SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT
ABYGA 500 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains:
Active substance:

Abiraterone acetate	500 mg

Excipients:

Lactose monohydrate (from cow's milk)	397.3 mg
Croscarmellose sodium	85.8 mg
Sodium lauryl sulfate	57.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet
Purple, oval-shaped biconvex, tablet.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
ABYGA is indicated with prednisone and prednisolone for the treatment of the following conditions:

- The treatment of newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) until disease progression or the occurrence of unacceptable toxicity (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 (ADT) 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.
- Docetaxel in combination with androgen suppression therapy (AST) is indicated for the treatment of adult male patients with metastatic hormone-sensitive prostate cancer (mHSPC) with high-volume disease (presence of visceral metastases or ≥4 bone metastases, of which at least 1 bone metastasis is outside the vertebrae and pelvis).

4.2. Posology and method of administration
This medicinal product should be prescribed by an appropriate healthcare professional.

Posology, frequency and duration of administration:
The recommended ABYGA dose is 1,000 mg (two 500 mg tablets) as a single daily dose that must not be taken with food (see "Method of administration" below). Taking the tablets with food increases systemic exposure to abiraterone (see Sections 4.5 and 5.2).

Dosage of Prednisone or Prednisolone

For patients with metastatic hormone sensitive prostate cancer, ABYGA is used with 5 mg prednisone or prednisolone daily.

For patients with metastatic castration resistant prostate cancer, ABYGA is used with 10 mg prednisone or prednisolone daily.

Medical castration with luteinizing hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.

In metastatic hormone-sensitive prostate cancer (mHSPC) with high-volume disease, if ABYGA is used in combination with androgen suppression therapy and docetaxel, the posology recommendations in the product information of ABYGA and docetaxel should be followed.

Even if a cycle of docetaxel is delayed, interrupted or discontinued, treatment with abiraterone should be continued until disease progresses or unacceptable toxicity develops.

Recommended monitoring
Serum transaminases should be measured prior to starting treatment with ABYGA, every 2 weeks for the first 3 months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. However, patients with a significant risk for congestive heart failure should be monitored every 2 weeks for the first 3 months of treatment and monthly thereafter (see Section 4.4).

In patients with pre-existing hypokalemia or those that develop hypokalemia whilst being treated with ABYGA, consider maintaining the patient's potassium level at ≥4 mM.

For patients who develop Grade ≥3 toxicities including hypertension, hypokalemia, edema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with ABYGA should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline.

In the event of a missed daily dose of either ABYGA, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Method of administration:

ABYGA is for oral use.

The tablets should be taken as a single dose once a day on an empty stomach. ABYGA should be taken at least 1 hour before or at least two hours after a meal. Tablets should be swallowed whole with water.

Additional information on special populations:

Hepatotoxicity

For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately (see Section 4.4). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (1 tablet) once daily. For patients being re-treated, serum transaminases should be monitored at a minimum of every 2 weeks for 3 months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued completely.

If patients develop severe hepatotoxicity (ALT or AST levels increased by 20 times the upper limit

of accepted as normal) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.

Hepatic impairment:
No dose change is required for patients with pre-existing mild hepatic failure (Child-Pugh Class A).

Moderate hepatic impairment (Child-Pugh Class B) has been shown to increase the systemic exposure to abiraterone by approximately 4-fold following single oral doses of abiraterone acetate 1,000 mg (see Section 5.2). There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. The use of ABYGA should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see Sections 4.2 and 5.2). ABYGA should not be used in patients with severe hepatic impairment (see Sections 4.3, 4.4 and 5.2).

Renal impairment:
No dose adjustment is necessary for patients with renal impairment (see Section 5.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients (see Section 4.4).

Pediatric population:
There is no relevant use of ABYGA in the pediatric population.

Geriatric population:
No studies have been conducted on dose adjustment for elderly patients.

4.3. Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Women who are or may potentially be pregnant (see Section 4.6).
- Contraindicated in severe hepatic impairment [Child-Pugh Class C (see Sections 4.2, 4.4 and 5.2)].
- ABYGA with prednisone or prednisolone is contraindicated in combination with Ra-223.

4.4. Special warnings and precautions for use
Hypertension, hypokalemia, fluid retention and cardiac failure due to mineralocorticoid excess
Abiraterone acetate may cause hypertension, hypokalemia and fluid retention (see Section 4.8) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see Section 5.1). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia (e.g., those on cardiac glycosides), or fluid retention (e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia and those with severe renal impairment).

ABYGA should be used cautiously in patients with a history of cardiovascular disease. The Phase 3 studies conducted excluded patients with uncontrolled hypertension, clinically significant 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 (NYHA) III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of <50%. In studies 3011 and 302, patients with atrial fibrillation, or other cardiac

arrhythmia requiring medical therapy were excluded. Safety in patients with left ventricular ejection fraction (LVEF) <50% or New York Heart Association Class (NYHA) Class III or IV heart failure (in study 301) or NYHA Class II to IV heart failure (in studies 3011 and 302) was not established (see Section 4.8 and 5.1).

Before treating patients with a significant risk for congestive heart failure (e.g. cardiac events such as heart failure, uncontrolled hypertension or ischemic heart disease), consider obtaining an assessment of cardiac function (e.g. echocardiogram). Before treatment with ABYGA, cardiac failure should be treated and cardiac function should be optimized. Hypertension, hypokalemia and fluid retention should be corrected and taken under control. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral edemas), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected. QT prolongation has been observed in patients experiencing hypokalemia in association with abiraterone acetate treatment. In the occurrence of a clinically significant decrease in cardiac function, cardiac function should be assessed according to the clinical indication, appropriate treatment should be initiated and discontinuation of ABYGA should be considered. (see Section 4.2).

Hepatotoxicity and hepatic impairment
Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred in controlled clinical studies (see Section 4.8). Serum transaminase levels should be measured prior to starting treatment, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. If at any time the ALT or AST rises above 5 times the upper limit of normal (ULN), treatment should be interrupted immediately and liver function closely monitored. Re-treatment may take place only after return of liver function tests to the patient's baseline and at a reduced dose level (see Section 4.2).

If patients develop severe hepatotoxicity (ALT or AST levels increased by 20 times the upper limit of accepted as normal) anytime while on therapy, ABYGA treatment should be discontinued and patients should not be re-treated.

Patients with active or symptomatic viral hepatitis were excluded from clinical trials; thus, there are no data to support the use of abiraterone acetate in this population.

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The use of abiraterone acetate should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see Sections 4.2 and 5.2). ABYGA should not be used in patients with severe hepatic impairment (see Sections 4.2, 4.3 and 5.2).

There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome (see Section 4.8).

Corticosteroid withdrawal and coverage of stress situations
Caution is advised and monitoring for adrenocortical insufficiency should occur if patients are withdrawn from prednisone or prednisolone. If ABYGA is to be continued after corticosteroids are withdrawn, patients should be monitored for symptoms related to mineralocorticoid excess (see Section 4.4. *Hypertension, hypokalemia, fluid retention and cardiac failure due to mineralocorticoid excess).*

In patients on prednisone or prednisolone who are subjected to unusual stress, an increased dose of corticosteroids may be indicated before, during and after the stressful situation.

Bone density
Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of ABYGA in combination with a glucocorticoid could increase this effect.

Prior use of ketoconazole
Lower rates of response might be expected in patients previously treated with ketoconazole for prostate cancer.

Hyperglycemia
The use of glucocorticoids could increase hyperglycemia, therefore blood sugar should be measured frequently in patients with diabetes.

Hypoglycemia
Cases of hypoglycemia were reported when abiraterone acetate plus prednisone or prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see Section 4.5); therefore, blood sugar should be monitored in patients with diabetes.

Use with chemotherapy
The safety and efficacy of concomitant use of ABYGA with cytotoxic chemotherapy has not been shown (see Section 5.1).

Potential risks
Anemia and sexual dysfunction may occur in men with metastatic prostate cancer including those undergoing treatment with ABYGA.

Skeletal muscle effects
Cases of myopathy and rhabdomyolysis have been reported in patients treated with abiraterone acetate. Most cases appeared within the first 6 months of treatment and recovered after abiraterone acetate withdrawal. Caution is recommended in patients concomitantly treated with medicinal products known to be associated with myopathy/rhabdomyolysis.

Interactions with other medicinal products
Strong inducers of CYP3A4 during treatment should be avoided unless there is noother treatment option, due to risk of decreased exposure to ABYGA (see Section 4.5).

Combination of abiraterone and prednisone/prednisolone with Ra-223
Therapy with abiraterone and prednisone/prednisolone in combination with Ra-223 is contraindicated (see Section 4.3) due to an increased risk of fractures and a tendency to increased mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in clinical trials.

It is not recommended that subsequent treatment with Ra-223 is initiated for at least 5 days after the last administration of ABYGA in combination with prednisone/prednisolone.

