PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] Abiraterone

Abiraterone acetate tablets, USP

Film-coated tablets, 250 mg and 500 mg, Oral

Androgen Biosynthesis Inhibitor

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Date of Initial Authorization:
FEB 17, 2022

Date of Revision:

NOV 02, 2022

Submission Control Number: 268106

RECENT MAJOR LABEL CHANGES

Not Applicable	

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Abiraterone (abiraterone acetate) is indicated in combination with prednisone for:

- the treatment of metastatic prostate cancer (castration-resistant prostate cancer, mCRPC) in patients who:
  - are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy
  - have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy

Abiraterone is also indicated in combination with prednisone and androgen deprivation therapy (ADT) for:

- the treatment of patients with newly diagnosed hormone-sensitive high-risk metastatic prostate cancer who may have received up to 3 months of prior ADT.

1.1 Pediatrics

Abiraterone has not been studied in children.

Pediatrics (≤ 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that the use in the geriatric population is not associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (See 7 WARNINGS AND PRECAUTIONS/ Hypersensitivity/Anaphylactic reaction). For a complete listing, see section 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING of the Product Monograph.
- Abiraterone is contraindicated in women who are or may potentially be pregnant.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Abiraterone may cause hypertension, hypokalemia and fluid retention due to mineralocorticoid excess (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- Abiraterone should be used with caution in patients with a history of cardiovascular disease (f specific conditions see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- Patients with severe and moderate hepatic impairment should not receive Abiraterone(see 7 WARNINGS AND PRECAUTIONS, Patients with Hepatic Impairment)
- Hepatotoxicity, including fatal cases has been observed (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

- **Recommended Dose**

The recommended dosage of Abiraterone is 1 g (two 500 mg tablets or four 250 mg tablets) as asingle daily dose that **must be taken on an empty stomach**. No solid or liquid food should beconsumed for at least two hours before the dose of Abiraterone is taken and for at least one hourafter the dose of Abiraterone is taken. The tablets should be swallowed whole with water.

- **Recommended Dose of Prednisone**

For metastatic castration-resistant prostate cancer (mCRPC), Abiraterone is used with 10 mg prednisone daily. For newly diagnosed high-risk metastatic prostate cancer, Abiraterone is used with 5 mg prednisone daily.

- **Dose Adjustment in Patients with Hepatic Impairment**

Abiraterone should not be used in patients with pre-existing moderate or severe hepaticimpairment (see 10 CLINICAL PHARMACOLOGY).

No dosage adjustment is necessary for patients with pre-existing mild hepatic impairment.

For patients who develop hepatotoxicity during treatment with Abiraterone(serum transaminases, ALT or AST rise above 5 times the upper limit of normal or bilirubin rises above 3 times the upper limit of normal) treatment should be withheld immediately until liver function tests normalize (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (one 500 mg tablet or two 250 mg tablets) once daily. For patients being re- treated, serum transaminases and bilirubin should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduceddose of 500 mg daily, discontinue treatment with Abiraterone. Reduced doses should not be taken with food.

If patients develop severe hepatotoxicity (ALT 20 times the upper limit of normal) anytime while on therapy, Abiraterone should be discontinued and patients should not be re-treated with Abiraterone.

Permanently discontinue Abiraterone for patients who develop a concurrent elevation of ALT greater than 3 times the upper limit of normal **and** total bilirubin greater than 2 times the upper limit of normal in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

- **Dose Adjustment in Patients with Renal Impairment**

No dosage adjustment is necessary for patients with renal impairment.

- Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Patients started on Abiraterone who were receiving a GnRH agonist should continue to receive a GnRH agonist.

Serum transaminases and bilirubin should be measured prior to starting treatment with Abiraterone, every two weeks for the first three months of treatment and monthly thereafter.

Blood pressure, serum potassium and fluid retention should be monitored monthly (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess).

4.5 Missed Dose

In the event of a missed daily dose of either Abiraterone or prednisone, treatment should beresumed the following day with the usual daily dose.

5 OVERDOSAGE

Human experience of overdose with Abiraterone is limited.

There is no specific antidote. Discontinue therapy immediately. General supportive measures should be undertaken, including monitoring for arrhythmias and liver function.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Film-coated Tablet/ 250 mg and 500 mg/ film-coated	Tablet core ingredients: Colloidal silicon dioxide, croscarmellose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, povidone (K 30), sodium lauryl sulphate. Tablet film coating: Ferrosoferric oxide (ingredient in 500 mg tablets only), iron oxide red, iron oxide yellow (ingredient in 250 mg tablets only), polyvinyl alcohol-part hydrolyzed, propylene glycol, talc, titanium dioxide.

Abiraterone 250 mg film-coated tablets are beige colored, oval shaped tablets debossed with “MA” on one side and “12” on other side.

Abiraterone 500 mg film-coated tablets are purple colored, oval shaped tablets debossed with “MA” on one side and “8” on the other.

Abiraterone 250 mg and 500 mg film-coated tablets are available in high-density polyethylene bottles fitted with a polypropylene cap. Package sizes are 60 tablets for 500 mg and 120 tablets for 250 mg. Tablets also available in blister carton of 10 x 14s.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Gonadotropin releasing hormone (GnRH) agonists must be taken during treatment with Abiraterone or patients must have been previously treated with orchiectomy.

Abiraterone must be taken on an empty stomach. No solid or liquid food should be consumed for at least two hours before the dose of Abiraterone is taken and for at least one hour after the dose of Abiraterone is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multipledoses of abiraterone acetate are taken with food has not been assessed (see 9.5 Drug-Food Interactions, 4 DOSAGE AND ADMINISTRATION, and 10 CLINICAL PHARMACOLOGY).

Use with Chemotherapy

The safety and efficacy of concomitant use of Abiraterone with cytotoxic chemotherapy has not been established.

