1.17 Summary of Product Characteristics (SmPC)

1.17.1 Product information for Health Professionals

Summary of Product Characteristics (SmPC) for BIRATO 250 (Abiraterone Acetate Tablets USP 250 mg) has been enclosed in the following pages.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Summary of Product Characteristics

Abiraterone Acetate Tablets USP 250 mg

1.Name of the medicinal product

Abiraterone Acetate Tablets USP 250 mg

2.Qualitative and quantitative composition

Each un coated tablet contains Abiraterone acetate USP 250 mg

Excipients with known effect

Product contains lactose.

For the full list of excipients, see section 6.1

3.Pharmaceutical form

Tablet

White to off-white, oval shaped tablets, debossed with “ABR” on one side and “250" on other side.

4. Clinical particulars

4.1 Therapeutic indications

Abiraterone Acetate is indicated with prednisone or prednisolone for:

• The treatment of metastatic castration resistant prostate cancer 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 metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

4.2 Posology and method of administration

This medicinal product should be prescribed by an appropriate healthcare professional.

Posology

The recommended dose is 1,000 mg (four 250 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).

Abiraterone Acetate is to be taken with low dose prednisone or prednisolone. The recommended

dose of prednisone or prednisolone is 10 mg daily.

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

Serum transaminases should be measured prior to starting treatment, every two weeks for the first three 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 three months of treatment and monthly thereafter (see section 4.4).

In patients with pre-existing hypokalaemia or those that develop hypokalaemia whilst being treated with Abiraterone Acetate , consider maintaining the patient's potassium level at ≥ 4.0 mM.

For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other nonmineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with Abiraterone Acetate 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 Abiraterone Acetate , prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

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 (two tablets) once daily. For patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued.

If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.

Hepatic impairment

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A.

Moderate hepatic impairment (Child-Pugh Class B) has been shown to increase the systemic exposure to abiraterone by approximately four-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 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). Abiraterone Acetate 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).

Paediatric population

There is no relevant use of Abiraterone Acetate in the paediatric population.

Method of administration

Abiraterone Acetate is for oral use.

The tablets should be taken at least two hours after eating and no food should be eaten for at least one hour after taking the tablets. These should be swallowed whole with water.

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).

- Severe hepatic impairment [Child-Pugh Class C (see sections 4.2, 4.4 and 5.2)].

4.4 Special warnings and precautions for use

Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess

Abiraterone Acetate may cause hypertension, hypokalaemia 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, hypokalaemia (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.

Abiraterone Acetate should be used with caution in patients with a history of cardiovascular disease. The phase 3 studies conducted with Abiraterone Acetate 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 (study 302) or cardiac ejection fraction measurement of < 50%. In study 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 NYHA Class III or IV heart failure (in study 301) or NYHA Class II to IV heart failure (in study 302) was not established (see sections 4.8 and 5.1).

Before treating patients with a significant risk for congestive heart failure (e.g.a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischaemic heart disease), consider obtaining an assessment of cardiac function (e.g. echocardiogram). Before treatment with Abiraterone Acetate , cardiac failure should be treated and cardiac function optimised. Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), 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 hypokalaemia in association with Abiraterone Acetate treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider

discontinuation of this treatment if there is a clinically significant decrease in cardiac function (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 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 20 times the ULN) anytime while on therapy, 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). Abiraterone Acetate 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 Abiraterone Acetate is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid

excess (see information above).

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 (castration resistant prostate cancer). The use of Abiraterone Acetate 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.

Hyperglycaemia

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

Use with chemotherapy

The safety and efficacy of concomitant use of Abiraterone Acetate with cytotoxic chemotherapy has not been established (see section 5.1).

Intolerance to excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Potential risks

Anaemia and sexual dysfunction may occur in men with metastatic castration resistant prostate cancer including those undergoing treatment with Abiraterone Acetate .

Skeletal muscle effects

Cases of myopathy have been reported in patients treated with Abiraterone Acetate . Some patients had rhabdomyolysis with renal failure. Most cases developed within the first month 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 are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to abiraterone (see section 4.5).

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 when given with food have not been established 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 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 therapeutic alternative.

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 to affect exposures to other medicinal products

Abiraterone is an inhibitor of the hepatic drug-metabolising 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 administering with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction

of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. Examples of medicinal products metabolised 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. Although these results indicate that no clinically meaningful increases in exposure are expected when Abiraterone Acetate is combined with medicinal products that are predominantly eliminated by CYP2C8, patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly.