Intolerance to excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase insufficiency or glucose-galactose malabsorption should not use this

medicine.

This medicinal product contains 24.12 mg sodium per dose (two tablets) equivalent to 1.2% of the WHO recommended maximum daily intake of 2 g sodium for adults.

4.5. Interaction with other medicinal products and other forms of interaction

Effect of food on abiraterone acetate

Administration with food significantly increases the absorption of abiraterone acetate. The efficacy and safety of ABYGA when given with food have not been demonstrated therefore this medicinal product must not be taken with food (see Sections 4.2 and 5.2).

Interactions with other medicinal products

Potential for other medicinal products to affect abiraterone exposures

In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer rifampicin, 600 mg daily for 6 days and followed by a single dose of abiraterone acetate 1,000 mg, the mean plasma AUC_{∞} of abiraterone was decreased by 55%.

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [*Hypericum perforatum*]) during treatment are to be avoided, unless there is no there is no other treatment option.

In a separate clinical pharmacokinetic interaction study of healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Potential for abiraterone to affect exposures to other medicinal products

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.9 fold. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when ABYGA is taken with medicinal products activated by or metabolized by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolized by CYP2D6 should be considered. Examples of medicinal products metabolized by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicinal products requiring CYP2D6 to form their active analgesic metabolites).

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Patients should be monitored for symptoms of toxicity when ABYGA is co-administered with drugs with a narrow therapeutic range that are CYP2C8 substrates. Examples of medicinal products metabolized by CYP2C8 include pioglitazone and repaglinide (see Section 4.4).

In vitro, the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the

concentrations of medicinal products eliminated by OATP1B1. There are no clinical data available to confirm transporter based interaction.

Use with products known to prolong QT interval
Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering ABYGA with medicinal products known to prolong the QT interval or medicinal products able to induce Torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Use with spironolactone
Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with ABYGA is not recommended (see Section 5.1).

Additional information on special populations
No interaction studies have been conducted.

Pediatric population
No interaction studies have been conducted.

4.6. Pregnancy and lactation
General recommendation
Pregnancy category: X

ABYGA is not for use in women. ABYGA is contraindicated in women who are or may potentially be pregnant (see Sections 4.3 and 5.3).

Women of childbearing potential
There are no clinical data on the use of ABYGA in pregnancy and ABYGA is not for use in women of childbearing potential.

Birth Control (contraception)
It is not known whether abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method. Studies in animals have shown reproductive toxicity (see Section 5.3).

Pregnancy
ABYGA is not for use in women and is contraindicated in women who are or may potentially be pregnant (see Sections 4.3 and 5.3).

Lactation
ABYGA is not for use in women.

Reproductive ability / Fertility
Abiraterone acetate affected fertility in male and female rats, but these effects were fully reversible (see Section 5.3).

4.7. Effects on ability to drive and use machines
ABYGA has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

In an analysis of adverse reactions of composite Phase 3 studies with abiraterone acetate, adverse reactions that were observed in ≥10% of patients were peripheral edema, hypokalemia, hypertension urinary tract infection, and alanine aminotransferase increased and/or aspartate aminotransferase increased.

Other important adverse reactions include cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis.

Abiraterone acetate may cause hypertension, hypokalemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies, anticipated mineralocorticoid adverse reactions were seen more commonly in patients treated with abiraterone acetate than in patients treated with placebo. In the study, hypokalemia was reported as 18% in abiraterone acetate-treated patients and 8% in placebo-treated patients, hypertension as 22% in abiraterone acetate-treated patients and 16% in placebo-treated patients, and fluid retention (peripheral edema) as 23% in abiraterone acetate-treated patients and 17% in placebo-treated patients. In patients treated with abiraterone acetate, grade 3 and 4 hypokalaemia (according to CTCAE, version 4.0 classification) was 6% compared with 1% in placebo-treated patients; grade 3 and 4 hypertension (according to CTCAE, version 4.0 classification) was 7% in patients treated with abiraterone acetate compared with 5% in placebo-treated patients; grade 3 and 4 fluid retention (peripheral edema) was 1% in patients treated with abiraterone acetate compared with 1% in placebo-treated patients. Mineralocorticoid reactions generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see Section 4.4).

Summary of adverse reactions

In studies of patients with metastatic advanced prostate cancer who were using a luteinizing hormone-releasing hormone (LHRH) analogue, or were previously treated with orchiectomy, abiraterone acetate was administered at a dose of 1,000 mg daily in combination with low dose prednisone or prednisolone (either 5 or 10 mg daily depending on the indication).

Adverse reactions observed during clinical studies and post-marketing experience are listed below by frequency category. Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Very common: Urinary tract infection
Common: Sepsis

Immune system disorders

Not known: Anaphylactic reactions

Endocrine disorders

Uncommon: Adrenal insufficiency

Metabolism and nutrition disorders
Very common: Hypokalemia
Common: Hypertriglyceridemia

Cardiac disorders
Common: Cardiac failure*, angina pectoris, atrial fibrillation, tachycardia
Uncommon: Other arrhythmias
Not known: Myocardial infarction, QT prolongation (see Sections 4.4 and 4.5)

Vascular disorders
Very common: Hypertension

Respiratory, thoracic and mediastinal disorders
Rare: Allergic alveolitis[a]

Gastrointestinal disorders
Very common: Diarrhea
Common: Dyspepsia

Hepatobiliary disorders
Very common: Alanine aminotransferase increased and/or aspartate aminotransferase increased[b]
Rare: Hepatitis fulminant, acute hepatic failure

Skin and subcutaneous tissue disorders
Common: Rash

Musculoskeletal and connective tissue disorders
Uncommon: Myopathy, rhabdomyolysis

Renal and urinary disorders
Common: Hematuria

General disorders and administration site conditions
Very common: Edema peripheral

Injury, poisoning and procedural complications
Common: Fractures**

* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased.
** Fractures includes osteoporosis and all fractures with the exception of pathological fractures.

[a] Spontaneous reports from post-marketing experience
[b] Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.

The following CTCAE (version 4.0) Grade 3 adverse reactions occurred in patients treated with abiraterone acetate: hypokalemia 5%; urinary tract infection 2%; alanine aminotransferase increased and/or aspartate aminotransferase increased 4%; hypertension 6%; fractures 2%; peripheral edema, cardiac failure, and atrial fibrillation 1%. CTCAE (version 4.0) Grade 3 hypertriglyceridemia and

angina pectoris occurred in <1% of patients. CTCAE (version 4.0) Grade 4 urinary tract infection, alanine aminotransferase increased and/or aspartate aminotransferase increased, hypokalemia, cardiac failure, atrial fibrillation, and fractures occurred in <1% of patients.

A higher incidence of hypertension and hypokalemia was observed in the hormone sensitive population (study 3011). Hypertension was reported in 36.7% of patients in the hormone sensitive population (study 3011) compared to 11.8% and 20.2% in studies 301 and 302, respectively. Hypokalemia was observed in 20.4% of patients in the hormone sensitive population (study 3011) compared to 19.2% and 14.9% in 301 and 302, respectively).

The incidence and severity of adverse events was higher in the subgroup of patients with baseline ECOG2 performance status grade and also in elderly patients (≥75 years).

Description of selected adverse reactions

Cardiovascular reactions

The three Phase 3 studies excluded patients with uncontrolled hypertension, clinically significant 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 (NYHA) Class III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of <50%. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominantly with the use of LHRH analogues, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the Phase 3 studies in patients taking abiraterone acetate vs. patients taking placebo were as follows: Atrial fibrillation 2.6% vs. 2%, tachycardia 1.9% vs. 1%, angina pectoris 1.7% vs. 0.8%, cardiac failure 0.7% vs. 0.2%, and arrhythmia 0.7% vs. 0.5%.

Hepatotoxicity

Hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone acetate. Across Phase 3 clinical studies, hepatotoxicity Grades 3 and 4 (e.g.,ALT and AST levels more than 5 times the upper limit of what is considered normal or bilirubin levels more than 1.5 times the upper limit of what is considered normal) were reported in approximately 6% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In Study 3011, grade 3 or 4 hepatotoxicity was observed in 8.4% of patients treated with abiraterone acetate. 10 patients who received abiraterone acetate were discontinued because of hepatotoxicity; 2 had Grade 2 hepatotoxicity, 6 had Grade 3 hepatotoxicity, and 2 had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011. In the Phase 3 clinical studies, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values.

