8 inducers.

PMDA's view:
Concomitant CYP3A or CYP2C8 inhibitors were suggested to increase exposure to apalutamide and M3, and the dose of apalutamide may need be reduced for concomitant use with CYP3A or CYP2C8 inhibitors irrespective of their inhibitory strength. Accordingly, concomitant use with CYP3A or CYP2C8 inhibitors should be avoided wherever possible, and if inevitable, the dose reduction of apalutamide should be considered and the patient should be carefully monitored for adverse events.

The applicant's explanation about concomitant use of apalutamide with CYP3A and CYP2C8 inducers is acceptable.

The applicant's current explanation about the justification of the PBPK model used to predict pharmacokinetic interactions of apalutamide mediated by CYP3A and CYP2C8 is acceptable. The applicant should continue collecting information and, if any new finding becomes available, the appropriateness of the PBPK model should be reassessed. A revision of the simulation result owing to a change of the PBPK model, if any, should be communicated to healthcare professionals without delay or any appropriate actions must be taken by the applicant.

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

The applicant submitted evaluation data on the efficacy and safety from a total of 4 studies consisting of 2 Japanese phase I studies, 1 global phase III study, and 1 foreign phase I/II study, as listed in Table 24. In addition, the applicant submitted reference data from a total of 10 studies consisting of 8 foreign phase I studies and 2 foreign phase Ib studies, as listed in Table 24.

Table 24. List of clinical studies for efficacy and safety

Data category	Region	Study	Phase	Study population	Number of enrollments	Dosage regimen	Major endpoints
Evaluation	Japan	21	I	Healthy adults	18	Single oral dose of apalutamide (tablet) 60, 120 or 240 mg	PK
		08	I	Patients with metastatic CRPC	6	Oral apalutamide (soft capsule or tablet) 240 mg QD with ADT	Safety Tolerability PK
	Global	003	III	Patients with non-metastatic CRPC defined by PSA doubling time of ≤10 months	1207 (a) 806 (b) 401	With ADT (a) Oral apalutamide (soft capsule or tablet) 240 mg QD (b) Oral placebo QD	Efficacy Safety
	Foreign	001	I/II	Phase I part Patients with metastatic CRPC Phase II part (a) Cohort 1: Patients with CRPC at high risk for distant metastasis (b) Cohort 2: Treatment-naive patients with metastatic CRPC (c) Cohort 3: Patients with metastatic CRPC who had received prior treatment with abiraterone	Phase I part 30 Phase II part 97 (a) 51 (b) 25 (c) 21	Phase I part Oral apalutamide (soft capsule or tablet) 30, 60, 90, 120, 180, or 240 mg QD or 300, 390 or 480 mg BID with ADT Phase II part Oral apalutamide (soft capsule or tablet) 240 mg QD with ADT	Efficacy Safety Tolerability PK
Reference	Foreign	006	I	Healthy adults	12 (a) 6 (b) 6	(a) Single oral dose of apalutamide (soft capsule) 240 mg and single intravenous dose of ^{14}C-apalutamide 100 μg (b) Single oral dose of apalutamide (soft capsule) 240 mg and ^{14}C-apalutamide (hard capsule)	PK Safety
		07	I	Healthy adults	120 (a) 15 (b) 105	(a) Single oral dose of apalutamide (soft capsule) 240 mg (b) Single oral dose of apalutamide (tablets in 7 different formulations) 240 mg	PK Safety
		11	I	Healthy adults	75 (a) 15 (b) 60	(a) Single oral dose of apalutamide (soft capsule) 240 mg (b) Single oral dose of apalutamide (tablets in 3 different formulations) 240 mg	PK Safety
		12	I	Healthy adults	45 (a) 15 (b) 15 (c) 15	(a) Single oral dose of apalutamide (soft capsule) 240 mg (b) Oral itraconazole 200 mg QD orally from Days 1 to 32; and single oral dose of apalutamide (soft capsule) 240 mg on Day 4 (c) Oral gemfibrozil (unapproved in Japan) QD from Days 1 to 32; and single oral dose of apalutamide (soft capsule) 240 mg on Day 4	PK Safety
		15	I	Healthy adults	56	Single oral crossover dose of apalutamide (tablets containing the drug substance with different particle size distributions) 60 mg	PK Safety
		17	I	Healthy adults	48	Single oral crossover dose of apalutamide (tablets in different batches) 60 mg	PK Safety

		18	I	Patients with normal hepatic function or hepatic impairment	24	Single oral dose of apalutamide (tablet)240 mg	PK Safety
		20	I	Patients with CRPC	23	In 42-day cycles, with ADT, different oral probe drugs QD on Days 1, 8, and 9; and oral apalutamide (tablet) 240 mg QD on Days 15 to 42.	PK Safety
		10	Ib	Patients with metastatic CRPC	57	In cycles, each consisting of 28 days, with ADT, abiraterone, and prednisone (unapproved in Japan), apalutamide (soft capsule or tablet) at 240 mg QD orally starting on Day 8	PK Safety
		19	Ib	Patients with metastatic CRPC or non-metastatic CRPC defined by PSA doubling time of ≤10 months	45	Oral apalutamide (tablet) 240 mg QD with ADT	PK Safety

Individual studies are summarized below. The major adverse events other than deaths observed in the individual clinical studies are presented in Section "7.3 Adverse events observed in clinical studies."

7.1 Evaluation data

7.1.1 Clinical pharmacology

In the following clinical pharmacology studies in healthy adults, no deaths occurred throughout the study treatment or within 56 days after the completion of treatment.

7.1.1.1 Japanese phase I study (CTD 5.3.3.1.1, Study 21, October to December 2016)

7.1.2 Japanese studies

7.1.2.1 Japanese phase I study (CTD 5.3.5.2.2, Study 08, ongoing since July 2014 [data cutoff on [redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and tolerability of apalutamide used with androgen deprivation therapy (ADT) (surgical or medical castration) in patients with metastatic CRPC[39] (target sample size, 6 patients) at 4 study centers in Japan.

Apalutamide (soft capsule or tablet[40]) 240 mg was orally administered QD[41] until the criteria for disease progression or study discontinuation met.

All 6 patients enrolled in this study received apalutamide and were included in the safety analysis.

Dose limiting toxicity (DLT) was evaluated until Day 35, and no DLT was observed.

No deaths occurred during apalutamide treatment or within 30 days after the completion of treatment.

39) The study included patients with CRPC meeting (a) serum testosterone within 4 weeks before inclusion <50 ng/dL; (b) PSA within 2 weeks before inclusion ≥2.0 ng/mL; and (c) 2 consecutive increases in PSA at an interval of ≥1 week.

40) Initially 30 mg soft capsules were used but later switched to 60 mg tablets (protocol, revised version 3 dated [redacted]).

41) A single oral dose of apalutamide 240 mg was administered 7 days before the start of Cycle 1.

7.1.3 Global studies

7.1.3.1 Global phase III study (CTD 5.3.5.1.1, Study 003, ongoing since September 2013 [data cutoff on May 19, 2017])

A double-blind, randomized, placebo-controlled comparative study was conducted in patients with non-metastatic CRPC,[42)] defined by PSA doubling time of ≤10 months[43)] (target sample size, 1200 patients) to compare the efficacy and safety between apalutamide and the placebo both administered in combination with ADT at 332 study centers in 26 countries or regions including Japan.

Apalutamide (soft capsule or tablet[44)]) 240 mg or placebo was orally administered QD until disease progression or a study discontinuation criterion met.

All of the 1207 patients enrolled and randomized in this study (806 in the apalutamide group, 401 in the placebo group) were included in the intention-to-treat (ITT) population and also in the efficacy analysis (Japanese patients, 34 in the apalutamide group and 21 in the placebo group). Of the ITT population, 1201 patients (803 in the apalutamide group, 398 in the placebo group) except for 6 patients (3 in the apalutamide group, 3 in the placebo group) who did not receive the study drug were included in the safety analysis (Japanese patients, 34 in the apalutamide group and 21 in the placebo group).

The primary endpoint in this study was MFS[45)] determined by the blinded independent central review (BICR) based on the Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1. An analysis was performed to verify the superiority of the apalutamide to the placebo in MFS at the timepoint at which the cumulative event number reached 372.

Efficacy results are presented based on from the primary analysis on MFS (data cutoff on May 19, 2017) in Table 25 and Kaplan-Meier curve in Figure 2. The apalutamide group was shown to be superior to the placebo group.

Table 25. Results from main analysis on MFS (BICR assessment, ITT population, data cutoff on May 19, 2017)

	Apalutamide	Placebo
Number of patients	806	401
Number of events (%)	209 (25.9)	210 (52.4)
Median [95% CI] (months)	40.51 [29.70, 40.51]	15.70 [14.55, 18.40]
Hazard ratio [95% CI]*[1]	0.297 [0.244, 0.362]	
P value (two-sided)*[2]	<0.0001	

*[1] Stratified Cox proportional hazard model with stratification factors of PSA doubling time (≤6 months, >6 months), antiresorptive agents (used, not used), and presence of locoregional disease (N0, N1); *[2] Stratified log-rank test with stratification factors of PSA doubling time (≤6 months, >6 months), antiresorptive agents (used, not used), and presence of locoregional disease (N0, N1), significance level (two-sided) 0.05

42) The study included patients with CRPC meeting (a) serum testosterone <50 ng/dL, (b) PSA >2.0 ng/mL, and (c) increases in PSA at intervals of ≥1 week observed 3 times.

43) PSA was measured ≥3 times during ADT. Patients with calculated PSA doubling time of ≤10 months were included.

44) Initially 30-mg soft capsules were used but later switched to 60-mg tablets (the protocol, revision 6 dated [redacted]).

45) Period until the day when distant metastasis is observed in the bone or soft tissue for the first time or the day of death of any cause, whichever occurred earlier.

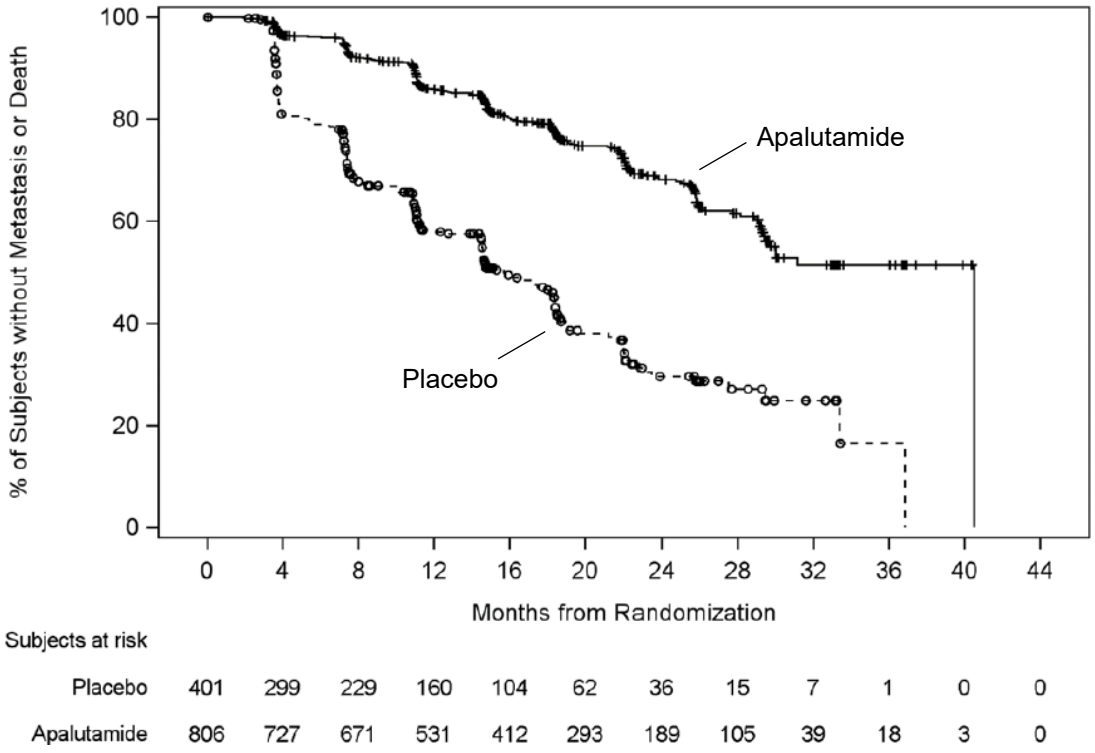

Figure 2. Kaplan-Meier curves as of main analysis on MFS
(BICR assessment, ITT population, data cutoff on May 19, 2017)

Deaths occurred in 10 of 803 patients (1.2%) in the apalutamide group and 1 of 398 patients (0.3%) in the placebo group (Japanese patients, 1 of 21 in the placebo group) during the study treatment or within 28 days after the completion of treatment. The causes of the deaths included disease progression in 3 patients, sepsis in 2 patients, and cardio-respiratory arrest, myocardial infarction, acute myocardial infarction, pneumonia, and cerebral haemorrhage in 1 patient each in the apalutamide group; and cardio-respiratory arrest in 1 patient in the placebo group. A causal relationship to the study drug could not be ruled out for acute myocardial infarction in 1 patient in the apalutamide group (the cause of death of 1 Japanese patient in the placebo group was cardio-respiratory arrest, for which a causal relationship to the study drug was ruled out).

