22 June 2023
EMA/317740/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Erleada

International non-proprietary name: apalutamide

Procedure No. EMEA/H/C/004452/X/0028/G

Note

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

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List of abbreviations

AE	adverse event
ANOVA	analysis of variance
AR	androgen receptor
AS	active substance
AUC	area under the plasma concentration - time curve
AUC0-72h	area under the plasma apalutamide concentration versus time curve from time 0 to 72 hours
BA	bioavailability
BCS	Biopharmaceutical Classification System
BE	bioequivalence
CC	calibrator
CI	confidence interval
CQA	critical quality attributes
Cmax	maximum plasma concentration
(n)CPP	(non-) critical process parameter
CSR	Clinical Study Report
ECG	electrocardiogram
FC	film-coated
FOIA	Freedom of Information Act
FP	finished product
GMR	geometric mean ratio
HDPE	high density polyethylene
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
PT	preferred term
KF	Karl Fischer titration
LLOQ	lower limit of quantitation
NIR	near infrared
PAR	proven acceptable ranges
Ph. Eur.	European Pharmacopoeia
PL	Package Leaflet
PVC-PCTFE	polyvinyl chloride – polychlorotrifluoroethylene
QC	quality control
QP	Qualified Person
QTPP	Quality Target Product Profile
RH	relative humidity
SAE	serious adverse event

SmPC	Summary of Product Characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
Tmax	time of maximum concentration
UHPLC	ultra high performance liquid chromatography
ULOQ	upper limit of quantitation
UV	ultraviolet spectrometry

1. Background information on the procedure

1.1. Submission of the dossier

Janssen-Cilag International N.V. submitted on 9 November 2022 a group of variations consisting of an extension application to add a new strength (240 mg) film-coated tablets of the marketing authorisation and the following variation:

Variation(s) requested		Type
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	IB

C.I.z (IB): to align the SmPC/PL for Erleada 60 mg with the SmPC/PL proposed for the registration of the new Erleada film-coated tablet strength, 240 mg.
The PL for Erleada 60 mg is proposed to be updated to ensure consistency.
The RMP (version 6.1) has also been submitted.
In addition, few minor revisions are proposed to the SmPC for Erleada 60 mg, to align the SmPC proposed for the 240 mg strength :
- SmPC Sections 5.1 and 5.2: Orthographic corrections
- SmPC Section 6.5: Further details on the description of the current packaging have been added, this change does not result from a change to the container.
- SmPC Section 6.6: The title of the section has been aligned with QRD template.

1.2. Legal basis

The legal basis for this application refers to:

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 of 23 July 2015 covering the application on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The Applicant received scientific advice on the development of apalutamide for the treatment of non-metastatic castration-resistant prostate cancer from the CHMP on 23/06/2022 (EMA/SA/0000083639).

1.6. Steps taken for the assessment of the product

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

Rapporteur: Carolina Prieto Fernandez Co-Rapporteur:N/A

The application was received by the EMA on	9 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 March 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 March 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	30 March 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	21 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 June 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 March 2023
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	N/A
The MAH submitted the responses to the CHMP List of Outstanding Issues on	16 June 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	19 June 2023
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Erleada on	22 June 2023

2. Scientific discussion

2.1. Problem statement

Apalutamide is currently commercially available as a film-coated (FC) tablet at a strength of 60 mg. The recommended clinical dose of apalutamide is 240 mg (i.e. 4×60 mg FC tablets) administered once daily with or without food.

To reduce the pill burden for patients and enhance compliance a new FC tablet with higher dose strength of 240 mg per tablet has been developed with the goal to lower the pill number from 4 tablets per day (based on the approved 60 mg tablet) to 1 tablet per day.

The purpose of this submission is to extend the current Marketing Authorisation (MA) to add a new immediate release oral FC tablet containing 240 mg of apalutamide. The proposed clinical use for the 240 mg film-coated tablet is for the same indications as the one approved for the 60 mg film-coated tablet. The lower tablet strength (i.e., 60 mg) will remain registered and available to allow dose reduction as per the guidance provided in the product label.

2.2. About the product

Apalutamide is an orally administered selective androgen receptor (AR) that binds directly to the ligand binding domain of the AR. Apalutamide prevents AR nuclear translocation, inhibits DNA binding, impedes AR mediated transcription, and lacks androgen receptor agonist activity.

Erleada is approved for the treatment of adult patients with non-metastatic castration-resistant prostate cancer and metastatic hormone-sensitive prostate cancer.

The recommended dose is 240 mg (one 240 mg tablet) as an oral single daily dose.

Multiple 240 mg tablet formulations were developed for clinical evaluation. Formulation G043 was selected to be tested in a pivotal bioequivalence trial.

The following two clinical studies support the new FC tablet formulation:

- Study 56021927PCR1027, a formulation selection study which investigated the relative Bioavailability (BA) of 240 mg FC tablet formulations compared with the current commercial FC tablets (G023) under fasting conditions.

  Based on relative BA Study 56021927PCR1027, formulation G043 was selected for further evaluation in pivotal Bioequivalence (BE) Study 56021927PCR1028. Study 56021927PCR1027 Part 2 was conducted to evaluate the relative BA of apalutamide using the 240 mg FC tablet formulation G043 with the intention to aid in the establishment of clinically relevant controls for the proposed commercial drug product.

- Study 56021927PCR1028 was conducted to evaluate the BE for the new tablet formulation (G043) compared with the current commercial 60 mg tablet formulation (G023). In the same study, the BA of the new tablet formulation (G043) when administered under fed or fasting conditions was also evaluated.

2.3. Type of Application and aspects on development

Erleada (apalutamide, 60mg film-coated tablets) was initially approved in the EU in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of

developing metastatic disease on 14 January 2019 and was subsequently approved for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) on 27 January 2020.

This extension of the Marketing Authorisation concerns the addition of a new strength ((240 mg) film-coated tablets) for Erleada. The clinical development program, based on two clinical studies, support the new FC tablet formulation (see 2.2. for the details of the clinical studies).

Scientific advice

The Applicant received scientific advice on the development of apalutamide for the treatment of non-metastatic castration-resistant prostate cancer from the CHMP on 23/06/2022 (EMA/SA/0000083639). The scientific advice pertained to the following quality aspects:

• The proposed dissolution method to support a line extension application of the 240 mg drug product.

2.4. Quality aspects

2.4.1. Introduction

The line extension application concerns the introduction of an additional higher strength of 240 mg to the already authorised 60 mg film-coated tablet.

The finished product is presented as an immediate release film-coated tablet containing 240 mg of apalutamide as the active substance.

Other ingredients are:
-Tablet core: colloidal anhydrous silica, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose (silicified)

-Film coating: glycerol monocaprylocaprate, iron oxide black (E172), polyvinyl alcohol, titanium dioxide (E171), macrogol poly (vinyl alcohol) grafted copolymer

The product is available either in transparent PVC-PCTFE film blister with an aluminium push-through foil sealed inside a child resistant wallet pack, or white HDPE bottle with child-resistant polypropylene closure and induction seal liner containing 2 grams of silica gel desiccant, as described in section 6.5 of the SmPC.

2.4.2. Active Substance

There are no changes in the active substance (AS) part other than the presentation of the risk assessment report on the presence of nitrosamines in the AS under Section 3.2.S.3.2 Impurities. The same active substance used for the currently authorised Erleada 60 mg film coated tablet strength is used for the new strength 240 mg strength. The outcome of the risk assessment is that there is no risk of presence of nitrosamines in apalutamide AS.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is oval shaped, bluish grey to grey film-coated 10 mm width and 21 mm length for oral administration, debossed with "E240" on one side and contains 240 mg of apalutamide.

The approved 60 mg strength is oblong shaped, greenish film-coated tablet of 9 mm width x 17 mm length for oral administration. The tablet is debossed with "AR 60" on one side and contains 60 mg of apalutamide. Therefore, both strengths can be differentiated by colour, shape and debossing.

The composition of the 240 mg strength is similar to the 60 mg film-coated tablet but does not contain cellulose microcrystalline.

The tablet is made from an intermediate which delivers 240 mg of apalutamide per tablet.

The AS is a BCS class 2 (insoluble in aqueous media) compound according to the biopharmaceutical classification system. The applicant has used enabling technology to improve the bioavailability; this was studied during the formulation of Erleada 60 mg tablet. The Applicant refers to the manufacturing process development of the intermediate of the 60 mg film-coated tablet and only the development of the downstream process of the 240 mg film-coated tablet is described; this is acceptable.

The excipients used in the proposed commercial formulation are commonly used excipients and have detailed monographs in relevant pharmacopoeias (USP/NF and Ph. Eur.). The coating powder is a non-compendial excipient; however, its components comply with relevant pharmacopoeias.

Multiple 240 mg film-coated tablet formulations were developed using enabling technology, as used for the commercial 60 mg tablet (G023).

The formulations were tested in a human bioavailability trial to evaluate the pharmacokinetics and the relative bioavailability compared with 4 tablets of the reference 60 mg reference formulation (G023). Based on the result of this in vivo study, the 240 mg formulation G043 was selected to be tested in a pivotal bioequivalence trial. The pivotal bioequivalence study demonstrated that the proposed 240 mg G043 formulation is bioequivalent to the already authorised 60 mg formulation (G023) under fasted and fed conditions.