Use in Combination with radium 223 dichloride
In a randomized clinical trial in patients with asymptomatic or mildly symptomatic bone-predominant metastatic castration resistant prostate cancer with bone metastases, the additionof radium 223 dichloride to abiraterone plus prednisone/prednisolone showed an increase in mortality and an increased rate of fracture. Radium 223 dichloride is not recommended for usein combination with Abiraterone plus prednisone/prednisolone outside of clinical trials.

Carcinogenesis and Mutagenesis

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 thepharmacological action of abiraterone. The clinical relevance of this finding is not known. Abiraterone acetate was not carcinogenic in female rats (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and Genotoxicity). Abiraterone acetate and abiraterone weredevoid of genotoxic potential in the standard panel of *in vitro* and *in vivo* genotoxicity tests (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and Genotoxicity).

Cardiovascular

Abiraterone should be used with caution in patients with a history of cardiovascular disease. The safety of abiraterone acetate in patients with myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or left ventricular ejection fraction (LVEF) <50% or New York Heart Association Class III or IV heart failure (in patients with mCRPC with prior treatment with docetaxel) or NYHA Class II to IV heart failure (in patients with asymptomatic or mildly symptomatic mCRPC, or newly diagnosed high-risk metastatic prostate cancer) has not been established because these patients were excluded from the pivotal studies.

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess Before treatment with Abiraterone, hypertension must be controlled, and hypokalemia must be corrected.

Abiraterone may cause hypertension, hypokalemia and fluid retention (see 8 ADVERSE REACTIONS) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see 10.1 Mechanism of Action). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severityof these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by potential increases in blood pressure, hypokalemia or fluidretention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. In post marketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia or have underlying cardiovascular conditions while taking abiraterone acetate. Blood pressure, serum potassium and fluid retention should be monitored at least monthly (see Monitoring and Laboratory Tests).

Dependence/Tolerance

Corticosteroid Withdrawal and Coverage of Stress Situations
Caution is advised if patients need to be withdrawn from prednisone. Monitoring for adrenocortical insufficiency should occur. If Abiraterone is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess.

In patients on prednisone who are subjected to unusual stress (e.g., surgery, trauma or severe infections), increased dosage of a corticosteroid may be indicated before, during and after the stressful situation.

Endocrine and Metabolism

Hypoglycemia
Isolated cases of hypoglycemia have been reported when abiraterone acetate plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see 9 DRUG INTERACTIONS). Blood glucose should be monitoredin patients with diabetes.

Hepatic/Biliary/Pancreatic

Hepatic impairment
Abiraterone should not be used in patients with pre-existing moderate or severe hepatic impairment. Abiraterone acetate has not been studied in mCRPC patients with moderate or severe (Child-Pugh Class B or C) hepatic impairment at baseline. For patients who develop hepatotoxicity during treatment, suspension of treatment and dosage adjustment may be required (see 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Hepatotoxicity
Cases of acute liver failure and hepatitis fulminant (including fatal outcomes) have been reported during post-marketing experience (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, and 8.5 Post-Market Adverse Reactions).

Marked increases in liver enzymes leading to drug discontinuation or dosage modification occurred in controlled clinical studies (see 8 ADVERSE REACTIONS). Serum transaminases (ALT and AST) and bilirubin levels should be measured prior to starting treatment with Abiraterone, every two weeks for the first three months of treatment, and monthly thereafter.

Promptly measure serum total bilirubin and serum transaminases (ALT and AST), if clinical symptoms or signs suggestive of hepatotoxicity develop. If at any time the serum transaminases(ALT or AST) rise above 5 times the upper limit of normal or the bilirubin rises above 3 times theupper limit of normal, treatment with Abiraterone should be interrupted immediately and liver function closely monitored.

Re-treatment with Abiraterone may only take place after the return of liver function tests to the patient's baseline and at a reduced dose level (see 4 DOSAGE AND ADMINSTRATION). Permanently discontinue Abiraterone for patients who develop a concurrent elevation of ALT greater than 3 times the upper limit of normal **and** total bilirubin greater than 2 times the upperlimit of normal in the absence of biliary obstruction or other causes responsible for the concurrent elevation (see 4 DOSAGE AND ADMINISTRATION).

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, Abiraterone should be discontinued and patients should not be re-treated with Abiraterone

Monitoring and Laboratory Tests

Serum transaminases and bilirubin should be measured prior to starting treatment with Abiraterone, every two weeks for the first three months of treatment and monthly thereafter.

Blood pressure, serum potassium and fluid retention should be monitored monthly (see 7 WARNINGS AND PRECAUTIONS). For patients taking 5 mg/day of prednisone, if hypokalemia persists despite optimal potassium supplementation and adequate oral intake, or ifany of the other mineralocorticoid effects persist, the dose of prednisone may be increased to 10 mg/day.

Caution is advised if patients need to be withdrawn from prednisone. Monitoring for adrenocortical insufficiency should occur. If Abiraterone is continued after corticosteroids arewithdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see 7 WARNINGS AND PRECAUTIONS, Corticosteroid Withdrawal and Coverage of Stress Situations).

Blood glucose levels should be monitored in patients with pre-existing diabetes receiving concomitant medications such as repaglinide or pioglitazone (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia).

Musculoskeletal

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 drugs known to be associated with myopathy/rhabdomyolysis.

Renal

Patients with Renal Impairment: No dosage adjustment is necessary for patients with renal impairment (see 4 DOSAGE AND ADMINISTRATION).

Reproductive Health: Female and Male Potential
For contraception measures, see 2 CONTRAINDICATIONS and 7.1.1 Pregnant Women.

- **Fertility**

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.

- **Teratogenic Risk**

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 (see16 NON-CLINICAL TOXICOLOGY, Reproductive Toxicology).

Sensitivity/Resistance

Hypersensitivity/Anaphylactic reaction
Cases of anaphylactic reactions (severe allergic reactions that include, but are not limited to, difficulty swallowing or breathing, swollen face, lips, tongue or throat, or an itchy rash (urticaria))requiring rapid medical interventions, have been reported during post-marketing experience (See 2 CONTRAINDICATIONS and 8.5 Post-Market Adverse Reactions).