Abiraterone acetate treatment was interrupted or discontinued if ALT or AST levels increased more than 5 times the upper limit of considered as normal or if bilirubin levels increased more than 3 times the upper limit of considered as normal. In two instances marked increases in liver function tests occurred (see Section 4.4). In two cases, liver function tests showed significant elevations (see section 4.4). In these two patients with normal baseline values, ALT or AST levels increased 15 to 40 times the upper limit of normal and bilirubin levels increased 2 to 6 times the upper limit of normal. Upon discontinuation of treatment, both patients had normalization of their liver function tests and one patient was re-treated without recurrence of the elevations. In study 302, Grade 3 or 4 ALT or AST elevations were observed in 35 (6.5%) patients treated with abiraterone acetate. Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases and 1 with AST elevation approximately 3 weeks after the last dose of abiraterone acetate). In Phase 3 clinical studies,

treatment discontinuations due to ALT and AST increases or abnormal hepatic function were reported in 1.1% of patients treated with abiraterone acetate and 0.6% of patients treated with placebo; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In Study 3011, patients with baseline ALT and AST values greater than 2.5 times the ULN, patients with bilirubin values greater than 1.5 times the upper limit of what is considered normal, and patients with active or symptomatic viral hepatitis or chronic liver disease; patients with ascites or bleeding disorders due to liver dysfunction were excluded. In Study 301, patients with baseline ALT and AST levels ≥2.5 times the upper limit of normal in the absence of liver metastases and >5 times the upper limit of normal in the presence of liver metastases were excluded. In the 302 trial, patients with liver metastases were not eligible and patients with baseline ALT and AST ≥2.5×ULN were excluded. When patients included in the clinical trial had abnormal liver function tests, their treatment was interrupted and actively managed by allowing them to resume treatment only after liver function tests returned to baseline levels (see Section 4.2). Patients with ALT and AST levels more than 20 times higher than the upper limit of what is considered normal were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity is not known.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9. Overdose
Human experience of overdose with abiraterone acetate is limited.

There is no specific antidote. In the event of an overdose, ABYGA administration should be withheld and general supportive measures undertaken, including monitoring for arrhythmias, hypokalemia and for signs and symptoms of fluid retention. Liver function also should be assessed.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Endocrine therapy, other hormone antagonists and related agents
ATC code: L02BX03

Mechanism of action
Abiraterone acetate (ABYGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal and prostatic tumor tissues and is required for androgen biosynthesis. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals (see Section 4.4).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with LHRH analogues or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor. Treatment with abiraterone acetate decreases serum testosterone to undetectable levels (using

commercial assays) when given with LHRH analogues (or orchiectomy).

Pharmacodynamic effects

Abiraterone acetate decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH analogues alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis. Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer. In a Phase 3 clinical study of patients who had not previously benefited from chemotherapy with taxanes, 38% of patients treated with abiraterone acetate, versus 10% of patients treated with placebo, had at least a 50% decline from baseline in PSA levels.

Clinical efficacy and safety

Efficacy of abiraterone acetate was established in three randomized placebo-controlled multicentre Phase 3 clinical studies (studies 3011, 302 and 301) of patients with metastatic hormone sensitive prostate cancer (mHSPC) and metastatic castration resistant prostate cancer (mCRPC). Study 3011 enrolled patients who were newly diagnosed (within 3 months of randomization) mHSPC who had high-risk prognostic factors. High-risk prognosis was defined as having at least 2 of the following 3 risk factors: (1) Gleason score of ≥8; (2) presence of 3 or more lesions on bone scan; (3) presence of measurable visceral (excluding lymph node disease) metastasis. In the active treatment arm, abiraterone acetate was administered at a dose of 1,000 mg daily in combination with low dose prednisone 5 mg once daily in addition to ADT (LHRH agonist or orchiectomy), which was the standard treatment Patients in the control arm received ADT and placebos for both abiraterone acetate and prednisone. Study 301 included patients who had previously received docetaxel and Study 302 included patients who had not received docetaxel. Patients were using an LHRH analogue or were previously treated with orchiectomy. In the active treatment arm, abiraterone acetate was administered at a dose of 1,000 mg daily in combination with low dose prednisone or prednisolone 5 mg twice daily. Control patients received placebo and low dose prednisone or prednisolone 5 mg twice daily.

Changes in PSA serum concentration independently do not always predict clinical benefit. Therefore, in all studies it was recommended that patients be maintained on their treatments until discontinuation criteria were met as specified below for each study.

In all studies spironolactone use was not allowed as spironolactone binds to the androgen receptor and may increase PSA levels.

Study 3011 (patients with newly diagnosed high risk mHSPC)

In Study 3011, (n=1,199) the median age of enrolled patients was 67 years. The number of patients treated with abiraterone acetate by racial group was Caucasian 832 (69.4%), Asian 246 (20.5%), Black or African American 25 (2.1%), other 80 (6.7%), unknown/not reported 13 (1.1%), and American Indian or Alaska Native 3 (0.3%). The ECOG performance status was 0 or 1 for 97% of patients. Patients with known brain metastasis, uncontrolled hypertension, significant heart disease, or NYHA Class II-IV heart failure were excluded. Patients that were treated with prior pharmacotherapy with the exception of up to 3 months of ADT or 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease, radiation therapy, or surgery for metastatic prostate cancer were excluded. Co-primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS). The median baseline pain score, as measured by the Brief Pain Inventory Short Form (BPI-SF) was 2 in both the treatment and Placebo groups. In addition to the co-primary endpoint measures, benefit was also assessed using time to skeletal-related event (SRE), time to subsequent therapy for prostate cancer, time to initiation of chemotherapy, time

to pain progression, and time to PSA progression. Treatment continued until disease progression, withdrawal of consent, the occurrence of unacceptable toxicity, or death.

Radiographic progression-free survival was defined as the time from randomization to the occurrence of radiographic progression or death from any cause. Radiographic progression included progression by bone scan (according to modified PCWG2) or progression of soft tissue lesions by CT or MRI (according to RECIST 1.1).

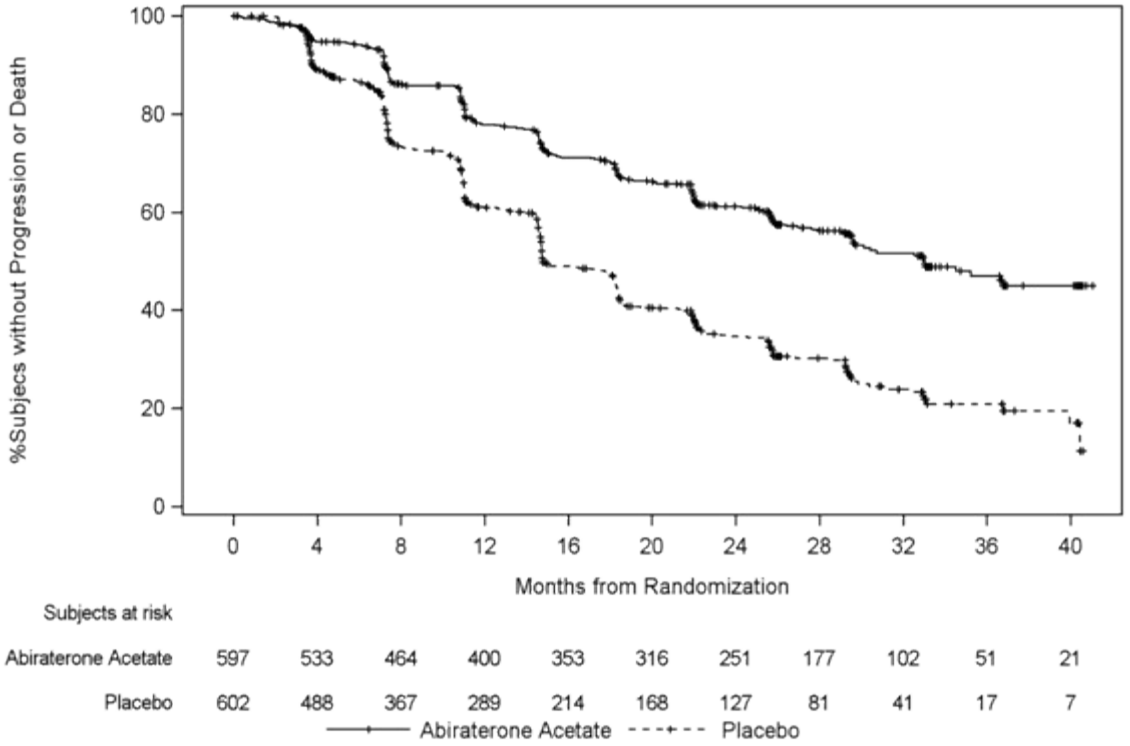
A significant difference in rPFS between treatment groups was observed (see Table 1 and Figure 1).

Table 1: Radiographic Progression-Free Survival -Stratified Analysis; Intent-to-treat Population (Study PCR3011)

	AA-P	**Placebo**
Subjects randomized	597	602
Event	239 (40.0%)	354 (58.8%)
Censored	358 (60.0%)	248 (41.2%)
Time to Event (months)		
Median (95% CI)	33.02 (29.57, NE)	14.78 (14.69, 18.27)
Range	(0.0+, 41.0+)	(0.0+, 40.6+)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.466 (0.394, 0.550)	

Note: + = Censored observation, NE = Not estimable. The radiographic progression and death are considered in defining the rPFS event. AA-P = Subjects who received abiraterone acetate and prednisone.
[a] p value is from a log-rank test stratified by ECOG PS score (0/1 or 2) and visceral lesion (absent or present).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors AA-P.