The dissolution method used for the quality control of the drug product was based on the method for the 60 mg strength and has been demonstrated to be sufficiently discriminatory. Sink conditions are not met for the selected medium, but it is justified because the medium needs to be below sink conditions to achieve a sufficiently slow dissolution profile. The use of a surfactant and the amount is also justified.

The compatibility of the finished product with soft foods and liquids to be administered to the patient, i.e. studies orange juice, green tea, yoghourt and applesauce has been sufficiently discussed. The tablet was first dispersed in a small amount of water (10 mL) and then mixed with these liquids and soft foods. The compatibility was assessed by different testings and the results were in compliance with the specifications. Section 4.2 of the SmPC contains the information about how to take the product with non-fizzy beverage or soft food, in line with the results presented in Module 3.

The compatibility of the dispersed finished product with nasogastric tubes of polyurethane, silicone and polyvinylchloride was also tested. The tablets were dispersed using water (10 mL) in a 20 mL syringe and then the content is passed through the nasogastric tubes. The compatibility was assessed by different testings and the results were in compliance with the specifications. Also no adsorption of drug product was observed on the tube and the prepared dose was freely flowing from the tube while dosing. Section 6.6 of the SmPC contains the information to administer the product through a nasogastric feeding tube, in line with the results presented in Module 3.

The manufacturing process development from the intermediate to the final film-coated tablet was presented. The quality target product profile (QTPP) for the finished product was defined as an immediate release oral film-coated tablet, containing 240 mg of apalutamide, which is bioequivalent to the commercial 60 mg FC tablet (G023) on an equivalent dose basis. The finished product should have a sufficiently low level of impurities and microbial burden, complying with the ICH requirements, and must meet its specifications over a shelf life of minimum 24 months when packaged in blisters or bottles. The QTTP was

linked with critical quality attributes (CQAs) that could impact the quality of the product. A number of proven acceptable ranges (PARs) were also defined for the process steps.

The container closure system is either transparent PVC-PCTFE film blister with an aluminium push-through foil sealed inside a child-resistant wallet pack, or white HDPE bottle with child-resistant polypropylene closure and induction seal liner containing 2 grams of silica gel desiccant.
Specifications for both containers were presented along with a confirmation that they comply with current EU Regulation. The child resistant features of both containers comply with ISO 8317.

2.4.3.2. Manufacture of the product and process controls

All relevant sites involved in the finished product manufacturing have valid manufacturing authorisations and/or valid GMP certificates.
The manufacturing process is a multistep process comprising preparation of intermediate, pre-blending, granulation, post granulation blending and lubrication, film-coating and packaging.

A detailed step by step description of the manufacturing process has been provided as well as tables with information on critical process parameters (CPPs) and noncritical process parameters (nCPPs) with operating targets and proven acceptable ranges (PARs) per step. The in process controls are acceptable. No design space is claimed. The proposed bulk holding time for film-coated tablets, manufactured at the proposed manufacturing site is supported by sufficient stability data.

The manufacturing process is validated and the process validation summary report has been provided. Three consecutive commercial scale finished product validation batches have been produced at the commercial facility. Each batch has been tested appropriately throughout the manufacturing process and has demonstrated that the manufacturing process consistently produces finished product meeting the proposed specifications.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (UV, UHPLC), assay (UHPLC), chromatographic purity (UHPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur. -UHPLC), solid state (NIR), water content (KF, NIR), and microbial purity (Ph. Eur.).

The proposed specification includes the relevant parameters for this type of products (immediate release coated tablets). Characterisation, mutagenicity, and toxicological qualification information for the specified degradation product and synthesis impurity has been presented and appropriate limits are set in the specification. The limit for unspecified degradation products has been set in accordance with ICH Q3B and, therefore it is also acceptable as is the limit proposed for total impurities. A test for solid state is included in the product´s specification and supported by the batch analysis results and the stability data.

An elemental impurities (EIs) risk assessment was performed on the FP. It can be concluded that none of the elemental impurities assessed are expected to exceed their corresponding control thresholds in the finished product. Therefore, the manufacturing process and analytical controls in place are considered adequate to assure that the levels of the elemental impurities from various sources in the finished product do not exceed the 30% threshold levels of the permitted levels for daily exposure. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in

human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the risk assessment conducted, no risk for presence of, or formation of, nitrosamines is identified for apalutamide 240 mg film-coated tablet. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and validated. The same reference standards and materials used for the testing of apalutamide AS are used for the testing of the finished product. the information regarding the reference standards is satisfactory.

All batches used in the clinical trials described in this dossier are presented in this section, including 60 mg apalutamide batches, which were used as a reference.

Batch analysis results for 10 batches of the 240 mg strength used throughout development were presented. All results comply well with the proposed specifications and are consisted also with the 60 mg tablets, suggesting that the process is well controlled and FP with a consistent quality profile is obtained.

2.4.3.4. Stability of the product

Stability data from six commercial scale batches (G043) manufactured at the commercial manufacturing site stored for up to 18 months under long term conditions (25 ºC/60 % RH and 30 ºC/75 %RH), and for 6 months under accelerated conditions (40 ºC/75 % RH), according to the ICH guidelines were provided. Three of the stability batches were packaged in the proposed HDPE bottles and three in the proposed blister.

Samples were tested for appearance, assay, chromatographic purity, dissolution, water content, solid and microbiological purity. The analytical procedures used were the same as for release and are stability indicating.

In addition, two G043 batches manufactured at the development site using aged intermediate batches have been placed on stability under the same ICH storage conditions mentioned above. The intermediate was studied on stability under various storage conditions for 12 months and the quality remains as initial. Aged intermediate batches, stored for 12 months at 30 °C/75% RH (end-to-end stability) were processed into finished product. The finished product produced from the aged intermediate meets the specifications upon storage under long term and accelerated conditions. It is thus justified to calculate the expiry date of the finished product from the date that the intermediate is mixed with the tablet excipients.

Forced degradation studies under stress conditions were performed to test the effects of thermal acidic, thermal alkaline, oxidative, neutral, dry heat, humid heat, light (ICH Q1B) and metal ions.

The product was stable under acidic, alkaline, neutral, metal ion, dry heat, humid heat and ICH 1QB photolytic conditions, and prone to minor degradation under oxidative conditions. These studies were also to demonstrate that the UHPLC test method for assay and impurities control is stability indicating.

Based on available stability data, the proposed shelf-life of 2 years without special the storage conditions but with the recommendation to *"store in original package to protect from moisture",* as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

None of the materials used for the manufacture of the finished product is of human or animal origin.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The information for the active substance remains the same as for the authorised 60 mg film coated tablets. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical pharmacology, pharmacokinetics and toxicology of apalutamide (JNJ-56021927-AAA) have been well characterized in a full non-clinical packaged included in the original Marketing Authorization Application (MAA) for Erleada.

2.5.2. Pharmacology

No additional nonclinical pharmacology studies have been submitted with this application.

2.5.3. Pharmacokinetics

No additional nonclinical pharmacokinetics studies have been submitted with this application.

2.5.4. Toxicology

No additional nonclinical toxicity studies have been submitted.

2.5.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): apalutamide /Erleada			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	2.89 at pH 4 2.91at pH 7 2.94 at pH 9	Potential PBT (N) PBT assessment is not necessary (Q6 in EMA QA Guideline)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.20	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(Y) Apalutamide is considered a potential endocrine disruptor

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 673 L/kg (soil) K_{oc} = 744 L/kg (soil) K_{oc} = 760 L/kg (soil) K_{oc} = 889 L/kg (soil) K_{oc} = 516 L/kg (sludge) K_{oc} = 601 L/kg (sludge)	KOC < 10000 L/kg therefore a Phase II Tier B terrestrial compartment studies are not necessary. Kd, Koc andKdes values for [14C] ARN-509 were determined. The Kd values were 42.8, 5.48, 17.6, 4.50, 166 and 215 mL/g for DU soil, RMN soil, MSL soil, PD soil, Wareham activated sludge and New Bedford activated sludge Kdes values for DU soil, RMN soil, MSL soil, PD soil, Wareham activated sludge and New Bedford activated sludge were 55.7, 6.34, 21.6, 5.24, 121 and 170, mL/g
Ready Biodegradability Test	OECD 301	0.59% CO2 evolution was achieved by day 28.	ARN-509 cannot be classified as "readily biodegradable" by the criteria set forth in OECD Guideline 301B
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, whole\ system}$ = 103 days % shifting to sediment =10% Taunton River (20oC): $DT_{50, water}$ = 30 d $DT_{50, sediment}$ = >1000 d $DT_{50, sediment}$ = 315 d (SFO) Weweantic River (20oC): $DT_{50, water}$ = 32 d (SFO) $DT_{50, sediment}$ =105 d $DT_{50, system}$ = = 92 d (SFO)	ARN-509 fulfill the criteria for classification as very persistent (vP) in the aquatic environment.

(Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	72h-NOEC	2.4	µg/L	Growth rate (*Pseudokirchneriella subcapitata*)
Daphnia sp. Reproduction Test	OECD 211	21- NOEC	1.9	mg/L	Juvenile production (*Daphnia magna*)

Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	3.7	mg/L	*Oncorhynchus mykiss*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	>1000	mg/L	

2.5.6. Discussion on non-clinical aspects

No pharmadynamics, pharmacokinetics and toxicology studies have been submitted for this application. Apalutamide is already used in existing marketed products and no significant increase in environmental exposure is anticipated, since calculations for Predicted Environmental Concentration and risk characterization ratios that were based on worst-case scenarios of the EU population that received apalutamide.