7.1 Special Populations

7.1.1 Pregnant Women

Abiraterone is contraindicated in women who are or may potentially be pregnant (see 2 CONTRAINDICATIONS and 16 NON-CINICAL TOXICOLOGY, Reproductive Toxicology).

There are no human data on the use of abiraterone acetate in pregnancy and abiraterone acetate is not for use in women of child-bearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the fetus (see 2 CONTRAINDICATIONS). Based on animal studies, there is potential of fetal harm (see 16 NON-CLINICAL TOXICOLOGY, Reproductive Toxicology).

It is not known if 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 witha woman of child-bearing potential, a condom is required along with another effective contraceptive method. These measures are required during and for one week after treatment with Abiraterone.

To avoid inadvertent exposure, women who are pregnant or women who may be pregnant should not handle Abiraterone without protection, e.g., gloves.

7.1.2 Breast-feeding

Abiraterone is not for use in women. It is not known if either abiraterone or its metabolites are excreted in human breast milk.

7.1.3 Pediatrics

Pediatrics (≤18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

In the Phase 3 studies of abiraterone acetate, 70% of patients were 65 years and over, and 27% of patients were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients (≥65 years) and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In combined data from Phase 3 trials, the adverse reactions seen with abiraterone acetate in ≥10% of patients were hypertension (21%), peripheral edema (19%), hypokalemia (18%), and alanine aminotransferase (ALT) increased and/or aspartate aminotransferase (AST) increased (13%).

The most common adverse reactions leading to dose interruption, reduction, or other modification in patients treated with abiraterone acetate versus placebo were hypokalemia (3% vs. 1%), hypertension (3% vs. 1%), AST elevation (2% vs. 1%), and ALT elevation (2% vs. 1%), and hepatic functional abnormal (2% vs. <1%). The most common adverse drug reactions that resulted in drug discontinuation in patients treated with abiraterone acetate were ALT increased, AST increased and hypokalemia (<1% each).

The most common serious adverse reactions (≥1%) observed with abiraterone acetate compared to placebo were pneumonia (2% vs. 1%) and urinary tract infection (2% vs. 1%).

Abiraterone acetate may cause hypertension, hypokalemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies, anticipated mineralocorticoid effects were seen more commonly in patients treated with abiraterone acetate versus patients treated with placebo: hypokalemia (18% vs. 8%), hypertension (22% vs. 16%) and fluid retention (peripheraledema) (23% vs. 17%), respectively. In patients treated with abiraterone acetate versus patients treated with placebo, Grades 3 and 4 hypokalemia were observed in 6% versus 1% of patients, Grades 3 and 4 hypertension were observed in 7% versus 5%, and Grades 3 and 4 fluid retention edema were observed in 1% versus 1% of patients, respectively. A higher incidence of hypertension and hypokalemia was observed in Study 3011 (see Study Tables 1-6 below). Generally, these effects due to mineralocorticoid excess were successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse drug reactions (see 7 WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Placebo-controlled Phase 3 Study in Asymptomatic or Mildly Symptomatic mCRPC Patients (Study 302)

In a placebo-controlled, multicentre Phase 3 clinical study of asymptomatic or mildly symptomatic patients with mCRPC who were using a GnRH agonist or were previously treated with orchiectomy, abiraterone acetate was administered at a dose of 1 g daily in combination with low dose prednisone (10 mg daily) in the active treatment arm. Placebo plus low dose prednisone (10 mg daily) was given to control patients. The median duration of treatment with abiraterone acetate was 18.8 months and 11.3 months for placebo.

The most common all grade adverse reactions observed with abiraterone acetate compared to placebo were joint pain or discomfort (32% vs. 27%), peripheral edema (25% vs. 20%), hot flush (22% vs. 18%), diarrhea (22% vs. 18%), hypertension (22% vs. 13%), cough (17% vs. 14%), hypokalemia (17% vs.13%),

upper respiratory tract infection (13% vs. 8%), dyspepsia (11% vs.5%), hematuria (10% vs. 6%), nasopharyngitis (11% vs. 8%), vomiting (13% vs. 11%), fatigue (39% vs. 34%), constipation (23% vs. 19%), contusion (13% vs. 9%), insomnia (14% vs. 11%), anemia (11% vs. 9%) and dyspnea (12% vs. 10%).

The most common serious adverse drug reactions observed with abiraterone acetate compared to placebo was urinary tract infection (1.5% vs. 0.6%), hypokalemia (0.4% vs. 0.2%) and hematuria (1.8% vs. 0.7%).

The most common adverse reactions leading to clinical intervention abiraterone acetate compared to placebo were AST elevation (4.2% vs. 0.6%), and ALT elevation (5.2% vs. 0.7%).

Anticipated mineralocorticoid effects were seen more commonly in patients treated with abiraterone acetate versus patients treated with placebo: hypokalemia (17% vs. 13%), hypertension (22% vs. 13%) and fluid retention (peripheral edema) (25% vs. 20%), respectively. In patients treated with abiraterone acetate Grades 3 and 4 hypokalemia and Grades 3 and 4 hypertension were observed in 2% and 4% of patients, respectively.

Table 1: Adverse Drug Reactions that Occurred in the Phase 3 Study with Asymptomatic or Mildly Symptomatic mCRPC Patients (Study 302) in ≥2% (all Grades) of Patients in the Abiraterone acetate Group