Figure 1: Kaplan-Meier Plot of Radiographic Progression-free Survival; Intent-to-treat Population (Study PCR3011)



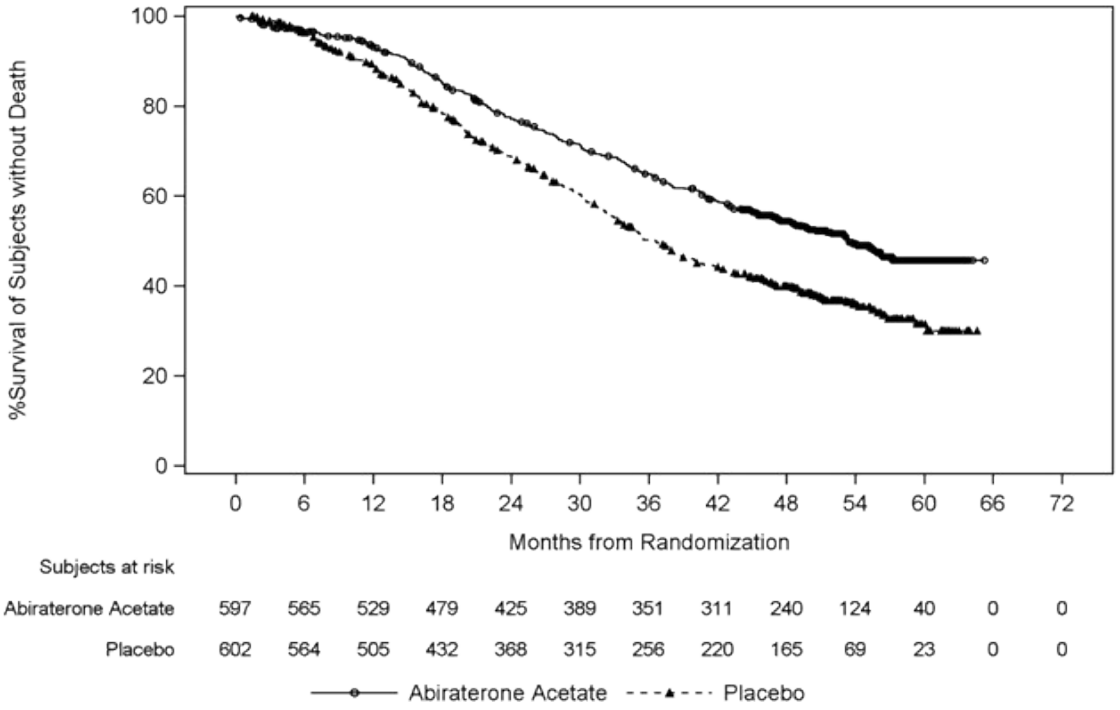
A statistically significant improvement in OS in favor of AA-P plus ADT was observed with a 34% reduction in the risk of death compared to Placebo plus ADT (HR=0.66; 95% CI: 0.56, 0.78; p<0.0001), (see Table 2 and Figure 2).

Table 2: Overall Survival of Patients Treated with Either Abiraterone Acetate or Placebo in Study PCR3011 (Intent-to-Treat Analysis)

Overall Survival	Abiraterone acetate and Prednisone (N = 597)	Placebo (N = 602)
Death (%)	275 (%46)	343 (%57)
Median Survival (Months)	53.3	36.5
(95% CI)	48.2, NE	33.5, 40
Hazard ratio (95% CI)[1]	0.66 (0.56, 0.78)	

NE = Not estimable.
[1] Hazard ratio is derived from stratified proportional hazards model. Hazard ratio <1 favors abiraterone acetate with prednisone.

Figure 2: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population Analysis (Study PCR3011)



Subgroup analyses consistently favour abiraterone acetate treatment. The treatment effect of AA-P on rPFS and OS in prespecified subgroups was superior and consistent in the overall study population, except in the subgroup with ECOG score 2, where no tendency to observe benefit was observed, however, the small sample size (n=40) limits the ability to provide a meaningful result.

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for abiraterone acetate vs. placebo treatment in all prospectively-defined secondary endpoints.

Study 302 (chemotherapy naïve patients)
This study enrolled chemotherapy naïve patients who were asymptomatic or mildly symptomatic and for whom chemotherapy was not yet clinically indicated. A score of 0-1 on Brief Pain Inventory-Short Form (BPI-SF) "worst pain in last 24 hours" was considered asymptomatic, and a score of 2-3 was considered mildly symptomatic.

In study 302, (n=1,088) the median age of enrolled patients was 71 years for patients treated with abiraterone acetate plus prednisone or prednisolone and 70 years for patients treated with placebo plus prednisone or prednisolone. The number of patients treated with abiraterone acetate by racial group was Caucasian 520 (95.4%), Black 15 (2.8%), Asian 4 (0.7%) and other 6 (1.1%). The Eastern Cooperative Oncology Group (ECOG) performance status was 0 for 76% of patients, and 1 for 24% of patients in both arms. 50% of patients had only bone metastases, 31% of patients had bone and soft tissue or lymph node metastases and 19% of patients had only soft tissue or lymph node metastases. Patients with visceral metastases were excluded. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). In addition to the co-primary endpoint measures, benefit was also assessed using time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, time to deterioration in ECOG performance score by ≥1 point and time to PSA progression based on Prostate Cancer Working Group-2 (PCWG2) criteria. Study treatments were discontinued at the time of unequivocal clinical progression. Treatments could also be discontinued at the time of confirmed radiographic progression at the discretion of the investigator.

Radiographic progression free survival (rPFS) was assessed with the use of sequential imaging studies

as defined by PCWG2 criteria (for bone lesions) and modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria (for soft tissue lesions). Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

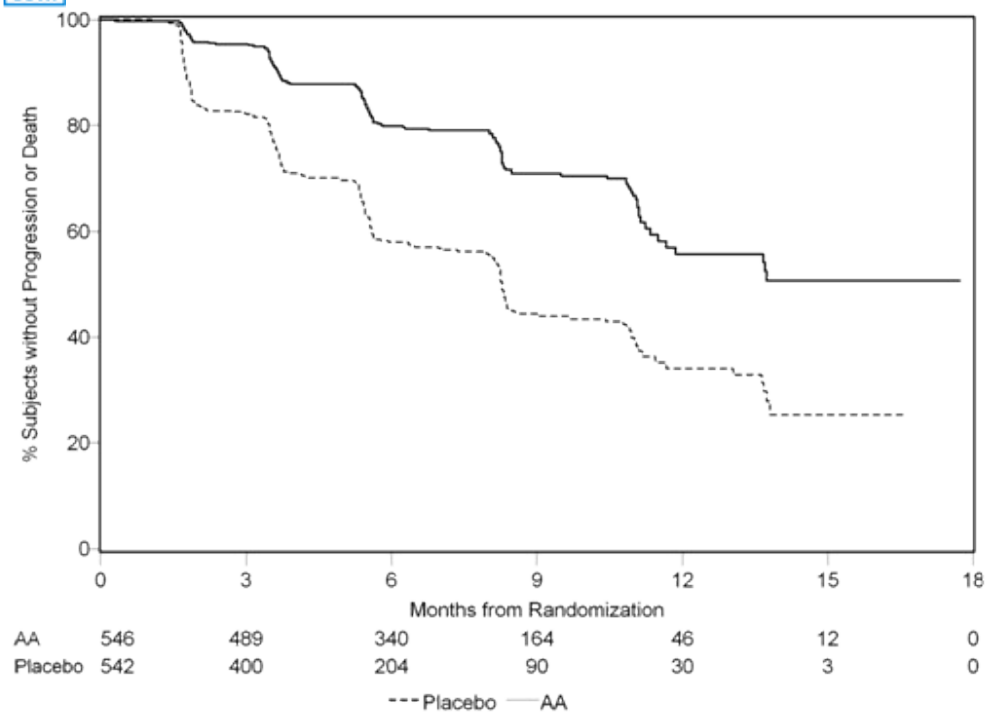
At the planned rPFS analysis included 401 events, 150 (28%) of patients treated with abiraterone acetate and 251 (46%) of patients treated with placebo had radiographic evidence of progression or had died. A significant difference in rPFS between treatment groups was observed (see Table 3 and Figure 3).

Table 3: Study 302: Radiographic progression-free survival of patients treated with either abiraterone acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

	Abiraterone acetate (N=546)	**Placebo (N=542)**
Radiographic Progression-free Survival (rPFS)		
Progression or death	150 (28%)	251 (46%)
Median rPFS in months (95% CI)	Not reached (11.66; NE)	8.3 (8.12; 8.54)
p-value*	<0.0001	
Hazard ratio** (95% CI)	0.425 (0.347; 0.522)	

NE=Not estimated
* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)
** Hazard ratio <1 favors abiraterone acetate

Figure 3: Kaplan Meier curves of radiographic progression-free survival in patients treated with either abiraterone acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA = Abiraterone acetate

However, subject data continued to be collected through the date of the second interim analysis of Overall survival (OS). The investigator radiographic review of rPFS performed as a follow up sensitivity analysis is presented in Table 4 and Figure 4.

