

Public Assessment Report

Scientific discussion

Abirateron Sandoz 250 mg and 500 mg, film-coated tablets (abiraterone acetate)

NL/H/5068/001-002/DC

Date: 18 June 2025

This module reflects the scientific discussion for the approval of Abirateron Sandoz 250 mg and 500 mg, film-coated tablets. The procedure was finalised on 21 April 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ADT	Androgen Deprivation Therapy
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
mCRPC	metastatic Castration Resistant Prostate Cancer
mHSPC	metastatic Hormone Sensitive Prostate Cancer
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Abirateron Sandoz 250 and 500 mg, film-coated tablets, from Sandoz B.V.

The product is indicated with prednisone or prednisolone for:

- the treatment of newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see section 5.1)
- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1)
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Abirateron Sandoz 500 mg is also indicated with prednisone or prednisolone for:

- the treatment of newly diagnosed high risk non-metastatic hormone sensitive prostate cancer (HSPC) in adult men in combination with ADT and radiotherapy (see section 5.1)

A comprehensive description of the indications and posology is given in the SmPC. The SmPC was updated on 12-07-2024 with the variation NL/H/5068/002/WS/003 (see annex 1).

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Zytiga 250 mg tablets and 500 mg film-coated tablets which have been registered in the EEA by Janssen-Cilag International N.V. since September 2011 via the centralised procedure (EU/1/11/714).

The concerned member state (CMS) involved in this procedure were:

For the 250 mg strength: Bulgaria , Croatia, Germany, Greece, Ireland, Italy, Northern Ireland, Poland, Portugal, and Slovakia . A repeat-use procedure (NL/H/5068/001/E/001) was used to register the product in Cyprus and Malta.

For the 500 mg strength: Austria, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Italy, Lithuania, Latvia, Norway, Poland, Portugal, Sweden, Slovakia, Bulgaria, Czechia and Northern Ireland. A repeat-use procedure (NL/H/5068/002/E/001) was used to register the product in Cyprus and Malta.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Abirateron Sandoz are film-coated tablets:

The 250 mg strength tablets are white to off-white, oval-shaped film-coated tablets, debossed with “250” on one side and contain as active substance 250 mg of abiraterone acetate.

The 500 mg strength tablets are purple, oval-shaped film-coated tablets, debossed with “500” on one side, and contain as active substance 500 mg of abiraterone acetate.

The tablets are packed in in Aluminium-OPA/Alu/PVC blisters or Aluminium-PVC/PE/PVDC blisters or High density polyethylene (HDPE) bottles with oxygen absorbing canister.

The excipients are:

Tablet core - croscarmellose sodium, sodium laurilsulfate, povidone K 30 (E1201), cellulose microcrystalline (E460), lactose monohydrate, silica colloidal anhydrous (E551), magnesium stearate (E470b).

Film-coating - poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide red (E172) (500 mg strength) and iron oxide black (E172) (500 mg strength).

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is abiraterone acetate, an established active substance described in the United States Pharmacopoeia (USP). The active substance is a crystalline powder and is practically insoluble in water. The active substance shows polymorphism and is consistently manufactured as polymorphic form A. Abiraterone acetate is a single enantiomer containing eight stereochemical elements, i.e. six chiral centres and two centres of geometrical isomerism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of four stages. There are six chemical reaction steps from the starting material to an intermediate which is then purified to produce the final product. The choice of the regulatory starting materials is justified. Adequate specifications have been adopted for starting materials, solvents and reagents. The manufacturing process has been described in sufficient detail, including process parameters, in-process controls, quantities of raw materials and yields. Also sufficient details on the micronisation, use of recovered solvents and reprocessing have been provided. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of in-house specifications established by the MAH, with additional requirements for particle size distribution and microbiological quality. The specification is acceptable in view of the route of synthesis and various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three pilot scaled and three production scaled batches manufactured according to the OLD route of synthesis that were stored at 30°C/65% RH (only full scaled batches; up to 24 months), 30°C/75% RH (up to 60 months) and 40°C/75% RH (six months). Stability data on nine production scaled batches manufactured according to the NEW (current) route of synthesis have also been provided that were stored at 30°C/65% RH (three to nine months), 30°C/75% RH (three to nine months) and 40°C/75% RH (three to six months) in accordance with applicable European guidelines demonstrating the stability of the active substance. The batches were stored in double LDPE bags, sealed in an aluminium foil bag and placed in a fibre drum. The stability batches were evaluated for description, identification, water content, related substances, assay and polymorphic form. Except for an increase in impurities no clear trends or changes in any of the tested parameters were observed. Results for impurities were variable. The stability data for the batches from the old route of synthesis are considered representative for stability of batches according to the new route of synthesis. Photostability of the drug substance was investigated showing no sensitivity of the drug substance to light exposure. Based on the data submitted, a retest period could be granted of 36 months without special storage conditions.

II.3 Medicinal Product

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies performed were the dissolution method development, formulation optimization studies, where the impact of different levels of excipients, particle size of the drug substance and polymorphic stability were investigated, and scale-up studies. A bioequivalence (BE) study was performed with the

500 mg product versus the 500 mg reference product. For the 250 mg product a biowaiver was claimed. The biobatch was manufactured according to the finalised composition and manufacturing process. Comparative *in vitro* dissolution testing at three pH's has been successfully studied in support of the bioequivalence study and biowaiver. The pharmaceutical development of the products has been adequately performed.

Manufacturing process

The main steps of the process are wet granulation, blending with extra-granular components and lubrication, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the products have been presented for three pilot scaled batches per strength. The products are manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients of the tablet cores comply with Ph.Eur. requirements and the film-coating materials comply with in-house requirements. These specifications are acceptable. Where relevant additional functionality-related characteristics have been specified. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, assay, related substances, dissolution, uniformity of mass, uniformity of dosage units, dimensions and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on three full scaled batches per strength and on one pilot scale batch per strength, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches and one pilot scaled batch per strength packed in Aluminium-OPA/Alu/PVC blisters, three production scaled batches and one pilot scaled batch per strength packed in Aluminium-PVC/PE/PVDC blisters and three production scaled batches per strength packed in High density polyethylene (HDPE) bottles with oxygen absorbing canister stored at 25°C/60% RH (12-18 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. The conditions used in the stability studies are according to the ICH stability guideline. The following parameters were investigated: description, assay, related substances, dissolution and microbiological quality. No clear trends or changes were seen in any of the tested parameters and all parameters remained within the specified limits. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of two years, without any special storage requirements.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose monohydrate and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Abirateron Sandoz have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Abirateron Sandoz are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

These products are generic formulations of Zytiga which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Abiraterone acetate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The

overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Abirateron Sandoz 500 mg, film-coated tablets (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Zytiga 500 mg, film-coated tablets (Janssen-Cilag International N.V., Belgium).

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH has requested a biowaiver for the lower strength Abirateron Sandoz 250 mg film-coated tablets based on the provided bioequivalence study with the 500 mg formulation. The biowaiver was based on the following conditions: The qualitative and quantitative composition of the different strengths are dose proportional and only differs in the film-coating. Both strengths of Abirateron Sandoz are manufactured by the same process. Dissolution studies supporting the biowaiver are acceptable. The results of study I with 500 mg formulation can be extrapolated to the 250 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Bioequivalence studies

Study I

Design

A randomised, open label, balanced, two-treatment, four-period, two sequence, single dose, crossover fully replicate, oral bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 22-44 years. Each subject received a single dose (500 mg) of one of the two abiraterone acetate formulations. The tablet was orally administered with water after at least ten hours of fasting. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after administration of the products.

The design of the study is acceptable.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a ten-fold (AUC) and up to a 17-fold (C_{max}) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking abiraterone with meals has the potential to result in highly variable exposures. Therefore, abiraterone must not be taken with food. It should be taken at least two hours after eating and no food should be eaten for at least one hour after taking abiraterone. The tablets should be swallowed whole with water.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

A total of 27 subjects completed at least two periods in the study, all of these subjects were included in the pharmacokinetics (PK)- and statistical analysis. 25 subjects completed all study periods. One subject completed only one period of the study and was therefore excluded from the analysis. Another subject completed three periods, two periods with reference and one period with test formulation. The third subject also completed 3 periods, two periods with test and one period with reference formulation.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of abiraterone under fasted conditions.

Treatment N=27	AUC _{0-t} (ng/h/ml)	AUC _{0-∞} (ng/h/ml)	C _{max} (ng/ml)	t _{max} (h)
Test	358.82 \pm 240.93	373.48 \pm 245.51	71.34 \pm 44.35	1.50 (0.67 – 5.00)
Reference	355.22 \pm 258.12	369.84 \pm 260.72	74.13 \pm 51.95	2.00 (0.67 – 5.00)
*Ratio (90% CI)	0.98 (0.87 – 1.11)	-	0.99 (0.85 – 1.15)	-
CV (%)	24.62	-	34.01	-
<p>AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum concentration CV coefficient of variation</p>				

**ln-transformed values*

Study II – Pilot study

Design

A randomised, open label, balanced, two-treatment, four-period, two sequence, single dose, crossover fully replicate, oral bioequivalence study was carried out under fasted conditions in

28 healthy male subjects, aged 22-44 years. Each subject received a single dose (500 mg) of one of the two abiraterone acetate formulations. The tablet was orally administered with water after at least ten hours of fasting. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

A total of 27 subjects completed at least two periods in the study, all of these subjects were included in the PK- and statistical analysis. 25 subjects completed all study periods. One subject completed only one period of the study and was therefore excluded from the analysis. Another subject completed 3 periods, two periods with reference and one period with test formulation. The third subject also completed three periods, two periods with test and one period with reference formulation.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of abiraterone under fasted conditions.