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 Abiraterone Acetate 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 Abiraterone Acetate is not recommended (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

There are no human data on the use of Abiraterone Acetate in pregnancy and this medicinal

product is not for use in women of childbearing potential.

Contraception in males and females

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

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

Breast-feeding

Abiraterone Acetate is not for use in women.

Fertility

Abiraterone 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

Abiraterone Acetate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions seen are peripheral oedema, hypokalaemia, hypertension and urinary tract infection.

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

Abiraterone Acetate may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In clinical studies, anticipated mineralocorticoid adverse reactions were seen more commonly in patients treated with abiraterone acetate than in patients treated with placebo: hypokalaemia 21% vs.11%, hypertension 16% vs. 11% and fluid retention (peripheral oedema) 26% vs. 20%, respectively. In patients treated with

abiraterone acetate, CTCAE (version 3.0) Grades 3 and 4 hypokalaemia and CTCAE (version 3.0) Grades 3 and 4 hypertension were observed in 4% and 2% of patients, respectively. 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).

Tabulated list of adverse reactions

In studies of patients with metastatic advanced prostate cancer who were using an 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 (10 mg daily).

Adverse reactions observed during clinical studies and post-marketing experience are listed below by frequency category. Frequency categories are defined as follows: 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) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions identified in clinical studies and post-marketing	
System Organ Class	**Adverse reaction and frequency**
Infections and infestations	very common: urinary tract infection common: sepsis
Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, arrhythmia, atrial fibrillation, tachycardia 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: diarrhoea common: dyspepsia
Hepatobiliary disorders	common: alanine aminotransferase increased, aspartate aminotransferase increased

	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: haematuria
General disorders and administration site conditions	very common: oedema peripheral
Injury, poisoning and procedural complications	common: fractures**
* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased ** Fractures includes all fractures with the exception of pathological fracture [a] Spontaneous reports from post-marketing experience	

The following CTCAE (version 3.0) Grade 3 adverse reactions occurred in patients treated with abiraterone acetate:

hypokalaemia 3%; urinary tract infection, alanine aminotransferase increased, hypertension, aspartate aminotransferase increased, fractures 2%; peripheral oedema, cardiac failure, and atrial fibrillation 1% each. CTCAE (version 3.0) Grade 3 hypertriglyceridaemia and angina pectoris occurred in < 1% of patients. CTCAE (version 3.0) Grade 4 peripheral oedema, hypokalaemia, urinary tract infection, cardiac failure and fractures occurred in < 1% of patients.

Description of selected adverse reactions

Cardiovascular reactions

Both phase 3 studiesexcluded 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 NYHA Class III or IV heart failure (study 301) or Class II to IV heart failure (study 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 versus patients taking placebo were as follows:

hypertension 14.5% vs. 10.5%, atrial fibrillation 3.4% vs. 3.4%, tachycardia 2.8% vs. 1.7%, angina pectoris 1.9% vs. 0.9%, cardiac failure 1.9% vs. 0.6%, and arrhythmia 1.1% vs. 0.4%.

Hepatotoxicity

Hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone acetate. Across all clinical studies, liver function test elevations (ALT or AST increases of > 5 x ULN or bilirubin increases > 1.5 x ULN) were reported in approximately 4% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In the 301 clinical study, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5 x ULN, or elevations in bilirubin > 3 x ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred (see section 4.4). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 x ULN and bilirubin elevations 2 to 6 x ULN. Upon discontinuation of treatment, both patients had normalisation 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). Treatment discontinuations due to ALT and AST increases were reported in 1.7% and 1.3% of patients treated with abiraterone acetate and 0.2% and 0% of patients treated with placebo, respectively; no deaths were reported due to hepatotoxicity event.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 301 trial, patients with baseline ALT and AST ≥ 2.5 x ULN in the absence of liver metastases and > 5 x ULN 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 x ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were vigorously managed by requiring treatment interruption and permitting re-treatment only after return of liver function tests to the patient's baseline (see section 4.2). Patients with elevations of ALT or AST > 20 x ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity is not understood.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Human experience of overdose with Abiraterone Acetate is limited.