7.1.4 Foreign studies

7.1.4.1 Foreign phase I/II study (CTD 5.3.5.2.1-1 to 5.3.5.2.1-2, Study 001, ongoing since July 2010 [data cutoff on [redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and tolerability of apalutamide administered in combination with ADT in patients with metastatic CRPC[46)47)] (target sample size, not specified) as the phase I part of Study 001 at 1 study center in a foreign country. The phase II part of Study 001 was an open-label, uncontrolled study conducted to investigate the efficacy and safety of apalutamide administered in combination with ADT at 16 study centers in 1 foreign country.

46) "Distant metastasis" was defined as a condition meeting ≥1 of the following criteria: (a) increases in PSA at intervals of ≥1 week observed 3 times and PSA within 2 weeks before inclusion of ≥2.0 ng/mL; (b) progression of soft tissue lesion or appearance of a new soft tissue lesion; and (c) appearance of ≥2 radiographically detectable new bone tissue lesions.

47) The study included patients with CRPC meeting serum testosterone of <50 ng/dL within 4 weeks before inclusion.

Of the phase II part, Cohort 1 included patients with CRPC at high risk for distant metastasis[48] (target sample size, 50 patients), Cohort 2 included treatment-naive patients with metastatic CRPC with no history of prior chemotherapy for metastatic prostate cancer or prior treatment with abiraterone acetate (abiraterone) (target sample size, 20 patients), and Cohort 3 included patients with metastatic CRPC with a history of prior treatment with abiraterone for ≥6 months (target sample size, 10-20 patients).

In the phase I part, apalutamide (soft capsule or tablet[49]) was orally administered at 30, 60, 90, 120, 180, or 240 mg QD or at 300, 390, or 480 mg BID.[50] In the phase II part, apalutamide (soft capsule or tablet[49]) was orally administered at 240 mg QD. Treatment with apalutamide was continued until disease progression or a study discontinuation criterion met.

In the phase I part, all 30 patients enrolled in any cohorts (3 each in the 30 mg, 60 mg, 90 mg, 120 mg, 180 mg, and 240 mg cohorts, 6 in the 300 mg cohort, 3 each in the 390 mg and 480 mg cohorts) received apalutamide and were included in the safety analysis. In the phase II part, all 97 patients enrolled in Cohorts 1 to 3 (51 in Cohort 1, 25 in Cohort 2, 21 in Cohort 3) received apalutamide and were included in the safety analysis. Of these, 90 patients (47 in Cohort 1, 25 in Cohort 2, 18 in Cohort 3) were included in the full analysis set (FAS) and the efficacy analysis, and 4 patients with bone metastasis in Cohort 1, 1 patient without definitive diagnosis of metastatic CRPC, and 2 patients without prior treatment with abiraterone in Cohort 3 were excluded.

DLT was evaluated until Day 35 in the phase I part. Although DLT occurred in 1 of 6 patients in the 300 mg cohort (Grade 3 abdominal pain), the maximum tolerated dose (MTD) was not determined.

The primary endpoint in the phase II part was PSA response rate based on the PSA value at Week 12. A ≥50% decrease from baseline to Week 12 was defined as an event, and the PSA response rate was estimated by the Exact method based on binomial distribution.

Table 26 shows results on PSA response rate at Week 12, the primary endpoint for the efficacy in the phase II part.

Table 26. Results from main analysis on PSA response rate (FAS, data cutoff on December 31, 2014)

	Cohort 1	Cohort 2	Cohort 3
Number of patients	47	25	18
Number of events	42	22	4
PSA response rate [95% CI] (%)	89.4 [76.9, 96.5]	88.0 [68.8, 97.5]	22.2 [6.4, 47.6]

Deaths did not occur during the study treatment or within 28 days after the completion of treatment in the phase I part, and 1 of 97 patients (1.0%) (1 in Cohort 2) died in the phase II part. The cause of death was disease progression, for which a causal relationship to apalutamide was ruled out.

48) "High risk for distant metastasis" was defined as a condition meeting either (a) PSA within 3 months before inclusion ≥8.0 ng/mL or (b) PSA doubling time ≤10 months.
49) Initially 30 mg soft capsules were used but later switched to 60 mg tablets (protocol, revised version 11 dated [redacted]).
50) A single oral dose of apalutamide was administered at 30, 60, 90, 120, 180, 240, 300, 390 or 480 mg 7 days before start of Cycle 1.

7.2 Reference data

7.2.1 Clinical pharmacology

The applicant submitted data from 10 clinical pharmacology studies in healthy adults, patients with normal hepatic function or hepatic impairment, and patients with CRPC listed below [see Section 6.2]. In these studies, deaths occurred in 6 patients (2 of 23 patients in Study 20, 4 of 57 patients in Study 10) during the study treatment or within 30 days after the completion of treatment. The causes of deaths were disease progression in 2 patients, and cerebral haemorrhage, pneumonia, prostate cancer metastatic, and metabolic encephalopathy in 1 patient each. A causal relationship to apalutamide was ruled out for all causes.

7.2.1.1 Foreign phase I study (CTD 5.3.1.1.1, Study 006, March to May 2013)

7.2.1.2 Foreign phase I study (CTD 5.3.1.2.1, Study 07, January to April 2014)

7.2.1.3 Foreign phase I study (CTD 5.3.1.2.2, Study 11, June to November 2014)

7.2.1.4 Foreign phase I study (CTD 5.3.3.4.1, Study 12, September to December 2014)

7.2.1.5 Foreign phase I study (CTD 5.3.1.2.3, Study 15, [redacted] to [redacted])

7.2.1.6 Foreign phase I study (CTD 5.3.1.2.4, Study 17, [redacted] to [redacted])

7.2.1.7 Foreign phase I study (CTD 5.3.3.3.1, Study 18, August 2015 to February 2017)

7.2.1.8 Foreign phase I study (CTD 5.3.3.4.2, Study 20, ongoing since March 2016)

7.2.1.9 Foreign phase Ib study (CTD 5.3.3.4.3-1 to 5.3.3.4.3-2, Study 10, ongoing since July 2014)

7.2.1.10 Foreign phase Ib study (CTD 5.3.4.2.1, Study 19, ongoing since January 2016)

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

In Study 003, 30 mg soft capsules were initially used but later switched to 60 mg tablets for convenience of storage. PMDA asked the applicant to explain any potential impact of the change in dosage form on the efficacy and safety evaluation of apalutamide.

The applicant's explanation:

The change in dosage form is unlikely to affect the efficacy and safety evaluation of apalutamide based on the results from a foreign phase I study (Study 11) [see Section 6.1.2.2] and the following reasons:

- The efficacy was investigated in each patient subgroup sorted by dosage form used in Study 003. Table 27 shows results of MFS as of the main analysis (data cutoff on May 19, 2017), indicating no clear differences among the subgroups.

Table 27. Efficacy by dosage form (Study 003, BICR assessment, data cutoff on May 19, 2017)

Dosage form	Treatment	Number of patients	MFS	
			Median [95% CI] (months)	Hazard ratio* [95% CI]
Tablet	Apalutamide	292	19.55 [-, -]	0.355
	Placebo	136	18.50 [11.53, -]	[0.238, 0.532]
Soft capsule and tablet	Apalutamide	411	40.51 [-, -]	0.323
	Placebo	157	22.01 [18.40, 23.06]	[0.241, 0.433]
Soft capsule	Apalutamide	100	15.93 [11.10, 22.11]	0.334
	Placebo	105	6.44 [3.78, 7.36]	[0.232, 0.481]

-, Estimation is not possible; * Non-stratified Cox proportional hazard model

- The safety was investigated in each patient subgroup sorted by dosage form used in Study 003. Table 28 summarizes the safety results, presenting no clear differences among the subgroups.

Table 28. Summary of safety (Study 003)

	Number of patients (%)		
	Patients receiving tablets only	Patients receiving both soft capsules and tablets	Patients receiving soft capsules only
	Apalutamide n = 292	Apalutamide n = 411	Apalutamide n = 100
All adverse events	276 (94.5)	401 (97.6)	98 (98.0)
Grade ≥3 adverse events	121 (41.4)	196 (47.7)	49 (49.0)
Adverse events resulting in death	4 (1.4)	2 (0.5)	4 (4.0)
Serious adverse events	55 (18.8)	118 (28.7)	31 (31.0)
Adverse events leading to treatment discontinuation	25 (8.6)	20 (4.9)	40 (40.0)
Adverse events leading to treatment interruption	82 (28.1)	123 (29.9)	32 (32.0)
Adverse events leading to dose reduction	30 (10.3)	31 (7.5)	16 (16.0)

PMDA's view:

The above applicant's explanation is acceptable. The review focused on the results of the global phase III study (Study 003), which was conducted to investigate the efficacy and safety of patients with non-metastatic CRPC defined by PSA doubling time of ≤10 months, recognizing as pivotal data submitted for the evaluation of the efficacy and safety of apalutamide. In addition, the efficacy in Japanese patients was investigated from a viewpoint of consistency between the entire population and Japanese population in Study 003 in accordance with "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), etc.

7.R.2 Efficacy

Based on the following review, PMDA has concluded that apalutamide is shown to be effective in treating patients with non-metastatic CRPC defined by PSA doubling time of ≤10 months.

7.R.2.1 Use of control group

The applicant's explanation about the use of the placebo as the control in Study 003:

When Study 003 was planned, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Prostate Cancer (NCCN guideline) (v.3. 2012) indicated clinical studies, observation, and secondary endocrine therapy as therapeutic options, but did not mention any recommended standard therapy. In this study, therefore, the placebo was used as the control.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints

The applicant's explanation about justification for selecting MFS as the primary endpoint in Study 003:
For the following reasons, MFS defined as the primary endpoint in Study 003 was assessed based on events including (a) bone or soft tissue distant metastasis or (b) death:

- In patients with non-metastatic CRPC, a high-risk factor for death is distant metastasis rather than locoregional lesion or disease progression of regional lymph node (*BJU Int.* 2012;109:32-9, etc.).

- In treatment of prostate cancer, if the progression of local lesions or regional lymph node occurs during systemic therapy (endocrine therapy and chemotherapy), radiation therapy and surgical intervention are performed in addition to the ongoing systemic therapy.

In patients with non-metastatic CRPC who have PSA doubling time of ≤10 months, the extension of MFS lead to the suppression of bone-related events associated with bone metastasis or ureteral obstruction associated with pelvic tissue metastasis, thereby facilitating the maintenance of physical functions and QOL of the patient, and thus is of a clinical significance. Therefore MFS is the appropriate primary endpoint.

PMDA's view:
Because the treatment of non-metastatic CRPC is aimed to extend the survival, and overall survival (OS) should be the appropriate primary endpoint of Study 003. However, the applicant's explanation that the extension of MFS in target patients in Study 003 has a certain clinical significance is understandable. Therefore, the efficacy of apalutamide may be evaluated based on results on MFS, the primary endpoint selected in Study 003, after the confirmation of the results of OS and progression free survival (PFS) in which the progression of local lesions and regional lymph node are counted as events.

7.R.2.3 Efficacy evaluation results

The superiority of apalutamide to the placebo was demonstrated in Study 003 in MFS determined by BICR, the primary endpoint [see Section 7.1.2.1].

When a statistically significant difference was observed in MFS between apalutamide and the placebo, a hypothesis test was to be performed on time to metastasis, PFS, time to symptomatic progression, OS, and time to initiation of cytotoxic chemotherapy in this order hierarchically. For the time to symptomatic progression, 1 interim analysis was scheduled. When a statistically significant difference was observed in the interim analysis, 1 interim analysis was to be performed for the OS and time to initiation of cytotoxic chemotherapy, otherwise 2 interim analyses. The purposes of the interim analyses were to evaluate the efficacy and to re-specify the number of events required. To adjustment of the type I error rate, the O'Brien-Fleming type alpha spending function based on the Lan-DeMets method and analysis method proposed by Wassmer (*Biom J.* 2006;48:714-29) were applied.

The hazard ratio [95% CI] of time to metastasis in the apalutamide group to that in the placebo group was 0.279 [0.227, 0.342] (stratified log-rank test, *P* value [two-sided] <0.0001, significance level [two-sided] of 0.05), showing a statistically significant difference, and thus the test was also performed on PFS. Results from the main analysis on PFS (data cutoff on May 19, 2017) and Kaplan-Meier curve are shown in Table 29 and Figure 3, respectively.