Treatment N=27	AUC _{0-t} (ng/h/ml)	AUC _{0-∞} (ng/h/ml)	C _{max} (ng/ml)	t _{max} (h)
Test	288.64 ± 195.92	302.09 ± 197.81	68.18 ± 53.05	2.00 (0.67 – 5.00)
Reference	280.37 ± 197.50	292.77 ± 198.18	64.18 ± 48.00	1.60 (0.67 – 5.00)
*Ratio (90% CI)	1.00 (0.84 – 1.20)	-	1.04 (0.86 – 1.25)	-
CV (%)	39.14	-	41.39	-
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum concentration CV coefficient of variation				

**In-transformed values*

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Abirateron Sandoz is considered bioequivalent with Zytiga.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Abirateron Sandoz.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> - Hepatotoxicity - Cardiac disorders - Osteoporosis including osteoporosis-related fractures - Rhabdomyolysis/myopathy - Allergic alveolitis - Increased exposure with food
Important potential risks	<ul style="list-style-type: none"> - Anaemia - Cataract - Drug-drug interaction (CYP2D6)
Missing information	<ul style="list-style-type: none"> - Use in patients with active or symptomatic viral hepatitis - Use in patients with moderate/severe hepatic impairment and chronic liver disease - Use in patients with severe renal impairment - Use in patients with heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association Class III or IV heart disease or cardiac ejection fraction measurement of <50%

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Zytiga. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the 500 mg product is similar to the pharmacokinetic profile of the 500 mg reference product. A biowaiver has been granted for the 250 mg strength. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Zytiga 250 mg tablets 500 mg film-coated tablets, EMEA/H/C/002321 for content and key safety message, and Felocord film-coated tablets, HU/H/0448/001-002/DC for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Abirateron Sandoz 250 and 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zytiga 250 and 500 mg, film-coated tablets. Zytiga are well-known medicinal products with established favourable efficacy and safety profiles.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Abirateron Sandoz with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 April 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5068/001-2/IA/001/G	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient)	No	17-11-2021	Approved	N.A.
NL/H/5068/002/E/001	Zero day RUP to add CY and MT		24-05-2022	Approved	N.A.
NL/H/5068/001-2/IB/002	Changes in the manufacturing process of the active substance <ul style="list-style-type: none"> Minor change to the restricted part of an Active Substance Master File. 	No	07-06-2022	Approved	N.A.
NL/H/5068/002/P/001	Art. 61(3): to add calendar days to unit dose blisters	Yes	03-02-2023	Approved	N.A.
NL/H/5608/001-2/IA/005/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product <ul style="list-style-type: none"> Secondary packaging site 	No	08-09-2023	Approved	N.A.
NL/H/5068/001-2/IA/WS/004	Changes in the manufacturing process of the active substance <ul style="list-style-type: none"> Minor change to the restricted part of an Active Substance Master File. 	No	23-10-2023	Approved	N.A.

	<p>Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance</p> <ul style="list-style-type: none"> Up to 10-fold increase compared to the originally approved batch size <p>Other variation</p>	No			
NL/H/5068/001-2/IA/WS/006	<p>Change in test procedure for the finished product</p> <p>Minor changes to an approved test procedure</p>	No	04-11-2023	Approved	N.A.
NL/H/5068/001-2/IA/007	<p>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product</p> <ul style="list-style-type: none"> Secondary packaging site 	No	27-02-2024	Approved	N.A.
NL/H/5068/001-2/IA/008/G	Change in the name and/or address of the marketing authorisation holder	Yes	30-03-2024	Approved	N.A.
NL/H/5068/001-2/IA/009/G	<p>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product</p> <ul style="list-style-type: none"> Secondary packaging site 	No	14-06-2024	Approved	N.A.
NL/H/5068/001-2/IA/010/G	Change in the name and/or address of the marketing authorisation holder	Yes	04-07-2024	Approved	N.A.
NL/H/5068/WS/003	Addition of a new therapeutic indication or modification of an approved one.	Yes	12-07-2024	Approved	N.A.

NL/H/5068 /002/II/00 3/G	Replacement of current Indication and Addition of new Indication for 500 mg strength				
NL/H/5068 /001- 002/WS/0 11	Changes in the manufacturing process of the active substance <ul style="list-style-type: none"> Minor change to the restricted part of an Active Substance Master File. <p>Other variation</p>	No No	14-11-2024	Approved	N.A.
NL/H/5068 /001- 002/IA/01 2/G	Change in the name and/or address of the marketing authorisation holder	Yes	01-11-2024	Approved	N.A.

ANNEX 1 - Replacement of current Indication and Addition of new Indication for 500 mg strength (NL/H/5068/002/WS/003)

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the RMS considers that the group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 for Abirateron Sandoz 500 mg, Bixodalan 500 mg and Abirateron 1A Pharma 500 mg (abiraterone acetate), in the treatment of prostate cancer, for the following proposed changes:

- Modification of an already approved indication
- Addition of a new indication
- Update of the SmPC and PIL in line with these prior changes

is approvable.

II. EXECUTIVE SUMMARY

- II.1 Scope of the variation

The MAH applied for a grouping of two type II, cat. C.I.6.a + C.I.6.a variation with the following content:

- **Change(s) to therapeutic indication(s).**
Addition of a new therapeutic indication or modification of an approved one (type II, no C.I.6.a).
This is to update an approved current indication metastatic hormone sensitive prostate cancer (mHSPC)
- **Change(s) to therapeutic indication(s).**
Addition of a new therapeutic indication or modification of an approved one (type II, no C.I.6.a).
Addition of new therapeutic indication non mHSPC in Section 4.1 and related text in Section 4.2 and Section 5.1 of the SmPC and section 1 of the PL are updated accordingly, active substance ABIRATERONE ACETATE for a grouping variation.

The MAH also declared that the adaptations in the SmPC and PL additionally included minor editorial changes and adaptations to the current QRD template.

The marketing authorisations for Abirateron Sandoz 500 mg, Bixodalan 500 mg and Abirateron 1A Pharma 500 mg film-coated tablets were granted pursuant to Article 10(1) of Directive 2001/83/EC [on 1 July 2021](#) via a decentralised procedure (NL/H/5068-5096-5070/002/DC). The procedure concerned a generic application claiming essential similarity with the innovator product [Zytiga](#) 250 mg tablets and 500 mg film-coated tablets which have been registered in the EEA by Janssen-Cilag International N.V. since 5 September 2011 via the centralised procedure (EU/1/11/714; [MAA EPAR](#)).

The currently approved indications (before the proposed changes) are:

"[Product name] is indicated with prednisone or prednisolone for:

- *the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see section 5.1)*
- *the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1)*
- *the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen."*

These are in line with the innovator ([Zytiga SmPC](#)).

Based on literature only, the MAH now proposes the following changes to the indications (deleted text strikethrough; added text bold):

"[Product name] is indicated with prednisone or prednisolone for:

- *the treatment of ~~newly diagnosed high risk~~ metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see section 5.1)*
- ***the treatment of high risk non metastatic hormone sensitive prostate cancer (HSPC) in adult men in combination with androgen deprivation therapy (ADT)***
- *the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1)*
- *the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen."*

In response to the RMS MOs in the D40 PVAR, the proposal above was amended as following (deleted text strikethrough; added text bold):

"[Product name] is indicated with prednisone or prednisolone for:

- *the treatment of **newly diagnosed** ~~high risk~~ metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see section 5.1)*
- *the treatment of **newly diagnosed** high risk non-metastatic hormone sensitive prostate cancer (HSPC) in adult men in combination with ADT and **radiotherapy (see section 5.1)***
- *the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1)*
- *the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen."*

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

N/A

III.2 Non clinical aspects

An environmental risk assessment was submitted in the second round of the procedure in response to invalidation issues raised by a CMS.

The product is intended as a substitute for the originator product on the market. The approval of this product will not result in an increase in the total quantity of Abiraterone Acetate/ Abiraterone released into the environment. The product does not contain any component which results in an additional hazard to the environment during storage, distribution, use and disposal.

In accordance with the Guideline and subsequent clarification in the Questions and Answers, the Applicant asserts that the absence of a completed Environmental Risk Assessment report is justified as there is no situation where a generic of this product is expected to lead to an increase of the environmental exposure.

- The proposed product has the same qualitative and quantitative composition of drug substance as the Innovator, the market strategy and expectation is to compete with the Innovator on price alone, without significantly influencing the overall use of the drug substance or formulated product, especially since the proposed product is a prescription only medication for cancer treatment.
- The proposed product is intended to treat exactly the same indications as the reference medicinal product, including the new indication for the treatment of high risk non metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT).
- The proposed product is only indicated for treatment in the same population group as the reference product and with the same dosing regime; thus keeping the maximum daily dosage of Generic Abiraterone Acetate/ Abiraterone, in the same range/value as the Innovator product.
- No new or additional markets or regions have been applied for.
- The product does not contain any component which results in an additional hazard to the environment during storage, distribution, use and disposal.
- Finally, the product does not contain any component which results in an additional hazard to the environment during storage, distribution, use and disposal.

Therefore, the applicant having accessed the publicly available data has decided to include in the Product Information- section 5.3, the same informative note that the Innovator texts contain:

“The active substance, abiraterone, shows an environmental risk for the aquatic environment, especially to fish.”

The justification for no increased exposure to the environment provided by the MAH is not agreed. There is clearly a new indication applied for, which results in an increase in the number of patients and therefore environmental exposure. An ERA is therefore warranted. However, it is also clear that an ERA has been performed by the innovator, which has resulted in paragraph in section 5.3 of the SmPC. Further ERA studies will not add to the current ERA conclusion, and therefore inclusion of the statement in SmPC section 5.3 is considered sufficient.

III.3 Clinical aspects

The clinical dossier does not contain any study reports and is based on bibliographical data.

The MAH provided a Clinical Overview dated April 2020 that is a combined version of the Clinical Overviews that were provided in 2019 and 2020, respectively, for the (original) marketing authorisation procedures for Abirateron Sandoz 500 mg, Bixodalan 500 mg, Abirateron 1A Pharma 500 mg (NL/H/5068-5069-5070/002/DC) and 1000 mg film-coated tablets (NL/H/5049-5165-

5166/001/DC). The Clinical Overview was scarcely updated, but this is acceptable. The provided Clinical Overview does not contain any specific justification for the proposed changes to the indications. As a justification for the proposed changes to the indications the MAH provided a nine-page Clinical Expert Statement and seven references, i.e. five articles from scientific literature published in 2017-2022 and two clinical guidelines. These are discussed below.