	Abiraterone acetate 1 g with Prednisone 10 mg Daily N=542			Placebo with Prednisone 10 mg Daily N=540		
System Organ Class / MedDRA Preferred Term (PT)	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Cardiac Disorders						
Cardiac failure[a]	10 (1.9%)	4 (0.8%)	1 (0.2%)	1 (0.2%)	0	0
Angina pectoris[b]	14 (2.6%)	2 (0.4%)	0	6 (1.1%)	2 (0.4%)	0
General Disorders and Administrative Site Conditions						
Edema peripheral	134 (24.7%)	2(0.4%)	0	108 (20.0%)	5 (0.9%)	0
Fatigue	212 (39.1%)	12 (2.2%)	0	185 (34.3%)	9 (1.7%)	0
Gastrointestinal Disorders						
Diarrhea	117 (21.6%)	5 (0.9%)	0	96 (17.8%)	5 (0.9%)	0
Dyspepsia	60 (11.1%)	0	0	27 (5.0%)	1 (0.2%)	0
Constipation	125 (23.1%)	2 (0.2%)	0	103 (19.1%)	3 (0.6%)	0
Vomiting	69 (12.7%)	4 (0.7%)	0	58 (10.7%)	0	0
Infections and Infestations						
Upper respiratory tract infection	69 (12.7%)	0	0	43 (8.0%)	0	0
Nasopharyngitis	58 (10.7%)	0	0	44 (8.1%)	0	0
Injury, Poisoning and Procedural Complications						
Contusion	72 (13.3%)	0	0	49 (9.1%)	0	0
Fall	32 (5.9%)	0	0	18 (3.3%)	0	0
Musculoskeletal and Connective Tissue Disorders						
Joint pain or discomfort[c]	172 (31.7%)	11 (2.0%)	0	144 (26.7%)	11 (2.0%)	0
Metabolism and Nutrition Disorders						
Hypokalemia	91 (16.8%)	12 (2.2%)	1 (0.2%)	68 (12.6%)	10 (1.9%)	0
Skin and Subcutaneous Tissue Disorders						
Rash	44 (8.1%)	0	0	20 (3.7%)	0	0
Skin lesion	19 (3.5%)	0	0	5 (0.9%)	0	0
Psychiatric Disorders						
Insomnia	73 (13.5%)	1 (0.2%)	0	61 (11.3%)	0	0

	Abiraterone acetate 1 g with Prednisone 10 mg Daily N=542			Placebo with Prednisone 10 mg Daily N=540		
System Organ Class / MedDRA Preferred Term (PT)	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Respiratory, Thoracic and Mediastinal Disorders						
Cough	94 (17.3%)	0	0	73 (13.5%)	1 (0.2%)	0
Dyspnea	64 (11.8%)	11 (2.0%)	2 (0.4%)	52 (9.6%)	4 (0.7%)	1 (0.2%)
Renal and Urinary Disorders						
Hematuria	56 (10.3%)	7 (1.3%)	0	30 (5.6%)	3 (0.6%)	0
Vascular Disorders						
Hot flush	121 (22.3%)	1 (0.2%)	0	98 (18.1%)	0	0
Hypertension	117 (21.6%)	21 (3.9%)	0	71 (13.1%)	16 (3.0%)	0
Hematoma	19 (3.5%)	0	0	6 (1.1%)	0	0

a. Cardiac failure also included: cardiac failure congestive, ejection fraction decreased, and left ventricular dysfunction.
b. Angina pectoris included due to its clinical relevance
c. Joint pain or discomfort included: arthralgia, arthritis, bursitis, joint swelling, joint stiffness, joint range of motion decreased, joint effusion, osteoarthritis, spinal osteoarthritis, tendonitis, rheumatoid arthritis

Placebo-controlled Phase 3 Study in mCRPC Patients with Prior Treatment with Docetaxel (Study 301)

In a placebo-controlled, multicentre Phase 3 clinical study of patients with mCRPC who were using a gonadotropin releasing hormone (GnRH) agonist or were previously treated with orchiectomy, and previously treated with docetaxel, abiraterone acetate was administered at a dose of 1 g daily in combination with low dose prednisone (10 mg daily) in the active treatment arm; placeboplus low dose prednisone (10 mg daily) was given to control patients. Patients enrolled were intolerant to or had failed up to two prior chemotherapy regimens, one of which contained docetaxel. The average duration of treatment with abiraterone acetate was 32 weeks and the duration of treatment for placebo was 16 weeks.

The most common all grade adverse reactions observed with abiraterone acetate compared to placebo were myopathy (36.3% vs. 30.9%), joint pain or discomfort (30.7% vs. 24.1%), peripheral edema (24.9% vs. 17.3%), hot flush (19.0% vs. 16.8%), diarrhea (17.6% vs. 13.5%), hypokalemia (17.1% vs. 8.4%), urinary tract infection (11.5% vs. 7.1%), and cough 10.6% vs. 7.6%).

The most common serious adverse reactions observed with abiraterone acetate compared to placebo were urinary tract infection (1.8% vs. 0.8%), bone fracture (1.6% vs. 0.6%), and hypokalemia (0.8% vs. 0%).

The most common adverse reactions leading to clinical intervention with abiraterone acetate compared to placebo were AST elevation (1.4% vs. 0.5%), ALT elevation (1.1% vs. 0%), hypokalemia (1.1% vs. 0.5%), urinary tract infection (0.9% vs. 0.3%), hypertension (0.9% vs. 0.3%), congestive heart failure (0.5% vs. 0%), and angina pectoris (0.3% vs. 0%).

Anticipated mineralocorticoid effects were seen more commonly in patients treated with abiraterone acetate versus patients treated with placebo: hypokalemia (17% vs. 8%), hypertension (9% vs. 7%) and fluid retention (peripheral edema) (25% vs. 17%), respectively. In patients treated with abiraterone acetate, Grades 3 and 4 hypokalemia and Grades 3 and 4 hypertension were observed in 4% and 1% of patients respectively.