Considering the above data, apalutamide should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

Based on the environmental risk assessment, no adverse environmental effects are anticipated as a consequence of the use of apalutamide for the treatment of prostate cancer as indicated in the SmPC.

2.5.7. Conclusion on the non-clinical aspects

There are no objections to an approval of this line extension from a nonclinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 1 - Clinical biopharmaceutic studies

Study ID	Objective(s)	Number of Treated Participants	Dose	Route	Formulation
56021927PCR1027	Part 1: To evaluate the PK and relative BA of new apalutamide tablet formulations compared to the current commercial tablet formulation	28 (healthy adult male participants)	240 mg, single dose	Oral	Fasting: • A (reference): 4×60 mg current commercial tablets (G023) • C (test): 1×240 mg tablet (G043)
	Part 2: To evaluate the PK and relative BA of new apalutamide tablet formulations being manufactured with a modified process compared to an apalutamide tablet	20 (healthy adult male participants)	240 mg, single dose	Oral	Fasting: • Reference: 1×240 mg tablet (G043) • Test: 1×240 mg tablet manufactured with a modified process

	formulation from Part 1				
56021927PCR1028	Part 1: To evaluate the BE of a new apalutamide tablet formulation relative to the current commercial tablet formulation	74 (healthy adult male participants)	240 mg, single dose	Oral	Fasting: • A (reference): 4×60 mg current commercial tablets (G023) • B (test): 1×240 mg tablet (G043)
	Part 2: To evaluate the BA of a new apalutamide tablet formulation under fed or fasting conditions	21 (healthy adult male participants)	240 mg, single dose	Oral	Fasting: • C (reference): 1×240 mg tablet (G043) Fed: • D (test): 1×240 mg tablet (G043)

2.6.2. Clinical pharmacology

The apalutamide drug substance is classified as BCS Class 2.

The current commercially available formulation of apalutamide is an immediate release oral film-coated (FC) tablet (G023) containing 60 mg of apalutamide drug substance. This formulation is produced using enabling technology.

Multiple 240 mg FC tablet formulations were developed for clinical evaluation. An enabling technology was selected to address the limited solubility of the drug substance and to increase the BA.

Formulation G043 was selected to be tested in a pivotal bioequivalence trial. As the proposed formulation (G043) is not proportional to that of the existing strength (G023), bioequivalence needs to be demonstrated between 1 x 240 mg strength and 4 x 60 mg strength. In addition, as the formulation is different, the food effect may also be different since the food effect is not only drug dependent but may also be product or formulation dependent.

2.6.2.1. Pharmacokinetics

Analytical methods

The applicant has submitted 3 bioanalytical methods: 11, 25 (partial validation) and 32 (partial validation).

Pharmacokinetic data analysis

Plasma concentration data has been analysed in both studies with non-compartmental approach to estimate the PK parameters of interest. The protocol of study 56021927PCR1027 did not define the method for the calculation of AUC, however this was stated in the Clinical Pharmacology Analysis Plan. The CSR identifies that AUC was estimated by the linear trapezoidal rule when explaining the abbreviation of $AUC_{0\text{-}72h}$. In the protocol of study 56021927PCR10278 the linear trapezoidal rule is pre-defined.

The PK analysis was conducted in both studies with Phoenix™ WinNonlin® (Certara L.P., Princeton, NJ, US).

Absorption

Bioavailability

The 240 mg biopharmaceutic development program consisted of the initial relative BA study (**PCR1027 Part 1**) to select the final 240 mg FC tablet formulation, the formal BE study under fasting conditions

(**PCR1028 Part 1**), and relative BA to demonstrate lack of food effect (**PCR1028 Part 2**). Additionally, the relative BA of the selected tablet was further evaluated in **PCR1027 Part 2**.

Protocol Number: 56021927PCR1027, Phase 1

A Single-Dose, Open-label, Randomized, 2-Part, 2-way Crossover Study to Assess the Relative Bioavailability of New Apalutamide Tablet Formulation with Respect to the Current Commercial Apalutamide Tablet Formulation in Healthy Male Participants.

Primary Objectives

Part 1: To evaluate the pharmacokinetics (PKs) and relative bioavailability of new apalutamide tablet formulation compared to the current commercial apalutamide tablet formulation in healthy male participants under fasted conditions at a single dose of 240 mg.

Part 2: To evaluate the PK and relative bioavailability of new apalutamide tablet formulations being manufactured with a modified process compared to an apalutamide tablet formulation from Part 1 when administered in healthy male participants under fasted conditions at a single dose of 240 mg.

Secondary Objective

To assess the safety profile of apalutamide following a single dose administration as a new tablet formulation and as the current commercial tablet formulation.

Study design

The study was conducted as a randomized, open-label, 2- part, 2-period, 2-way crossover, single centre, Phase 1 study. A single dose of 240 mg apalutamide was administered for each treatment period in a 2-way crossover pattern under fasted conditions in healthy male participants.

There was a minimum washout of 6 weeks in between the 2 periods as planned.

Principle Investigator: Danielle Armas, M.D

Clinical facility: Celerion 2420 West Baseline Road Tempe, AZ, 85283 United States of America.

Date of the protocol: 10 July 2020. Amendment 1: 14 August 2020 and Amendment 2: 30 April 2021.

The overall reason for the first amendment was to incorporate the Food and Drug Administration (FDA) recommendation to discontinue a participant if he experiences any ≥ Grade 2 adverse event (AE) at least possibly related to study treatment as per investigator assessment.

The overall reasons for the second amendment were to update study treatments for crossover procedure and to update the number of participants for Part 2 of study.

Date of IRB approval of protocol: 20/08/2020. The IRB was Advarra, 6940 Columbia Gateway Drive, Suite 110, Columbia, MD, 21046. United States of America

Dates of the clinical phases of the study: 4 October 2020 – 21 November 2020 (Part 1) and 19 October 2021 to 30 November 2021 (Part 2).

Study Period: 17 September 2020 (date first participant signed informed consent form) to 02 January 2022 (date of last contact of the participant who had last completed the study).

Dates of the bioanalytical part: 27 November 2020 to 15 December 2021.

Blood samples were taken pre-dose and at 0h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h and 72h after administration of the products. Samples were collected in tubes containing heparin and centrifuged at 3000 rpm for 10 min at 4ºC. Plasma samples were stored at -20ºC until analysis.

Test and Reference products

Treatment A (Reference): 240 mg apalutamide given as a single dose of 4×60 mg current commercial formulation tablets (G023).

Treatment C (Test): 240 mg apalutamide given as a single dose of 1×240 mg in a tablet formulation (G043).

Study Treatment Information

Study interventions and dose strength	Formulation	Batch Number (bulk)	Packaged Lot Number	Expiry. Date
Treatment A (Reference) 240 mg (4×60 mg)	Commercial formulation tablets (G023)	19AG7990x	CSU 4381013	24 Jan 2022
Treatment C (Test for Part 1 and reference for Part 2) 240 mg	Tablet (G043)	20F16/G043 21F17/G043	CSU 4381141 CSU 4383246	15 Jun 2021 25 May 2022

Population(s) studied

The planned sample size was 68 male participants (approximately, 28 participants in Part 1 and 40 participants in Part 2), although 48 male participants were analysed (28 participants in Part 1 and 20 participants in Part 2). Of the 48 participants enrolled, 46 participants completed the study and 2 participants terminated study participation prematurely.

The participants were randomized to treatment sequences (AC, CA) and were treated as follows:

- Six participants randomized to Treatment Sequence AC were administered Treatment A on Period 1 Day 1 and Treatment C on Period 2 Day 1. One participant randomized to Treatment Sequence AC who was administered Treatment A was withdrawn from the study on Period 1 Day 1 due to a failed urine drug screen for cotinine and was not administered Treatment C on Period 2 Day 1.

- Seven participants randomized to Treatment Sequence CA were administered Treatment C on Period 1 Day 1 and Treatment A on Period 2 Day 1.

Analytical methods

Plasma samples of apalutamide (JNJ-56021927) and metabolite JNJ-56142060 were analysed using a validated bioanalytical method using liquid chromatography for separation and tandem mass spectrometry (LC-MS/MS) for detection (25). This method is supported by the following method validation reports: **25**; **11**.

Plasma concentrations of apalutamide and metabolite JNJ-56142060 were determined within the range of quantitation of 0.00500 to 5.00 µg/mL for apalutamide and metabolite JNJ-56142060.

Incurred sample reproducibility was performed in 120/1316 (9.1%) of the study samples. 100% of the ISR results were within acceptance criteria for JNJ-56021927 and 97.5% of the ISR results were within acceptance criteria for JNJ-56142060.

The maximum frozen storage for study samples was 61 days. Samples and calibration/QC samples were analyzed within proven frozen stability of 630 days at -70°C.

The samples (1316) were received on the 20 and 26 November 2020 as well as on the 08 December 2021 frozen at -70ºC.

The blank and zero samples of each run were used to assess selectivity (signal-to-noise ratio).

All study samples from a subject were initially analyzed in the same analytical run. The calibrators were 0.00500 (LLOQ), 0.0100, 0.0250, 0.100, 0.250, 1.00, 2.50, 4.00, and 5.00 (ULOQ) µg/mL for both analytes and the QC samples were 0.0150, 0.300, 1.50 and 3.75 µg/mL for both analytes, up to run ID 12; 0.0150, 0.300, 2.40 and 3.75 µg/mL for both analytes, as of run ID 13.