III.3.1 Clinical pharmacology

N/A

III.3.2 Clinical efficacy

The main part of the Clinical Expert Statement begins with the following statement:

Since the approval of Abiraterone in the abovementioned indications, several new trial results have emerged demonstrating significantly improved overall survival (OS) benefit for the use of Abiraterone in further clinical scenarios including low-risk mHSPC, high-volume mHSPC and high-risk localized prostate cancer. The respective data are discussed in the following sections.

Metastatic hormone-sensitive prostate cancer (mHSPC)

a) Results for Abiraterone in low risk mHSPC

In Europe, Abiraterone is limited to mHSPC patients with newly diagnosed, high risk mHSPC. This limitation in the European label of Abiraterone is based on the findings in the LATITUDE trial, which recruited 1199 newly diagnosed patients with high risk mHSPC and demonstrated significant OS benefit for Abiraterone in combination with ADT compared to ADT alone.

In contrast, the US FDA approved Abiraterone without this limitation and the approved indication in the US label is as follows:

Metastatic castration-sensitive prostate cancer

This broader FDA approval was based not only on the results of the LATITUDE trial but also on the results of the randomized phase 3 clinical trial STAMPEDE. This is a multistage, multi-arm study with adaptive trial design. One analysis of this trial compared treatment with abiraterone and low-dose prednisone (AAP) plus ADT to ADT alone in patients with mHSPC (irrespective of risk or volume status), localized high-risk or node-positive disease. It demonstrated a significantly improved OS for AAP plus ADT over ADT alone ([James et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017](#)).

Unlike LATITUDE, STAMPEDE eligibility permitted not only mHSPC patients (52%, N=941) but also patients with high-risk NO M0 disease (28%, N= 50); definition 2 of 3 high-risk factors: stage T3/4, PSA >40 ng/ml, or Gleason score 8–10) or N1 M0 disease (20%, N=369; pelvic nodal metastases).

In the first publication in the New England Journal of Medicine 2017 the mHSPC patient group was not subdivided according to risk status (low vs high risk). This subgroup analysis was for the first time published in 2019 ([Hoyle et al. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer. Eur Urol. 2019](#)) and updated again in 2022 ([James et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5 year follow-up results from the STAMPEDE randomised trial \(NCT00268476\). Int J Cancer. 2022](#)). These analyses confirm the OS benefit for the mHSPC population regardless of risk status. More in detail, 1003 patients with mHSPC were

randomized to receive AAP plus ADT vs ADT alone. 94% were newly diagnosed, 48% had high risk disease and 44% low risk disease (according to LATITUDE definition), 8% were not assessable. Median follow up was 6.1 years in the updated analysis. There was significant and clinically meaningful OS benefit for AAP + standard of care (SOC) compared to SOC alone: adjusted HR = 0.60 (95% CI: 0.50-0.71; $p= 0.31 \times 10^{-9}$) favouring AAP + SOC. The 5-years survival improved from 41% on SOC alone to 60% on AAP + SOC. This OS benefit was similar in low-risk (HR = 0.55; 95% CI: 0.41-0.76) and high-risk (HR = 0.54; 95% CI: 0.43-0.69) patients with significant improvement.

The analysis from the large randomized phase 3 STAMPEDE trial thus provides clear evidence for the significant OS benefit for Abiraterone not only in high risk but also in low risk patients.

Based on these results, the use of Abiraterone for patients with metastatic hormone-sensitive prostate cancer is recommended by the major European guidelines of both the European Association of Urology (EAU) and the European Society of Medical Oncology (ESMO) irrespective of the risk or volume status of the disease and irrespective of the time of diagnosis (newly diagnosed or metachronous).

EAU guidelines 2023 for mHSPC (<https://uroweb.org/guidelines/prostate-cancer>):

Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease and who are fit for the regimen.

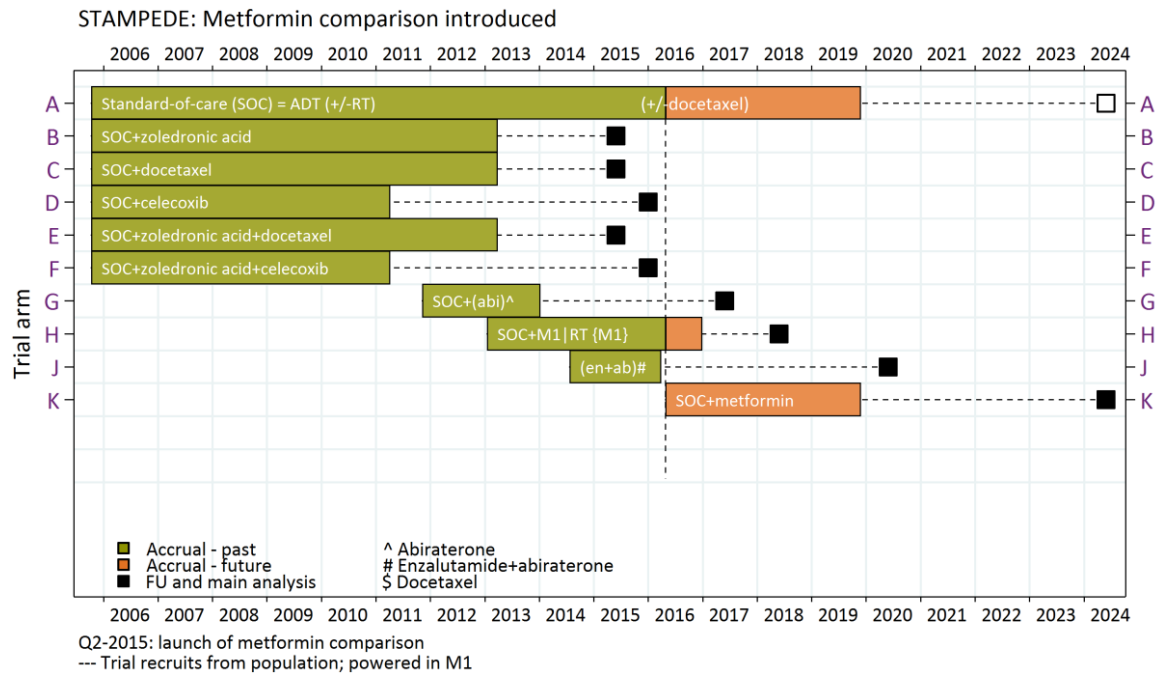
ESMO guidelines 2020 for mHSPC ([Parker et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Ann Oncol. 2020](#)):

ADT is recommended as first-line treatment of mHSPC in combination with abiraterone/prednisone [ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4] or apalutamide [ESMO-MCBS v1.1 score: 4] or docetaxel [ESMO-MCBS v1.1 score: 4] or enzalutamide [ESMO-MCBS v1.1 score: 4] [I, A].

Main study

STAMPEDE is a multi-centre, randomised controlled trial for patients with locally advanced or metastatic prostate cancer who are commencing long-term ADT. The trial has a multigroup, multistage platform design, incorporating a seamless phase 2-3 component. The trial assesses the effects of adding different agents, both as single agents and in combinations, to the standard-of-care. When the trial opened in 2005 there were five "original comparisons". Since then, the trial has been amended to include additional research arms in order to evaluate among other things abiraterone (Arm G) in the "abiraterone comparison". The trial has multiple arms; the control arm of the trial (Arm A) receives standard therapy alone. When the trial started standard treatment was androgen deprivation therapy (ADT) only, achieved through the use of luteinising hormone releasing hormone (LHRH) analogues or antagonist or bilateral orchidectomy according to local practice. Standard treatment may now include docetaxel chemotherapy for all men entering STAMPEDE. Radiotherapy is also mandated for men with node negative non-metastatic disease. The treatment arms open to recruitment over time are shown in **Figure 1**.

Figure 1: Arms of the STAMPEDE trial open to recruitment over time



For each comparison of research arm against control, the trial will be conducted in a number of stages: a Pilot/Safety Phase, Activity Stages and a final Efficacy Stage. The primary outcome measure of the Pilot/Safety Phase is safety. Research arms will only continue to recruitment in the next stage if they have been shown to be both safe and feasible, although patient data from all patients and all stages will be included in the final analyses. In the Activity Stages the primary outcome measure is failure-free survival (FFS). Some evidence of activity will be required for a research arm to continue past each stage. The Efficacy Stage will take place when a pre-specified number of deaths are observed amongst the control arm patients for that relevant comparison. This will be when around 267 deaths are reported in the control arm for the “abiraterone comparison”.

Methods

Eligible patients had prostate cancer that was newly diagnosed and metastatic, node-positive, or high-risk locally advanced (with at least two of following: a tumour stage of T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥ 40 ng per millilitre) or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (in men no longer receiving therapy, a PSA level > 4 ng per millilitre with a doubling time of < 6 months, a PSA level > 20 ng per millilitre, nodal or metastatic relapse, or < 12 months of total ADT with an interval of > 12 months without treatment).

Patients were randomly assigned in a 1:1 ratio (with stratification according to among other things the presence or absence of metastases [yes vs no]) to receive ADT alone or ADT plus abiraterone acetate (1000 mg daily) and prednisolone (5 mg daily) (combination therapy). The trial was open label. For patients with metastatic disease, treatment continued until radiologic, clinical, or prostate-specific antigen (PSA) progression. The primary outcome measure was OS. The intermediate primary outcome was failure-free survival, with treatment failure defined as radiologic, clinical, or PSA progression or death from prostate cancer.

The sample size was calculated with the use of Stata nstage and predecessor programs that allow for the design of multigroup, multistage trials. Assuming a median failure-free survival of 2 years and a

median OS between 4 and 5 years for ADT, a 25% relative difference between the combination group and the ADT-alone group was targeted for both failure-free survival (hazard ratio for treatment failure, 0.75) and OS (hazard ratio for death, 0.75). The main analysis for the comparison of combination therapy against control for survival could be performed after the occurrence of approximately 267 deaths in the control group for 90% power and a one-sided alpha level of 2.5%, after accounting for three intermediate lack-of-benefit analyses of failure-free survival. Prior to analysis, the hypothesis was pre-specified that there would be no difference in the treatment effect from adding AAP across the subgroups.