There is no specific antidote. In the event of an overdose, administration should be withheld and general supportive measures undertaken, including monitoring for arrhythmias, hypokalaemia 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 (Abiraterone Acetate Tablets) 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 and is required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. 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 tumour. 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. PSA serves as a biomarker in patients with prostate cancer. In a phase 3 clinical study of patients who failed prior 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 was established in two randomised placebo-controlled multicentre phase 3 clinical studies (studies 301 and 302) of patients with metastatic castration resistant prostate cancer. Study 302 enrolled docetaxel naïve patients; whereas, study 301 enrolled patients who had received prior 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 both studies it was recommended that patients be maintained on their study treatments until discontinuation criteria were met as specified below for each study.

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

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. Fifty percent of patients had only bone metastases, an additional 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 utilised centrally-reviewed radiographic assessment of progression.

At the planned rPFS analysis there were 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 2 and Figure 1).

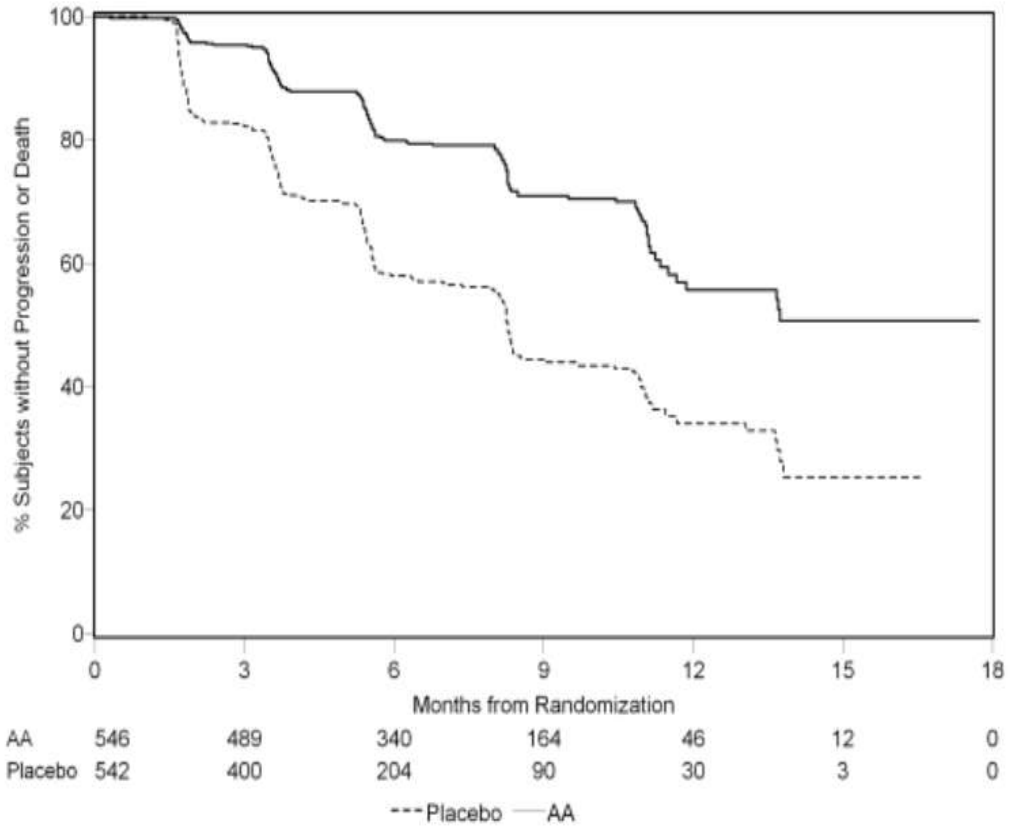
Table 2: Study 302: Radiographic progression-free survival of patients treated with either Abiraterone Acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

	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 favours Abiraterone Acetate