No dilution was validated. When study samples were diluted, overcurve QC samples (diluted 2-fold at 7.50 µg/mL) were analyzed in 6-fold in the analytical runs concerned, applying the same method of dilution as used for the study samples.

In each run containing a calibration curve, 3 zero plasma samples were analyzed directly following the sample at the highest calibration level and all QC samples at the highest level to discard the existence of carry-over in the equipment. The analyte response in all zero samples had to be <20.0% of the response (peak area) found in the sample at the LLOQ level analyzed in the same run.

The response of the internal standard had to be between 30% and 170% of the mean of the internal standard area of each analytical run. The internal standard response was evaluated in each run containing study samples. No samples were repeated for inadequate internal standard response.

The total number of samples selected for the assessment of incurred sample reproducibility was 120. For each reproducibility result, the relative difference from the original result was calculated. For at least 2/3 of the samples, the absolute relative difference had to be ≤20.0%.

One sample was reanalyzed because the original result was out of range (>5.00 µg/mL) for JNJ-56021927, and because not enough internal standard working solution was added for JNJ-56142060. Inadvertently, the sample was initially reanalyzed undiluted. Reanalysis was repeated after 2-fold dilution.

Run ID 2 was rejected for both analytes and completely reanalyzed in run ID 5, run ID 3 was rejected for JNJ-56021927 and completely reanalyzed in run ID 6, and run ID 4 was rejected and completely reanalyzed in run ID 9.

No samples were reanalyzed for non-analytical reasons, and no reintegrations were carried out.

Chromatograms of the first 5.0% of the study samples, including blank, zero, calibration and QC samples of the involved analytical runs were shown.

Pharmacokinetic variables

The primary PK parameters of interest for the statistical analysis were C_{max} and AUC_{0-72h} of apalutamide after dosing.

PK parameters were calculated with a non-compartmental analysis with Phoenix™ WinNonlin® (Certara L.P., Princeton, NJ, US).

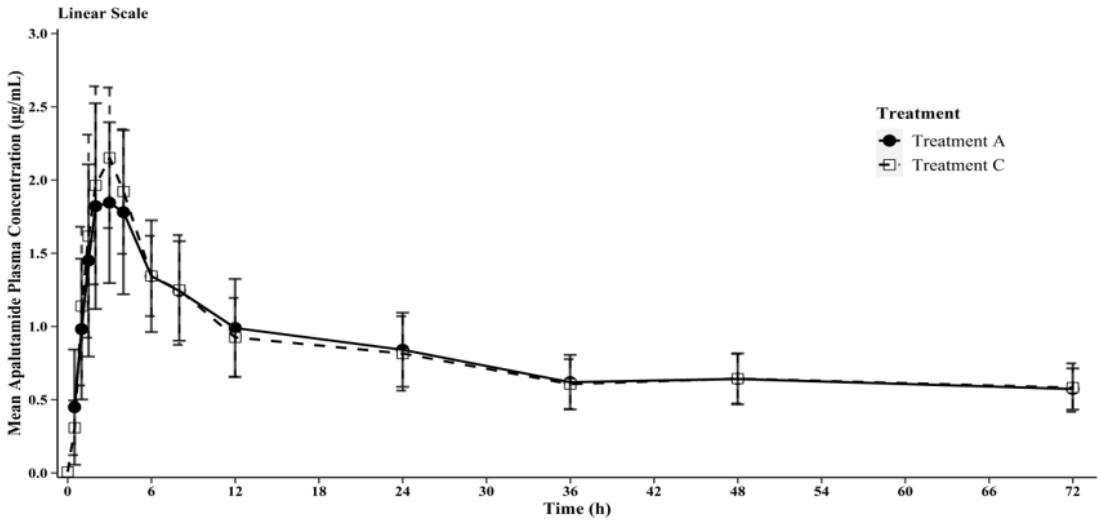
Statistical methods

The 90% confidence intervals for the ratio of Test formulation over the Reference formulation were calculated for ln-transformed C_{max} and AUC_{0-72} by ANOVA using Mixed-procedure.

Results

The mean plasma concentration-time curves for apalutamide treatment C (test G043) vs reference G023 (treatment A) part 1 are shown in **Figure 1**.

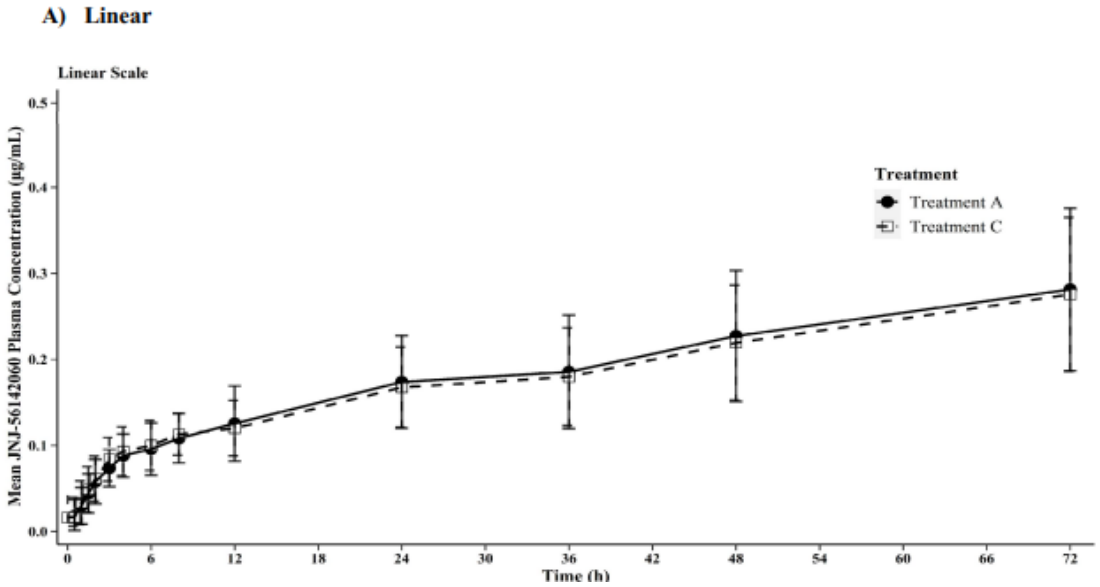
Figure 1. Mean apalutamide plasma concentration (µg/mL) over time (h) for apalutamide treatment C (test G043) vs reference G023 (treatment A) part 1



Treatment A (Reference): 240 mg apalutamide given as a single dose of 4x60 mg current commercial formulation tablets (G023)
Treatment C (Test): 240 mg apalutamide as a single dose of 1 x 240 mg in a tablet formulation (G043)

The mean plasma concentration-time curves for apalutamide metabolite treatment C (test G043) vs reference G023 (treatment A) are shown in **Figure 2**.

Figure 2. Mean apalutamide metabolite plasma concentration (µg/mL) over time (h) for apalutamide metabolite treatment C (test G043) vs reference G023 (treatment A)



Part 1: All 14 participants were included in descriptive statistics for Treatment A and 13 participants were included in descriptive statistics for Treatment C. One participant in Treatment C Period 2 discontinued due to failed urine drug screening.

Pre-dose plasma PK concentrations were observed for 19 participants in period 2 for respective treatments for analyte apalutamide. These pre-dose concentrations were below 5% of Cmax in period 2. Hence these participants were included for PK and inferential statistical evaluations.

Pre-dose plasma PK concentrations were observed for 25 participants in period 2 for respective treatments for analyte JNJ-56142060. These pre-dose concentrations were above 5% of C_{max} except for 3 participants

(below 5% of C_{max}). Participants with pre-dose above 5% of C_{max} were excluded from calculation of descriptive statistics.

The pharmacokinetic variables of apalutamide of the Test and the Reference products are shown in the next

Table 2 together with the statistical analysis.

Table 2. Relative bioavailability: Statistical comparison of apalutamide exposure parameters after oral administration of 240mg apalutamide under fasted conditions in healthy adult participants (pharmacodynamic data analysis set – study 56021927PCR1027)

Statistical Comparison of Apalutamide Exposure Parameters After Oral Administration of 240 mg Apalutamide under Fasted Conditions in Healthy Adult Participants; Pharmacokinetic Data Analysis Set (Study 56021927PCR1027); (Relative Bioavailability)

		Geometric Means				
Treatment Comparison (Test Vs Reference)	PK Parameter	Reference	Test	Ratio of Geometric Means (%)	90% CI (%)	Intra-participant CV (%)
Part 1: Treatment C Vs Treatment A	C_{max} (µg/mL)	1.95	2.25	115.2	101.16-131.20	18.6
	AUC_{0-72h} (h*µg/mL)	54.7	55.8	102.02	99.05-105.07	4.2

N = 13 for Treatment C Vs Treatment A for each treatment per PK parameter (C_{max}, AUC_{0-72h})

Note: Analysis done on log transformed data and the results were back-transformed using anti-logarithm.

Mixed effects model, controlling for treatment, sequence, and period as fixed effects, and participant as a random effect.

Treatment A (Reference): 240 mg apalutamide given as a single dose of 4×60 mg current commercial formulation tablets (G023).