Table 29. Results from main analysis on PFS (BICR assessment, ITT population, data cutoff on May 19, 2017)

	Apalutamide	Placebo
Number of patients	806	401
Number of events (%)	220 (27.3)	219 (54.6)
Median [95% CI] (months)	40.51 [29.40, 40.51]	14.65 [11.27, 17.97]
Hazard ratio [95% CI]*[1]	0.300 [0.247, 0.364]	
P value (two-sided)*[2]	<0.0001	

*[1] Stratified Cox proportional hazard model with stratification factors of PSA doubling time (≤6 months, >6 months), use of antiresorptive agents (used, not used), and presence of locoregional disease (N0, N1); *[2] Stratified log-rank test with stratification factors of PSA doubling time (≤6 months, >6 months), use of antiresorptive agents (used, not used), and presence of locoregional disease (N0, N1), significance level (two-sided) 0.05

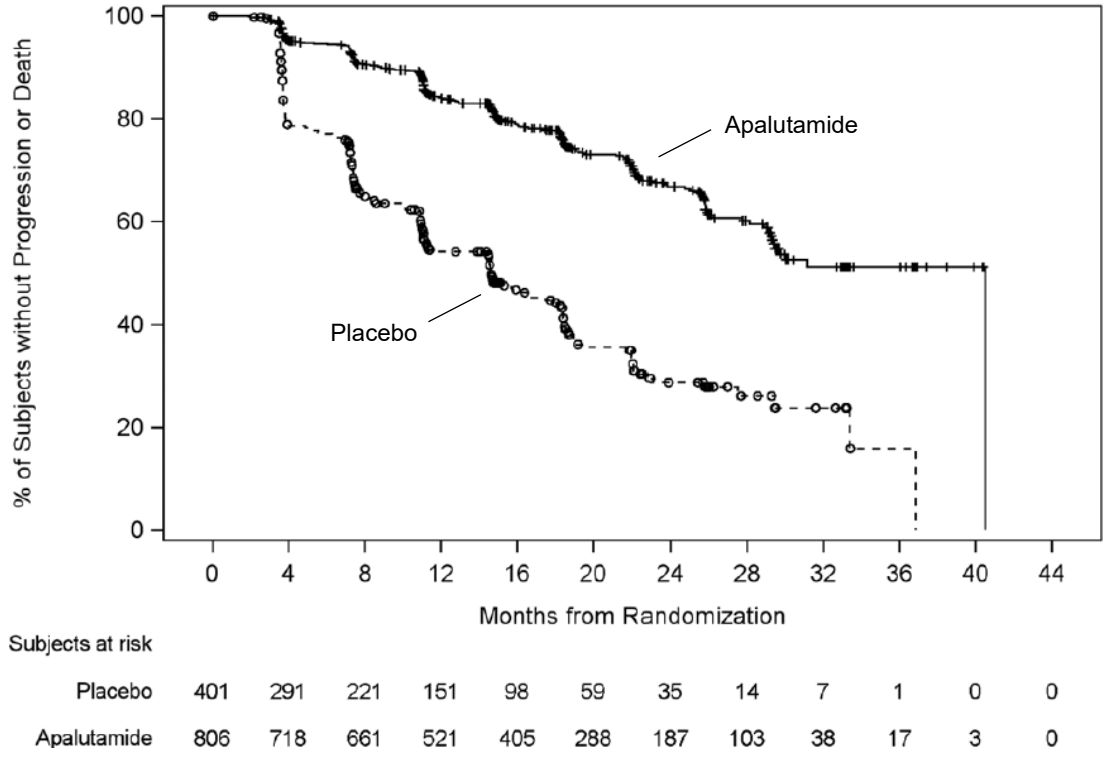

Figure 3. Kaplan-Meier curves as of main analysis on PFS (BICR assessment, ITT population, data cutoff on May 19, 2017)

Furthermore, the interim analysis on the time to symptomatic progression showed that the hazard ratio [95% CI] of time to metastasis in the apalutamide group to that in the placebo group was 0.447 [0.315, 0.634] (stratified log-rank test, *P* value [two-sided] = 0.00000356, significance level [two-sided] of 0.00008), showing a statistically significant difference, and thus the test was also performed on the OS. Results from the interim analysis on OS (data cutoff on May 19, 2017) and Kaplan-Meier curve are shown in Table 30 and Figure 4, respectively.

Table 30. Results from interim analysis on OS (ITT population, data cutoff on May 19, 2017)

	Apalutamide	Placebo
Number of patients	806	401
Number of events (%)	62 (7.7)	42 (10.5)
Median [95% CI] (months)	- [-, -]	39.03 [39.03, -]
Hazard ratio [95% CI]*[1]	0.700 [0.472, 1.038]	
P value (two-sided)*[2]	0.0742	

-, Estimation is not possible; *[1] Stratified Cox proportional hazard model with stratification factors of PSA doubling time (≤6 months, >6 months), use of antiresorptive agents (used, not used), and presence of locoregional disease (N0, N1); *[2] Stratified log-rank test with stratification factors of PSA doubling time (≤6 months, >6 months), use of antiresorptive agents (used, not used), and presence of locoregional disease (N0, N1), significance level (two-sided) 0.000012

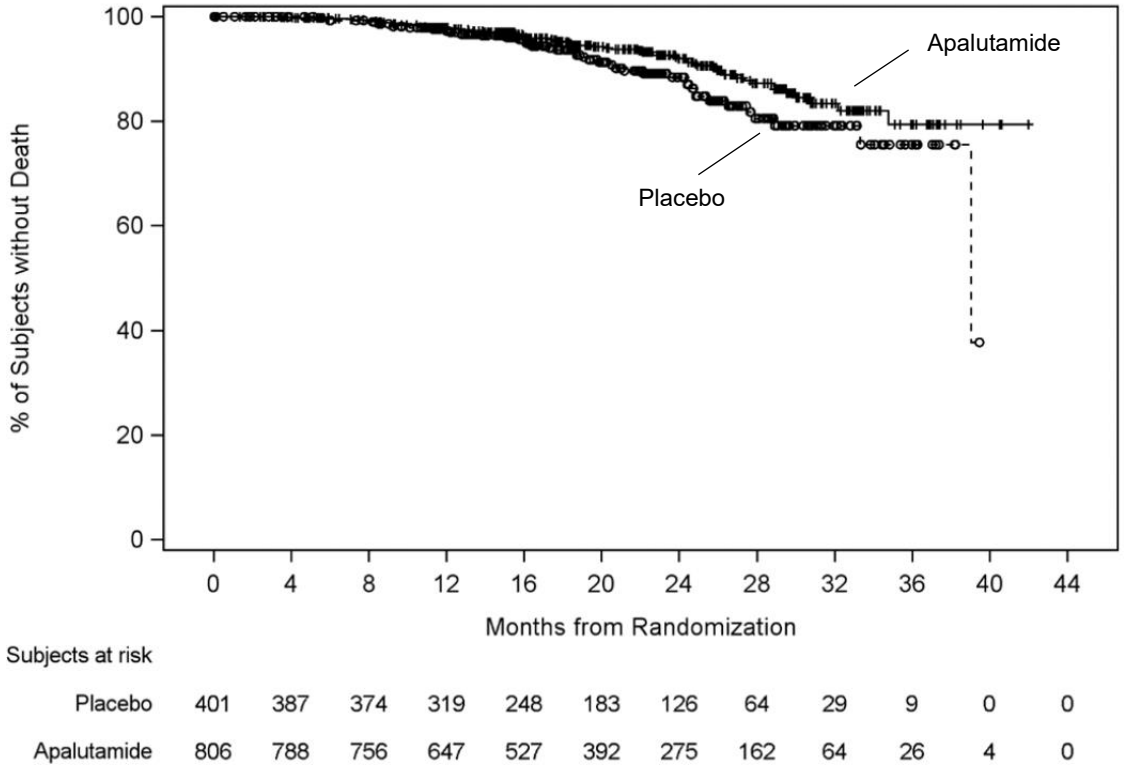

Figure 4. Kaplan-Meier curves as of interim analysis on OS (ITT population, data cutoff on May 19, 2017)

The MFS analysis results in Japanese patients in Study 003 and Kaplan-Meier curves are shown in Table 31 and Figure 5, respectively.

Table 31. MFS analysis results MFS in Japanese patients (BICR assessment, ITT population, data cutoff on May 19, 2017)

	Apalutamide	Placebo
Number of patients	34	21
Number of events (%)	5 (14.7)	8 (38.1)
Median MFS [95% CI] (months)	- [10.97, -]	18.23 [11.04, 18.50]
Hazard ratio [95% CI]*[1]	0.565 [0.181, 1.766]	
P value (two-sided)*[2]	0.3207	

-, Estimation is not possible; *[1] Non-stratified Cox proportional hazard model; *[2] Non-stratified log-rank test

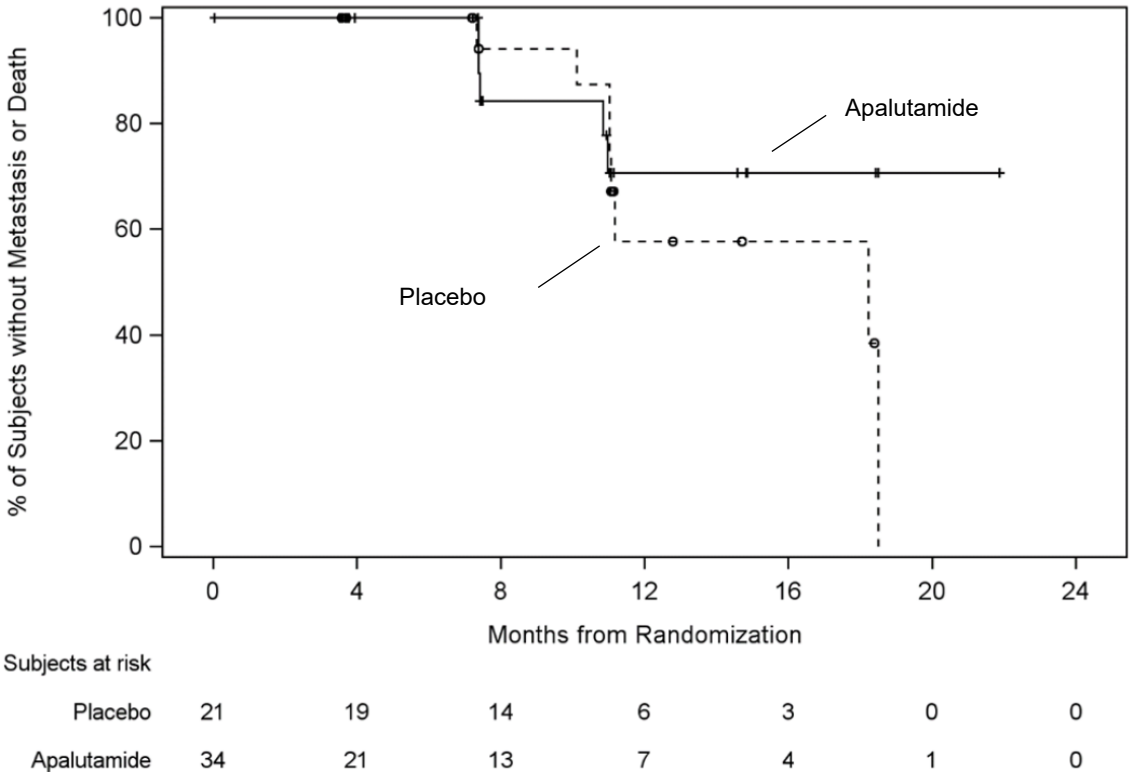

Figure 5. Kaplan-Meier curves in Japanese patients as of analysis on MFS (BICR assessment, ITT population, data cutoff on May 19, 2017)

PMDA's view:

Apalutamide is shown to be effective in the target patients in Study 003 for the following reasons:

- As mentioned above, the applicant's explanation is understandable in that the extension of MFS, the primary endpoint, has clinical significance to a certain degree. Furthermore, apalutamide was shown to be superior to the placebo and have a clinically significant effect.

- Apalutamide was shown to be superior to the placebo and have a clinically significant effect in PFS, the secondary endpoint.

- OS, the secondary endpoint, showed no trend to be shortened in the apalutamide group as compared with the placebo group.

- The small numbers of Japanese patients and events in this population in Study 003 imposed a limitation on the evaluation of the efficacy of apalutamide in Japanese patients based on the results on MFS in the Japanese population. However, no clearly different trends were observed between the above results of the Japanese population and the entire population.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events observed in clinical studies"]

PMDA's conclusions:

Based on the following review, adverse events requiring particular attention during treatment with apalutamide in patients with non-metastatic CRPC are severe skin disorder, cardiac disorder, seizure, and fracture. Caution should be exercised against these adverse events in the use of apalutamide.

At the same time, although caution should be used against the above-mentioned adverse events during treatment, apalutamide is tolerated by patients under appropriate follow-up by physicians with adequate knowledge and experience in cancer drug therapy, through monitoring and controlling of the adverse events, dose reduction, interruption or discontinuation of apalutamide, etc.

7.R.3.1 Safety profile of apalutamide

The applicant's explanation about the safety profile of apalutamide, based on the safety data from Study 003:

Table 32 outlines safety in Study 003.

Table 32. Outline of safety (Study 003)

	Number of patients (%)	
	Apalutamide n = 803	Placebo n = 398
All adverse events	775 (96.5)	371 (93.2)
Grade ≥3 adverse events	366 (45.6)	137 (34.4)
Adverse events resulting in death	10 (1.2)	1 (0.3)
Serious adverse events	204 (25.4)	93 (23.4)
Adverse events leading to treatment discontinuation	85 (10.6)	28 (7.0)
Adverse events leading to treatment interruption	237 (29.5)	71 (17.8)
Adverse events leading to dose reduction	77 (9.6)	7 (1.8)

All adverse events with ≥5% higher incidence in the apalutamide group than in the placebo group in Study 003 were fatigue (244 patients [30.4%] in the apalutamide group; 84 patients [21.1%] in the placebo group), hypertension (199 [24.8%], 79 [19.8%]), diarrhoea (163 [20.3%], 60 [15.1%]), weight decreased (129 [16.1%], 25 [6.3%]), arthralgia (128 [15.9%], 30 [7.5%]), fall (125 [15.6%], 36 [9.0%]), hot flush (113 [14.1%], 34 [8.5%]), rash (87 [10.8%], 13 [3.3%]), and dysgeusia (57 [7.1%], 6 [1.5%]). The Grade ≥3 adverse event with ≥2% higher incidence in the apalutamide group than in the placebo group was hypertension (115 [14.3%], 47 [11.8%]). There were no adverse events resulting in death, serious adverse events, adverse events leading to treatment discontinuation, treatment interruption, or dose reduction showed the incidence of ≥2% higher in the apalutamide group than in the placebo group.