All the patients were included in the efficacy analyses under their assigned treatment on an intention-to-treat (ITT) basis. Pre-specified subgroup analyses looked at the consistency of treatment effect according to stratification factors (including metastatic status). Relevant to the currently proposed broadening of the mHSPC indication is that the metastatic disease risk group was retrospectively classified according to the definition used in the LATITUDE trial ([Fizazi et al. N Engl J Med. 2017](#); [Zytiga II/47 EPAR](#)), with high-risk disease defined as at least two of: ≥ 3 bone metastases; visceral metastases; Gleason score ≥ 8 . Patients were excluded from this analysis only if they had incomplete information precluding classification into low or high risk.

Results

The below efficacy results were extracted from [Hoyle et al. Eur Urol. 2019](#).

Between 15 November 2011 and 17 January 2014, 990 mHSPC patients were in the “abiraterone comparison” randomised to receive ADT alone or with AAP. The data lock date for the retrospective scan data was 1 August 2018. Patients with incomplete information precluding radiological risk-based classification were excluded as follows: absent Gleason score (n = 34), unobtainable bone scintigraphy (n = 41), and bone metastases diagnosed using nonconventional imaging (n = 14). A total of 901 mHSPC patients underwent stratification using the LATITUDE risk criteria. Baseline characteristics by LATITUDE-defined risk subgroups were balanced between the two treatment arms (see [Table 1 in article](#)). In all, 428 (48%) patients were classified as having a low risk by the LATITUDE criteria. High-risk disease using the LATITUDE criteria was seen in 473 (52%) patients. Median follow-up was 42 months. Of 901 patients, 330 (195 ADT; 135 ADT + AAP) had died.

The ADT + AAP combination therapy demonstrated a survival advantage over ADT alone (HR: 0.61, 95% CI [0.49–0.79], **Figure 2**). Also, when stratified according to the LATITUDE criteria for low risk, ADT + AAP demonstrated a survival advantage (HR: 0.66, 95% CI [0.44–0.98]): absolute 3-year survival was 83% with ADT + AAP and 78% with ADT alone (**Figure 2**,

Figure 3A). Improvement was also seen in the high-risk disease subgroup (HR: 0.54, 95% CI [0.41–0.70]): absolute 3-year survival was 65% with ADT + AAP and 45% with ADT (**Figure 2**,

Figure 3B). The heterogeneity of treatment effect between high- and low-risk groups was not statistically significant (p-interaction = 0.39, **Figure 2**), although for OS, the number of patients needed treatment (20 vs five) to prevent one death after 3 years in the low-risk group was four times more than that in the high-risk group.

Figure 2: Forest plot of hazard ratios (HRs) for AAP from adjusted Cox models on overall survival LATITUDE low- and high-risk subgroups

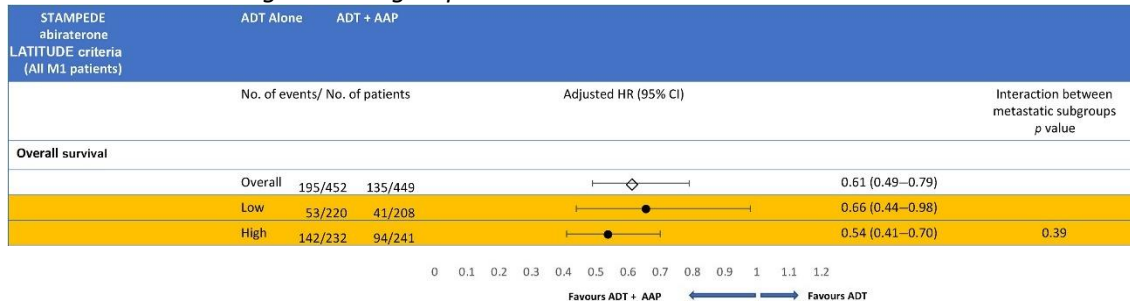
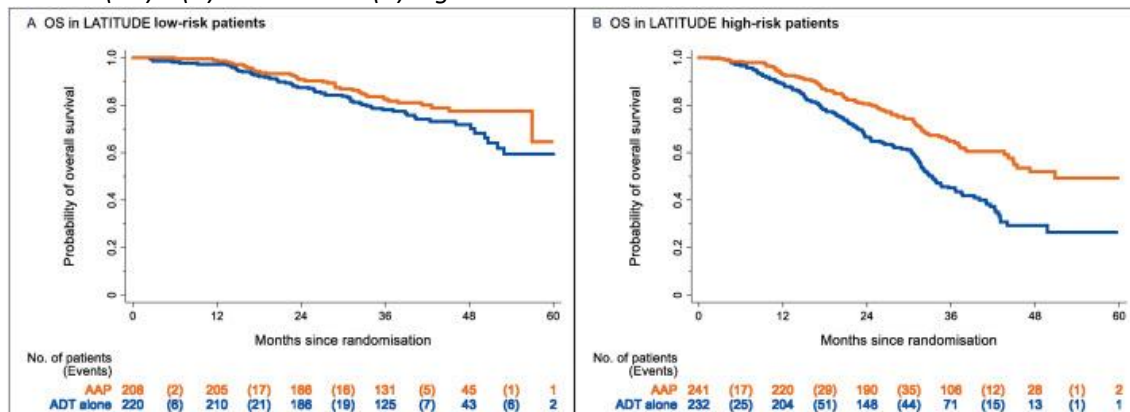


Figure 3: Kaplan-Meier curves according to M1 risk stratification using the LATITUDE criteria for overall survival (OS)—(A) low risk and (B) high risk



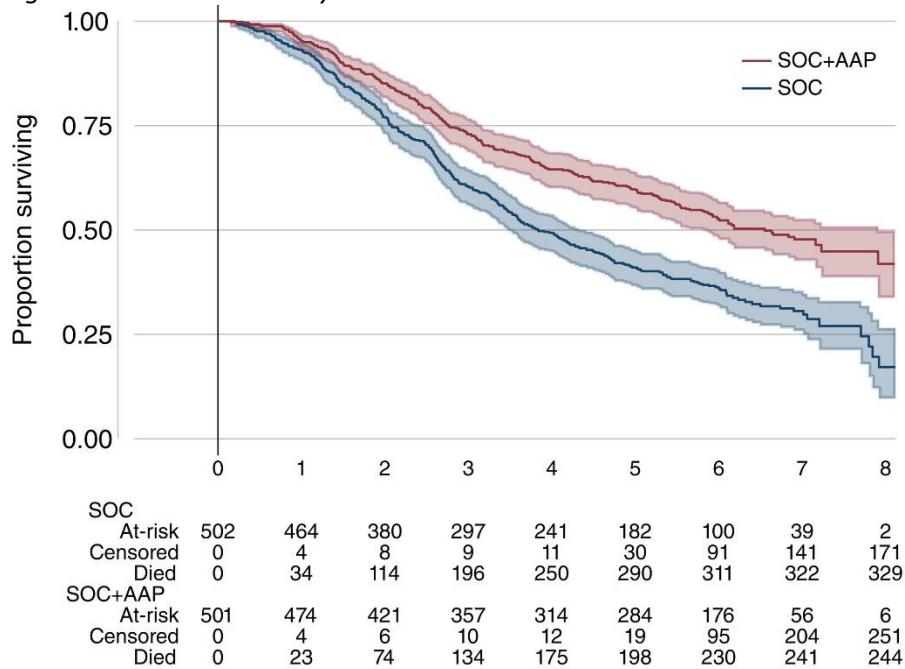
The analysis of STAMPEDE patients by metastatic burden may be influenced by patients with recurrent disease following previous radical treatment. Exclusion of patients receiving prior radical therapy provided a de novo cohort of 859 patients (95% of the original cohort). The cohort was stratified according to the LATITUDE risk criteria. Benefit of ADT + AAP over ADT alone was observed for both subgroups, irrespective of risk stratification. The relative hazard for survival in de novo low-risk patients was slightly superior to the original cohort analysis (HR: 0.64, 95% CI [0.42-0.97]). A similar result was seen for low-volume subgroup survival analysis (HR: 0.60, 95% CI [0.39-0.92]).

The below updated results were extracted from [James et al. Int J Cancer. 2022.](#)

Between 15 November 2011 and 17 January 2014, 1917 patients were randomised to the arms of STAMPEDE constituting the “abiraterone comparison”. Of these, all 1003 patients with metastatic disease were analysed here: 502 (50%) allocated to standard treatment (SOC alone group) and 501 (50%) to standard treatment plus abiraterone and prednisolone (SOC + AAP group). Median age at randomisation was 67 years (IQR 62-71), 941 (94%) had newly diagnosed disease. Metastatic disease risk group was retrospectively classified as low-risk in 428 (43%) patients, high in 473 (47%) and was unclassified in a further 102 (10%).

The database was locked for this analysis on 3 April 2020. Median follow-up was 73 months (6.1 years). Deaths were reported in 573/1003 (57%) participants including 329 (66%) in the SOC alone group and 244 (49%) in the SOC + AAP group: HR = 0.60 for SOC + AAP (95% CI: 0.50-0.71, P < .0001) (**Figure 4**). Median survival was 46 months (IQR 25, 92) in the SOC alone group and 79 months (IQR 33, not reached) in the SOC + AAP group; 5-year survival was 41% (95% CI: 37%-45%) for SOC alone and 60% (95% CI: 50%-71%) for SOC + AAP.

Figure 4: Overall survival by allocated treatment



Focusing on the 91% (909/1003) of patients for whom metastatic disease risk group could be calculated, the relative effect of SOC + AAP on OS was similar in both low-risk and high-risk metastatic disease risk groups (

Table 1;

Figure 5) [Correction added on 6 June 2022, after first online publication].