Treatment C (Test [Reference in Part 2]): 240 mg apalutamide given as a single dose of 1×240 mg in a tablet formulation (G043).

Intra- participant CV(%) = 100* (sqrt(exp(MSE)-1).

Protocol deviations:

Major protocol deviations reported during the study were:

- According to the Time and Events Schedule defined in the protocol, blood samples for safety laboratory assessments (chemistry and haematology) were to be collected during the Day 2 visit. However, they were not collected in 6 participants randomized to Treatment Sequence CA.

The reported major protocol deviations did not have any impact on the interpretation of study data. No minor protocol deviations were reported during the study.

<u>Bioequivalence</u>

Protocol Number: 56021927PCR1028, Phase 1

A Single-Dose, Open-label, Randomized, 2 Part Pivotal Study to Assess Bioequivalence of a New Apalutamide Film-Coated Tablet with Respect to Current Commercial Film-Coated Tablets and Food Effect of the New Tablet in Healthy Male Participants

The primary objective the first part was to evaluate the bioequivalence of a new apalutamide film-coated tablet formulation with respect to the current commercial apalutamide film-coated tablet formulation.

The primary objective of the second part was to estimate the bioavailability of a new apalutamide film-coated tablet formulation when administered under fed or fasted conditions.

Study design

This was a randomized, open-label, single-dose, single-center, 2-part Phase 1 study in healthy male participants. Each part consisted of 2-sequence, 2-treatment, 2-period, 2-way crossover design. A single-dose of 240 mg apalutamide was administered orally in each treatment period. Part 1 assessed the bioequivalence of a new apalutamide film-coated tablet formulation relative to the current commercial apalutamide film-coated tablet formulation under fasted conditions and Part 2 assessed the food effect of a new 240 mg apalutamide film-coated tablet when administered with or without food.

Table 3. Randomization scheme

Randomization Scheme

Part	Sequence Number	No. of Participants	Period 1	Period 2	Period 1 Prandial Condition	Period 2 Prandial Condition
1	1	37	A	B	Fasting	Fasting
	2	37	B	A	Fasting	Fasting
2	3	12	C	D	Fasting	Fed
	4	12	D	C	Fed	Fasting

A: Treatment A (Reference): 240 mg apalutamide given as a single-dose of 4×60 mg current commercial formulation film-coated Reference Tablet A (G023).
B: Treatment B (Test): 240 mg apalutamide given as a single-dose of 1×240 mg film-coated Test Tablet B (G043).
C: Treatment C (Reference): 240 mg apalutamide given as a single-dose of 1×240 mg film-coated Test Tablet B (G043).
D: Treatment D (Test): 240 mg apalutamide given as a single-dose of 1×240 mg film-coated Test Tablet B (G043).

Hypothesis:

Part 1: The apalutamide component of a new apalutamide 240 mg film-coated tablet formulation is bioequivalent with respect to the current commercial 60 mg film-coated tablet formulation when administered at the same dose under fasted conditions as determined by the GMR for Cmax and AUC0-72 (test/reference) and their corresponding 90% CIs being contained within the 80.00% to 125.00% criteria for bioequivalence.

Part 2: This was an estimation study to provide the precision of the point estimates for bioavailability (as assessed by the GMR for C_{max} and AUC_{0-72}) between fed and fasted conditions and no formal hypothesis was tested.

A minimum washout period of 7 weeks or a maximum of 8 weeks separated the dose administrations in the 2 treatment periods. The duration of participation in the study for an individual participant was approximately 12 weeks (including screening, open-label treatment phase, and EOS/EW assessments). Further information is listed below:

Principle Investigator: Danielle Armas, M.D

Clinical facility: Celerion 2420 West Baseline Road Tempe, AZ, 85283 United States of America.

Date of the protocol: 09 August 2021.

Date of IRB approval of protocol: 30/09/2021. The IRB was Advarra, 6940 Columbia Gateway Drive, Suite 110, Columbia, MD, 21046. United States of America.

Dates of the clinical phases of the study:16 November 2021 to 29 November 2021 (Period 1) and 4 January 2022 to 17 January 2022.

Study Period: 28 October 2021 for Part 1; 12 November 2021 for Part 2 (Date first participant signed informed consent) to 15 March 2022 for Part 1; 16 March 2022 for Part 2 (Date of last participant last visit).

Dates of the bioanalytical part: 23 January 2022 to 21 February 22.

Blood samples were taken pre-dose and at 0h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h and 72h after administration of the products. Samples were collected in tubes containing K2-EDTA and centrifuged at 2500-3000 rpm for 15 min at 4ºC. Plasma samples were stored at -20ºC until analysis..

Test and Reference products

The following reference and test tablet formulations were administered during the study:

Part 1

Treatment A (Reference): 240 mg apalutamide given as a single-dose of 4×60 mg Reference Tablet A (G023) administered under fasted conditions.

Treatment B (Test): 240 mg apalutamide given as a single-dose of 1×240 mg Test Tablet B (G043) administered under fasted conditions.

Part 2

Treatment C (Reference): 240 mg apalutamide given as a single-dose of 1×240 mg Test Tablet B (G043) administered under fasted conditions.

Treatment D (Test): 240 mg apalutamide given as a single-dose of 1×240 mg Test Tablet B (G043) administered under fed conditions.

Table 4. Study treatment information

Study Part	Treatment	Treatment Condition	Dose (Formulation)	Batch/ Lot Number	Expiry Date
Part 1	Treatment A	Fasted	240 mg apalutamide given as a single dose of 4×60 mg Reference Tablet A (G023)	21BG4517X	5 March 2024
	Treatment B	Fasted	240 mg apalutamide given as a single-dose of 1×240 mg Test Tablet B (G043)	4586786	9 April 2023
Part 2	Treatment C	Fasted	240 mg apalutamide given as a single dose of 1×240 mg Test Tablet B (G043)	4586786	9 April 2023
	Treatment D	Fed	240 mg apalutamide given as a single dose of 1×240 mg Test Tablet B (G043)	4586786	9 April 2023

Population(s) studied

Approximately, 98 healthy male participants (74 participants in Part 1 and 24 participants in Part 2) were to be enrolled and randomized in the study to ensure that at least 84 participants (64 participants in Part 1 and 20 participants in Part 2) complete all required assessments.

A total of 95 healthy male participants (74 participants in Part 1 and 21 participants in Part 2), were randomized. in this study. Of the 74 participants in the study Part 1, 64 participants completed the study and 10 participants terminated study participation prematurely. Of the 21 participants in the study Part 2, 20 participants completed the study and 1 participant terminated study participation prematurely.

In Part 1:

- Five (6.8%) participants terminated study participation prematurely due to COVID-19 related AEs (3 [8.1%] participants randomized to Treatment Sequence AB post administration of Treatment A and 2 [5.4%] participants randomized to Treatment Sequence BA post administration of Treatment B).

- One (1.4%) participant (1 [2.7%] participant randomized to Treatment Sequence AB) was terminated prematurely due to an TEAE of hypercholesterolaemia post administration of Treatment A.

- One (1.4%) participant (1 [2.7%] participants randomized to Treatment Sequence AB terminated study participation prematurely due to withdrawal by the participant post administration of both Treatment A and Treatment B.

- Three (4.1%) participants (none randomized to Treatment Sequence AB and 3 [8.1%] participants randomized to Treatment Sequence BA) terminated study participation prematurely due to other reasons (1 participant discontinued on Day 1 of Period 2 due to positive COVID-19 result post administration of both Treatment A and Treatment B; 1 participant was withdrawn from the study on Period 2 Day -1 due to a failed urine drug screen for cocaine prior to administration of Treatment A in Period 2; and 1 participant was withdrawn from the study on Period 2 Day -1 due to a positive urine drug screen for tetrahydrocannabinol (THC) prior to administration of Treatment A in Period 2).

In part 2:

Study participation was terminated prematurely in 1 (4.8%) participant (1 [9.1%] participant randomized to Treatment Sequence CD) post administration of Treatment C in Period 1 due to a positive urine drug screen result for cannabinoids

Analytical methods

Plasma samples of apalutamide (JNJ-56021927) were analyzed using a validated bioanalytical method using liquid chromatography for separation and tandem mass spectrometry for analysis (25). This method is supported by the following method validation reports: **25** / **11**.

Plasma concentrations of apalutamide were determined using lower limit of quantification (LLOQ) of 0.005 µg/mL. The range of quantitation was 0.005 to 5.00 µg/mL for apalutamide.

The in-study validation or study sample analysis is submitted as an appendix to the CSR where the Compliance and/or Drug Concentration Data should be submitted instead of in its location in section 5.3.1.4.

Incurred sample reproducibility was performed in 180/2527 (7.1%) of the study samples, and 99.4% of the ISR results were within acceptance criteria.

The maximum frozen storage for study samples was 97 days. Samples and calibration/QC samples were analyzed within proven frozen stability of 630 days at -70°C.

The samples (2527) were received on the 31 Jan 2022, 7 and 15 Fed 2022 frozen at -70ºC.

The blank and zero samples of each run were used to assess selectivity (signal-to-noise ratio).

All study samples from a subject were initially analyzed in the same analytical run. The calibrators were 0.00500 (LLOQ), 0.0100, 0.0250, 0.100, 0.250, 1.00, 2.50, 4.00, and 5.00 (ULOQ) µg/mLand the QC samples 0.0150, 0.300, 2.40 and 3.75 µg/mL. No diluted QC samples were included because no samples required dilution.