PMDA's view:

In Study 003, some adverse events occurred more frequently in the apalutamide group than in the placebo group, but most events were Grade ≤2 and controlled by the interruption or dose reduction. Apalutamide is thus tolerated by patients under appropriate follow-up by physicians with adequate knowledge and experience in cancer drug therapy, through monitoring and controlling of the adverse events, interruption of apalutamide, etc.

7.R.3.2 Difference in safety between Japanese and non-Japanese patients

The applicant's explanation about difference in safety between Japanese and non-Japanese patients:
Table 33 outlines the safety in Japanese and non-Japanese patients in the apalutamide group in Study 003.

Table 33. Outline of safety in Japanese and non-Japanese patients (Study 003)

	Number of patients (%)	
	Japanese patients n = 34	Non-Japanese patients n = 769
All adverse events	32 (94.1)	734 (96.6)
Grade ≥3 adverse events	15 (44.1)	351 (45.6)
Adverse events resulting in death	0	10 (1.3)
Serious adverse events	8 (23.5)	196 (25.5)
Adverse events leading to treatment discontinuation	7 (20.6)	78 (10.1)
Adverse events leading to treatment interruption	17 (50.0)	220 (28.6)
Adverse events leading to dose reduction	4 (11.8)	73 (9.5)

All-Grade adverse events with ≥10% higher incidence in Japanese patients than in non-Japanese patients in Study 003 were rash maculo-papular (8 Japanese patients [23.5%], 35 non-Japanese patients [4.6%]), rash generalized (6 [17.6%], 13 [1.7%]), and dysgeusia (6 [17.6%], 51 [6.6%]). The Grade ≥3 adverse event reported by ≥2 Japanese patients was rash maculo-papular (2 [5.9%], 13 [1.7%]). Adverse events leading to treatment interruption reported by ≥2 Japanese patients were rash maculo-papular (5 [14.7%], 11 [1.4%]), rash generalized (4 [11.8%], 5 [0.7%]), and decreased appetite (2 [5.9%], 5 [0.7%]). There were no adverse events resulting in death, serious adverse events, and adverse events leading to treatment discontinuation or dose reduction that reported by ≥2 Japanese patients.

PMDA's view:
The small number of Japanese patients who received apalutamide imposes a limitation on the comparison of safety profiles between Japanese and non-Japanese patients. Although the incidences of rash maculo-papular, rash generalized, and dysgeusia were higher in Japanese patients than in non-Japanese patients, apalutamide is tolerable even in Japanese patients in light of the following observations:

- In Japanese patients, no serious adverse events occurred, and adverse events leading to treatment discontinuation or dose reduction were rash maculo-papular and rash generalized, both of which occurred only in 1 patient each.

- Apalutamide is administered by physicians with adequate knowledge and experience in cancer drug therapy.

In the following subsections, PMDA reviews safety with the focus on the adverse events with a higher incidence in the apalutamide group than in the placebo group mainly observed in Study 003.

7.R.3.3 Skin disorders

The applicant's explanation about skin disorders associated with apalutamide:

Skin disorder-related adverse events were tabulated based on a Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA queries (SMQ) of "severe cutaneous adverse reactions" and MedDRA high level group terms (HLGT) of "rash and skin eruption NEC."

Table 34 shows the incidences of skin disorders in Study 003.

Table 34. Incidences of skin disorders (Study 003)

PT (MedDRA ver. 19.1)	Number of patients (%)			
	Apalutamide n = 803		Placebo n = 398	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Skin disorder	191 (23.8)	42 (5.2)	22 (5.5)	1 (0.3)
Rash	87 (10.8)	10 (1.2)	13 (3.3)	1 (0.3)
Rash maculo-papular	43 (5.4)	15 (1.9)	2 (0.5)	0
Rash generalised	19 (2.4)	7 (0.9)	1 (0.3)	0
Urticaria	16 (2.0)	2 (0.2)	1 (0.3)	0
Rash pruritic	11 (1.4)	1 (0.1)	2 (0.5)	0
Rash macular	10 (1.2)	5 (0.6)	1 (0.3)	0
Conjunctivitis	7 (0.9)	0	0	0
Rash papular	4 (0.5)	1 (0.1)	1 (0.3)	0
Erythema multiforme	4 (0.5)	2 (0.2)	0	0
Skin exfoliation	4 (0.5)	0	0	0
Stomatitis	3 (0.4)	0	1 (0.3)	0
Genital rash	3 (0.4)	0	0	0
Rash erythematous	3 (0.4)	0	0	0
Drug eruption	2 (0.2)	1 (0.1)	1 (0.3)	0
Mouth ulceration	2 (0.2)	1 (0.1)	1 (0.3)	0
Rash pustular	2 (0.2)	0	0	0
Blister	1 (0.1)	0	1 (0.3)	0
Pemphigoid	1 (0.1)	1 (0.1)	1 (0.3)	0
Papule	1 (0.1)	0	0	0
Skin erosion	1 (0.1)	0	0	0
Rash vesicular	0	0	1 (0.3)	0

In Study 003, there was no skin disorder that resulted in deaths. Serious skin disorders occurred in 2 of 803 patients (0.2%, erythema multiforme and mouth ulceration in 1 each) in the apalutamide group and did not occur in the placebo group. A causal relationship to apalutamide could not be ruled out for the event in 1 of 803 patients (0.1%, erythema multiforme in 1). Skin disorders leading to treatment discontinuation occurred in 19 of 803 patients (2.4%; rash maculo-papular in 6, rash generalized in 4, rash in 3, erythema multiforme in 2, and drug eruption, mouth ulceration, pemphigoid, and rash macular in 1 each) in the apalutamide group and did not occur in the placebo group. Skin disorders leading to treatment interruption occurred in 55 of 803 patients (6.8%; rash in 19, rash maculo-papular in 16, rash generalized in 9, rash macular in 5, urticaria and rash pruritic in 3 each, erythema multiforme in 2, pemphigoid and rash papular in 1 each [some patients had >1 adverse event]) in the apalutamide group and 5 of 398 patients (1.3%; rash in 2, and rash maculo-papular, urticaria, and rash vesicular in 1 each) in the placebo group.

The median time (range) to the first onset of skin disorder in the apalutamide group in Study 003 was 82.0 days (1-994 days).

Table 35 shows details of patients who received apalutamide and experienced serious skin disorder in all the clinical studies included in the submitted data for this application.

Table 35. List of patients who experienced serious skin disorders

Study	Age	PT (MedDRA ver. 19.1)	Grade	Day of onset (Day)	Duration (Day)	Apalutamide treatment	Causal relationship to apalutamide	Outcome
Study 003	7[redacted]	Erythema multiforme	3	41	17	Discontinued	Related	Resolved
	6[redacted]	Mouth ulceration	3	401	17	Discontinued	Not related	Resolved

PMDA's view:

Because skin disorders associated with apalutamide are mainly rash or skin eruption, and most events are Grade ≤2, these events is controllable with appropriate measures. However, serious skin disorders for which a causal relationship to apalutamide could not be ruled out such as erythema multiforme occurred, and caution should be used against severe skin disorders during apalutamide treatment. Therefore, the occurrence of skin disorders in the clinical studies should be appropriately communicated to healthcare professionals via the package insert.

7.R.3.4 Cardiac disorders

The applicant's explanation about cardiac disorders associated with apalutamide:

Cardiac disorder-related adverse events related to were tabulated according to MedDRA SMQ of "myocardial infarction," "supraventricular tachyarrhythmias," "ventricular tachyarrhythmias," "arrhythmia related investigations, signs and symptoms," "cardiac failure," and "other ischaemic heart disease."

Table 36 shows the incidences of cardiac disorders in Study 003.

Table 36. Incidences of cardiac disorders with an incidence of ≥1% in any group (Study 003)

PT (MedDRA ver. 19.1)	Number of patients (%)			
	Apalutamide n = 803		Placebo n = 398	
	All Grades	Grades ≥3	All Grades	Grades ≥3
Cardiac disorders	179 (22.3)	44 (5.5)	65 (16.3)	16 (4.0)
Oedema peripheral	69 (8.6)	0	29 (7.3)	0
Atrial fibrillation	21 (2.6)	9 (1.1)	7 (1.8)	3 (0.8)
Syncope	17 (2.1)	17 (2.1)	4 (1.0)	4 (1.0)
Chest pain	14 (1.7)	0	5 (1.3)	0
Palpitations	14 (1.7)	0	0	0
Angina pectoris	13 (1.6)	0	2 (0.5)	0
Peripheral swelling	12 (1.5)	0	4 (1.0)	0
Tachycardia	9 (1.1)	1 (0.1)	1 (0.3)	0
Cardiac failure congestive	8 (1.0)	1 (0.1)	1 (0.3)	1 (0.3)
Bradycardia	6 (0.7)	1 (0.1)	6 (1.5)	1 (0.3)

In Study 003, cardiac disorders leading to deaths occurred in 3 of 803 patients (0.4%; cardio-respiratory arrest, acute myocardial infarction, and myocardial infarction in 1 each) in the apalutamide group and 1 of 398 patients (0.3%, cardio-respiratory arrest in 1) in the placebo group. A causal relationship to apalutamide could not be ruled out for the event in 1 of 803 patients (0.1%, acute myocardial infarction in 1) in the apalutamide group. Serious cardiac disorders occurred in 37 of 803 patients (4.6%; atrial fibrillation in 7; syncope in 5; cardiac failure congestive and myocardial infarction in 4 each; coronary artery disease and cardiac failure in 3 each; acute myocardial infarction and cardiomyopathy in 2 each; acute coronary syndrome, angina pectoris, cardio-respiratory arrest, myocardial ischaemia, angina unstable, atrial flutter, bradycardia, chest pain, coronary artery occlusion, oedema peripheral, pulmonary oedema, right ventricular dysfunction, sinus node dysfunction, supraventricular tachycardia, and ventricular tachycardia in 1 each [some patients had >1 adverse event]) in the apalutamide group, and 12 of 398 patients (3.0%; atrial fibrillation in 2; syncope, cardiac failure congestive, coronary artery disease, acute coronary syndrome, angina pectoris, cardio-respiratory arrest, myocardial ischaemia, cardiac failure acute, acute myocardial infarction, and stress cardiomyopathy in 1 each) in the placebo group. A causal relationship to apalutamide could not be ruled out for the events in 6 of 803 patients (0.7%; atrial fibrillation in 2; atrial flutter, cardiac failure, myocardial infarction, acute myocardial infarction, and cardiac failure congestive in 1 each [some patients had >1 adverse event]) in the apalutamide group. Cardiac disorders leading to treatment discontinuation occurred in 8 of 803 patients (1.0%; angina pectoris in 2; cardio-respiratory arrest, atrial fibrillation, cardiac failure congestive, myocardial infarction, acute myocardial infarction, oedema peripheral, and right ventricular dysfunction in 1 each [some patients had >1 adverse event]) in the apalutamide group and 3 of 398 patients (0.8%; cardio-respiratory arrest, acute coronary syndrome, and stress cardiomyopathy in 1 each) in the placebo group. Cardiac disorders leading to treatment interruption occurred in 17 of 803 patients (2.1%; atrial fibrillation in 6; angina pectoris and syncope in 2 each; atrial flutter, bradycardia, cardiac failure, cardiomegaly, coronary artery disease, myocardial infarction, oedema peripheral, palpitations, supraventricular tachycardia, and ventricular tachycardia in 1 each [some patients had >1 adverse event]) in the apalutamide group and 6 of 398 patients (1.5%; atrial fibrillation in 2; angina pectoris, cardiac failure acute, acute myocardial infarction, and cardiac failure congestive in 1 each) in the placebo group.

The median time (range) to the first onset of cardiac disorder in the apalutamide group in Study 003 was 201.0 days (1-970 days).

Table 37 shows details of patients who received apalutamide and experienced a serious cardiac disorder (causally related to apalutamide) in Study 003.

Table 37. List of patients who experienced serious cardiac disorder (causally related to apalutamide) (Study 003)

Age	PT (MedDRA ver. 19.1)	Grade	Day of onset (Day)	Duration (Day)	Apalutamide treatment	Outcome
7[redacted]	Atrial fibrillation	3	239	4	Interrupted	Resolved
	Atrial flutter	3	239	4	Interrupted	Resolved
8[redacted]	Myocardial infarction	4	200	9	Continued	Resolved
8[redacted]	Cardiac failure	3	159	7	Continued	Resolved
8[redacted]	Acute myocardial infarction	5	102	-*	Discontinued	Died
6[redacted]	Atrial fibrillation	3	327	39	Discontinued	Resolved
8[redacted]	Cardiac failure congestive	2	38	16	Discontinued	Resolved

* Death occurred on the day of onset.