Six hundred and seven (607) subjects had radiographic progression or died: 271 (50%) in the abiraterone acetate group and 336 (62%) in the placebo group. Treatment with abiraterone acetate decreased the risk of radiographic progression or death by 47% compared with placebo (HR=0.530; 95% CI: [0.451; 0.623], p <0.0001). The median rPFS was 16.5 months in the abiraterone acetate group and 8.3 months in the placebo group.

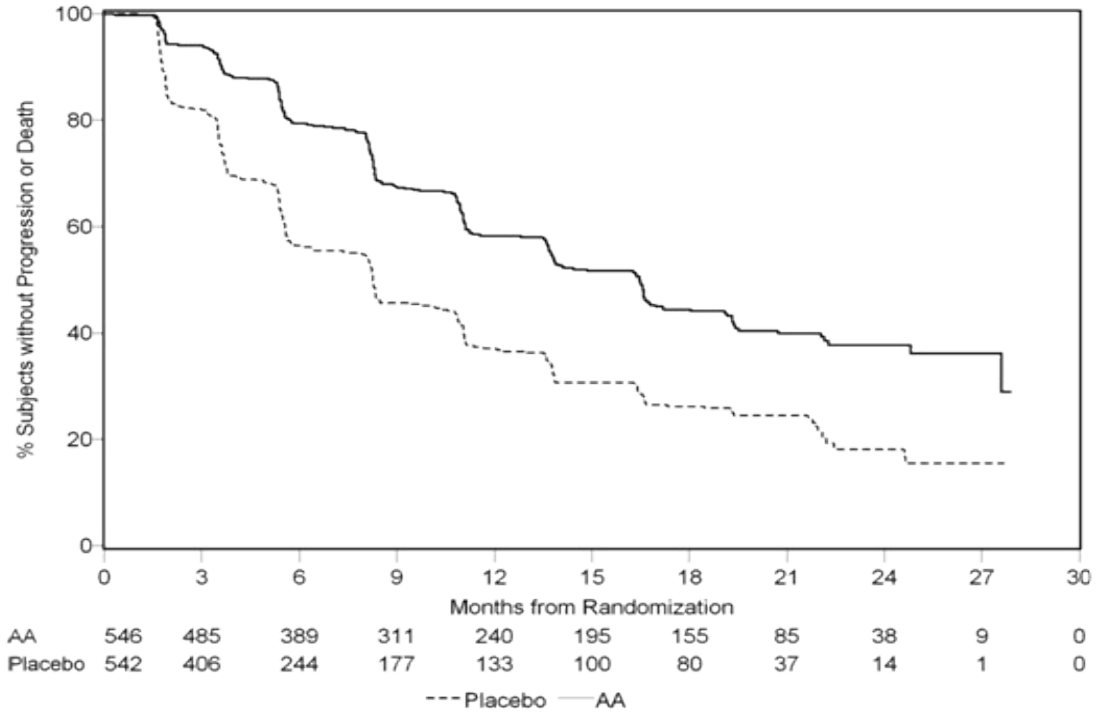
Table 4: Study 302: Radiographic progression-free survival of patients treated with either abiraterone acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator Review)

	Abiraterone acetate (N=546)	**Placebo (N=542)**
Radiographic Progression-free Survival (rPFS)		
Progression or death	271 (50%)	336 (62%)
Median rPFS in months (95% CI)	16.5 (13.80; 16.79)	8.3 (8.05; 9.43)
p-value*	<0.0001	
Hazard ratio** (95% CI)	0.530 (0.451; 0.623)	

* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)
** Hazard ratio <1 favors abiraterone acetate

Figure 4: Kaplan Meier curves of radiographic progression-free survival in patients treated with either abiraterone acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator

Review)



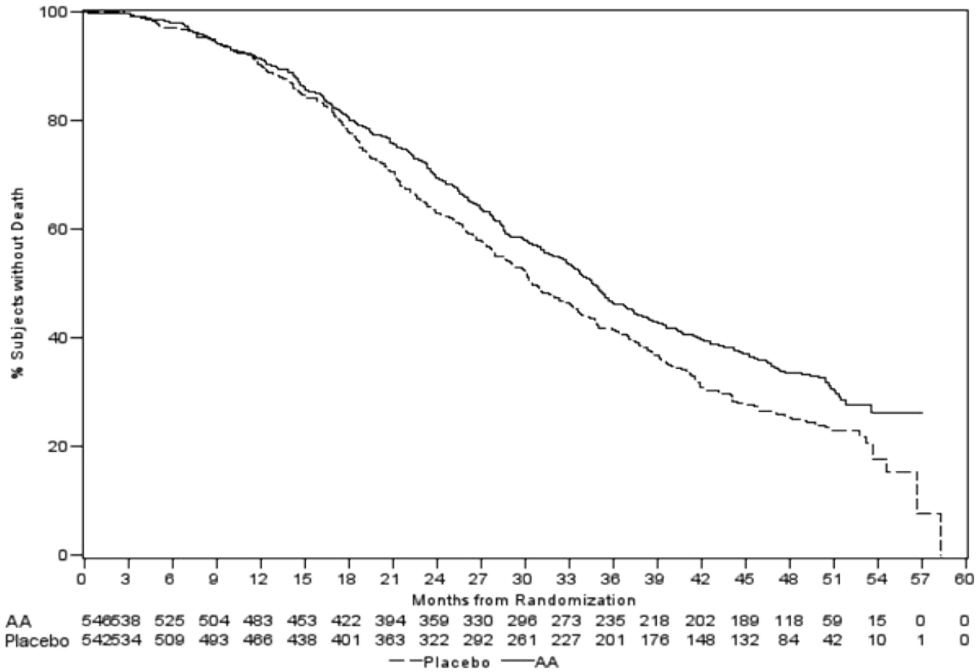
AA = Abiraterone acetate

A planned interim analysis (IA) for OS was conducted after 333 deaths were observed. The study was unblinded based on the magnitude of clinical benefit observed and patients in the placebo group were offered treatment with abiraterone acetate. Abiraterone acetate reduced the risk of death by 25%, providing a longer overall survival compared to placebo. (HR=0.752; 95% CI: [0.606; 0.934], p=0.0097), but OS was not mature and interim results did not meet the pre-specified stopping boundary for statistical significance (see Table 4). Survival continued to be followed after this interim analysis. The planned final analysis for OS was conducted after 741 deaths were observed (median follow up of 49 months). 65% (354 of 546) of patients treated with abiraterone acetate, compared with 71% (387 of 542) of patients treated with placebo, had died. A statistically significant OS benefit in favor of the abiraterone acetate-treated group was demonstrated with a 19.4% reduction in risk of death (HR=0.806; 95% CI: [0.697; 0.931], p=0.0033) and an improvement in median OS of 4.4 months (abiraterone acetate 34.7 months, placebo 30.3 months) (see Table 5 and Figure 5). This improvement was demonstrated even though 44% of patients in the placebo arm received abiraterone acetate as subsequent therapy.

Table 5: Study 302: Overall survival of patients treated with either abiraterone acetate or

placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy		
	Abiraterone acetate (N=546)	**Placebo (N=542)**
Interim survival analysis		
Deaths (%)	147 (27%)	186 (34%)
Median survival (months) (95% CI)	Not reached (NE; NE)	27.2 (25.95; NE)
p-value*	0.0097	
Hazard ratio** (95% CI)	0.752 (0.606; 0.934)	
Final survival analysis		
Deaths	354 (65%)	387 (71%)
Median overall survival (months, 95% CI)	34.7 (32.7; 36.8)	30.3 (28.7; 33.3)
p-value*	0.0033	
Hazard ratio** (95% CI)	0.806 (0.697; 0.931)	
NE = Not Estimated * p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1) ** Hazard ratio <1 favors abiraterone acetate		

Figure 5: Kaplan Meier survival curves of patients treated with either abiraterone acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy, final analysis



AA = Abiraterone acetate

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for abiraterone acetate vs. placebo treatment in all secondary endpoint measures as follows:

Time to PSA progression based on PCWG2 criteria: The median time to PSA progression was 11.1 months for patients receiving abiraterone acetate and 5.6 months for patients receiving placebo (HR=0.488; 95% CI: [0.420; 0.568], p <0.0001). The time to PSA progression was approximately doubled with abiraterone acetate treatment (HR=0.488). The proportion of subjects with a confirmed

PSA response was greater in the abiraterone acetate group than in the placebo group (62% vs. 24%; p <0.0001). In subjects with measurable soft tissue disease, significantly increased numbers of complete and partial tumor responses were seen with abiraterone acetate treatment.