In each run containing a calibration curve, 3 zero plasma samples were analyzed directly following the sample at the highest calibration level and all QC samples at the highest level to discard the existence of carry-over in the equipment. The analyte response in all zero samples had to be <20.0% of the response

(peak area) found in the sample at the LLOQ level analyzed in the same run. In run ID 5, the response of the first zero sample following the fourth QC sample at the highest level exceeded 20.0% of the LLOQ. Evaluation as per procedure PRA-QMS-00662 [12] by the Project Manager showed that this did not affect the results of the study samples. In run ID 10, the JNJ-56021927 response in multiple carry-over zero samples was >20.0% of its response at the LLOQ level. This was investigated. See IUR number 2022-NL-0069 in Section 6.3.1. Run ID 10 was rejected and all samples in the run were reanalyzed.

The response of the internal standard had to be between 30% and 170% of the mean of the internal standard area of each analytical run. The internal standard response was evaluated in each run containing study samples. No samples were repeated for inadequate internal standard response.

The total number of samples selected for the assessment of incurred sample reproducibility was 180. For each reproducibility result, the relative difference from the original result was calculated. For at least 2/3 of the samples, the absolute relative difference had to be ≤20.0%.

Fifteen samples were reanalyzed because of a preparation error. Run ID 10 was rejected and the samples were reanalyzed in run IDs 17 and 18. No samples were reanalyzed for non-analytical reasons and no reintegrations were carried out.

No samples were reanalyzed for non-analytical reasons and no reintegrations were carried out.

Chromatograms of the first 20.0% of the study samples, plus the contingent chromatograms of ISR analysis of these study samples, including test, blank, zero, calibration and QC samples of the involved analytical runs are submitted.

Pharmacokinetic variables

The primary PK parameters of interest for the statistical analysis were C_{max} and $AUC_{0\text{-}72h}$ of apalutamide after dosing.

PK parameters were calculated with a non-compartmental analysis with Phoenix™ WinNonlin® (Certara L.P., Princeton, NJ, US). AUC was calculated according to the linear trapezoidal rule as pre-defined in the protocol.

Two AUC values were excluded from the statistical analysis of Part 1 because the sample at 72 h was missing and the primary PK parameter cannot be calculated.

Statistical methods

Part 1:

A linear mixed effect model that included treatment, period, and treatment sequence as fixed effects, and participant as a random effect, was applied to estimate the least squares means and intra-participant variance. Using these estimated least squares means and intra-participant variance, the point estimate and 90% CIs for the difference in means on a log scale between tests and reference were constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the GMRs of C_{max} and AUC0-72h of the following pairs of treatments: Treatment B (Test) versus Treatment A (Reference).

Part 2:

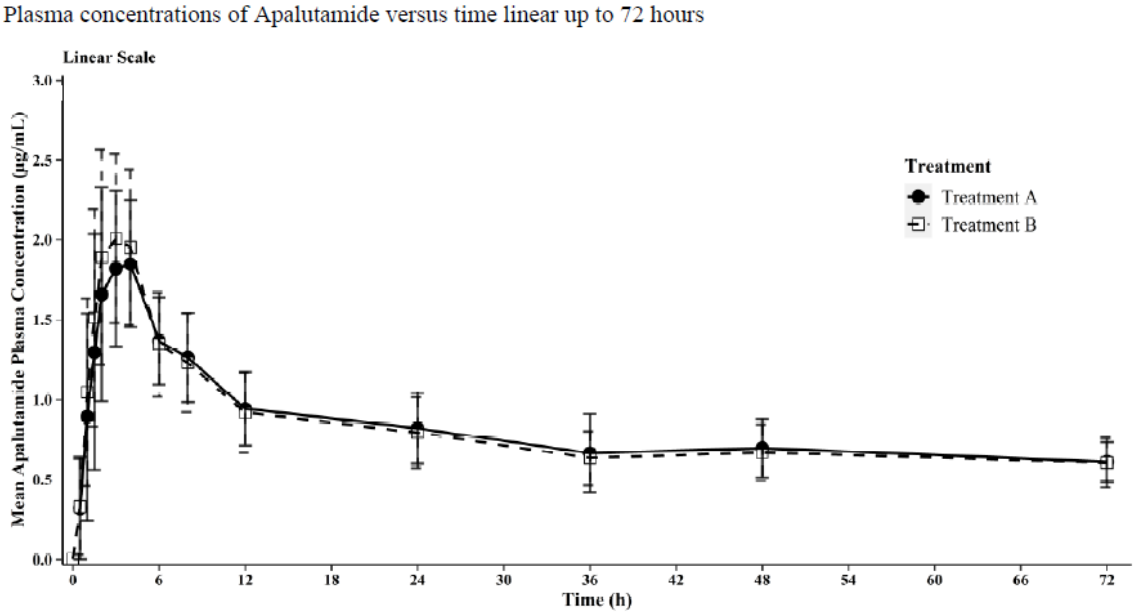
A linear mixed effect model that included treatment, period, and treatment sequence as fixed effects, and participant as a random effect, was applied to construct the 90% CI for the GMR of the PK parameters between D and C.

Results

Part 1:

The mean plasma concentration-time curves for apalutamide are shown in **Figure 3** below.

Figure 3. Mean apalutamide plasma concentration (µg/mL) over time (h) for apalutamide treatment B (test G043) vs reference G023 (treatment A), administered under fasting conditions

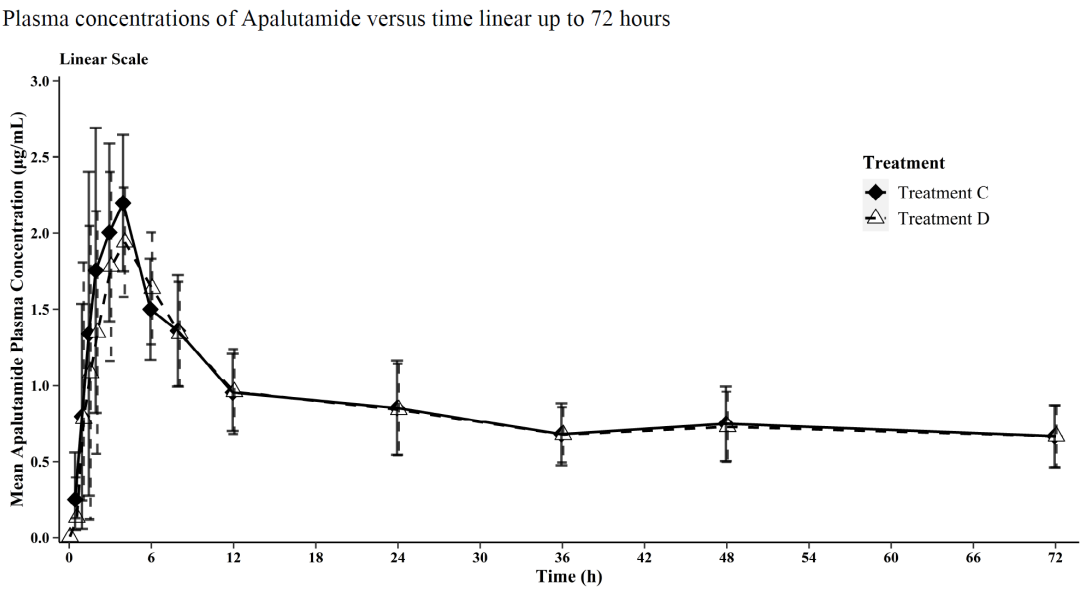


Treatment A (Reference): 240 mg apalutamide given as a single-dose of 4×60 mg current commercial formulation film-coated Reference Tablet A (G023) administered under fasting conditions
Treatment B (Test): 240 mg apalutamide given as a single-dose of 1×240 mg film-coated Test Tablet B (G043) administered under fasting conditions.

Part 2:

The mean plasma concentration-time curves for apalutamide are shown in **Figure 4** below.

Figure 4. Mean apalutamide plasma concentration (µg/mL) over time (h) for apalutamide treatment C (Reference, test G043, fasting) vs treatment D (test, test G043, fed)



Treatment C (Reference): 240 mg apalutamide given as a single-dose of 1×240 mg film-coated Test Tablet B (G043) administered under fasting conditions.
Treatment D (Test): 240 mg apalutamide given as a single-dose of 1×240 mg film-coated Test Tablet B (G043) administered under fed conditions.

Part 1: All 14 participants were included in descriptive statistics for Treatment A and 13 participants were included in descriptive statistics for Treatment C. One participant in Treatment C Period 2 discontinued due to failed urine drug screening.

Pre-dose plasma PK concentrations were observed for 19 participants in period 2 for respective treatments for analyte apalutamide. These pre-dose concentrations were below 5% of C_{max} in period 2. Hence these participants were included for PK and inferential statistical evaluations.

Pre-dose plasma PK concentrations were observed for 25 participants in period 2 for respective treatments for analyte JNJ-56142060. These pre-dose concentrations were above 5% of Cmax except for 3 participants (below 5% of C_{max}). Participants with pre-dose above 5% of C_{max} were excluded from calculation of descriptive statistics.

Part 2: 19 participants were included in descriptive statistics for Treatment C and all 20 participants were included in descriptive statistics for Treatment D. One participant in Treatment C Period 2 discontinued due to due to AE.