PMDA's view:

Serious cardiac disorders for which a causal relationship to apalutamide could not be ruled out such as atrial fibrillation occurred in Study 003, and caution should be used against cardiac disorders during apalutamide treatment. Healthcare professionals should be properly advised via the package insert to take appropriate actions, i.e., the monitoring of symptoms associated with cardiac disorders such as atrial fibrillation and cardiac failure and cardiac function examination as necessary. The occurrence of cardiac disorders and actions taken against the events in the clinical studies should be communicated to healthcare professionals appropriately via the package insert.

7.R.3.5 Seizures

The applicant's explanation about seizures associated with apalutamide:

Seizure-related adverse events were tabulated according to MedDRA SMQ of "convulsions."

Table 38 shows the incidences of seizure in Study 003.

Table 38. Incidences of seizure (Study 003)

PT (MedDRA ver. 19.1)	Number of patients (%)			
	Apalutamide n = 803		Placebo n = 398	
	All Grades	Grades ≥3	All Grades	Grades ≥3
Seizure	2 (0.2)	0	0	0

In Study 003, there was no seizure resulting in deaths or leading to treatment interruption. Serious seizures occurred in 2 of 803 patients (0.2%; seizure in 2) in the apalutamide group and none occurred in the placebo group. A causal relationship to apalutamide could not be ruled out for the event in 1 of 803 patients (0.1%; 1 patient) in the apalutamide group. Seizures leading to treatment discontinuation occurred in 2 of 803 patients (0.2%, seizures in 2) in the apalutamide group and none occurred in the placebo group.

The median time (range) to the first onset of seizure in the apalutamide group in Study 003 was 414.5 days (354-475 days).

Table 39 shows details of patients who received apalutamide and experienced a seizure in the clinical study and in the post-marketing setting in a foreign country.

Table 39. List of patients who experienced seizure

Study	Age	Sex	PT (MedDRA ver. 19.1)	Grade	Seriousness	Day of onset (Day)	Duration (Day)	Apalutamide treatment	Causal relationship to apalutamide	Outcome
Study 003	7	Male	Seizure	1	Serious	475	8	Discontinued	Related	Resolved
	8	Male	Seizure	2	Serious	354	1	Discontinued	Not related	Resolved
Post-marketing use in foreign countries	6	Male	Seizure	Unknown	Serious	Unknown	Unknown	Unknown	Related	Unknown

PMDA asked the applicant to explain the mechanism of onset and the risk factors of seizure.

The applicant's response:
Seizure may be caused by the off-target inhibition of apalutamide and its metabolite, M3 (*N*-desmethyl apalutamide), against GABA receptors. However, the mechanism remains unclear and the definite risk factors have not been identified at present.

PMDA's view:
Caution should be used against seizures during apalutamide treatment for the following reasons: Seizures were reported from the clinical studies and the post-marketing setting outside Japan, and serious seizures for which a causal relationship to apalutamide could not be ruled out occurred. Seizure is likely to occur in light of the action mechanism of apalutamide, and therefore caution should be used against the event. Healthcare professionals should be appropriately informed via the package insert of the occurrence of seizure in the clinical studies and the fact that patients with a history of or predisposition to seizure were excluded from Study 003 according to the exclusion criteria.

7.R.3.6 Fractures

The applicant's explanation about fractures during apalutamide treatment in light of reported fractures in patients with prostate cancer due to osteoporosis associated with enhanced bone turnover and decreased bone density by ADT (*Osteoporos Int.* 2005;16:707-11):

Fracture-related adverse events were tabulated according to MedDRA SMQ of "accidents and injuries" and "osteoporosis/osteopenia."

Table 40 shows the incidences of fractures in Study 003.

Table 40. Incidences of fractures reported by ≥5 patients in any group (Study 003)

PT (MedDRA ver. 19.1)	Number of patients (%)			
	Apalutamide n = 803		Placebo n = 398	
	All Grades	Grades ≥3	All Grades	Grades ≥3
Fracture	94 (11.7)	22 (2.7)	26 (6.5)	3 (0.8)
Rib fracture	29 (3.6)	2 (0.2)	14 (3.5)	0
Lumbar vertebral fracture	9 (1.1)	1 (0.1)	0	0
Spinal compression fracture	8 (1.0)	1 (0.1)	1 (0.3)	0
Spinal fracture	6 (0.7)	3 (0.4)	1 (0.3)	0
Foot fracture	5 (0.6)	2 (0.2)	0	0
Hip fracture	5 (0.6)	2 (0.2)	0	0
Humerus fracture	5 (0.6)	0	0	0

In Study 003, there was no fracture leading to deaths. Serious fractures occurred in 27 of 803 patients (3.4%, femur fracture, lumbar vertebral fracture, and spinal fracture in 3 each; acetabulum fracture, foot fracture, hip fracture, humerus fracture, pubis fracture, and rib fracture in 2 each; ankle fracture, compression fracture, facial bones fracture, lower limb fracture, radius fracture, thoracic vertebral fracture, and upper limb fracture in 1 each [some patients had >1 adverse event]) in the apalutamide group, and 3 of 398 patients (0.8%; femur fracture, avulsion fracture, and femoral neck fracture in 1 each) in the placebo group. A causal relationship to apalutamide could not be ruled out for the events in 4 of 803 patients (0.5%; lumbar vertebral fracture, humerus fracture, rib fracture, and upper limb fracture in 1 each) in the apalutamide group. Fracture led to treatment discontinuation in 1 of 803 patients (0.1%, rib fracture in 1) in the apalutamide group, but a causal relationship to apalutamide was ruled out for the event. No fracture leading to treatment discontinuation occurred in the placebo group. Fracture led to treatment interruption in 6 of 803 patients (0.7%; lumbar vertebral fracture in 2; compression fracture, femur fracture, fibula fracture, thoracic vertebral fracture and upper limb fracture in 1 each [some patients had >1 adverse event]) in the apalutamide group and 3 of 398 patients (0.8%; rib fracture in 2; femoral neck fracture in 1) in the placebo group. A causal relationship to apalutamide could not be ruled out for the event in 1 of 803 patients (0.5%; upper limb fracture in 1) in the apalutamide group.

The median time (range) to the first onset of fracture in the apalutamide group in Study 003 was 313.5 days (20-953 days).

Table 41 show details of patients who received apalutamide and experienced serious fracture (causally related to apalutamide) in all the clinical studies included in the submitted data for this application.

Table 41. List of patients who experienced serious fracture (causally related to apalutamide)

Study	Age	PT (MedDRA ver. 19.1)	Grade	Day of onset (Day)	Duration (Day)	Apalutamide treatment	Outcome
Study 003	7[redacted]	Lumbar vertebral fracture	1	415	Continued	Unknown	Not resolved
	8[redacted]	Upper limb fracture	3	696	20	Interrupted	Resolved
	8[redacted]	Rib fracture	2	920	3	None	Resolved
	6[redacted]	Humerus fracture	2	602	1	None	Resolved

PMDA's view:
Regarding patients who experienced fracture for which a causal relationship to apalutamide could not be ruled out, information about the course of event is insufficient; most of these patients were the elderly; and many of reported events were fall-related [see Section 7.R.3.1]. These observations leave the possibility that fractures were attributable to other influential factors, precluding a definite conclusion on the relationship between fractures and apalutamide based on the information currently available. In Study 003, however, the incidence of fracture was higher in the apalutamide group than in the placebo group, and there were serious cases of fracture in the clinical studies, raising concerns about increasing seriousness of the condition depending on the site affected. Therefore, caution should be used against fractures during apalutamide treatment.

Based on the above, the occurrence of fracture in the clinical studies should be appropriately communicated to healthcare professionals via the package insert.

7.R.4 Clinical positioning and indication

The proposed indication of apalutamide was "Castration-resistant prostate cancer." The "Precautions for Indication" section presented the following statement:

- The safety and efficacy of apalutamide have not been established in patients with distant metastasis.

Based on the reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the discussion in following subsection, PMDA concluded that the indication of apalutamide should be defined as "Non-metastatic castration-resistant prostate cancer" with the following cautionary advice presented in the "Precautions for Indication" section:

- Before selecting eligible patients, physicians should become well-acquainted with information provided in the "CLINICAL STUDIES" section and thoroughly understand the efficacy and safety of apalutamide.

7.R.4.1 Clinical positioning of apalutamide and eligible patients

Major clinical practice guidelines in or outside Japan or clinical oncology textbooks describe apalutamide used in patients with non-metastatic CRPC as shown below. At present, the Clinical practice guideline in Japan and the New Clinical Oncology, textbook version 5 (Nankodo Co., Ltd. 2018) do not have descriptions about apalutamide used in patients with non-metastatic CRPC.

- NCCN guideline (v.4.2018):
  Apalutamide is recommended for the treatment of non-metastatic CRPC with PSA doubling time of ≤10 months.

PMDA asked the applicant to explain detailed attributes of patients with non-metastatic CRPC eligible for apalutamide and its indication.

The applicant's explanation:
Based on results from Study 003, apalutamide is recommended for the treatment of patients with non-metastatic CRPC, defined by PSA doubling time of ≤10 months, who were eligible for Study 003.

In contrast, apalutamide is not recommended to treat patients with non-metastatic CRPC based on PSA doubling time of >10 months, who were not included in Study 003, because of no data showing the clinical benefits of apalutamide in this population at present. However, patients may miss an opportunity to receive apalutamide treatment before the ≤10-month PSA doubling time is confirmed. Thus the PSA doubling time of patients should not be specified in the indication of apalutamide but be noted in the "CLINICAL STUDIES" section of the package insert as a piece of information about Study 003.

- In Study 003, PSA was initially measured ≥3 times to calculate the PSA doubling time within 6 months before enrollment and randomization, and patients with the calculated PSA doubling time of ≤10 months were enrolled. However, some patients with the calculated PSA doubling time of ≤10

months were not included in Study 003 because their PSA was not measured 3 times within 6 months before enrollment and randomization. The protocol was then revised so that PSA doubling time was calculated from PSA values measured within 24 months before enrollment and randomization (protocol, revised version 5 dated [redacted], [redacted]). As a result, the number of patients failing to meet the inclusion criteria declined at the imaging examination before enrollment in this study.

- In Study 003, of 2132 patients screened, 925 patients (43.4%) were excluded at the enrollment. Of these, 517 patients were found to have distant metastasis at the imaging examination before enrollment even though their PSA doubling time was ≤10 months.

Based on the above, the proposed "Precautions for Indication" section provided the following cautionary note, and the indication was proposed as "castration-resistant prostate cancer."

- The safety and efficacy of apalutamide have not been established in patients with distant metastasis.

In terms of the choice between apalutamide and enzalutamide for treatment of non-metastatic CRPC, physicians are required to have a good understanding of the efficacy and safety of each drug and to select whichever suitable to each patient's condition, because of currently unknown priority owing to the lack of clinical data comparing efficacy and safety between the 2 drugs.

PMDA's view:
The applicant's explanation is generally acceptable. However, the target population of Study 003, which demonstrated clinical benefit of apalutamide, was patients with non-metastatic cancer, and this information is important in terms of the selection of patients eligible for apalutamide and should be clearly mentioned in the indication of apalutamide.

Accordingly, the indication of apalutamide should be "Non-metastatic castration-resistant prostate cancer." The package insert should note in the "CLINICAL STUDIES" section that Study 003 was conducted in patients with non-metastatic CRPC defined by PSA doubling time of ≤10 months, and give the following advice in the "Precautions for Indication" section.

- Before selecting eligible patients, physicians should become well-acquainted with information provided in the "CLINICAL STUDIES" section and thoroughly understand the efficacy and safety of apalutamide.

7.R.5 Dosage and administration

The proposed description of dosage and administration was "The usual adult dosage is 240 mg of apalutamide orally administered once daily." In addition, the following descriptions were presented in the "Precautions for Dosage and Administration" section. The "Important Precautions" section of the package insert was to advise that apalutamide be permanently discontinued in case of seizure during the treatment.

- The efficacy and safety of apalutamide without concomitant surgical or medical castration have not been established.

- If a Grade ≥3 or intolerable adverse drug reaction occurs, apalutamide should be interrupted until recovery to Grade ≤1 or baseline. The treatment may be resumed at the dose before interruption or a reduced dose of 180 or 120 mg.

After the reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the following subsections, PMDA concluded that the dosage regimen of apalutamide should be modified as "The usual adult dosage is 240 mg of apalutamide orally administered once daily. The dose may be reduced according to the patient's condition," along with the following cautionary notes in the "Precautions for Dosage and Administration" section.

- The efficacy and safety of apalutamide without concomitant surgical or medical castration have not been established.

- In case of an adverse drug reaction, apalutamide should be interrupted or discontinued, or the dose of apalutamide should be reduced in accordance with the following criteria.