Table 2: Adverse Drug Reactions that Occurred in a Phase 3 Study with mCRPC Patients with Prior Treatment with Docetaxel (Study 301) in ≥2% (all Grades) of Patients in the Abiraterone acetate Group

	Abiraterone acetate 1 g with Prednisone 10 mg Daily N=791			Placebo with Prednisone 10 mg Daily N=394		
System Organ Class / MedDRA Preferred Term (PT)	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Cardiac Disorders						
Arrhythmia[a]	56 (7.0%)	7 (0.9%)	2 (0.2%)	15 (4.0%)	2 (0.5%)	1 (0.3%)
Cardiac failure[b]	16 (2.0%)	12 (1.5%)	1 (0.1%)	4 (1.0%)	0	1 (0.3%)
Angina pectoris[c]	10 (1.3%)	2 (0.3%)	0	2 (0.5%)	0	0
General Disorders and Administrative Site Conditions						
Edema peripheral	197 (24.9%)	11 (1.4%)	1 (0.1%)	68 (17.3%)	3 (0.8%)	0
Gastrointestinal Disorders						
Diarrhea	139 (17.6%)	5 (0.6%)	0	53 (13.5%)	5 (1.3%)	0
Dyspepsia	48 (6.1%)	0	0	13 (3.3%)	0	0
Injury, Poisoning and Procedural Complications						
Fractures[d]	47 (5.9%)	8 (1.0%)	3 (0.4%)	9 (2.3%)	0	0
Infections and Infestations						
Urinary tract infection	91 (11.5%)	17 (2.1%)	0	28 (7.1%)	2 (0.5%)	0
Upper respiratory tract infection	43 (5.4%)	0	0	10 (2.5%)	0	0
Musculoskeletal and Connective Tissue Disorders						
Joint pain or discomfort[e]	243 (30.7%)	37 (4.7%)	0	95 (24.1%)	17 (4.3%)	0
Myopathy[f]	287 (36.3%)	43 (5.4%)	2 (0.2%)	122 (30.9%)	14 (4.6%)	1 (0.3%)
Metabolism and Nutrition Disorders						
Hypokalemia	135 (17.1%)	27 (3.4%)	3 (0.4%)	33 (8.4%)	3 (0.8%)	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	84 (10.6%)	0	0	30 (7.6%)	0	0
Renal and Urinary Disorders						
Urinary frequency	57 (7.2%)	2 (0.3%)	0	20 (5.1%)	1 (0.3%)	0
Nocturia	49 (6.2%)	0	0	16 (4.1%)	0	0

	Abiraterone acetate 1 g with Prednisone 10 mg Daily N=791			Placebo with Prednisone 10 mg Daily N=394		
System Organ Class / MedDRA Preferred Term (PT)	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Vascular Disorders						
Hot flush	150 (19.0%)	2 (0.3%)	0	66 (16.8%)	1 (0.3%)	0
Hypertension	67 (8.5%)	10 (1.3%)	0	27 (6.9%)	1 (0.3%)	0

a. Arrhythmia included: tachycardia, atrial fibrillation, arrhythmia, bradycardia, supraventricular tachycardia, atrial tachycardia, atrioventricular block complete, conduction disorder, ventricular tachycardia, atrial flutter, bradyarrhythmia.
b. Cardiac failure also included cardiac failure congestive, ejection fraction decreased, and left ventricular dysfunction.
c. Angina pectoris included due to its clinical relevance.
d. Fractures included all fractures with the exception of pathological fracture.
e. Joint pain or discomfort included: arthralgia, arthritis, arthropathy, bursitis, joint swelling, joint stiffness, joint range of motion decreased, joint effusion, joint ankylosis, osteoarthritis, rheumatoid arthritis, spinal osteoarthritis, spondylolisthesis, tendonitis
f. Myopathy included: musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia, muscular weakness, musculoskeletal discomfort, myopathy, limb discomfort, blood creatine phosphokinase increased, muscle atrophy, muscle fatigue, muscle twitching, myopathy steroid.

Placebo-controlled Phase 3 Study in Patients with Newly Diagnosed High-Risk Metastatic Prostate Cancer (Study 3011 – LATITUDE)

In a Phase 3 study of patients with newly diagnosed high-risk metastatic hormone-sensitive prostate cancer who may have received up to 3 months of prior ADT, abiraterone acetate was administered at a dose of 1 g daily in combination with low-dose prednisone (5 mg daily) and ADT (a GnRH agonist or orchiectomy) in the active treatment arm; ADT and placebo were givento control patients. The median duration of treatment was 26 months with abiraterone acetate and 14 months with placebo. For patients who had crossed over from the placebo arm to abiraterone acetate, themedian total treatment duration on abiraterone acetate was 12 months.

The results from the final analysis of safety were consistent with those presented in the first interim analysis. With an additional 22 months of data collection since the time of the first interimanalysis, there were no clinically relevant changes in the safety profile of abiraterone acetate profile.

The most common all grade adverse reactions observed with abiraterone acetate compared to placebo were hypertension (38.4% versus 22.1%), hypokalemia (24.0% versus 3.8%), and hot flushes (15.4% versus 12.6%).

The most common serious adverse reactions observed with abiraterone acetate compared to placebo were pneumonia (2.0% versus 0.3%), urinary tract infection (1.3% versus 0.8%), and hematuria (1.3% versus 0.5%).

The most common adverse reactions leading to clinical intervention with abiraterone acetate compared to placebo were hypokalemia (9.5% versus 0.8%), hypertension (7.2% versus 2.7%), AST increased (5.7% versus 1.7%), and ALT increased (5.5% versus 1.8%).

Anticipated mineralocorticoid effects were seen more commonly in study 3011 in patients treated with abiraterone acetate versus patients treated with placebo: hypertension (40.7% versus 23.9%), hypokalemia (24.0% versus 3.8%) and fluid retention/edema (13.6% versus 11.8%). In patients treated with abiraterone acetate, Grade 3 and 4 hypokalemia was reported in 10.9% and 0.8% patients respectively. Grade 3 and 4 hypertension was 21.8% and 0.2% respectively.

Table 3: Adverse Drug Reactions that Occurred in the Phase 3 Study of Newly Diagnosed High-Risk Metastatic Hormone-sensitive Prostate Cancer Patients (Study 3011) with ≥2% increase in frequency (all Grades) in the Abiraterone acetate Group compared to Placebo.