Figure 1: 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



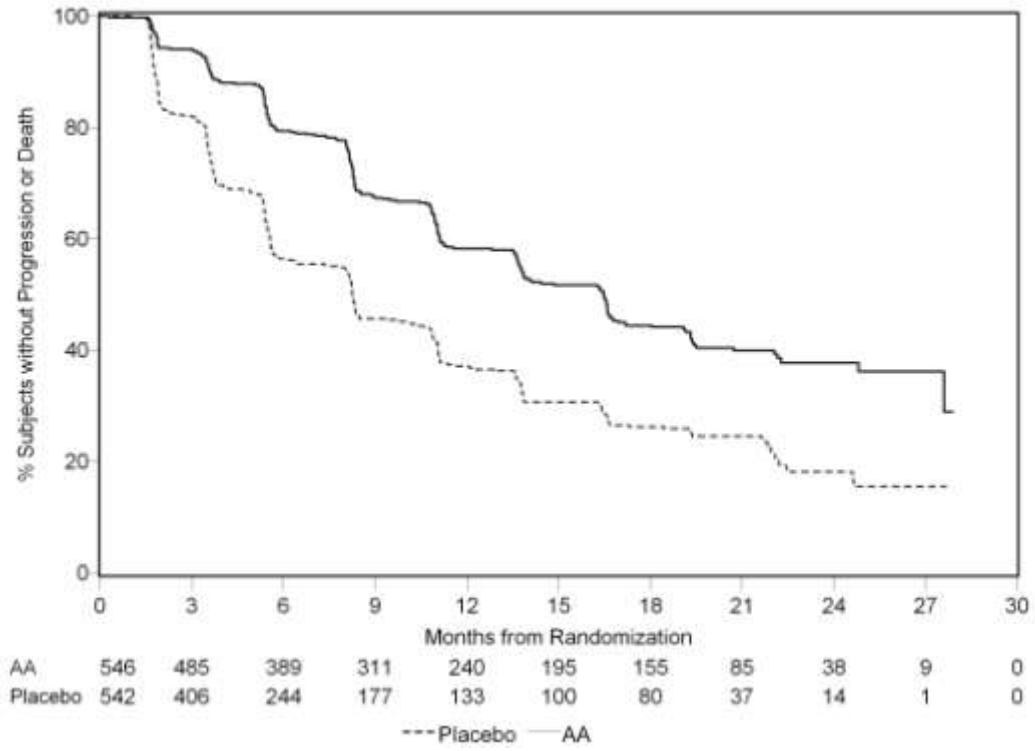
AA = Abiraterone Acetate

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 3 and Figure 2.

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 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 (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 (8.12; 8.54)
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 favours Abiraterone Acetate		

Figure 2: 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

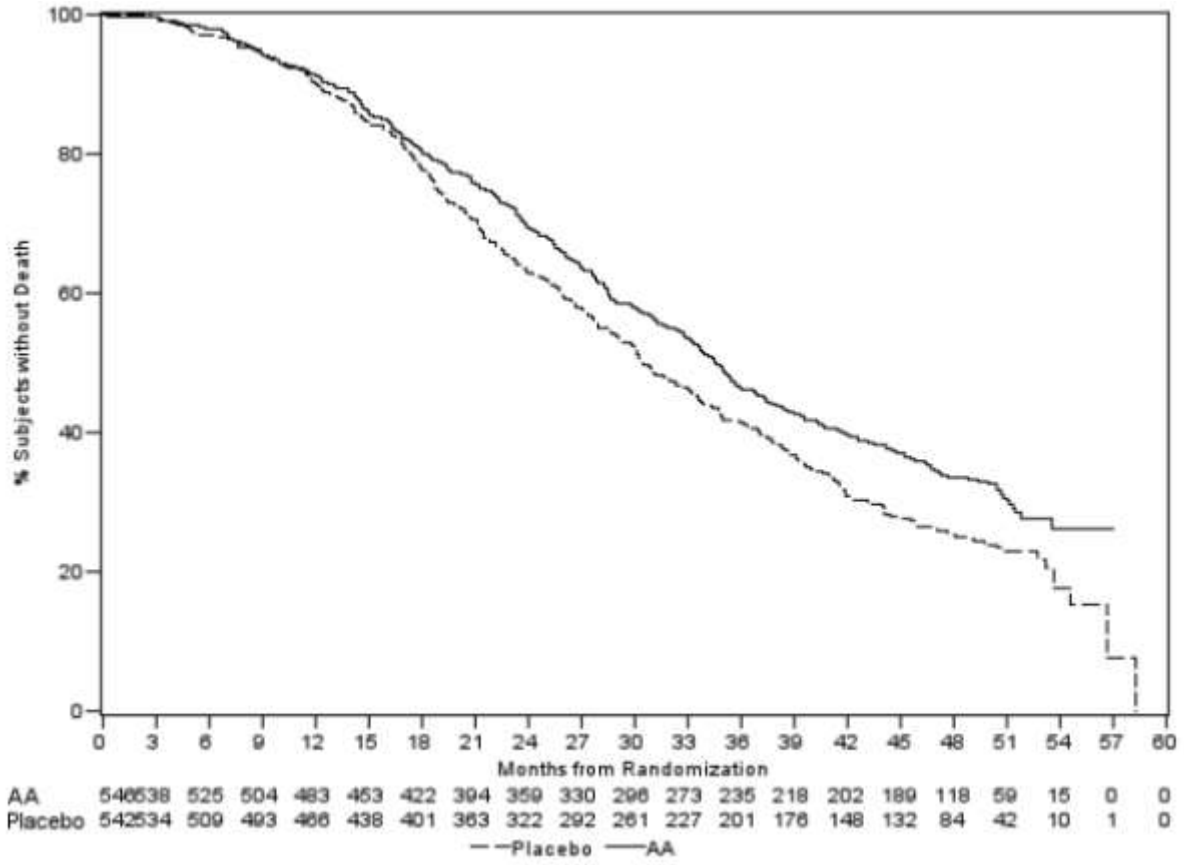
A planned interim analysis (IA) for OS was conducted after 333 deaths were observed. The study was unblinded based on the magnitude of clinical benefit observed and patients in the placebo group were offered treatment with Abiraterone Acetate .