Time to opiate use for cancer pain: The median time to opiate use for prostate cancer pain at the time of final analysis was 33.4 months for patients receiving abiraterone acetate and was 23.4 months for patients receiving placebo (HR=0.721; 95% CI: [0.614; 0.846], p <0.0001).

Time to initiation of cytotoxic chemotherapy: The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving abiraterone acetate and 16.8 months for patients receiving placebo (HR=0.580; 95% CI: [0.487; 0.691], p <0.0001).

Time to deterioration in ECOG performance score by ≥1 point: The median time to deterioration in ECOG performance score by ≥1 point was 12.3 months for patients receiving abiraterone acetate and 10.9 months for patients receiving placebo (HR=0.821; 95% CI: [0.714; 0.943], p=0.0053).

The following study endpoints demonstrated a statistically significant advantage in favor of abiraterone acetate treatment:

Objective response: Objective response was defined as the proportion of subjects with measurable disease achieving a complete or partial response according to RECIST criteria (baseline lymph node size was required to be ≥2 cm to be considered a target lesion). The proportion of subjects with measurable disease at baseline who had an objective response was 36% in the abiraterone acetate group and 16% in the placebo group (p <0.0001).

Pain: Treatment with abiraterone acetate significantly reduced the risk of average pain intensity progression by up to 18% compared with placebo (p=0.049). The median time to progression was 26.7 months in the abiraterone acetate group and 18.4 months in the placebo group.

Time to degradation in the FACT-P (Total Score): Treatment with abiraterone acetate decreased the risk of FACT-P (Total Score) degradation by 22% compared with placebo (p=0.0028). The median time to degradation in FACT-P (Total Score) was 12.7 months in the abiraterone acetate group and 8.3 months in the placebo group.

Study 301 (patients who had received prior chemotherapy)
Study 301 enrolled patients who had received prior docetaxel. Patients were not required to show disease progression on docetaxel, as toxicity from this chemotherapy may have led to discontinuation.
Patients were maintained on study treatments until there was PSA progression (confirmed 25% increase over the patient's baseline/lowest confirmed level) together with protocol-defined radiographic progression and symptomatic or clinical progression. Patients with prior ketoconazole treatment for prostate cancer were excluded from this study. The primary efficacy endpoint was overall survival.

The median age of enrolled patients was 69 years (range 39-95). The number of patients treated with abiraterone acetate by racial group was Caucasian 737 (93.2%), Black 28 (3.5%), Asian 11 (1.4%) and other 14 (1.8%). 11% of patients enrolled had an ECOG performance score of 2; 70% had radiographic evidence of disease progression with or without PSA progression; 70% had received one prior cytotoxic chemotherapy and 30% received two. Liver metastasis was present in 11% of patients treated with abiraterone acetate.

In a planned analysis conducted after 552 deaths were observed, 42% (333 of 797) of patients treated with abiraterone acetate compared with 55% (219 of 398) of patients treated with placebo, had died. A statistically significant improvement in median overall survival was seen in patients treated with abiraterone acetate (see Table 6).

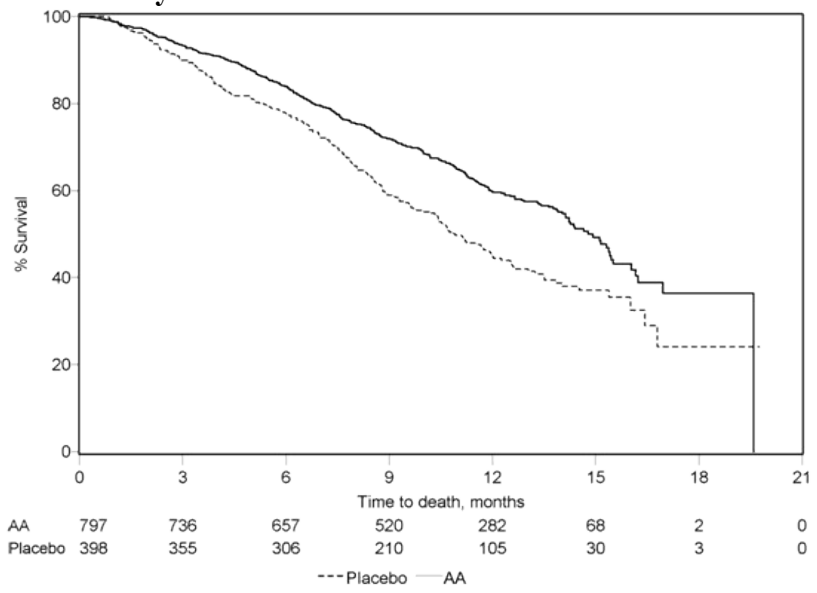
Table 6: Overall survival of patients treated with either abiraterone acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

	Abiraterone acetate (N=797)	**Placebo (N=398)**
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1; 15.4)	10.9 (10.2; 12.0)
p-value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.646 (0.543; 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8; 17.0)	11.2 (10.4; 13.1)
Hazard ratio (95% CI)[b]	0.740 (0.638; 0.859)	

[a] p-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).
[b] Hazard ratio is derived from a stratified proportional hazards model. Hazard ratio < 1 favors abiraterone acetate

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with abiraterone acetate remained alive, compared with the proportion of patients treated with placebo (see Figure 6).

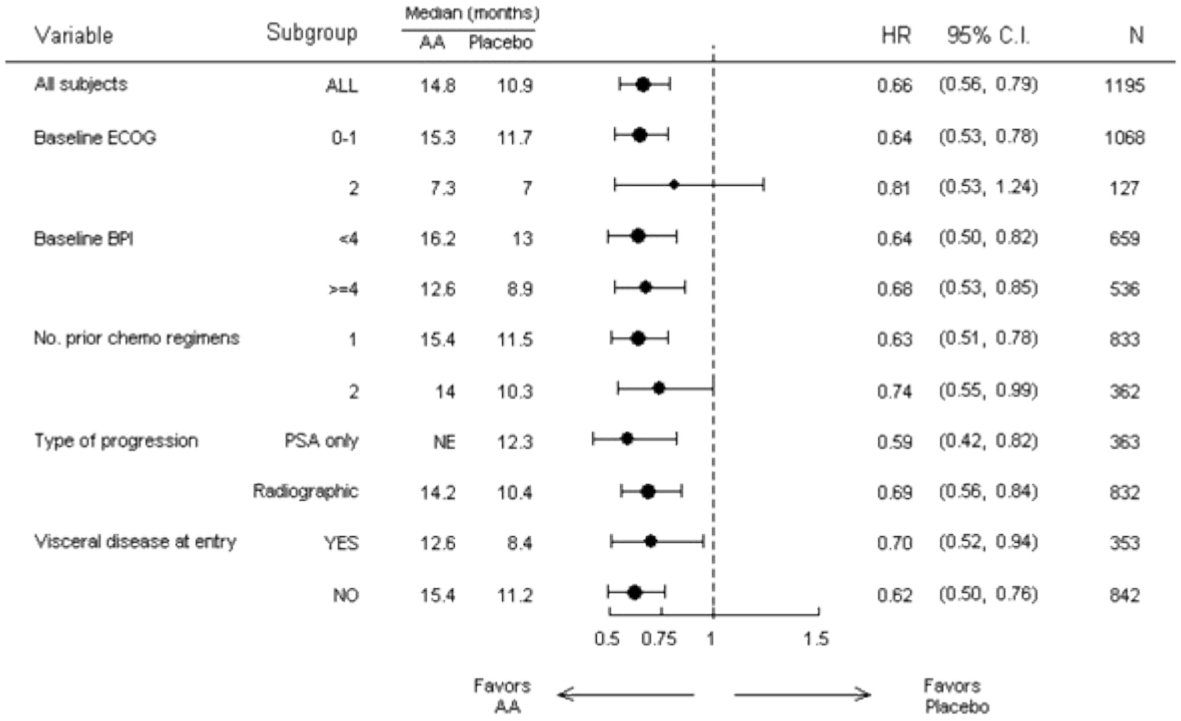
Figure 6: Kaplan Meier survival curves of patients treated with either abiraterone acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA=Abiraterone acetate

Subgroup survival analyses showed a consistent survival benefit for treatment with abiraterone acetate (see Figure 7).

Figure 7: Overall survival by subgroup: Hazard ratio and 95% confidence interval



AA = Abiraterone acetate; BPI = Brief Pain Inventory; C.I. = Confidence interval; ECOG = Eastern Cooperative Oncology Group performance score; HR = Hazard ratio; NE = Not evaluable

In addition to the observed improvement in overall survival, all secondary study endpoints favored abiraterone acetate and were statistically significant after adjusting for multiple testing as follows:

In patients receiving abiraterone acetate, a statistically significantly higher overall PSA response rate (defined as ≥50% reduction from baseline) was achieved compared to patients receiving placebo, 38% with abiraterone acetate compared to 10% with placebo, p<0.0001.