	Abiraterone acetate 1 g with Prednisone 5mg and ADT[a] Daily N=597[b]			**Placebo and ADT[a] Daily N=602[b]**		
System Organ Class / MedDRA Preferred Term (PT)	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Cardiac Disorders						
Cardiac Failure	9 (1.5%)	2 (0.3%)	1 (0.2%)	2 (0.3%)	0	0
Angina pectoris	10 (1.7%)	3 (0.5%)	1 (0.2%)	5 (0.8%)	0	0
Atrial fibrillation	10 (1.7%)	2 (0.3%)	0	2 (0.3%)	1 (0.2%)	0
Infections and Infestations						
Urinary tract infection	44 (7.4%)	6 (1%)	0	23 (3.8%)	5 (0.8%)	0
Upper respiratory tract infection	42 (7.0%)	1 (0.2%)	0	29 (4.8%)	1 (0.2%)	0
Influenza	42 (7.0%)	0	0	20 (3.3%)	0	0
Bronchitis	24 (4.0%)	2 (0.3%)	0	8 (1.3%)	0	0
Injury, Poisoning and Procedural Complications						
Rib fracture	15 (2.5%)	0	0	2 (0.3%)	0	0
Metabolism and Nutrition Disorders						
Hypokalemia[c]	143 (24.0%)	65 (10.9%)	5 (0.8%)	23 (3.8%)	9 (1.5%)	1 (0.2%)
Nervous System Disorders						
Headache	46 (7.7%)	2 (0.3%)	0	31 (5.1%)	1 (0.2%)	0
Psychiatric Disorders						
Depression	17 (2.8%)	0	0	5 (0.8%)	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	41 (6.9%)	0	0	18 (3.0%)	0	0
Vascular Disorders						
Hypertension	229 (38.4%)	125 (20.9%)	0	133 (22.1%)	59 (9.8%)	1(0.2%)
Hot flush	92 (15.4%)	0	0	76 (12.6%)	1 (0.2%)	0

a. All patients were receiving a GnRH agonist or had undergone orchiectomy.
b. n=patients assessed for safety.
c. investigator assessed AE based on reported symptoms

Cardiovascular Effects: The Phase 3 studies excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, arterial thrombotic events in the past 6 months, severe or unstable angina, or LVEF <50% or New York Heart Association (NYHA)

Class III or IV heart disease (Study 301), or NYHA Class II to IV heart disease (Studies 302 and 3011). All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy (ADT), predominantly with the use of GnRH agonists, which has been associated with diabetes, myocardial infarction,cerebrovascular accident and sudden cardiac death.

In combined data from Phase 3 trials, the incidence of cardiovascular adverse reactions in patients taking abiraterone acetate versus patients taking placebo were as follows: atrial fibrillation, 2.6%vs. 2.0%; tachycardia, 1.9% vs. 1.0%; angina pectoris, 1.7% vs. 0.8%; cardiac failure, 0.7% vs. 0.2%; and arrhythmia, 0.7% vs. 0.5%.

Hepatotoxicity: Drug-associated hepatotoxicity with elevated serum transaminases (ALT and 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 or AST increases of >5X ULN or bilirubin increases >1.5X ULN) were reported in approximately 6% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment.

In the Phase 3 clinical study in mCRPC patients with prior treatment with docetaxel (Study 301), patients whose baseline ALT or AST were elevated were more likely to experience liver functiontest elevations than those beginning with normal values. When elevations of either ALT or AST >5X ULN, or elevations in bilirubin >3X ULN were observed, abiraterone acetate was withheld ordiscontinued. In two instances marked increases in liver function tests occurred (see 7 WARNINGS AND PRECAUTIONS). These two patients with normal baseline hepatic functionexperienced ALT or AST elevations 15X to 40X ULN and bilirubin elevations 2X to 6X ULN. Upon interruption of abiraterone acetate, both patients had normalization of their liver function tests. One patient was re-treated with abiraterone acetate. Recurrence of the elevations was not observed in this patient.

In the Phase 3 clinical study of asymptomatic or mildly symptomatic mCRPC patients (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 three patients (two with new multiple liver metastases, and one with AST elevation approximately three weeks after the last dose of abiraterone acetate).

In the Phase 3 clinical study of newly diagnosed high-risk metastatic prostate cancer (Study 3011), Grade 3 and Grade 4 hepatotoxicity was observed in 8.2% and 0.7% of patients treatedwith abiraterone acetate. Ten patients (1.7%) who received abiraterone acetate were discontinued because of hepatotoxicity; two had Grade 2 hepatotoxicity, six had Grade 3 hepatotoxicity, and two had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011.

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, respectively; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with active hepatitis or baseline hepatitis or significant abnormalities of liver function tests. In the trial with mCRPC patients who had received prior treatment with docetaxel (Study 301), patients with baseline ALT and AST ≥2.5X ULN in the absence of liver metastases and >5X ULN in the presence of liver metastases were excluded. In the trial with asymptomatic or mildly symptomatic mCRPC patients (Study 302), those with liver metastases were not eligible and patients with baseline ALT and AST ≥2.5X ULN were excluded. In the trial of newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (Study 3011), patients with baseline ALTand AST >2.5X ULN, bilirubin >1.5X ULN or those with active or symptomatic viral hepatitis or chronic liver disease, ascites or bleeding disorders secondary to hepatic dysfunction were excluded. Abnormal liver function tests developing in patients participating in clinical trials were managed by treatment interruption and by permitting re-treatment only after return of liver function tests to the patient's baseline (see 4 DOSAGE AND ADMINISTRATION). Patients with elevations of ALT or AST >20X ULN were not re-treated. The safety of re-treatment in such patients is unknown.

8.3 Less Common Clinical Trial Adverse Reactions

Endocrine Disorders: Adrenal insufficiency
General Disorders and Administrative Site Conditions: Influenza-like illness
Infections and Infestations: Lower respiratory tract infection
Investigations: Blood creatinine increased, weight increased
Metabolism and Nutrition Disorders: Hypertriglyceridemia

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 4, Table 5 and Table 6 show laboratory values of interest from the placebo-controlled Phase 3 trials.