Overall survival was longer for Abiraterone Acetate than placebo with a 25% reduction in risk of death (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 IA.

The planned final analysis for OS was conducted after 741 deaths were observed (median follow up of 49 months). Sixtyfive percent (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 favour 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 4 and Figure 3). This improvement was demonstrated even though 44% of patients in the placebo arm received Abiraterone Acetate as subsequent therapy.

Table 4: 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 *	0.01	
Hazard ratio** (95% CI)	0.752 (0.606; 0.934)	
Final survival analysis		
Deaths	354 (65%)	387 (71%)
Median overall survival in 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 favours Abiraterone Acetate		

Figure 3: 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 favour 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 18% compared with placebo (p = 0.0490). 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/nadir) 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%). Eleven percent 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 5).

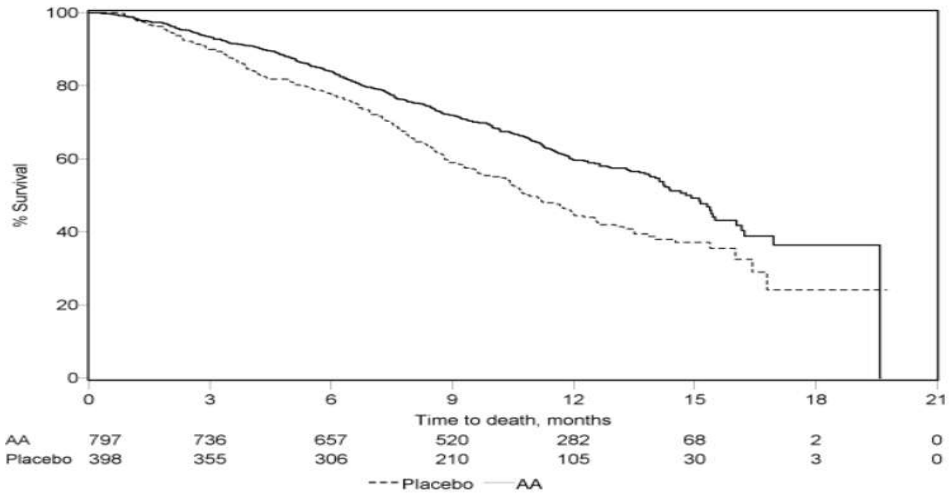
Table 5: Overall survival of patients treated with either Abiraterone Acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

	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 overall survival in 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 favours 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 4).