The median time to PSA progression was 10.2 months for patients treated with abiraterone acetate and 6.6 months for patients treated with placebo (HR=0.58; 95% CI: [0.462; 0.728], p <0.0001).

The median radiographic progression-free survival was 5.6 months for patients treated with abiraterone acetate and 3.6 months for patients who received placebo (HR=0.673; 95% CI: [0.585; 0.776], p < 0.0001).

Pain
The proportion of patients with pain palliation was statistically significantly higher in the abiraterone acetate group than in the placebo group (44% vs. 27%, p=0.0002). A responder for pain palliation was defined as a patient who experienced at least a 30% reduction from baseline in the BPI-SF worst pain intensity score over the last 24 hours without any increase in analgesic usage score observed at two consecutive evaluations four weeks apart. Only patients with a baseline pain score of ≥4 and at least one post-baseline pain score were analyzed (N=512) for pain palliation.

Patients treated with abiraterone acetate had a lower rate of pain progression than those treated with placebo: 22% of those treated with abiraterone acetate versus 28% of those treated with placebo at 6 months, 30% of those treated with abiraterone acetate versus 38% of those treated with placebo at 12 months, and 35% of those treated with abiraterone acetate versus 46% of those treated with placebo at 18 months. Pain progression was defined as an increase from baseline of ≥30% in the BPI-SF worst pain intensity score over the previous 24 hours without a decrease in analgesic usage score observed at 2 consecutive visits, or an increase of ≥30% in analgesic usage score observed at 2 consecutive visits. The time to pain progression at the 25th percentile was 7.4 months in the abiraterone acetate group, versus 4.7 months in the placebo group.

Skeletal-related events
At 6 months, 12 months and 18 months, the proportion of patients with skeletal-related events was lower in the abiraterone acetate group compared with placebo (18% vs 28% at 6 months, 30% vs 40% at 12 months and 35% vs 40% at 18 months, respectively). The time to first skeletal-related event at the 25th percentile in abiraterone acetate group was twice that of the control group at 9.9 months versus 4.9 months. A skeletal-related event was defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.

PEACE 1 study
Metastatic hormone-sensitive prostate cancer (mHSPC)
The efficacy and safety of abiraterone in combination with androgen deprivation therapy and docetaxel were evaluated in a multicentre, open-ended, randomised, phase III trial (PEACE 1) with a 2x2 factorial design in mHSPC patients.

A total of 1173 patients were randomized into 4 separate groups (1:1:1:1:1). 296 patients received ADT and/or docetaxel in the standard care arm (SOC). 293 patients received SOC + radiotherapy, 292 patients received SOC + abiraterone + prednisone and 291 patients received SOC + abiraterone + prednisone + radiotherapy.

The number of patients receiving 1000 mg abiraterone orally once daily in the general population was n=583. The number of patients receiving abiraterone 1000 mg orally once daily concurrently with docetaxel is n = 355 (+/- radiotherapy)

In total, 355 patients received abiraterone 1000 mg orally once daily concurrently with docetaxel 75 mg/m^2 during 6 cycles.

Treatment with abiraterone was continued until symptomatic progressive disease developed, antineoplastic therapy was changed, unacceptable toxicity developed, death occurred or the study was dropped.

Patient demographics and disease features are balanced across treatment arms. The median age was 67 years (range 37-94). Most patients (75%) had a Gleason score of 8 or higher at diagnosis. ECOG PS score was 0 in 71% of patients and ECOG PS score was 1 in 29%. Lymph node metastasis was positive in 55% of patients. Bone metastasis was positive in 81% of patients, only lymph node metastasis in 8%, and visceral metastasis in 11%.

57% of patients have high-volume disease and 43% have low-volume disease. High-volume disease was defined as the presence of four or more bone metastases and one or more outside the vertebral body or pelvis or visceral metastases. All other evaluable conditions were categorized as low-volume disease.

The common primary endpoints of the study were radiographic progression-free survival (rPFS) and overall survival (OS).

The median follow-up time was 3.5 years for rPFS and 4.4 years for OS. This study showed that 'Triplet Therapy' (ADT+ docetaxel+ abiraterone (in combination with prednisone)) improved overall survival (OS) and radiographic progression-free survival (rPFS) in patients with de novo metastatic castration-sensitive prostate cancer (p<0.0001).

In the general population, patients assigned to receive abiraterone (n: 583) had longer rPFS (hazard ratio [HR] 0.54, 99.9% confidence interval [CI] 0.41-0.71; p<0.0001) and longer OS (HR 0.82, 95.1% CI 0.69-0.98; p= 0.030) than patients not receiving abiraterone (n: 589). Median rPFS was 4.5 years in patients taking abiraterone, 2.2 years in those not taking abiraterone, and adding abiraterone to standard therapy provided a 2.3-year advantage in rPFS. The median OS was 5.72 years in patients receiving abiraterone and 4.72 years in patients not receiving abiraterone, and the addition of abiraterone to standard treatment added 1 year of additional survival. In docetaxel-populated ADT (355 patients in both abiraterone and non-abiraterone groups), CTRs were consistent for both rPFS (CTR 0.5, 99.9% CI 0.34-0.71; p < 0.0001) and OS (CTR 0.75, 95.1% CI 0.59-0.95; p = 0.017). Among patients receiving ADT plus abiraterone together with docetaxel, the median rPFS was 4.46 years. The median OS was not reached, with a median rPFS of 2.03 years and a median OS of 4.43 years compared with a median rPFS of 2.03 years and a median OS of 4.43 years among those who received ADT plus abiraterone together with docetaxel.

Adding abiraterone to ADT plus docetaxel did not increase the side effect incidences of neutropenia, febrile neutropenia, fatigue or neuropathy compared with ADT plus docetaxel alone. Adding abiraterone to standard treatment improved OS and rPFS with a slight increase in side effects.

Table 7: Effectiveness results of the PEACE 1 study

	Patients evaluated, n		Median, years		Median difference, years	Hazard ratio	p value
	With abiraterone groups SOC	SOC without abiraterone groups	With abiraterone groups SOC	SOC without abiraterone groups			
Primary results in the general population							
Overall survival	583	589	5,7	4,7	0,9 (%95,1 CI, 0–2)	0,82 (%95,1 CI 0,69–0,98)	0,03
Radiographic progression-free survival	583	589	4,5	2,2	2,1 (%99,9 CI 0,7–2,9)	0,54 (%99,9 CI 0,41–0,71)	<0,0001
Secondary results in the general population							
Survival without CRPC	583	589	3,8	1,5	2,3 (%95 CI 1,6–3)	0,4 (%95 CI 0,35–0,47)	<0,0001
Prostate cancer-specific	583	589	NR	5,8	NA	0,75 (%95 CI	0,0038

survival						0,61–0,91)	
Primary results in ADT with docetaxel population							
Overall survival	355	355	NR	4,4	NA	0,75 (%95,1 CI 0,59–0,95)	0,017
Radiographic progression-free survival	355	355	4,5	2	2,2 (%99,9 CI 0,6-2,8)	0,5 (%99,9 CI 0,34–0,71)	<0,0001
Secondary results in ADT with docetaxel population							
Overall survival in patients with low-volume metastatic burden	131	123	NR	NR	NA	0,83 (%95,1 CI 0,5–1,39)	0,66
Overall survival in patients with high-volume metastatic burden	224	232	5,1	3,5	1,1 (%95,1 CI 0,2-1,9)	0,72 (%95,1 CI 0,55–0,95)	0,019
Radiographic progression-free survival in patients with low-volume metastatic burden	129	122	NR	2,7	NA	0,58 (%99,9 CI 0,29–1,15)	0,0061
Radiographic progression-free survival in patients with high-volume metastatic burden	225	231	4,1	1,6	2,2 (%99,9 CI 0,6-3,2)	0,47 (%99,9 CI 0,3–0,72)	<0,0001
Survival without CRPC	355	355	3,2	1,4	2 (%95 CI 1,5-3,1)	0,38 (%95 CI 0,31–0,47)	<0,0001
Prostate cancer-specific survival	355	355	NR	4,7	NA	0,69 (%95 CI 0,53–0,9)	0,0062

ADT= androgen deprivation therapy. CRPC= castration-resistant prostate cancer. NA= not available. NR= not reached. SOC= standard of care (with or without radiotherapy).