Table 4: Selected Laboratory Abnormalities in mCRPC Asymptomatic or Mildly Symptomatic Patients who Received Abiraterone acetate (Study 302)

	Abiraterone acetate 1 g with Prednisone10 mg Daily N=542		Placebo with Prednisone 10 mg Daily N=540	
	All Grades %	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
ALT increased	41	6	28	1
AST increased	36	3	27	1
Bilirubin increased	11	<1	4	<1
Hypokalemia	14	2	8	1
Hypophosphatemia	26	5	14	2
Hypertriglyceridemia	22	0	17	0
Hypernatremia	30	<1	24	<1
Hypercalcemia	10	0	4	0
Lymphopenia	36	7	30	0

Table 5: Selected Laboratory Abnormalities in mCRPC Patients with Prior Treatment with Docetaxel who Received Abiraterone acetate (Study 301)

	Abiraterone acetate 1 g with Prednisone5 mg Daily N=791		Placebo with Prednisone 10 mg Daily N=394	
	All Grades %	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
ALT increased	11	1	10	<1
AST increased	30	2	34	1
Bilirubin increased	6	<1	3	0
Hypokalemia	19	3	10	<1
Hypercholesterolemia	55	<1	48	<1
Low phosphorus	23	7	15	5
Hypertriglyceridemia	62	<1	53	0

Table 6: Selected Laboratory Abnormalities in Patients with Newly Diagnosed High-Risk Metastatic Hormone-sensitive Prostate Cancer who Received Abiraterone acetate (Study 3011)

	Abiraterone acetate 1 g with Prednisone5 mg Daily N= 597		Placebo N=602	
	All Grades %	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
ALT increased	45	6	45	1
AST increased	46	5	46	2
Bilirubin increased	16	<1	6	<1
Hypokalemia	30	10	7	1
Lymphopenia	20	5	13	2

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of abiraterone acetate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory, thoracic and mediastinal disorders: allergic alveolitis
Musculoskeletal and connective tissue disorders: rhabdomyolysis, myopathy
Hepatobiliary disorders: hepatitis fulminant, acute hepatic failure with fatalities (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, and 7 WARNINGS AND PRECAUTIONS, **Hepatic/Biliary/Pancreatic**)
Cardiac disorders: QT prolongation and Torsades de Pointes (observed in patients who developed hypokalemia or had underlying cardiovascular conditions, see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
Endocrine and metabolism: isolated cases of hypoglycemia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia).
Immune system disorders-Hypersensitivity: anaphylactic reaction (severe allergic reactions that include, but are not limited to, difficulty swallowing or breathing, swollen face, lips, tongue or throat, or an itchy rash (urticaria).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro studies indicated that CYP3A4 and SULT2A1 are the major isoenzymes involved in the metabolism of abiraterone (see 10.3 Pharmacokinetics, Non-clinical Pharmacokinetics). Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2C8 and CYP2D6(see 9.4 Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

No studies on the effects of abiraterone acetate on the ability to drive or use machines have been performed. It is not anticipated that Abiraterone will affect the ability to drive and use machines.

9.4 Drug-Drug Interactions

Potential for other medicinal ingredients to affect Abiraterone

CYP3A4 inducers: Based on *in vitro* data, the active metabolite abiraterone is a substrate of CYP3A4. 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 1000 mg, the mean plasma AUC_∞ of abiraterone was decreased by 55%.Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital) during treatment with Abiraterone are to be avoided. If patients must be co- administered a strong CYP3A4 inducer, careful evaluation of clinical efficacy must be undertaken as there are no clinical data recommending an appropriate dose adjustment.

CYP3A4 inhibitors: In a clinical pharmacokinetic interaction study, healthy subjects were administered ketoconazole, a strong CYP3A4 inhibitor, 400 mg daily for 6 days. No clinicallymeaningful effect on the pharmacokinetics of abiraterone was demonstrated following co- administration of a single dose of abiraterone acetate, 1000 mg at day 4.

Potential for Abiraterone to affect other drugs

CYP1A2: In a clinical study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

CYP2D6: In the same 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 by approximately 200%. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased by approximately 33%.

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Caution is advised when Abiraterone is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic indexdrugs metabolized by CYP2D6 should be considered.

CYP2C8: 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 the CYP2C8 substrate pioglitazone, each decreased by 10%, when a single dose of pioglitazone was giventogether with a single dose of 1000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a

CYP2C8 substrate with a narrow therapeutic index if used concomitantly with Abiraterone. Examples of medicinal products metabolized by CYP2C8 include pioglitazone and repaglinide (see 7 WARNINGS AND PRECAUTIONS).

CYP2C9, CYP2C19 and CYP3A4/5: *In vitro* studies with human hepatic microsomes demonstrated that abiraterone was a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5.No clinical DDI studies have been performed to confirm these *in vitro* findings (see 10.3 Pharmacokinetics, Non-clinical Pharmacokinetics).

OATP1B1: *In vitro*, abiraterone and its major metabolites were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations ofdrugs that are eliminated by OATP1B1. There are no clinical data available to confirm transporter-based interaction.

9.5 Drug-Food Interactions

Administration of Abiraterone with food significantly increases the absorption of abiraterone. Theefficacy and safety of abiraterone acetate given with food has not been established. **Abiraterone must not be taken with solid or liquid food** (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

Co-administration of Abiraterone with St. John's wort (*Hypericum perforatum*) may potentially reduce the plasma concentrations of Abiraterone. Concomitant use with St. John's wort or products containing St. John's wort is to be avoided.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Abiraterone acetate 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 tumor tissues. It catalyzes the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17-α hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals (see 7 WARNINGS AND PRECAUTIONS, Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor. Abiraterone acetate decreases serum testosterone and other androgens in patients to levels lower than those achieved by the use of GnRH agonists alone or by orchiectomy. Commercial testosterone assays have inadequate sensitivity to detect the effect of abiraterone acetate on serum testosterone levels, therefore, it is not necessary to monitor the effect of abiraterone acetate on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

10.2 Pharmacodynamics

Cardiac Electrophysiology: A multicentre, open-label, uncontrolled, single arm ECG assessment study was performed in 33 patients with metastatic castration-resistant prostate cancer who were medically (N=28) or surgically castrated (N=5). Patients had serial ECG recordings at baseline and on day 1 of the first and second 28-day cycles of treatment with abiraterone acetate 1 g daily in combination with prednisone 5 mg twice daily. At steady-stateon day 1 of cycle 2, the QTc interval was significantly shortened at most time points, with a maximum decrease from baseline of mean -10.7 (90% CI - 14.8, -6.5) ms at 24 h post-dosing.