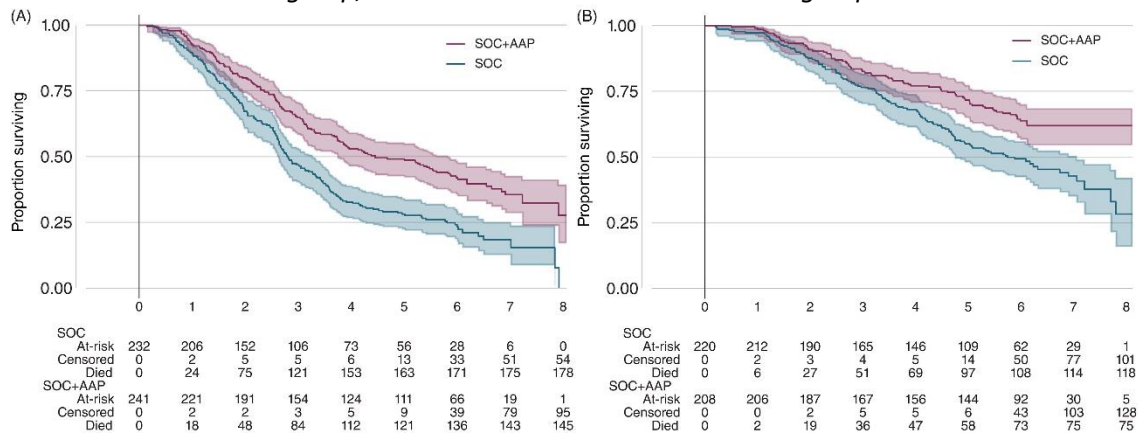
Table 1: Primary outcome, by metastatic disease risk group using LATITUDE criteria

	Metastatic disease risk group					
	Low-risk		High-risk		Unclassified ^a	
	SOC-alone n = 220	SOC ± AAP n = 208	SOC-alone n = 232	SOC ± AAP n = 241	SOC-alone n = 45	SOC ± AAP n = 43
Overall survival						
Events	118	75	178	145	29	22
% alive at 5 years, (95% CI)	55% (48-61)	72% (65-77)	28% (22-34)	49% (43-55)	40% (26-54)	59% (42-72)
HR = vs SOC-alone (95% CI), P	0.54 (0.40-0.74)	<.0001	0.54 (0.43-0.69)	<.0001	0.63 (0.33-1.23)	.180

^aScans were unavailable for patients at sites in Switzerland, 14 further patients therefore do not appear in this table.

Abbreviations: 95% CI, 95% confidence interval; AAP, abiraterone acetate + prednisolone/prednisone; P, P-value; Ref, reference arm; RMST, restricted mean survival time; SOC, standard-of-care.

Figure 5: Overall survival by allocated treatment and metastatic disease risk group: 3A - high-risk metastatic disease risk group; 3B - low-risk metastatic disease risk group



Further treatment was reported for most patients within 1 year of first disease progression (Table 2). Patients allocated to the SOC alone group were more likely to receive abiraterone or enzalutamide within 1 year (abiraterone, 19% vs 2%; enzalutamide, 16% vs 8%). Reported use of docetaxel within 1 year after first progression was higher among patients allocated to SOC + AAP (32% SOC alone and 40% SOC + AAP).

Table 2: Post-progression treatment

Patients with reported progression*	SOC-alone		SOC+AAP		p
	n=437	(100%)	n=282	(100%)	
Any second-line treatment	405	(93%)	217	(77%)	<0.0001
Anti-androgen	316	(72%)	84	(30%)	<0.0001
Abiraterone	131	(30%)	10	(4%)	<0.0001
Enzalutamide	157	(36%)	46	(16%)	<0.0001
Docetaxel	199	(46%)	137	(49%)	0.424
Zoledronic acid	81	(19%)	51	(18%)	0.88
Dexamethasone	116	(27%)	66	(23%)	0.344
Prednisolone	93	(21%)	43	(15%)	0.044

Regarding safety, patients in the safety population (all patients who started treatment in the arms of STAMPEDE constituting the “abiraterone comparison”) who reported adverse events (AEs) of grade 3 or higher during their entire time in the trial numbered 443 of 948 (47%) in the combination group and 315 of 960 (33%) in the ADT-alone group (see Table 2 from James et al. N Engl J Med. 2017). There were 12 grade 5 AEs, including 9 in the combination group (2 events of pneumonia [1 including sepsis], 2 events of stroke, and 1 event each of dyspnoea, lower respiratory tract infection, liver failure, pulmonary haemorrhage, and chest infection) and 3 in the ADT-alone group (2 events of myocardial infarction and 1 event of bronchopneumonia). The main additional AEs over and above the control therapy were hypertension, mild increases in aminotransferase levels, and respiratory disorders.

The MAH originally proposes to change the wording of the mHSPC indication as follows (deleted text strikethrough): “the treatment of ~~newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) ...~~”. Therefore, the MAH has to justify an extension of the indication to patients with low-risk mHSPC, plus the MAH has to justify an extension of the indication to patients with relapsing (not newly diagnosed) mHSPC. The results from STAMPEDE may be used for the first, but do not seem appropriate for the latter.

Already in 2017, the STAMPEDE results demonstrated an OS benefit of SOC + AAP over SOC alone in patients with newly diagnosed metastatic prostate cancer, irrespective of risk ([James et al. N Engl J Med. 2017](#)). However, the pivotal study for the Zytiga extension of indication to mHSPC was LATITUDE, in which only patients with newly diagnosed *high-risk* disease were included ([Fizazi et al. N Engl J Med. 2017](#); [Zytiga II/47 EPAR](#)). It is noted that the results of both studies were published simultaneously and that the STAMPEDE results are mentioned in the Zytiga EPAR.

To specifically address the uncertainty regarding the treatment benefit for patients with low-risk metastatic disease, Hoyle *et al.* conducted a post-hoc subset analysis of the patients in the STAMPEDE “abiraterone comparison”, stratified retrospectively by baseline staging risk according to the LATITUDE criteria ([Hoyle et al. Eur Urol. 2019](#)). James *et al.* provided confirmatory updated results with extended follow-up for both the overall group of patients with metastatic disease and the subset analysis ([James et al. Int J Cancer. 2022](#)).

Importantly, almost all patients (95%) in STAMPEDE had *newly diagnosed* (or *de novo*) disease. It is, therefore, uncertain whether the results are also applicable to patients who develop metastatic disease after prior local therapy ([Hoyle et al. Eur Urol. 2019](#)).

From a statistical perspective, given the results presented by Hoyle *et al.* are based on a subgroup analysis at the time of the pre-specified number of events for the primary analysis, it is considered that these results are more suitable for regulatory decision-making, with the updated results provided by James *et al.* considered to be supportive. Importantly, with reference to the guideline on the investigation of subgroups in confirmatory clinical trials ([EMA/CHMP/539146/2013](#)), the evaluation of the low-risk subgroup is in the context of an overall statistically persuasive effect in the primary analysis population, and with no strong signals of inconsistent treatment effects among the high- and low-risk subgroups.

The above efficacy results from Hoyle *et al.* clearly demonstrate an OS benefit (with 37% maturity) for SOC + AAP over SOC alone in the overall group of patients with newly diagnosed metastatic disease, irrespective of risk. James *et al.* provided confirmatory updated OS data with 57% maturity. The results of the subset/-group analysis in both articles confirm consistency of effect in both low-risk and high-risk disease subgroups.

Regarding safety, the toxicity of AAP is not expected to differ between patients with newly diagnosed high- or low-risk mHSPC. Indeed, the toxicity of AAP in STAMPEDE as reported in [James et al. N Engl J Med. 2017](#) appears similar to the known safety profile in the abiraterone SmPC. Therefore, it can be accepted that section 4.8 of the SmPC is unchanged.

The information provided by the MAH to support broadening the currently approved mHSPC indication is limited. Moreover, STAMPEDE was not conducted under the responsibility of the MAH and no Clinical Study Report (CSR) was provided. Then again, another comparison from STAMPEDE, i.e. the “docetaxel comparison” was used as a pivotal study for the Taxotere extension of indication to mHSPC ([Taxotere WS1550 EPAR](#)). Therefore, results from STAMPEDE have already been considered for regulatory decision making.

The MAH correctly quotes the recommendations from current clinical guidelines. It is, however, clearly shown in the [2023 EAU guidelines](#) that this recommendation was based on studies in which almost exclusively patients with newly diagnosed metastatic disease were included. Moreover, in the ESMO guidelines is clearly stated that as a result the benefit of adding AAP to ADT in patients with relapsing

(not newly diagnosed) metastatic disease is uncertain ([Parker et al. Ann Oncol. 2020](#)). Plus, for example in the [Dutch guidelines](#) the recommendation is limited to patients with newly diagnosed disease only.

In conclusion, the STAMPEDE results in [Hoyle et al. Eur Urol. 2019](#) demonstrate an OS benefit of adding AAP to ADT in patients with newly diagnosed mHSPC, irrespective of risk. In [James et al. Int J Cancer. 2022](#), confirmatory updated results with extended follow-up are presented. The toxicity of AAP in this broader indication is in line with the known safety profile of AAP and (thus) acceptable. Therefore, the benefit-risk balance (B/R) is considered positive for this patient population.

The MAH agrees to maintain the restriction of the indication to patients with newly diagnosed disease. The currently proposed indication is acceptable (deleted text strikethrough): “the treatment of newly diagnosed ~~high-risk~~ metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see section 5.1)”.

The Clinical Expert Statement continues as follows:

High risk non-metastatic localized prostate cancer

Although high-risk localized prostate cancer diseases account for only one-fifth of all primary diagnoses, they account for two-thirds of the 10-year prostate cancer specific mortality. These findings support targeting research toward the optimal treatment of high-risk localized disease.

STAMPEDE is a multi-arm, multi-stage trial with adaptive trial design evaluating different therapies or localized high risk, relapsed or metastatic prostate cancer.

A recent analysis included 1,974 men with high-risk localized prostate cancer ([Attard et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet. 2022](#)). Newly diagnosed patients with high risk disease (defined as at least two of the following factors: clinical T-stage T3 or T4, Gleason score 8–10, PSA > 40 ng/mL), node positive patients (pelvic lymph nodes) or relapsing patients with high-risk features (definition: ≤12 months of total ADT with an interval of ≥12 months without treatment and PSA concentration ≥4 ng/mL with a doubling time of <6 months, or a PSA concentration ≥20 ng/mL, or nodal relapse) **non-metastatic prostate cancer**, and a WHO performance status of 0–2 were included. Patients were randomised to ADT alone, or ADT plus abiraterone, with or without enzalutamide. Radiotherapy was mandated for N0 disease and recommended for N1 disease. Androgen deprivation therapy was administered for 3 years, and abiraterone/enzalutamide for 2 years.