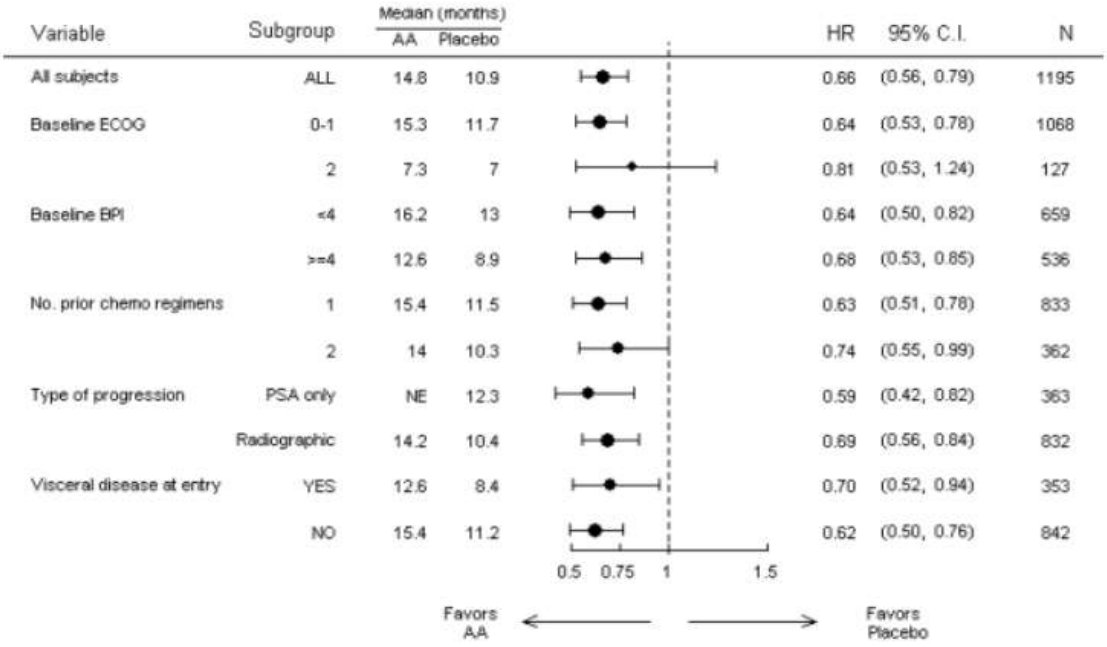
Figure 4: Kaplan Meier survival curves of patients treated with either Abiraterone Acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA = Abiraterone Acetate

Subgroup survival analyses showed a consistent survival benefit for treatment with Abiraterone Acetate (see Figure 5).

Figure 5: 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 favoured Abiraterone Acetate and were statistically significant after adjusting for multiple testing as follows:

Patients receiving Abiraterone Acetate demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 38% vs. 10%, $p < 0.0001$.

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 = 0.580; 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 analysed (N = 512) for pain palliation.

A lower proportion of patients treated with Abiraterone Acetate had pain progression compared to patients taking placebo at 6 (22% vs. 28%), 12 (30% vs. 38%) and 18 months (35% vs. 46%). 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 two consecutive visits, or an increase of ≥ 30% in analgesic usage score observed at two consecutive visits. The time to pain progression at the 25^{th} percentile was 7.4 months in the Abiraterone Acetate group, versus 4.7 months in the placebo group.

Skeletal-related events

A lower proportion of patients in the Abiraterone Acetate group had skeletal-related events compared with the placebo group at 6 months (18% vs. 28%), 12 months (30% vs. 40%), and 18 months (35% vs. 40%). The time to first skeletal-related event at the 25th percentile in the 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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Abiraterone Acetate in all subsets of the paediatric population in advanced prostate cancer. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate 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 (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 Acetate with meals has the potential to result in highly variable exposures. Therefore, Abiraterone Acetate 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 Acetate . The tablets should 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 5,630 l, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolysed 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 recovered in faeces and approximately 5% in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Hepatic impairment

The pharmacokinetics of abiraterone acetate was examined 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 preexisting 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 AUC to 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, suspension 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 haemodialysis 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. 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, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped.

In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced foetal 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 reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse. 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 carcinogenic in female rats.

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

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate, Microcrystalline cellulose (PH 101), Croscarmellose sodium, Povidone K 30, Sodium laurylsulfate, Colloidal silicon dioxide and Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Do not store above 30ºC. Keep out of the sight and reach of children.

6.5 Nature and contents of container

120's HDPE container.

6.6 Special precautions for disposal and other handling

Based on its mechanism of action, this medicinal product may harm a developing foetus; therefore, women who are pregnant or may be pregnant should not handle it without protection, e.g., gloves. 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 authorisation holder

MSN LABORATORIES PRIVATE LIMITED

MSN House, Plot No. : C-24,

Anrich Industrial Estate,

Sanath Nagar, Hyderabad - 500 018, India.

8. Marketing authorisation number(s)

Not applicable

9. Date of first authorisation/renewal of the authorisation

Not applicable

10. Date of revision of the text: November 2017.