Dose reduction for continued treatment with apalutamide

Dose-reduction level	Dose
Normal dose	240 mg
1-level reduction	180 mg
2-level reduction	120 mg

Criteria for dose adjustment following an adverse drug reaction

Adverse drug reaction	Grade*	Measure
Seizure	-	Discontinue apalutamide.
Other	3 or 4	Interrupt apalutamide until recovery to Grade ≤1. Apalutamide may be resumed but at a reduced dose according to the following guidelines: • After the recovery from the initial adverse reaction, resume apalutamide at the usual dose. • After the recovery from a recurrent adverse reaction, resume apalutamide at the 1-level lower dose.

* Graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver4.0

7.R.5.1 Dosage and administration for apalutamide

The applicant's explanation about the rationale for the proposed dosage and administration:
The dosage regimen in Study 003 was designed based on the results from the following studies, which demonstrated the clinical benefit of apalutamide in patients with non-metastatic CRPC defined by PSA doubling time of ≤10 months. The proposed dosage and administration of apalutamide were therefore determined based on the dosage regimen in Study 003.

- In the phase I part of Study 001, apalutamide 30, 60, 90, 120, 180, 240, 300, 390, or 480 mg QD in combination with ADT was tolerated.

- In the phase I part of Study 001, the plasma trough concentration (mean) of apalutamide 240 mg QD on Day 22 of Cycle 1 was 4.42 μg/mL, which fell within the range of plasma trough concentrations (mean) in castrated SCID mice subcutaneously implanted with LNCaP/AR (cs) cell line after repeated doses of apalutamide 10 and 30 mg/kg QD[51)] for 42 days (3.91 and 6.14 μg/mL, respectively).

- In the phase II part of Study 001, apalutamide 240 mg QD in combination with ADT in Cohort 1 achieved a certain level of PSA response rate [see Section 7.1.4.1].

PMDA's view:
The applicant's explanation is acceptable. The dosage regimen should be modified as "The usual adult dosage is 240 mg of apalutamide orally administered once daily. The dose may be reduced according to the patient's condition."

7.R.5.2 Dose adjustment for apalutamide

The applicant's explanation about guidelines for dose-reduction, interruption or discontinuation of apalutamide:
In Study 003, the criteria for dose-reduction, interruption, and discontinuation of apalutamide were specified, and the clinical benefit of apalutamide was demonstrated based on the criteria. Accordingly, the dose adjustment guidelines will be provided in the "Precautions for Dosage and Administration" section as per below. The protocol of Study 003 stipulates that apalutamide be permanently discontinued in case of seizure, and this advice will be provided in the "Important Precautions" section of the package insert.

- If a Grade ≥3 or intolerable adverse drug reaction occurs, apalutamide should be interrupted until recovery to Grade ≤1 or baseline. The treatment may be resumed at the dose before interruption or a reduced dose of 180 or 120 mg.

PMDA's view:
PMDA generally accepted the applicant's explanation. However, the dose adjustment criteria should be modified as described below, including measures to be taken following a seizure, and be presented in the "Precautions for Dosage and Administration" section.

Dose reduction for continued treatment with apalutamide

Dose-reduction level	Dose
Normal dose	240 mg
1-level reduction	180 mg
2-level reduction	120 mg

51) As compared with the control, apalutamide inhibited tumor growth statistically significantly [see Section 3.1.4.2].

Criteria for dose adjustment to accommodate an adverse drug reaction

Adverse drug reaction	Grade*	Measure
Seizure	-	Discontinue apalutamide.
Other	3 or 4	Interrupt apalutamide until recovery to Grade ≤1. Apalutamide may be resumed but at a reduced dose according to the following guidelines: • After the recovery from the initial adverse reaction, resume apalutamide at the usual dose. • After the recovery from a recurrent adverse reaction, resume apalutamide at the 1-level reduced dose.

* Graded in accordance with NCI-CTCAE ver4.0.

7.R.5.3 Combination with surgical or medical castration

The applicant's explanation about the combination of apalutamide with surgical or medical castration:
Efficacy and safety data of apalutamide used without surgical or medical castration are not available at present, and caution will be advised against it through the "Precautions for Dosage and Administration" section.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan:
Post-marketing surveillance is being planned to investigate the safety of apalutamide in patients with CRPC receiving apalutamide in the post-marketing setting.

The planned safety specification of the surveillance includes skin eruption, fall, and non-pathological fracture in light of the incidences of adverse events in Study 003.

A planned sample size is 200. This sample size is presumed to be sufficient to obtain data from ≥5 patients who have experienced Grade ≥3 skin eruption at the probability of ≥95%, based on a focus on skin eruption owing to its high incidence in Japanese patients in Study 003.

The follow-up period is 52 weeks. The initial onsets of the events included in the above safety specification were observed mostly within 12 months in Study 003, and none of the events showed an increasing trend in their incidences with increasing apalutamide doses.

PMDA's view:
Safety information of apalutamide in Japanese patients with CRPC is limited. Severe skin disorders and seizures are risks of apalutamide requiring careful attention and should be specified in safety specification of the surveillance. The post-marketing surveillance should be conducted to investigate the occurrence of these events.

The planned sample size and follow-up period should be reconsidered in light of the occurrence, etc. of these events added in the safety specification of the surveillance

7.3 Adverse events observed in clinical studies

Deaths reported in the safety evaluation data were detailed in Sections "7.1 Evaluation data" and in "7.2 Reference data." Other main adverse events are summarized below.

7.3.1 Japanese phase I study (Study 21)

Adverse events occurred in 2 of 6 subjects (33.3%) in the 60 mg group, 4 of 6 subjects (66.7%) in the 120 mg group, and 5 of 6 subjects (83.3%) in the 240 mg group. Adverse events for which a causal relationship to apalutamide could not be ruled out occurred in 2 of 6 subjects (33.3%) in the 60 mg group, 4 of 6 subjects (66.7%) in the 120 mg group, and 4 of 6 subjects (66.7%) in the 240 mg group. Adverse events reported by ≥2 subjects in each group were blood testosterone increased in 2 subjects (33.3%) in the 60 mg group, blood testosterone increased in 3 subjects (50.0%) in the 120 mg group, and blood testosterone increased in 4 subjects (66.7%) in the 240 mg group, and a causal relationship to apalutamide could not be ruled out for all these events,.

Neither serious adverse events nor adverse events leading to the discontinuation of apalutamide occurred.

7.3.2 Japanese phase I study (Study 08)

Adverse events occurred in 6 of 6 patients (100%), and adverse events for which a causal relationship to apalutamide could not be ruled out occurred in all the patients. Adverse events reported by ≥2 patients were abdominal discomfort, rash, nasopharyngitis, dysgeusia, and hot flush in 2 patients (33.3%) each.

A serious adverse event occurred in 1 of 6 patients (16.7%). The reported serious adverse event was spinal cord compression in 1 patient (16.7%), for which a causal relationship to apalutamide was ruled out.

Adverse event leading to the discontinuation of apalutamide occurred in 1 of 6 patients (16.7%). The reported adverse event leading to the discontinuation of apalutamide was spinal cord compression in 1 patient (16.7%), for which a causal relationship to apalutamide was ruled out.

7.3.3 Global phase III study (Study 003)

Adverse events occurred in 775 of 803 patients (96.5%) in the apalutamide group and 371 of 398 patients (93.2%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 565 of 803 patients (70.4%) in the apalutamide group and 216 of 398 patients (54.3%) in the placebo group. Table 42 shows adverse events with an incidence of ≥15% in any group.

Table 42. Adverse events with an incidence of ≥15% in any group

SOC PT (MedDRA/J ver. 19.1)	Number of patients (%)			
	Apalutamide n = 803		Placebo n = 398	
	All Grades	Grades ≥3	All Grades	Grades ≥3
All adverse events	775 (96.5)	366 (45.6)	371 (93.2)	137 (34.4)
Gastrointestinal disorders				
Diarrhoea	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)
Nausea	145 (18.1)	0	63 (15.8)	0
General disorders and administration site conditions				
Fatigue	244 (30.4)	7 (0.9)	84 (21.1)	1 (0.3)
Musculoskeletal and connective tissue disorders				
Arthralgia	128 (15.9)	0	30 (7.5)	0
Angiopathy				
Hypertension	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)
Injury, poisoning and procedural complications				
Fall	125 (15.6)	14 (1.7)	36 (9.0)	3 (0.8)
Investigations				
Weight decreased	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)

Serious adverse events occurred in 204 of 803 patients (25.4%) in the apalutamide group and 93 of 398 patients (23.4%) in the placebo group. Serious adverse events reported by ≥4 patients in each group were haematuria in 13 patients (1.6%), urinary retention and urinary tract infection in 10 patients (1.2%) each, pneumonia in 9 patients (1.1%), sepsis and hydronephrosis in 8 patients (1.0%) each, atrial fibrillation in 7 patients (0.9%), fall and acute kidney injury in 6 patients (0.7%) each, urosepsis, diarrhoea, syncope, osteoarthritis, and pyrexia in 5 patients (0.6%) each, and cardiac failure congestive and myocardial infarction in 4 patients (0.5%) each in the apalutamide group; and urinary retention in 15 patients (3.8%), haematuria and hydronephrosis in 8 patients (2.0%) each, acute kidney injury and urinary tract obstruction in 4 patients (1.0%) each in the placebo group. A causal relationship to the study drug could not be ruled out for diarrhoea (3 patients), atrial fibrillation (2 patients), cardiac failure congestive, myocardial infarction, fall, pyrexia, acute kidney injury and sepsis (1 patient each) in the apalutamide group and hydronephrosis (1 patient) in the placebo group.

Adverse events leading to the discontinuation of the study drug occurred in 85 of 803 patients (10.6%) in the apalutamide group and 28 of 398 patients (7.0%) in the placebo group. Adverse events leading to the discontinuation of the study drug reported by ≥4 patients in each group were fatigue in 8 patients (1.0%), rash maculo-papular in 6 patients (0.7%), and rash generalised and sepsis in 4 patients (0.5%) each in the apalutamide group. A causal relationship to the study drug could not be ruled out for fatigue (7 patients), rash maculo-papular (6 patients), and rash generalized (4 patients).

7.3.4 Foreign phase I/II study (Study 001)

7.3.4.1 Phase I part

Adverse events occurred in 15 of 15 patients (100%) in the <240 mg (30 mg, 60 mg, 90 mg, 120 mg, and 180 mg) group, 3 of 3 patients (100%) in the 240 mg group, and 11 of 12 patients (91.7%) in the >240 mg (300 mg, 390 mg, and 480 mg) group. Adverse events for which a causal relationship to apalutamide could not be ruled out occurred 14 of 15 patients (93.3%) in the <240 mg group, 3 of 3 patients (100%) in the 240 mg group, and 11 of 12 patients (91.7%) in the >240 mg group. Adverse events reported by ≥2 patients in each of the <240 mg and >240 mg groups were fatigue in 10 patients

(66.7%); constipation in 7 patients (46.7%); back pain and arthralgia in 6 patients (40.0%) each; oedema peripheral in 5 patients (33.3%); diarrhoea, headache and dyspnoea in 4 patients (26.7%) each; musculoskeletal pain, pain in extremity, musculoskeletal chest pain, nausea, abdominal pain, peripheral motor neuropathy, cough, and hot flush in 3 patients (20.0%) each; and pain, pyrexia, muscle spasms, neck pain, dizziness, hypoaesthesia, dysuria, haematuria, haemorrhage urinary tract, nocturia, urethral pain, helicobacter infection, upper respiratory tract infection, anaemia, and visual acuity reduced in 2 patients (13.3%) each in the <240 mg group and peripheral sensory neuropathy in 6 patients (50.0%); fatigue, back pain, nausea, and diarrhoea in 5 patients (41.7%) each; abdominal pain and arthralgia in 4 patients (33.3%) each; musculoskeletal pain, cough, pain, bone pain, constipation, dyspnoea, dyspnoea exertional, hyperkalaemia, and hypothyroidism in 3 patients (25.0%) each; and headache, pain in extremity, muscle spasms, dysuria, haematuria, and insomnia in 2 patients (16.7%) each in the >240 mg group.

Serious adverse events occurred in 2 of 15 patients (13.3%) in the <240 mg group and 5 of 12 patients (41.7%) in the >240 mg group. There was no serious adverse event reported by ≥2 patients in any group.

Adverse events leading to the discontinuation of apalutamide occurred in 2 of 15 patients (13.3%) in the <240 mg group and 2 of 12 patients (16.7%) in the >240 mg group. There was no adverse event leading to the discontinuation of apalutamide reported by ≥2 patients in any group.

7.3.4.2 Phase II part

Adverse events occurred in 51 of 51 patients (100%) in Cohort 1 of patients with CRPC at high risk for distant metastasis, 25 of 25 patients (100%) in Cohort 2 of treatment-naive patients with metastatic CRPC, and 21 of 21 patients (100%) in Cohort 3 of patients with metastatic CRPC who had received prior treatment with abiraterone. Adverse events for which a causal relationship to apalutamide could not be ruled out occurred in 47 of 51 patients (92.2%) in Cohort 1, 21 of 25 patients (84.0%) in Cohort 2, and 17 of 21 patients (81.0%) in Cohort 3. Table 43 shows adverse events with an incidence of ≥20% in any cohort.