Table 7: Efficacy results in the population intended to be treated

Figure 8: Kaplan-Meier overall survival (OS) and radiographic progression-free survival (rPFS) data:

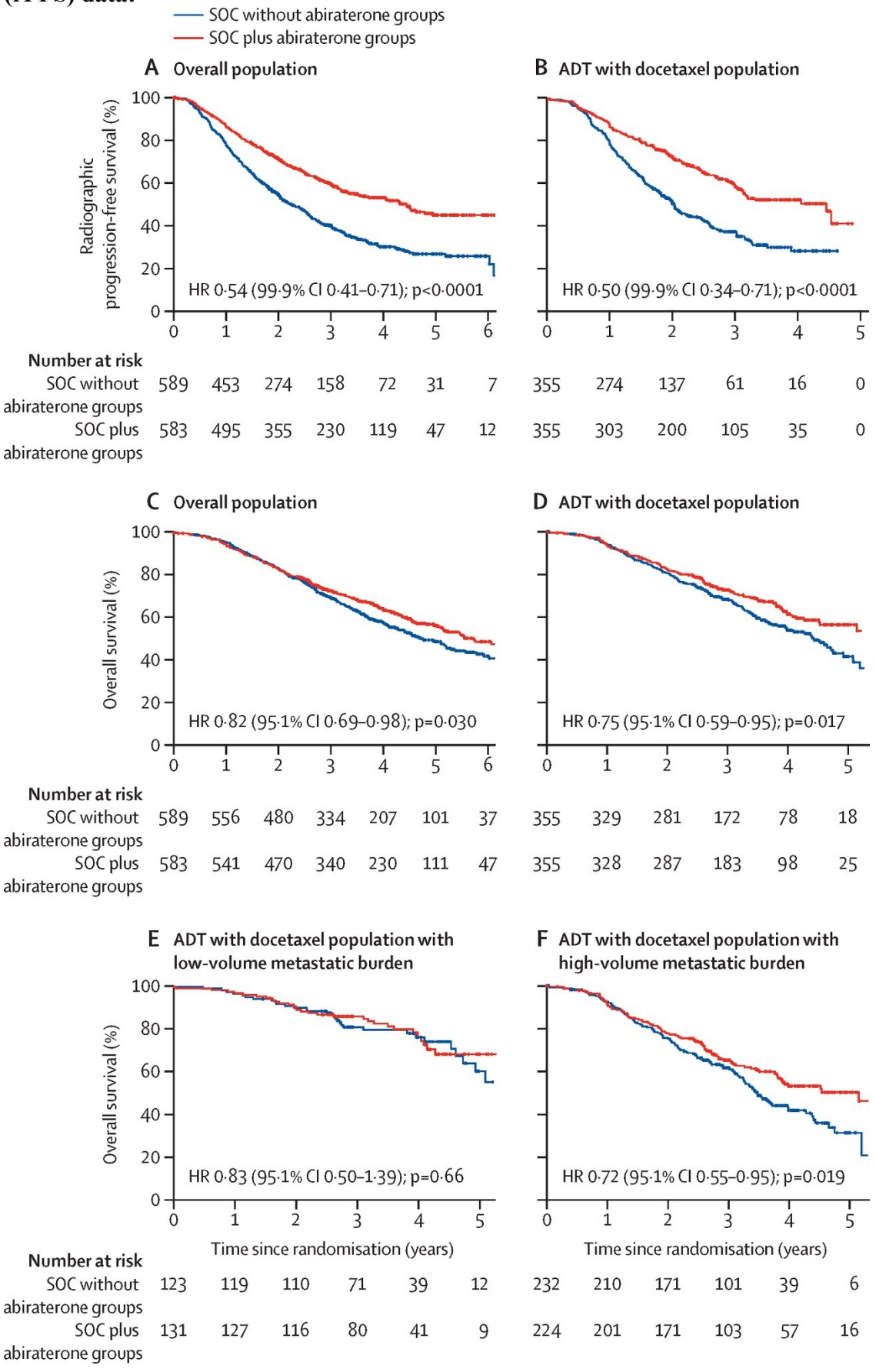


Figure 8: Kaplan-Meier estimates of radiographic progression-free survival and overall survival in the general population and in the ADT with docetaxel population Event-time curves, radiographic progression-free survival (A) and overall survival (C) in the general population in patients with low-volume metastatic burden (E) and high-volume metastatic burden (F), presented for radiographic progression-free survival (B) and overall survival (D) in the ADT with docetaxel population and overall survival in the ADT with docetaxel population. SOC in the overall population was ADT with or without docetaxel. SOC in the ADT with docetaxel population was ADT with docetaxel. ADT=androgen deprivation therapy. SOC=standard of care (with or without radiotherapy).

Pediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with abiraterone acetate in all subgroups of the pediatric population in advanced prostate cancer. See Section 4.2 for information on pediatric use.

5.2. Pharmacokinetic properties
General particulars
Following administration of abiraterone acetate, the pharmacokinetics of abiraterone have been studied in healthy subjects, patients with metastatic advanced prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor (see Section 5.1).

Absorption:
Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 10-fold (in AUC) and up to a 17-fold (in 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 acetate with meals has the potential to result in highly variable exposures. Therefore, ABYGA must not be taken with food. ABYGA tablets must be taken as a single dose once daily on an empty stomach. ABYGA must be taken at least 2 hours after eating and food must not be eaten for at least 1 hour after taking ABYGA. The tablets must be swallowed whole with water (see Section 4.2).

Distribution:
The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5.63 liters, shows that abiraterone intensively distributes to peripheral tissues.

Biotransformation:
Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found in the form of metabolites of abiraterone. Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represents approximately 43% of total radioactivity.

Elimination:
The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following oral administration of ^{14}C-abiraterone acetate 1,000 mg, approximately 88% of the radioactive dose is appeared in feces and approximately 5% in urine. The major compounds

present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Characteristics in patients

Hepatic impairment:

The pharmacokinetics of abiraterone acetate was studied in subjects with pre-existing mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) and in healthy control subjects. Systemic exposure to abiraterone after a single oral 1,000 mg dose increased by approximately 11% and 260% in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with pre-existing severe (n=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic effect (AUC) of abiraterone increased by approximately 600% and the fraction of free drug increased by 80% in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment. The use of abiraterone acetate should be cautiously assessed in patients with moderate hepatic impairment in whom the benefit clearly should outweigh the possible risk (see Sections 4.2 and 4.4). Abiraterone acetate should not be used in patients with severe hepatic impairment (see Sections 4.2, 4.3 and 4.4).

For patients who develop hepatotoxicity during treatment ABGYA, stopping of treatment and dose adjustment may be required (see Sections 4.2 and 4.4).

Renal impairment:

The pharmacokinetics of abiraterone acetate was compared in patients with end-stage renal disease on a stable hemodialysis schedule versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis. ABYGA administration in patients with renal impairment, including severe renal impairment, does not require dose reduction (see Section 4.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

5.3. Preclinical safety data

In all animal toxicity studies, circulating testosterone levels were significantly reduced. As a result, reduction in organ weights and morphological and/or histopathological changes in the reproductive organs, and the adrenal, pituitary and mammary glands were observed. All changes showed complete or partial reversibility. The changes in the reproductive organs and androgen-sensitive organs are consistent with the pharmacology of abiraterone. All treatment-related hormonal changes reversed or were shown to be resolving after a 4-week recovery period.

In fertility studies in both male and female rats, abiraterone acetate reduced fertility, however, fertility was completely restored at 4 to 16 weeks after abiraterone acetate was stopped.

In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced fetal weight and survival. Effects on the external genitalia were observed though abiraterone acetate

was not teratogenic.

In these fertility and developmental toxicity studies performed in the rat, all effects were related to the pharmacological activity of abiraterone.

Aside from reproductive organ changes seen in all animal toxicology studies, non-clinical data based on classical safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential studies did not indicate a specific hazard for humans. In a 6-month study in transgenic mice (Tg.rasH2), abiraterone acetate was not found to be carcinogenic. In a 24-month carcinogenicity study in the rat, abiraterone acetate increased the incidence of interstitial cell neoplasms in the testes. This finding is considered related to the pharmacological action of abiraterone and rat specific. Abiraterone acetate was not found to be carcinogenic in female rats.

Environmental Risk Assessment:

The active substance, abiraterone, shows an environmental risk for the aquatic environment (especially fish).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate (from cow's milk)
Microcrystalline cellulose
Croscarmellose sodium
Povidone
Sodium lauryl sulfate
Colloidal silicon dioxide
Magnesium stearate

Opadry 85F200050 purple

Polyvinyl alcohol
Titanium dioxide
Macrogol/PEG MW 3350
Talc
Iron oxide black
Iron oxide red

6.2. Incompatibilities

There are no known incompatibilities.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 25°C.

Keep out of the reach and sight of children and in its packaging.

6.5. Nature and contents of container

PA/ALU/PVC Foil/Aluminum Foil blister is used as the primary packaging material of the product. Each cardboard box contains a package leaflet and blister packs containing 60 tablets.

6.6. Special precautions for disposal and other handling

Based on its mechanism of action, this medicinal product may harm a developing fetus; therefore, women who are pregnant or may be pregnant should not contact ABYGA without protection, e.g., gloves (see Section 4.6).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This medicinal product may pose a risk to the aquatic environment (see Section 5.3).

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

2021/463

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 24.11.2021
Date of last renewal :

10. DATE OF REVISION OF THE SPC