Median follow up was 6 years. 39% of patients had node positive disease and 85% were planned to receive local radiotherapy. Overall, metastasis-free survival was significantly longer in the combination-therapy groups than in the control groups (HR 0.53; 95% CI 0.44–0.64, p<0.0001).

6-year metastasis-free survival was 82% (95% CI 79–85) in the combination-therapy group and 69% (66–72) in the control group. There was no evidence of a difference in metastasis-free survival when enzalutamide and abiraterone were administered concurrently compared with abiraterone alone (interaction HR 1.02, 0.70–1.50, p=0.91) and no evidence of between-trial heterogeneity (I² p=0.90).

OS was also significantly longer in the combination-therapy groups (HR 0.60, 95% CI 0.48–0.73, p<0.0001). Moreover, prostate cancer-specific survival (HR 0.49, 0.37–0.65,

p<0.0001), biochemical failure-free-survival (HR 0.39, 0.33–0.47, p<0.0001), and progression-free survival (HR 0.44, 0.36–0.54, p<0.0001) were also significantly longer in the combination therapy groups than in the control groups.

AEs grade 3 or higher during the first 24 months were reported in 37% of patients in the abiraterone therapy group and in 29% of patients in the control group whereas this rate was 58% in the abiraterone/enzalutamide combination group.

The two most common events more frequently reported in the abiraterone/enzalutamide combination-therapy groups were hypertension (abiraterone 5% vs abiraterone/enzalutamide 14%) and liver enzyme elevation (abiraterone 6% vs abiraterone and enzalutamide 13%).

The addition of enzalutamide therefore did not improve outcomes but increased toxicity.

Based on these positive results with clear demonstration of OS benefit, the combination of ADT plus Abiraterone for 2 years has become a new standard of care treatment in addition to radiotherapy for patients with high risk localized prostate cancer as included in the STAMPEDE study.

The European Association of Urology has therefore adapted its recommendations accordingly.

EAU guidelines 2023 for locally advanced disease (<https://uroweb.org/guidelines/prostate-cancer>):

For node negative high risk disease: Offer IMRT/VMAT plus IGRT to the prostate in combination with long-term ADT and 2 years of abiraterone to cN0M0 patients with > 2 high-risk factors (cT3-4, Gleason > 8 or PSA > 40 ng/mL).

For node positive disease: Offer IMRT/VMAT plus IGRT to the prostate plus pelvis in combination with long-term ADT and 2 years of abiraterone to cN1M0 patients

The MAH has provided the above brief justification for the new indication for the treatment of patients with high-risk non-metastatic HSPC in combination with ADT. For a proper assessment of the benefits of abiraterone in the proposed indication, the below information was extracted from the provided reference/article and its accompanying supplementary appendix ([Attard et al. Lancet. 2022](#)).

Main study

See above for a description of the **STAMPEDE** study design. Also, in **Figure 1** can be seen the SOC control arm (Arm A), the abiraterone Arm G, and the abiraterone and enzalutamide Arm J.

In STAMPEDE, two separate comparisons/trials with the same eligibility criteria and no overlapping control patients were undertaken to evaluate the efficacy of adding abiraterone with prednisolone (the Arms A-G “abiraterone comparison” henceforth called abiraterone trial) or abiraterone with prednisolone and enzalutamide (the Arms A-J “abiraterone and enzalutamide comparison” henceforth referred to as abiraterone and enzalutamide trial). See also Figure S1 in the [supplementary appendix of Attard et al. Lancet. 2022](#). Because of the data that emerged after completion of accrual to both trials, namely the greater than expected efficacy of abiraterone and prednisolone in metastatic patients ([James et al. N Engl J Med. 2017](#)) and the absence of a survival benefit from combination of enzalutamide with abiraterone and prednisone in metastatic castration-resistant prostate cancer ([Morris et al. J Clin Oncol. 2023](#), but results published as abstract in 2019), it was concluded that a difference in treatment effect between the two trials would not be able to be observed. Given the clinical need to determine the efficacy of treatment intensification in non-metastatic patients, a set of decisions was made by the trial management group before inspection of any efficacy outcomes by randomised group in the abiraterone and enzalutamide trial and with no subsequent efficacy analysis of non-metastatic patients in the abiraterone trial. These decisions were to (1) formally separately

report non-metastatic and metastatic patients, (2) combine the non-metastatic patients from both trials (both trials assigned control patients to the same SOC treatment, had no overlapping control patients and included the same dose and regimen of abiraterone acetate, given either with prednisolone or with both prednisolone and enzalutamide), (3) change the primary outcome measure for the non-metastatic population from OS to metastasis-free survival (MFS), and (4) extend follow-up of both trials until sufficient events in the non-metastatic population. This change in reporting plan was approved by the trial steering committee, which functions independently from the trial management group, on 2 December 2019, and was subsequently published as a prespecified declaration of the study team's intentions ([Attard et al. Eur Urol. 2023](#)).

Regarding (3) the change of the primary endpoint to MFS, as for other STAMPEDE comparisons, A-G and A-J were designed to use OS as the final primary outcome. However, the ICECaP meta-analysis of patients with non-metastatic disease has demonstrated that MFS is a robust surrogate outcome measure for OS ([Xie et al. J Clin Oncol. 2017](#)). Therefore, MFS will be the primary outcome measure for the non-metastatic patients.

Methods

Eligible patients had prostate cancer that was newly diagnosed and metastatic, node-positive, or high-risk locally advanced (with at least two of following: a tumour stage of T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥ 40 ng per millilitre) or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (in men no longer receiving therapy, a PSA level >4 ng per millilitre with a doubling time of <6 months, a PSA level >20 ng per millilitre, nodal or metastatic relapse, or <12 months of total ADT with an interval of >12 months without treatment).

In both trials separately, as there were no overlapping control patients (**Figure 1**), patients were randomly assigned in a 1:1 ratio to SOC alone (control group) or with combination therapy, with stratification according to among other things the presence or absence of metastases (yes vs no), planned use of prostate radiotherapy (yes vs no), nodal involvement (negative vs indeterminate vs positive). Both trials were open label. The protocol recommended that patients received SOC treatment with 3 years ADT. Radiotherapy after randomisation was mandated (unless contraindicated) for patients with node-negative disease and encouraged for node-positive disease. Abiraterone acetate (1000 mg daily) with prednisolone (5 mg daily) alone or with enzalutamide (160 mg daily), hereafter referred to as combination therapy, were given orally once daily and were to continue for 2 years or until progression, whichever came first. In the abiraterone and enzalutamide trial, enzalutamide was taken for the same duration as the co-administered abiraterone, unless either abiraterone or enzalutamide was stopped for toxicity, in which case the other drug was allowed to continue. When radiotherapy was omitted, treatment could continue until disease progression. The primary endpoint of this meta-analysis was MFS, defined as time from randomisation to death from any cause or to distant metastases confirmed by imaging. Secondary endpoints included OS.

Both trials recruited to their originally required overall target sample size; there was no pre-defined sample size for non-metastatic patients. To determine how many MFS events were required to be reported in the control patients, the nstage function within Stata was used (Stata Corp, Texas, TX, USA; version 16.1). Assuming a MFS of 70% at 5.5 years for control patients, a 25% relative improvement between the combination-therapy and control groups was targeted (target hazard ratio [HR] 0.75). For 90% power and a one-sided α level set at 1.25% (to account for previous reporting of overall survival [but not MFS] of patients in the abiraterone trial [[James et al. N Engl J Med. 2017](#)]), approximately 315 MFS events were required in the control groups. Patients without an event of interest were censored when they were last known to be event-free according to a received follow-up case record form.

All patients were included in the efficacy analyses under their assigned treatment on an ITT basis. For toxicity and AEs, patients were included if any treatment was administered as per randomised allocation. Pre-specified subgroup analyses of MFS and OS explored the consistency of treatment effect between both trials and across randomisation stratification factors including nodal status and planned radiotherapy. The proportion of heterogeneity between trials was calculated based on Cochran's Q test (quantified by the I^2 value).

Results

The below efficacy results were extracted from [Attard et al. Lancet. 2022](#).

Between 15 November 2011, and 31 March 2016, 1974 non-metastatic patients were randomly assigned in both trials (455 to the control group and 459 to the combination-therapy group of the abiraterone trial from 15 November 2011 to 17 January 2014, and 533 to the control group and 527 to the combination-therapy group of the abiraterone and enzalutamide trial from 29 July 2014 to 31 March 2016). Database lock and extraction occurred on 3 August 2021. The baseline characteristics of the patients were well balanced between randomised groups (see [table in article](#)). The median age was 68 years (IQR 63–73), median PSA was 34 ng/ml (IQR 15–74), 774 (39%) of 1974 patients were node-positive, and 1563 (79%) of 1968 had a Gleason score sum of 8–10. The median follow-up was 72 months (IQR 63–73; 85 months [83–96] in the abiraterone trial and 60 months [59–71] in the abiraterone and enzalutamide trial). The planned rate of use of local radiotherapy was 1684 (85%) of 1974, namely for newly diagnosed patients, 99% for node-negative patients and 71% for node-positive patients, and 7% for previously treated patients.