Pre-dose plasma PK concentrations were observed for 25 participants in Period 2 for respective treatments for analyte apalutamide. These pre-dose concentrations were below or equal to 5% of C_{max} in period 2. Hence these participants were included for PK and inferential statistical evaluations.

Pre-dose plasma PK concentrations were observed for 19 participants in Period 2 for respective treatments for analyte JNJ-56142060. These pre-dose concentrations were above 5% of C_{max}. Participants with pre-dose above 5% of C_{max} were excluded from calculation of descriptive statistics.

The pharmacokinetic variables of apalutamide of the Test and the Reference products are shown in the next table **Table 5** together with the statistical analysis.

Part 1 results

Table 5. Part 1 / Bioequivalence - Primary analysis results – statistical comparison of apalutamide exposure parameters after single oral administration of 240mg apalutamide as Treatment B (G043, Test) and Treatment A (G023, Reference) under fasted conditions in healthy adult participants (pharmacodynamic data analysis set – Study 56021927PCR1028)

Statistical Comparison of Apalutamide Exposure Parameters After Single Oral Administration of 240 mg Apalutamide as Treatment B (G043, Test) and Treatment A (G023, Reference), Under Fasted Conditions in Healthy Adult Participants; Pharmacokinetic Data Analysis Set (Study 56021927PCR1028); Part 1 (Bioequivalence)

Primary analysis					
Geometric Means					
PK Parameter	Treatment A (Reference)	Treatment B (Test)	Ratio of Geometric Means (%)	90% CI (%)	Intra-Participant CV (%)
C_{max} (µg/mL)	2.05	2.25	109.67	104.55-115.04	16.4
AUC_{0-72h} (h*µg/mL)	57.7	59.3	102.71	100.78-104.68	6.4

N=65 for C_{max} and N=63 for AUC_{0-72h} per each treatment
Note: Analysis done on log transformed data and the results were back-transformed using anti-logarithm.
Primary Analysis: Mixed effects model, controlling for treatment, sequence, and period as fixed effects, and participant within sequence as a random effect.
Treatment A (Reference): 240 mg apalutamide given as a single-dose of 4×60 mg current commercial formulation film-coated Reference Tablet A (G023) administered under fasting conditions.
Treatment B (Test): 240 mg apalutamide given as a single dose of 1×240 mg film-coated Test Tablet B (G043) administered under fasting conditions.

Part 2 results

Table 6. Part 2 / Food Effect - statistical comparison of apalutamide exposure parameters after single oral administration of 240mg apalutamide as Treatment D (G043, Test, Fed) and Treatment C (G043, Reference, Fasted) in healthy adult participants (pharmacodynamic data analysis set – Study 56021927PCR1028)

Statistical Comparison of Exposure Parameters of Apalutamide After Oral Administration of 240 mg Apalutamide as Treatment D (single oral dose of 1×240 mg film-coated Test Tablet B [G043], Test, Fed) and Treatment C (single oral dose of 1×240 mg film-coated Test Tablet B [G043], Reference, Fasted), in Healthy Adult Participants; Pharmacokinetic Data Analysis Set (Study 56021927PCR1028); Part 2 (Food Effect)

Food Effect					
Geometric Means					
PK Parameter	Treatment C (Reference)	Treatment D (Test)	Ratio of Geometric Means (%)	90% CI (%)	Intra- participant CV (%)
C_{max} (µg/mL)	2.36	2.15	90.96	83.06-99.61	16.7
AUC_{0-72h} (h*µg/mL)	59.2	59.2	99.94	97.12-102.84	5.2

N=20 each for C_{max} and AUC_{0-72h} per each treatment
Note: Analysis done on log transformed data and the results were back-transformed using anti-logarithm
Mixed effects model, controlling for treatment, sequence, and period as fixed effects, and participant within sequence as a random effect
Treatment C (Reference): 240 mg apalutamide given as a single dose of 1×240 mg film-coated Test Tablet B (G043) administered under fasting conditions
Treatment D (Test): 240 mg apalutamide given as a single dose of 1×240 mg film-coated Test Tablet B (G043) administered under fed conditions.
Intra- participant CV (%) = 100* (sqrt(exp(MSE)-1)

Protocol deviations:

Major protocol deviations reported during Part 1 of the study were:

- Physical examination was not conducted in 1 participant randomized to Treatment Sequence BA on Period 2 Day 4.

- One participant randomized to Treatment Sequence BA was withdrawn from the study due to a failed urine drug screen for cocaine on Period 2 Day -1. The site staff conducted only Period 2 Day -1

procedures and following withdrawal did not complete the procedures for early termination that included ECG, full physical examination (only brief PE was performed), and TSH/testosterone labs. Although the site staff contacted the participant to return to the clinic to complete missed procedures, the participant refused to return as the compensation offered was not enough for him to return to the site.

- One participant randomized to Treatment Sequence BA was withdrawn from the study due to a failed urine drug screen for THC on Period 2 Day -1. The site staff conducted only Period 2 Day -1 procedures and following withdrawal did not complete the procedures for early termination that included ECG, full physical examination (only brief PE was performed), and TSH/testosterone labs. Although the site staff contacted the participant to return to the clinic to complete missed procedures, the participant did not respond to the certified letter and was deemed lost to follow-up.

No major protocol deviations were reported during Part 2 of the study.

Pharmacokinetic conclusion on study 56021927PCR1028:

Part 1 (Bioequivalence): Formulation G043 versus G023 under Fasted Conditions

- Treatment B (G043) is bioequivalent to Treatment A (G023). The 90% CI of the GMR of Cmax and AUC0-72h fell completely within the BE limits of 80.00%-125.00%.

Part 2 (Food Effect): Fed versus Fasted for Formulation G043

- Treatment D (G043-Fed) is comparable to Treatment C (G043-Fasted). The 90% CI of the GMR of Cmax and AUC0-72h fell completely within the limits of 80.00%-125.00%.

2.6.3. Discussion on clinical pharmacology

The biopharmaceutic development program for the new 240 mg strength consisted of the initial bioavailability (BA) study (**56021927PCR1027 Part 1**) to select the final (240 mg) film-coated tablet formulation, the formal bioequivalence (BE) study performed under fasting conditions (**56021927PCR1028 Part 1**), and the relative BA study to demonstrate lack of food effect (**56021927PCR1028 Part 2**). Additionally, the relative BA of the selected tablet with a modified process was further evaluated in study **56021927PCR1027 Part 2**.

The study (56021927PCR1027) to assess the systemic exposure of the new tablet formulation (test G043) vs. the reference one (i.e. G023 - the currently commercial 60 mg FC tablet) in healthy male participants, is considered adequate. The statistical analysis is acceptable (i.e. based on log-transformation and conventional ANOVA factors considered: treatment, sequence, period and subject (sequence)). The PROC MIXED method reports the same results as PROC GLM since missing data has been excluded and the designs can be considered as 2x2 designs. The G043 formulation was selected for further development based on favourable exposure profiles, formulation composition, and manufacturing process. This is acceptable.

Study 56021927PCR1028 was a randomized, open-label, single-dose, single-center, 2-part Phase 1 study in healthy male participants. Each part consisted of 2-sequence, 2-treatment, 2-period, 2-way crossover design. A single-dose of 240 mg apalutamide was administered orally in each treatment period. As outlined above, Part 1 was a bioequivalence study to confirm that the new 240 mg strength is equivalent to 4 tablets of the current 60 mg strength (under fasted conditions) and Part 2 was a food effect study to confirm that the food effect is negligible and bioequivalence is shown between the fasted and fed state. The employed design is overall considered adequate for the two PK objectives. The mean and individual plots of parent concentrations versus time have been submitted within the CSR. Truncation of AUC at 72 h is considered sufficiently representative of extent of absorption for drugs with long half-life. As in the

PCR1027 study, the statistical analysis is considered acceptable (i.e. based on log-transformation and conventional ANOVA factors considered: treatment, sequence, period and subject (sequence)). The PROC MIXED method reports the same results as PROC GLM since missing data has been excluded and the designs can be considered as 2x2 designs. Based on the results from study PCR1028 the new 240 mg strength can be considered bioequivalent to 4 tablets of 60 mg administered simultaneously. Further, the bioavailability of the new strength formulation is not affected by the concomitant intake of food and can be taken irrespective of meals, like the currently marketed strength.

2.6.4. Conclusions on clinical pharmacology

From a clinical pharmacology point of view, the application is acceptable and the new 240 mg strength can be considered bioequivalent to 4 tablets of 60 mg administered simultaneously.

2.6.5. Clinical efficacy

No new efficacy data have been provided as part of this submission. This is acceptable. The clinical information supports the use of the proposed 240 mg film-coated tablets formulation in the same indications as the 60 mg film-coated tablets.

2.6.6. Clinical safety

2.6.6.1. Patient exposure

Safety data is provided from 48 participants randomized in the relative bioavailability study 56021927PCR1027 and from 74 + 21 subjects in the bioequivalence study 56021927PCR1028. Both studies included healthy male participants that received single doses of apalutamide.

2.6.6.2. Adverse events

Most of the reported AEs were of mild grade. The number of subjects experiencing at least one AE in study 56021927PCR1027 was 11 (22.9%) subjects and in study 56021927PCR1028 was 18 (24.3%) and 4 (19.0%) subjects in Parts 1 and 2, respectively.

Three grade 3 TEAEs were reported in study 56021927PCR1028 (two in part 1, one with treatment A and one with treatment B; and an additional one in part 2 with treatment D). All the three were reported as resolved. No higher grade AEs were reported.