Table 43. Adverse events with an incidence of ≥20% in any cohort

SOC PT (MedDRA/J ver. 19.1)	Number of patients (%)					
	Cohort 1 n = 51		Cohort 2 n = 25		Cohort 3 n = 21	
	All Grades	Grades ≥3	All Grades	Grades ≥3	All Grades	Grades ≥3
All adverse events	51 (100)	25 (49.0)	25 (100)	12 (48.0)	21 (100)	10 (47.6)
Gastrointestinal disorders						
Diarrhoea	22 (43.1)	1 (2.0)	11 (44.0)	0	8 (38.1)	0
Nausea	20 (39.2)	0	14 (56.0)	0	7 (33.3)	0
Abdominal pain	10 (19.6)	0	12 (48.0)	1 (4.0)	1 (4.8)	0
Constipation	9 (17.6)	0	3 (12.0)	1 (0.4)	5 (23.8)	1 (4.8)
General disorders and administration site conditions						
Fatigue	34 (66.7)	2 (3.9)	15 (60.0)	0	11 (52.4)	1 (4.8)
Musculoskeletal and connective tissue disorders						
Arthralgia	12 (23.5)	1 (2.0)	7 (28.0)	0	6 (28.6)	0
Back pain	14 (27.5)	0	6 (24.0)	0	4 (19.0)	2 (9.5)
Musculoskeletal pain	5 (9.8)	0	2 (8.0)	0	6 (28.6)	1 (4.8)
Musculoskeletal chest pain	2 (3.9)	0	7 (28.0)	0	3 (14.3)	0
Nervous system disorders						
Dysgeusia	11 (21.6)	0	2 (8.0)	0	2 (9.5)	0
Infections and infestations						
Nasopharyngitis	10 (19.6)	0	5 (20.0)	0	1 (4.8)	0
Respiratory, thoracic and mediastinal disorders						
Cough	10 (19.6)	0	6 (24.0)	0	2 (9.5)	0
Dyspnoea	4 (7.8)	0	7 (28.0)	2 (8.0)	3 (14.3)	0
Skin and subcutaneous tissue disorders						
Rash generalised	2 (8.0)	0	5 (20.0)	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	7 (13.7)	1 (2.0)	4 (16.0)	0	5 (23.8)	0
Angiopathy						
Hot flush	10 (19.6)	0	5 (20.0)	0	0	0
Blood and lymphatic system disorders						
Anaemia	9 (17.6)	2 (3.9)	5 (20.0)	3 (12.0)	3 (14.3)	0
Endocrine disorders						
Hypothyroidism	11 (21.6)	0	3 (12.0)	0	1 (4.8)	0

Serious adverse events occurred in 16 of 51 patients (31.4%) in Cohort 1, 10 of 25 patients (40.0%) in Cohort 2, and 6 of 21 patients (28.6%) in Cohort 3. Serious adverse events reported by ≥2 patients in each cohort were cerebrovascular accident and urinary retention in 2 patients (3.9%) each in Cohort 1 and constipation and back pain in 2 patients (9.5%) each in Cohort 3.

Adverse events leading to the discontinuation of apalutamide occurred in 9 of 51 patients (17.6%) in Cohort 1, 6 of 25 patients (24.0%) in Cohort 2, and 1 of 21 patients (4.8%) in Cohort 3. An adverse event leading to the discontinuation of apalutamide reported by ≥2 patients in each cohort was fatigue in 2 patients (3.9%) in Cohort 1, and a causal relationship to apalutamide could not be ruled out for either events.

7.3.5 Foreign phase I (Study 006)

Adverse events occurred in 6 of 6 subjects (100%) in Part A (a single oral dose of apalutamide followed by a single intravenous dose of ^{14}C-apalutamide) and 5 of 6 subjects (83.3%) in Part B (a single oral dose of apalutamide and ^{14}C-apalutamide). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 5 of 6 subjects (83.3%) in Part A and 3 of 6 subjects (50.0%) in Part B. Adverse events reported by ≥2 subjects in each part were headache in 3 subjects (50.0%) and

contusion in 2 subjects (33.3%) in Part A and nasopharyngitis, musculoskeletal stiffness, pain in extremity, and headache in 2 subjects (33.3%) each in Part B.

Neither serious adverse events nor adverse events leading to the discontinuation of the study drug occurred.

7.3.6 Foreign phase I (Study 07)

Adverse events occurred in 6 of 15 subjects (40.0%) in the Soft Capsule A group, 5 of 15 subjects (33.3%) in the Tablet B group, 6 of 15 subjects (40.0%) in the Tablet C group, 6 of 15 subjects (40.0%) in the Tablet D group, 1 of 15 subjects (6.7%) in the Tablet E group, 4 of 15 subjects (26.7%) in the Tablet F group, 1 of 15 subjects (6.7%) in the Tablet G group, and 4 of 15 subjects (26.7%) in the Tablet H group. Adverse events for which a causal relationship to apalutamide could not be ruled out occurred in 6 of 15 subjects (40.0%) in the Soft capsule A group, 1 of 15 subjects (6.7%) in the Tablet B group, 4 of 15 subjects (26.7%) in the Tablet C group, 5 of 15 subjects (33.3%) in the Tablet D group, 1 of 15 subjects (6.7%) in the Tablet E group, and 3 of 15 subjects (20.0%) in the Tablet H group. Adverse events reported by ≥2 subjects in each group were headache in 2 subjects (13.3%) in the Soft Capsule A group, upper respiratory tract infection in 3 subjects (20.0%) in the Tablet C group, and viral infection in 2 subjects (13.3%) in the Tablet F group.

A serious adverse event occurred in 1 of 15 subjects (6.7%) in the Tablet B group. The reported serious adverse event was appendicitis in 1 subject (6.7%), for which a causal relationship to apalutamide was ruled out.

No adverse events leading to the discontinuation of apalutamide occurred.

7.3.7 Foreign phase I study (Study 11)

Adverse events occurred in 3 of 15 subjects (20.0%) in the Soft Capsule A fasted-state group, 4 of 15 subjects (26.7%) in the Tablet B fasted-state group, 6 of 15 subjects (40.0%) in the Tablet C fasted-state group, 4 of 15 subjects (26.7%) in the Tablet D fasted-state group, and 1 of 15 subjects (6.7%) in the Tablet B high-fat meal group. Adverse events for which a causal relationship to apalutamide could not be ruled out occurred in 3 of 15 subjects (20.0%) in the Soft Capsule A fasted-state group, 2 of 15 subjects (13.3%) in the Tablet B fasted-state group, 5 of 15 subjects (33.3%) in the Tablet C fasted-state group, 2 of 15 subjects (13.3%) in the Tablet D fasted-state group, and 1 of 15 subjects (6.7%) in the Tablet B high-fat meal group. Adverse events reported by ≥2 subjects in each group were pollakiuria and insomnia in 2 subjects (13.3%) each in the Soft Capsule A fasted-state group and headache in 2 subjects (13.3%) in the Tablet C fasted-state group.

Neither serious adverse events nor adverse events leading to the discontinuation of apalutamide occurred.

7.3.8 Foreign phase I study (Study 12)

Adverse events occurred in 9 of 15 subjects (60.0%) in Group A (apalutamide alone), 7 of 15 subjects (46.7%) in Group B (apalutamide + itraconazole), and 8 of 15 subjects (53.3%) in Group C (apalutamide + gemfibrozil). Adverse events for which a causal relationship to apalutamide could not be ruled out

occurred in 8 of 15 subjects (53.3%) in Group A, 7 of 15 subjects (46.7%) in Group B, and 8 of 15 subjects (53.3%) in Group C. Adverse events reported by ≥2 subjects in each group were upper respiratory tract infection in 4 subjects (26.7%) and abdominal pain, erythema, and feeling hot in 2 subjects (13.3%) each in Group A, oropharyngeal pain in 2 subjects (13.3%) in Group B, and upper respiratory tract infection in 3 subjects (20.0%), and oropharyngeal pain and rhinorrhea in 2 subjects (13.3%) each in Group C.

No serious adverse events occurred.

An adverse event leading to the discontinuation of apalutamide occurred in 1 of 15 subjects (6.7%) in the Group C. The reported adverse event was hepatic function abnormal in 1 subject (6.7%), for which a causal relationship to apalutamide could not be ruled out.

7.3.9 Foreign phase I study (Study 15)

The study consisted of the Tablet A/Tablet B group, Tablet B/Tablet A group, Tablet A/Tablet C group, Tablet C/Tablet A group, Tablet A/Tablet D group, Tablet D/Tablet A group, Tablet A/Tablet E group, and Tablet E/Tablet A group. Adverse events occurred in 3 of 7 subjects (42.9%) in the Tablet B/Tablet A group, 3 of 7 subjects (42.9%) in the Tablet A/Tablet C group, 1 of 7 subjects (14.3%) in the Tablet C/Tablet A group, 2 of 7 subjects (28.6%) in the Tablet A/Tablet D group, 2 of 7 subjects (28.6%) in the Tablet D/Tablet A group, 3 of 7 subjects (42.9%) in the Tablet A/Tablet E group, and 4 of 7 subjects (57.1%) in the Tablet E/Tablet A group. Adverse events for which a causal relationship to apalutamide could not be ruled out occurred in 3/7 subjects (42.9%) in the Tablet B/Tablet A group, 1 of 7 subjects (14.3%) in the Tablet D/Tablet A group, 1 of 7 subjects (14.3%) in the Tablet A/Tablet E group, and 2 of 7 subjects (28.6%) in the Tablet E/Tablet A group. There was no adverse event reported by ≥2 subjects in any group.

Neither serious adverse events nor adverse events leading to the discontinuation of apalutamide occurred.

7.3.10 Foreign phase I study (Study 17)

Adverse events occurred in 2 of 12 subjects (16.7%) in the Tablet A/Tablet B group, 6 of 12 subjects (50.0%) in the Tablet B/Tablet A group, 3 of 12 subjects (25.0%) in the Tablet A/Tablet C group, and 4 of 12 subjects (33.3%) in the Tablet C/Tablet A group. Adverse events for which a causal relationship to apalutamide could not be ruled out occurred in 2 of 12 subjects (16.7%) in each of the Tablet A/Tablet B, Tablet B/Tablet A, and Tablet A/Tablet C groups and 1 of 12 subjects (8.3%) in the Tablet C/Tablet A group. Adverse events reported by ≥2 subjects in each group were upper respiratory tract infection in 2 subjects (16.7%) in the Tablet B/Tablet A group and weight increased in 3 subjects (25.0%) in the Tablet C/Tablet A group.

Neither serious adverse events nor adverse events leading to the discontinuation of apalutamide occurred.

7.3.11 Foreign phase I study (Study 18)

Adverse events occurred in 3 of 8 patients with mild hepatic impairment (37.5%) and 4 of 8 patients with moderate hepatic impairment (50.0%). Adverse events for which a causal relationship to

apalutamide could not be ruled out occurred in 1 of 8 patients with moderate hepatic impairment (12.5%). Adverse events reported by ≥2 patients in each group were skin abrasion in 2 patients with mild hepatic impairment (25.0%).

Serious adverse events occurred in 2 of 8 patients with moderate hepatic impairment (25.0%). There was no serious adverse event reported by ≥2 patients.

No adverse events leading to the discontinuation of apalutamide occurred.

7.3.12 Foreign phase I study (Study 20)

Adverse events occurred in 14 of 23 patients (60.9%), and adverse events for which a causal relationship to apalutamide could not be ruled out occurred in 10 of 23 patients (43.5%). Adverse events reported by ≥2 patients were asthenia and blood thyroid stimulating hormone increased in 4 patients (17.4%) each; nausea in 3 patients (13.0%); and diarrhoea, thyroxine free decreased, decreased appetite, hypercholesterolaemia, back pain, and cancer pain in 2 patients (8.7%) each.

Serious adverse events occurred in 3 of 23 patients (13.0%). There was no serious adverse event reported by ≥2 patients.

Adverse events leading to the discontinuation of apalutamide occurred in 2 of 23 patients (8.7%). There was no adverse event leading to the discontinuation of apalutamide reported by ≥2 patients.

7.3.13 Foreign phase Ib study (Study 10)

Adverse events occurred in 57 of 57 patients (100%), and adverse events for which a causal relationship to apalutamide could not be ruled out occurred in 52 of 57 patients (91.2%). Adverse events with an incidence of ≥30% were fatigue in 32 patients (56.1%), nausea and vomiting in 23 patients (40.4%) each, back pain in 19 patients (33.3%), and decreased appetite in 18 patients (31.6%).

Serious adverse events occurred in 22 of 57 patients (38.6%). Serious adverse events reported by ≥2 patients were pneumonia in 4 patients (7.0%), back pain in 3 patients (5.3%), and constipation, pyrexia and fall in 2 patients (3.5%) each. A causal relationship to apalutamide could not be ruled out for pneumonia (1 patient).

Adverse events leading to the discontinuation of apalutamide occurred in 5 of 57 patients (8.8%). Adverse events leading to the discontinuation of apalutamide reported by ≥2 patients were bone pain in 2 patients (3.5%), for which a causal relationship to apalutamide was ruled out.

7.3.14 Foreign phase Ib study (Study 19)

Adverse events occurred in 37 of 45 patients (82.2%), and adverse events for which a causal relationship to apalutamide could not be ruled out occurred in 23 of 45 patients (51.1%). Adverse events with an incidence of ≥10% were fatigue in 18 patients (40.0%), decreased appetite in 11 patients (24.4%), back pain in 7 patients (15.6%), diarrhoea and dyspnoea in 6 patients (13.3%) each, and constipation and nausea in 5 patients (11.1%) each.