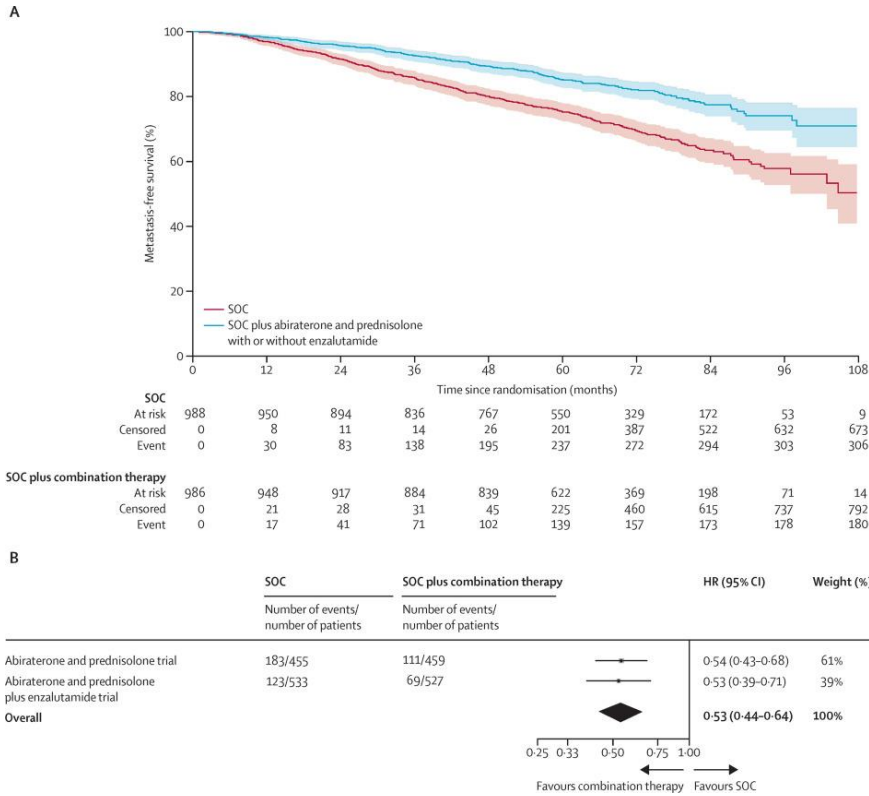
There were 180 MFS events in the combination-therapy groups and 306 in the control groups. Of the 180 MFS events in the combination-therapy groups, 93 (52%) were deaths and 87 (48%) were a report of extra-pelvic metastases. Of the 306 events in the control groups, 117 (38%) were deaths and 189 (62%) were a report of metastases. See **Table 3** for a breakdown of MFS events by study arm.

Table 3: Breakdown of metastasis-free survival events

	Control group (abiraterone trial)	Control group (abiraterone and enzalutamide trial)	Combination therapy (abiraterone trial)	Combination therapy (abiraterone + enzalutamide trial)
MFS events	183	123	111	69
event = death (% of events)	73 (40%)	44 (36%)	60 (54%)	33 (48%)
event = metastasis	110 (60%)	79 (64%)	51 (46%)	36 (52%)

MFS was significantly longer in the combination-therapy groups (median not reached, IQR not estimable [NE]–NE) than in the control groups (not reached, 97–NE; HR 0.53, 95% CI 0.44–0.64; $p < 0.0001$) (**Figure 6**). A pre-planned subgroup analysis included 294 MFS events in the abiraterone trial and 192 in the abiraterone and enzalutamide trial. This analysis showed a strong effect in each trial separately (abiraterone trial HR 0.54, 95% CI 0.43–0.68, $p < 0.0001$; abiraterone and enzalutamide trial 0.53, 0.39–0.71, $p < 0.0001$; **Figure 6B**) with no evidence of a difference in treatment effect (interaction HR 1.02, 0.70–1.50, $p = 0.91$) and no evidence of between-trial heterogeneity (I^2 $p = 0.90$). In an analysis of subgroups defined by randomisation stratification factors, no statistically significant heterogeneity of effect was for WHO nodal status or planned radiotherapy (see [Figure 3 in article](#)). **Figure 7** shows the MFS Kaplan-Meier curve for the abiraterone trial.

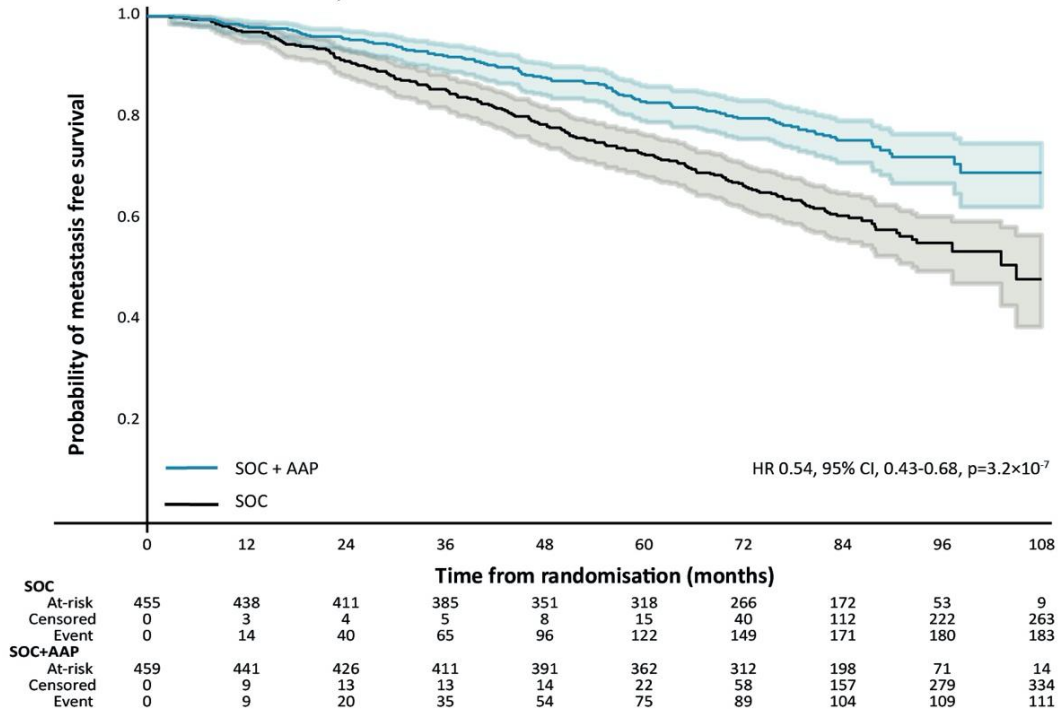
Figure 6: Metastasis-free survival in both trials combined



(A) Kaplan-Meier estimates of all patients in individual patient data meta-analysis; shaded regions represent 95% CIs. (B) Pre-specified subgroup analysis by trial. HR=hazard ratio. SOC=standard of care.

Figure 7: Metastasis-free survival in abiraterone trial

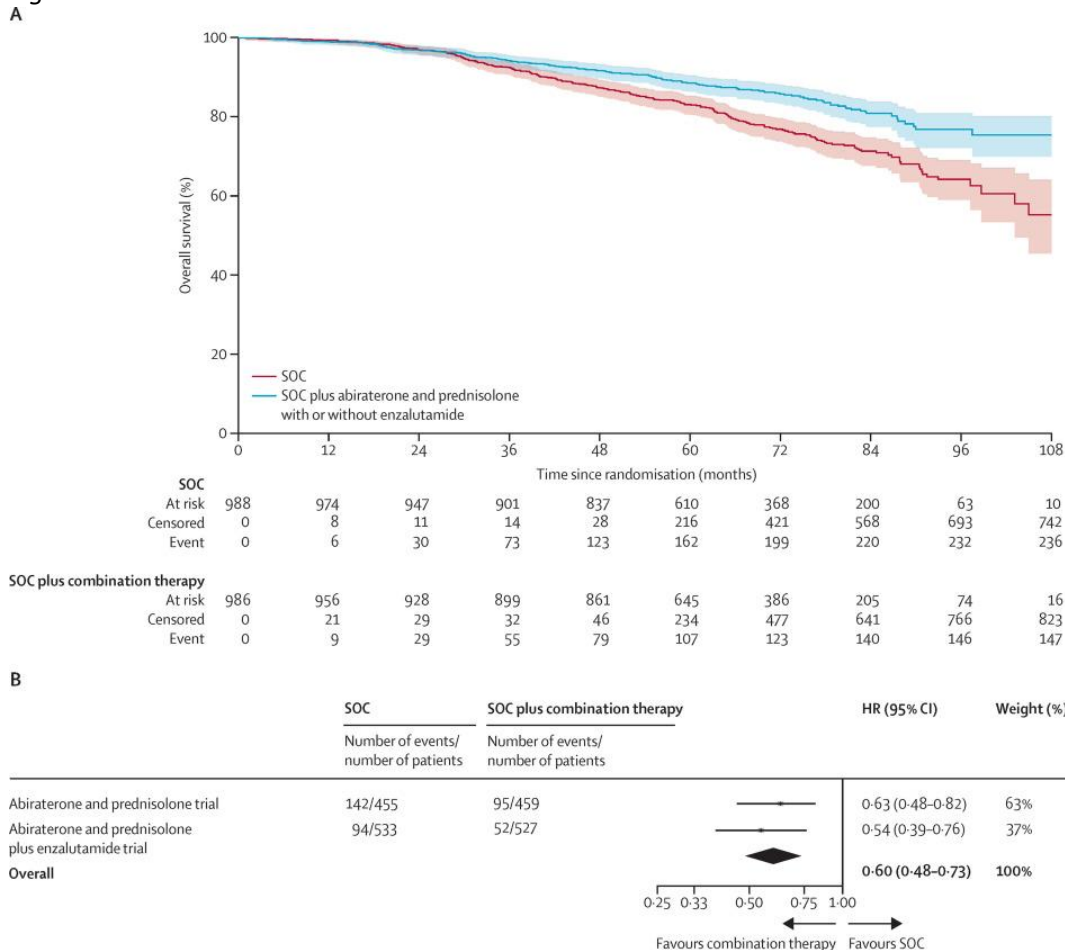
A. Metastasis-free survival, SOC vs SOC with abiraterone



Kaplan-Meier estimates; 95% confidence interval represented by lighter shade. Sensitivity analysis excluding 22 patients (1%) who were classified as protocol deviations due to excursions from eligibility criteria was also performed: hazard ratio (95% confidence intervals) 0.54 (0.43, 0.68). SOC, standard of care; AAP, abiraterone; ENZ, enzalutamide.

There were 147 deaths in the combination-therapy groups and 236 in the control groups. Overall survival was significantly longer in the combination-therapy groups (median not reached, IQR NE–NE) than in the control groups (not reached, 103–NE; HR 0.60, 95% CI 0.48–0.73, $p < 0.0001$) (Figure 8). A pre-planned subgroup analysis included 237 deaths in the abiraterone trial and 146 deaths in the abiraterone and enzalutamide trial. The effect was strongly observed in both trials (abiraterone trial HR 0.63, 95% CI 0.48–0.82, $p = 0.0005$; abiraterone and enzalutamide trial 0.54, 0.39–0.76, $p = 0.0004$) with no evidence of between-trial heterogeneity ($I^2 p = 0.51$; Figure 8). Figure 9 shows the OS Kaplan-Meier curve for the abiraterone trial.