2.6.6.3. Serious adverse event/deaths/other significant events

No subject in either study reported a fatal or serious AE.

2.6.6.4. Laboratory findings

Overall, no clinically relevant mean changes from baseline over time were observed in any of the haematology and chemistry parameters in studies 56021927PCR1027 and 56021927PCR1028. No clinically significant abnormalities in vital signs, physical examinations, or ECG parameters were reported during any of the two studies

2.6.6.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.6.6. Discontinuation due to adverse events

One participant was assessed with a Grade 1 TEAE of symptomatic COVID-19 in study 56021927PCR1027 that led to the discontinuation of the study intervention. In part 1 of study 56021927PCR1028 6 subjects (4 in Treatment A and 2 in Treatment B) were assessed with TEAEs that led to discontinuation. Only one (Grade 1 hypercholesterolemia) was considered drug related. The other 5 were four Grade 1 asymptomatic COVID-19 and one Grade 2 symptomatic COVID-19. No subjects experienced TEAEs leading to discontinuation in part 2 of study 56021927PCR1028.

2.6.6.7. Post marketing experience

No new data on safety have been reported.

2.6.7. Discussion on clinical safety

Overall, the safety profile of the apalutamide 240 mg FC tablet is considered to be in line with that of the currently available 60 mg tablet. No new safety concerns have been identified. Of note, there were no changes to safety concerns, PhV plan and RMM resulting from the clinical development of the 240mg tablet.

From a general safety perspective, the informative value of data coming from single-dose administrations in healthy individuals is limited. From a comparative perspective there is no trend suggesting a different safety or tolerability profile when the proposed new strength vs. four tablets of the currently marketed strength are given. This is expected since bioequivalence has been demonstrated.

2.6.8. Conclusions on the clinical safety

AE data observed in studies 56021927PCR1027 and 56021927PCR1028 were consistent with the known safety profile for apalutamide. No new safety concerns have been identified.

Taking into account that bioequivalence has been shown, the safety profile of the proposed strength can be assumed to be equivalent to that of the existing 60 mg strength.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 7. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Seizures Fall Non-pathological fracture Ischemic heart disease Ischemic cerebrovascular disorders

Summary of safety concerns	
Important potential risks	None
Missing information	Use in patients with severe hepatic impairment Use in patients with clinically significant cardiovascular disease

2.7.2. Pharmacovigilance plan

Table 8. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
56021927PCR1026 A single-dose, open-label study to evaluate the pharmacokinetics of apalutamide in subjects with severe hepatic impairment compared with subjects with normal hepatic function. Ongoing	To characterize the single dose PK and safety of apalutamide in subjects with severe hepatic impairment relative to subjects with normal hepatic function.	Use in patients with severe hepatic impairment	Protocol submission Study start Final results Final report	September 2019 January 2020 31 May 2024 31 May 2025

2.7.3. Risk minimisation measures

2.7.3.1. Summary of risk minimisation measures from the RMP

No additional information was added to this section. The corresponding data remains unchanged.

- **Additional Risk Minimization Measures**

Routine risk minimization activities are sufficient to manage the safety concerns of the medicinal product.

2.7.3.2. Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are considered sufficient to minimise the risks of the product in the proposed indications.

Table 9. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Seizures	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Advice on the use of apalutamide if a seizure develops is provided in SmPC Section 4.4 and PL Section 4 • Advice on the use of apalutamide in patients with a history of seizures or other predisposing factors is provided in SmPC Section 4.4 • Warning to the use of apalutamide with concomitant medicinal products that lower the seizure threshold is provided in SmPC Section 4.4 and PL Section 2 • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • TFUQ to obtain structured information on reported suspected adverse reaction of seizures **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Fall	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to evaluate patients for fall risk is provided in SmPC Section 4.4 and PL Section 4 • A warning for patients to take extra care to reduce risk of fall is provided in PL Section 2 • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • TFUQ to obtain structured information on reported suspected adverse reaction of fall **Additional pharmacovigilance activities:** • None
Non-pathological fracture	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to evaluate patients for fracture risk is provided in SmPC Section 4.4 and PL Section 4 • Recommendation to monitor and manage patients at risk for fractures according to established treatment guidelines, and to consider use of bone targeted agents is provided in SmPC Section 4.4 • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • TFUQ to obtain structured information on reported suspected adverse reaction of fractures **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Ischemic heart disease	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor for signs and symptoms of ischemic heart disease is provided in SmPC Section 4.4, PL Section 2, and PL Section 4 • Recommendation to optimize management of risk factors for ischemic heart disease is provided in SmPC Section 4.4 • Advice for patients experiencing signs and symptoms of heart disease is provided in PL Section 2 and PL Section 4 • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Ischemic cerebrovascular disorders	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor for signs and symptoms of ischemic cerebrovascular disorders is provided in SmPC Section 4.4, PL Section 2, and PL Section 4 • Recommendation to optimize management of risk factors for ischemic cerebrovascular disorders is provided in SmPC Section 4.4 • Advice for patients experiencing signs and symptoms of stroke or mini-stroke is provided in PL Section 2 and PL Section 4 • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Missing Information		

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with severe hepatic impairment	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 5.2 • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • 56021927PCR1026 Final report: 31 May 2025
Use in patients with clinically significant cardiovascular disease	**Routine risk minimization measures:** • SmPC Section 4.4 • Recommendation to monitor patients with clinically significant cardiovascular disease for risk factors such as hypercholesterolemia, hypertriglyceridemia, or other cardio-metabolic disorders, and to treat, if appropriate, after initiating apalutamide for these conditions according to established treatment guidelines is provided in SmPC Section 4.4 • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

2.7.4. Conclusion

The CHMP considered that the risk management plan version 6.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. Labelling exemptions

A request to omit certain particulars from the immediate labelling (blister foil) has been submitted by the applicant and has been found acceptable, in line with the one granted for Erleada 60 mg film-coated tablets at the time of MAA, for the following reasons:

The product will be marketed as film-coated tablets supplied in blisters sealed in a wallet card. The company requested to omit printing certain of the minimum particulars on the blister foil as patients will not be able to see it since it will be completely sealed in an inner wallet. The inner wallet will contain all the required minimum particulars for the primary packaging and will be translated in all languages.

It was considered acceptable to print the minimum particulars on the blister foil as follows: invented name, INN, strength, EXP/Lot. The only particulars that would need translation on the blister foil are the INN, EXP and Lot, and it was agreed to have these particulars in English only, in line with the exemption granted for Erleada 60 mg film-coated tablets.

The labelling subject to translation exemption above will however be translated in all languages in the Annexes published with the EPAR on the EMA website, but the printed materials will only be in English as agreed.

2.9.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.* Indeed, the user consultation complies with the requirements and recommendations of articles 59(3) and 61(1) of Directive 2001/83/EC (as amended by Directive 2004/27/EC).

3. Benefit-Risk Balance

The bioequivalence study 56021927PCR1028 together with the bioavailability study 56021927PCR1027 form the pivotal basis as phase I, single-dose, open-label, randomized studies conducted in healthy males. The study design is considered adequate to evaluate the bioequivalence of the 240mg tablet. Choice of dose, sampling points and overall sampling times were adequate. The analytical methods were validated. Pharmacokinetic and statistical methods applied are adequate.

The 240 mg tablet met the protocol-defined criteria for bioequivalence when compared with the 4x60mg tablet. The point estimates and their 90% confidence intervals for the pharmacokinetic parameters AUC_{0-72} and C_{max} were all contained within the protocol-defined acceptance range of 80.00%-125.00%. Bioequivalence of the two tablets was demonstrated.

The benefit/risk ratio of the 240mg tablet can be considered comparable to the 4x60mg tablet.

3.1. Conclusions

The overall benefit/risk balance of Erleada 240 mg film-coated tablets is positive subject to the conditions stated in the 'Recommendations' section.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, bioavailability, bioequivalence and safety, the CHMP considers by consensus that the benefit-risk balance of, Erleada 240 mg film-coated tablets is favourable in the following indication(s):

- adult men for the treatment of non metastatic castration resistant prostate cancer (NM CRPC) who are at high risk of developing metastatic disease (see section 5.1).
- in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) (see section 5.1).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Erleada subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

In addition, CHMP did recommend the variation(s) to the terms of the marketing authorisation, concerning the following change:

Variations requested		**Type**	**Annexes affected**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type IB	I and IIIB

C.I.z (IB): to align the SmPC/PL for Erleada 60 mg with the SmPC/PL proposed for the registration

of the new Erleada film-coated tablet strength, 240 mg.
The PL for Erleada 60 mg is proposed to be updated to ensure consistency. The RMP version 6.1 has also been submitted.
In addition, few minor revisions are proposed to the SmPC for Erleada 60 mg, to align the SmPC proposed for the 240 mg strength:

- SmPC Section 3: Correction of the tablets size
- SmPC Section 4.2: Further details on the method of administration
- SmPC Section 4.8: Correction in line with the SmPC Guideline
- SmPC Sections 5.1 and 5.2 : Orthographic corrections
- SmPC Section 6.5 : Further details on the description of the current packaging have been added, this change does not result from a change to the container
- SmPC Section 6.6 : The title of the section has been aligned with QRD template.

The revised annexes I, IIIA, IIIB and A are included in the annexes to this opinion