Serious adverse events occurred in 5 of 45 patients (11.1%). A serious adverse event reported by ≥2 patients was back pain in 2 patients (4.4%), for which a causal relationship to apalutamide was ruled out.

No adverse events leading to the discontinuation of apalutamide occurred.

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 assessment is ongoing. 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 assessment is ongoing. 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 the product has efficacy in the treatment of non-metastatic CRPC, and that the product has acceptable safety in view of its benefits. Apalutamide is a drug with a new active ingredient that competitively inhibits androgen binding to the ligand binding domain of AR and blocks nuclear import of AR, a transcription factor, consequently inhibiting AR binding to the transcription factor binding region on DNA and subsequent transcription of the target gene. Apalutamide inhibits AR-mediated signaling, and is thereby expected to suppress androgen-dependent tumor growth. Therefore, the product has clinical significance as a therapeutic option for non-metastatic CRPC. The indication and post-marketing investigations need to be further discussed.

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

Review Report (2)

January 21, 2019

Product Submitted for Approval

Brand Name	Erleada Tablets 60 mg
Non-proprietary Name	Apalutamide
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 28, 2018

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

Following the review in Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of apalutamide was demonstrated in patients with non-metastatic CRPC[52)] defined by PSA doubling time of ≤10 months,[53)] because the global phase III study (Study 003) in this patient population demonstrated the superiority of apalutamide to the placebo in MFS, the primary endpoint.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

Following the review in Section "7.R.3 Safety" of the Review Report (1), PMDA identified severe skin disorder, cardiac disorder, seizure, and fracture as adverse events particularly requiring attention during the treatment with apalutamide in patients with non-metastatic CRPC.

Although extra attention is required to the above–mentioned adverse events during apalutamide treatment, PMDA has concluded that apalutamide is tolerated by patients under appropriate follow-up

52) The study included patients with CRPC meeting (a) serum testosterone <50 ng/dL, (b) PSA >2.0 ng/mL, and (c) 3 increases in PSA at an interval ≥1 week.
53) PSA was measured ≥3 times during ADT. Patients with PSA doubling time calculated to be ≤10 months were included.

by physicians with adequate knowledge and experience in cancer drug therapy, through monitoring and controlling of the adverse events and interruption of apalutamide, etc.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

As a result of the review in Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA concluded that the indication of apalutamide should be "Non-metastatic castration-resistant prostate cancer," and the package insert should note that Study 003 targeted patients with non-metastatic CRPC defined by PSA doubling time of ≤10 months in the "CLINICAL STUDIES" section and present the following cautionary advice in the "Precautions for Indication" section.

Precautions for Indication

- Before selecting eligible patients, physicians should become well-acquainted with information provided in the "CLNICAL STUDIES" section and thoroughly understand the efficacy and safety of apalutamide.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to describe the "Indication" and "Precautions for Indication" sections as above, and the applicant agreed.

1.4 Dosage and administration

As a result of the review in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the following cautionary advice be presented in the "Precautions for Dosage and Administration" section and that the dosage and administration for apalutamide be described as "The usual adult dosage is 240 mg of apalutamide orally administered once daily. The dose may be reduced according to the patient's condition."

Precautions for Dosage and Administration

- The efficacy and safety of apalutamide without concomitant surgical or medical castration have not been established.

- In case of an adverse drug reaction, apalutamide should be interrupted or discontinued, or the dose of apalutamide should be reduced in accordance with the following criteria.

Dose reduction for continued treatment with apalutamide

Dose-reduction level	Dose
Normal dose	240 mg
1-level reduction	180 mg
2-level reduction	120 mg

Criteria for dose adjustment following an adverse drug reaction

Adverse drug reaction	Grade*	Measure
Seizure	-	Discontinue apalutamide.
Other	3 or 4	Interrupt apalutamide until recovery to Grade ≤1 or baseline. Apalutamide may be resumed but at a reduced dose according to the following guidelines: • After the recovery from the initial adverse reaction, resume apalutamide at the usual dose. • After the recovery from a recurrent adverse reaction, resume apalutamide at the 1-level lower dose.

* Graded in accordance with NCI-CTCAE ver4.0.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to present the above statements in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections, and the applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance covering patients with non-metastatic CRPC who have received apalutamide to investigate the safety of apalutamide in its post-marketing clinical use, with a planned sample size of 200 and a follow-up period of 52 weeks.

As a result of the review in Section "7.R.6 Post-marketing specifications" of the Review Report (1), PMDA concluded that the safety specification of post-marketing surveillance should include severe skin disorder and seizure.

PMDA also concluded that the planned sample size and follow-up period should be discussed again in light of the occurrence of the events included in the safety specification in Study 003.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above discussion, PMDA instructed the applicant to discuss the post-marketing surveillance plan again.

The applicant's reply:

- The safety specification will include severe skin disorder and seizure.

- The planned sample size will be 200 based on the data from Study 003 on the occurrence of events included in the safety specification.

- The follow-up period will be 52 weeks based on the data from Study 003 on the occurrence of events included in the safety specification.

PMDA accepted the applicant's reply.

Based on the discussion above, PMDA has concluded that the risk management plan (draft) for apalutamide should include the safety specification presented in Table 44, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 45 and 46.

Table 44. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Severe skin disorder • Seizure	• Cardiac disorders • Fracture	Not applicable
Efficacy specification		
Not applicable		

Table 45. Summary of additional pharmacovigilance activities, efficacy surveillance and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy surveillance and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results surveys • Post-marketing clinical study (extension study from Study 003)	Not applicable	• Provision of information obtained from early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals

Table 46. Outline of use-results survey (draft)

Objective	To investigate the incidences of severe skin disorder and seizure in clinical use
Survey method	Central registry system
Population	Patients with non-metastatic CRPC who have received apalutamide
Observation period	52 weeks
Planned sample size	200
Main survey items	Safety specification: Severe skin disorder and seizure Other main survey items: Patient characteristics (age, ECOG PS, prior treatment of the primary disease, past illness, concurrent illness, etc.), status of treatment with apalutamide, concomitant therapies, etc.

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

2.1 PMDA's conclusion concerning the results of 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.

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.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that Apalutamide may be approved after modifying the indication and the dosage and administration as shown below, with the following condition. At the same time, necessary cautionary advice should be provided in the package insert and information on the proper use of Apalutamide should be provided appropriately in its post-marketing use. Furthermore, the proper use of Apalutamide should be strictly ensured under the supervision of physicians with adequate knowledge and experience in cancer drug therapy at medical institutions capable of emergency care. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product, and the drug product and its drug substance are both classified as a powerful drug.

Indication

Non-metastatic castration-resistant prostate cancer

Dosage and Administration

The usual adult dosage is 240 mg of apalutamide orally administered once daily. The dose may be reduced according to the patient's condition.

Approval Condition

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

Contraindications

Patients with a history of hypersensitivity to any ingredients of apalutamide

Precautions for Indication

Before selecting eligible patients, physicians should become well-acquainted with information provided in the "CLINICAL STUDIES" section and thoroughly understand the efficacy and safety of apalutamide.

Precautions for Dosage and Administration

1) In case of an adverse drug reaction, apalutamide should be interrupted or discontinued, or the dose of apalutamide should be reduced in accordance with the following criteria.

Dose reduction for continued treatment with apalutamide

Dose-reduction level	Dose
Normal dose	240 mg
1-level reduction	180 mg
2-level reduction	120 mg

Criteria for dose adjustment following an adverse drug reaction

Adverse drug reaction	Grade[Note)]	Measure
Seizure	-	Discontinue apalutamide.
Other	3 or 4	Interrupt apalutamide until recovery to Grade ≤1 or baseline. Apalutamide may be resumed but at a reduced dose according to the following guidelines: • After the recovery from the initial adverse reaction, resume apalutamide at the usual dose. • After the recovery from a recurrent adverse reaction, resume apalutamide at the 1-level lower dose.

Note) Graded in accordance with NCI-CTCAE ver4.0.

2) The efficacy and safety of apalutamide without concomitant surgical or medical castration have not been established.

Appendix

List of Abbreviations

Abiraterone	abiraterone acetate
ADT	androgen deprivation therapy
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apalutamide	apalutamide
APD_{60}	action potential duration at 60% repolarization
APD_{90}	action potential duration at 90% repolarization
Application	Application for marketing approval
APTT	activated partial thromboplastin time
AR	androgen receptor
ARE	androgen response element
AST	aspartate aminotransferase
$AUC_{24h,ss}$	area under the concentration curve during 24 hours after dosing at steady state
BA	bioavailability
BCRP	breast cancer resistance protein
BE	bioequivalence
BICR	blinded independent central review
BID	bis in die
ChIP	chromatin immunoprecipitation
CHO cell line	Chinese hamster ovary cell line
CI	confidence interval
Clinical practice guideline in Japan	Evidenced-based clinical practice guideline for prostate cancer 2016 edition, the Japanese Urological Association
CL_m/F	apparent clearance of M3
$C_{max,ss}$	maximum plasma concentration at steady state
CMC	carboxymethyl cellulose
CPP	critical process parameter
CQA	critical quality attribute
CRPC	castration-resistance prostate cancer
CYP	cytochrome P450
^{14}C-apalutamide	^{14}C-labeled apalutamide
^{14}C-M3	^{14}C-labeled M3 (*N*-desmethyl apalutamide)
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
ERα	estrogen receptor α
F	relative bioavailability
FAS	full analysis set
FC	film coating
FDHT	16β-fluoro-5α-dihydrotestosterone
GABA	γ-aminobutyric acid
GC	gas chromatography
GGT	γ-glutamyl transferase
GR	glucocorticoid receptor
HDL	high-density lipoprotein
hERG	human *ether-a-go-go* related gene
HLGT	high level group terms
HR	hormone receptor

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH M7 guideline	"Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" (PSEHB/ELD Notification No. 1110-3 dated November 10, 2015)
ICH Q1A guideline	"Revision of the Guidelines on Stability Testing of New Drug Substances and Products" (PFSB/ELD Notification No. 0603001 dated June 3, 2003)"
ICH Q1E guideline	"Evaluation for Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3D guideline	"Guideline for Elemental Impurities" (PFSB/ELD Notification No. 0930-4 dated September 30, 2015)
IR	infrared absorption spectrum
ITT	intention-to-treat
K_a	absorption rate constant
LC	liquid chromatography
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LDL	low-density lipoprotein
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MFS	metastasis-free survival
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Prostate Cancer
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIR	near infrared absorption spectrum
NMR	nuclear magnetic resonance spectrum
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
$P_{app\ B \rightarrow A}$	apparent permeability in basolateral to apical direction
PBPK	physiologically based pharmacokinetic
PEG	polyethylene glycol
PFS	progression free survival
P-gp	P-glycoprotein
PgR	progesterone receptor
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PS	performance status
PSA	prostate-specific antigen
PT	preferred term
PTP	press through packaging
Q/F	apparent inter-compartmental clearance of apalutamide
QbD	quality by design

QD	quaque die
Q_m/F	apparent inter-compartmental clearance of M3
QTcB	QT corrected with Bazzet formula
QTcF	QT interval corrected with Fridericia formula
ΔQTcF	change in QTcF from baseline
QTcR	QT corrected for heart rate
QTcV	QT corrected with Van de Water formula
RDW	red blood cell distribution width
RECIST	Response Evaluation Criteria in Solid Tumors
SCID mouse	severe combined immunodeficient mouse
SMQ	standardized MedDRA queries
SOC	system organ class
Study 001	Study ARN-509-001
Study 003	Study ARN-509-003
Study 006	Study ARN-509-006
Study 07	Study 56021927PCR1007
Study 08	Study 56021927PCR1008
Study 11	Study 56021927PCR1011
Study 12	Study 56021927PCR1012
Study 15	Study 56021927PCR1015
Study 17	Study 56021927PCR1017
Study 18	Study 56021927PCR1018
Study 19	Study 56021927PCR1019
Study 20	Study 56021927PCR1020
Study 21	Study 56021927PCR1021
Tablet A (B)/Tablet B (A) group	Group of subjects who received Tablet A (B) in the first term and then Tablet B (A) in the second term
Tablet A (C)/Tablet C (A) group	Group of subjects who received Tablet A (C) in the first term and then Tablet C (A) in the second term
Tablet A (D)/Tablet D (A) group	Group of subjects who received Tablet A (D) in the first term and then Tablet D (A) in the second term
Tablet A (E)/Tablet E (A) group	Group of subjects who received Tablet A (E) in the first term and then Tablet E (A) in the second term
TMPRSS2	transmembrane protease serine 2
3T3-NRU	3T3 neutral red uptake phototoxicity test
TPGS	D-α-tocopherol polyethylene glycol succinate conjugate
TUNEL	terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling
UV/VIS	ultraviolet/visible spectrum
V_c/F	apparent volume of distribution of central compartment of apalutamide
V_{cm}/F	apparent volume of distribution of central compartment of M3
V_{max}	maximum rate of depolarization
V_p/F	apparent peripheral volume of distribution of apalutamide
VP16	virion protein 16
V_{pm}/F	apparent volume of distribution of peripheral compartment of M3