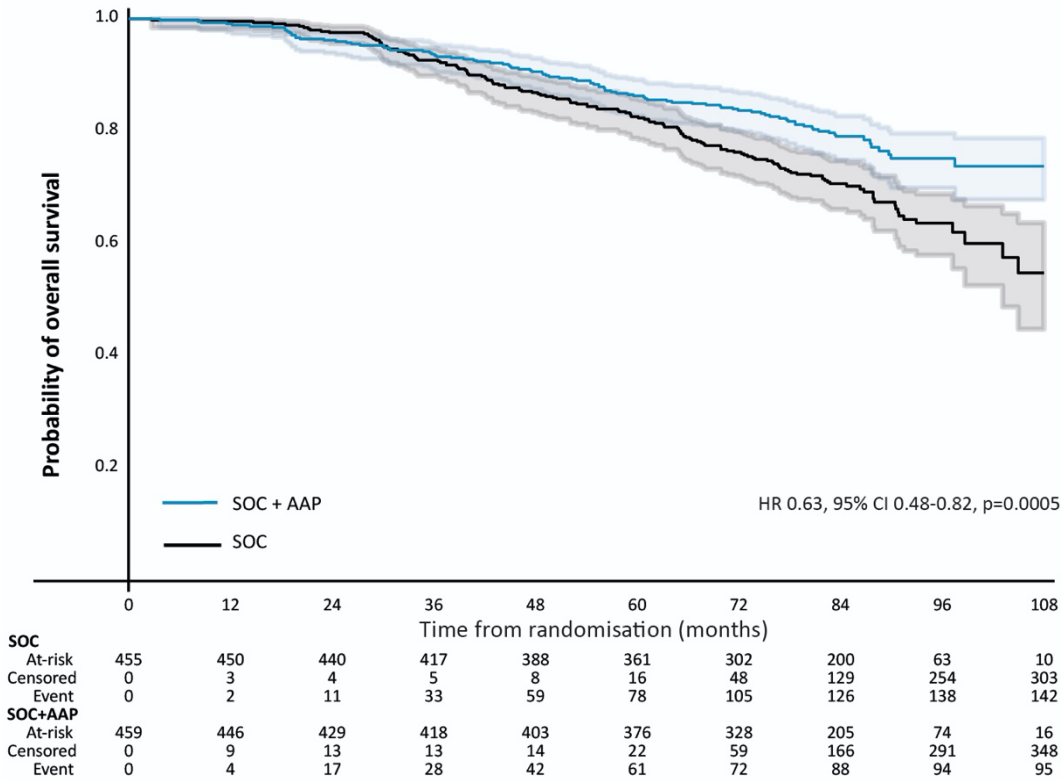
Figure 8: Overall survival in both trials combined



(A) Kaplan-Meier estimates of all patients in individual patient data meta-analysis; shaded regions represent 95% CIs. (B) Pre-specified subgroup analysis by trial. HR=hazard ratio. SOC=standard of care.

Figure 9: Overall survival in abiraterone trial

A. Overall survival, SOC vs SOC with abiraterone



Kaplan-Meier estimates; 95% confidence interval represented by lighter shade. SOC, standard of care; AAP, abiraterone; ENZ, enzalutamide.

In the safety population, 130 (29%) of 455 control patients in the abiraterone trial and 172 (32%) of 533 control patients in the abiraterone and enzalutamide trial had grade 3 or worse AEs during the first 24 months. In the combination-therapy groups, 169 (37%) of 451 patients in the abiraterone trial and 298 (57%) of 513 patients in the abiraterone and enzalutamide trial had grade 3 or worse AEs during the first 24 months. Seven grade 5 events were reported: none in the control groups, three (1%) in the abiraterone and prednisolone group (one [$<1\%$] event each of rectal adenocarcinoma, pulmonary haemorrhage, and a respiratory disorder), and four (1%) in the abiraterone and prednisolone with enzalutamide group (two events [$<1\%$] each of septic shock and sudden death). The most common AEs reported in the combination-therapy groups compared with the control groups were hypertension (153 [5%] of 988 in the control groups vs 393 [41%] of 964 in the combination-therapy groups) and aminotransaminases (136 [14%] vs 332 [34%]). The most common grade 3 or worse AEs when enzalutamide and abiraterone were combined were hypertension (23 [5%] of 451 in the abiraterone trial vs 73 [14%] of 513 in abiraterone and enzalutamide trial), fatigue (ten [2%] vs 49 [10%]), and increases in aminotransferases (25 [5%] vs 69 [13%]). See [table 2 in article](#). In the abiraterone trial 13% of patients stopped abiraterone because of excessive toxicity, whereas in the abiraterone and enzalutamide trial 31% and 25% of patients stopped abiraterone and enzalutamide, respectively, for this reason.

In summary, men with high-risk non-metastatic prostate cancer who receive ADT with combination therapy have significantly better metastases-free survival and overall survival than those who receive ADT alone. Two years of abiraterone and prednisolone added to ADT and, if indicated, radiotherapy

should be considered a new standard treatment for non-metastatic prostate cancer with high-risk features.

The MAH agrees to restrict the indication to patients with newly diagnosed disease and agrees to include radiotherapy as part of combination treatment. The currently proposed indication is acceptable: *“the treatment of newly diagnosed high risk non-metastatic hormone sensitive prostate cancer (HSPC) in adult men in combination with ADT and radiotherapy (see section 5.1)”*.

III.3.3 Clinical safety

N/A

III.3.4 RMP

The MAH submitted an updated RMP (version 2.1, dated on 05-03-2024) as requested.

The major changes compared to the currently approved version: inclusion of the newly proposed indication, update of safety concerns to none, additional RMM updated to not applicable, targeted follow-up questionnaires removed.

No safety concerns were identified, which is in line with the RMP of the reference product Zytiga (version 15.1). The reference product does not have the applied for indication that is proposed for this generic product. No difference in safety profile is expected in the applied indication of “newly diagnosed non-metastatic HSPC” compared to the existing indication “newly diagnosed metastatic HSPC”.

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are proposed. No additional pharmacovigilance activities are proposed. No post-authorization efficacy studies are in place or planned. This is in line with the reference product.

Therefore, the updated RMP (version 2.1, dated on 05-03-2024) is considered acceptable.

III.4 Product information

III.4.1 Summary of Product Characteristics

See SmPC

III.4.2 Package leaflet and user test

See PL

III.4.3 Labelling

N/A

IV. UPDATED OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Abirateron Sandoz 500 mg, Bixodalan 500 mg and Abirateron 1A Pharma 500 mg (abiraterone acetate) were granted a marketing authorisation pursuant to Article 10(1) of Directive 2001/83/EC via a decentralised procedure (NL/H/5068-5069-5070/002/DC). The procedure concerned a generic application claiming essential similarity with the innovator product [Zytiga](#) 250 mg tablets and 500 mg film-coated tablets registered in the EEA via the centralised procedure ([MAA EPAR](#); [Zytiga SmPC](#)).

With the current procedure, the MAH initially proposed the following changes to the approved indications

(deleted text strikethrough; added text bold):

“[Product name] is indicated with prednisone or prednisolone for:

- *the treatment of ~~newly diagnosed high-risk~~ metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see section 5.1)*
- ***the treatment of newly diagnosed high risk non-metastatic hormone sensitive prostate cancer (HSPC) in adult men in combination with androgen deprivation therapy (ADT) and radiotherapy (see section 5.1)***
- *the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1)*
- *the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.”*

The clinical dossier does not contain any study reports and is based on bibliographical data. The MAH, as a justification for the proposed changes to the indications, provided a nine-page Clinical Expert Statement and seven references, i.e. five published articles from scientific literature and two clinical guidelines.

For a proper assessment of the benefits of abiraterone in the proposed indications, information was extracted from the provided references/articles and their accompanying supplementary materials ([James et al. N Engl J Med. 2017](#); [Hoyle et al. Eur Urol. 2019](#); [James et al. Int J Cancer. 2022](#); [Attard et al. Lancet. 2022](#)). All these references/articles concern [the STAMPEDE trial](#). STAMPEDE was not conducted under the responsibility of the MAH and no CSR was provided. Then again, another comparison from STAMPEDE was used as a pivotal study for the extension of indication of another medicinal product ([Taxotere WS1550 EPAR](#)). Therefore, results from STAMPEDE have already been considered for regulatory decision making.

Of note, the STAMPEDE results were obtained with the innovator product [Zytiga](#). It is considered though, that these results can be extrapolated to Abirateron Sandoz 500 mg, Bixodalan 500 mg, Abirateron 1A Pharma 500 mg film-coated tablets which are generic medicinal products for which essential similarity has been demonstrated with this innovator product.

Based on the extracted information and the considerations discussed above, the following conclusions can be drawn:

1. It is acceptable to change the wording of the mHSPC indication as follows (deleted text strikethrough): *“the treatment of newly diagnosed ~~high-risk~~ metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see section 5.1)”*.

The STAMPEDE results in [Hoyle et al. Eur Urol. 2019](#) demonstrate an OS benefit of adding AAP to ADT in patients with newly diagnosed mHSPC, irrespective of risk. In [James et al. Int J Cancer. 2022](#), confirmatory updated results with extended follow-up are presented. The toxicity of AAP in this broader indication is in line with the known safety profile of AAP and (thus) acceptable. Therefore, the benefit-risk balance (B/R) is considered positive for this patient population.

2. It is acceptable to add the following new indication: *“the treatment of newly diagnosed high risk non-metastatic hormone sensitive prostate cancer (HSPC) in adult men in combination with ADT and radiotherapy (see section 5.1)”*.

The results of the abiraterone trial in STAMPEDE demonstrate a MFS and OS benefit of adding AAP to ADT and radiotherapy in patients with (very) high-risk non-metastatic HSPC ([Attard et al. Lancet. 2022](#)). The toxicity of AAP in this new indication is in line with the known safety profile of AAP and (thus) acceptable. Therefore, the B/R of adding AAP to ADT and radiotherapy in patients with (very) high-risk non-metastatic HSPC is considered positive.

Therefore, the group of variations following a worksharing procedure NL/H/5068/002/WS/003 is approved.