Androgen deprivation is associated with QTc prolongation. In this study the QTc interval averaged 435−440 ms at baseline and 57.6% of subjects had baseline QTc values > 450 msprior to initiation of abiraterone acetate. Because the subjects in this trial were already androgen-deprived, the results of this study cannot be extrapolated to non-castrated populations.

Mineralocorticoid receptor antagonists: Patients in the pivotal clinical trials (COU-AA-302 and COU-AA-301) were not allowed to use the mineralocorticoid receptor antagonist spironolactone with abiraterone acetate since spironolactone has the ability to bind and activate the wild type androgen receptor, which could stimulate disease progression. The use of spironolactone with Abiraterone should be avoided.

Prior use of ketoconazole: Based on experience in an early abiraterone acetate trial, lower rates of response might be expected in patients previously treated with ketoconazole for prostate cancer.

10.3 Pharmacokinetics

Non-clinical pharmacokinetics

Several isoenzymes (CYP, UGT and SULT) are responsible for the metabolism of abiraterone into 15 detectable metabolites, accounting for approximately 92% of circulating radioactivity. CYP3A4 and SULT2A1 are the major single isoenzymes involved in metabolite formation with aminor contribution from UGT1A4, SULT1E1 and UGT1A3.

In vitro studies with human hepatic microsomes demonstrated that abiraterone was not an inhibitor for human CYP2A6 and CYP2E1. In these same studies, abiraterone was a moderateinhibitor of CYP2C9, CYP2C19 and CYP3A4/5. However, the concentrations of abiraterone in patients were lower than the concentration required for clinically meaningful inhibition of these enzymes. Abiraterone was also determined *in vitro* to be a potent inhibitor of CYP1A2, CYP2D6and CYP2C8 (see 9.4 Drug-Drug Interactions).

The pharmacokinetics of abiraterone in the presence of strong inducers or inhibitors of the above enzymes have not been evaluated *in vitro* or *in vivo* with the exception of CYP3A4 (see9.4 Drug-Drug Interactions, ***CYP3A4 inducers*** and ***CYP3A4 inhibitors***).

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone has been studied in healthy subjects, patients with metastatic prostate cancer and subjects without cancerwith hepatic or renal impairment. Abiraterone acetate is rapidly converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Absorption:

The AUC and C_{max} values in patients with castration-resistant prostate cancer were 979 ng•h/mL and 216.5 ng/mL respectively. In addition, there was large inter-patient variabilityobserved for healthy subjects and patients with castration-resistant prostate cancer.

There was an observed reduction in the clearance of patients with castration-resistant prostate cancer (33%) compared to healthy subjects. This reduction could translate to a 40% mean increase of mean population predicted exposure in patients relative to healthy subjects, but thisincrease may be confounded with effects of concomitant medications and food intake conditions. This difference is not considered to be clinically relevant.

Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours in patients with castration-resistant prostate cancer.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and AUC were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10- fold higher, respectively when abiraterone acetate was administeredwith a high-fat meal (57% fat, 825 calories).

Given the normal variation in the content and composition of meals, taking Abiraterone with meals has the potential to result in highly variable exposures. Therefore, Abiraterone tablets **must be taken** as a single dose once daily **on an empty stomach**. No solid or liquid food should be consumed at least two hours before taking Abiraterone and for at least one hour after taking Abiraterone. The tablets should be swallowed whole with water (see 4 DOSAGE AND ADMINISTRATION).

Distribution:

The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5630 L, suggesting that abiraterone extensively distributes to peripheral tissues. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp). *In vitro* studies show thatabiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

Metabolism:

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is rapidly hydrolyzed to the active metabolite abiraterone. This reaction is not CYP mediated but hypothesized to occur via an unidentified esterase(s). Abiraterone then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. This results in the formation of two main plasma circulating inactive metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each accounting for approximately 43% of total radioactivity. The formation of N-oxide abiraterone sulphate is predominantly catalyzed by CYP3A4 and SULT2A1while the formation of abiraterone sulphate is catalyzed by SULT2A1.

Excretion:

The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy

subjects and approximately 12 hours based on data from patients with metastatic castration-resistant prostate cancer. Following oral administration of ^{14}C-abiraterone acetate, approximately 88% of the radioactive dose is recovered 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).

Special Populations and Conditions:
The effect of intrinsic factors such as age and body weight has been evaluated using population pharmacokinetic approaches and no statistically significant effect was evident for any of these covariates.

- **Pediatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

- **Sex:** All clinical study information thus far is derived from male subjects.

- **Genetic Polymorphism:** The effect of genetic differences on the pharmacokinetics of abiraterone has not been evaluated.

- **Hepatic Insufficiency:** The pharmacokinetics of abiraterone was examined in non-mCRPC subjects with pre-existing mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh class A and B, respectively) and in healthy control subjects (N=8). Systemic exposure (AUC)to abiraterone after a single oral 1 g dose increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone was prolonged from approximately 13 hours in healthy subjects to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. No dosage adjustment is necessary formCRPC patients with pre-existing mild hepatic impairment. Abiraterone should not be used in patients with pre-existing moderate or severe hepatic impairment. The safety of abiraterone acetate has not been studied in mCRPC patients with moderate or severe (Child-Pugh Class B or C) hepatic impairment at baseline.

  For patients who develop hepatotoxicity during treatment with Abiraterone suspension of treatment and dosage adjustment may be required (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

- **Renal Insufficiency:** The pharmacokinetics of abiraterone following the administration of a single oral 1 g dose of abiraterone acetate was compared in patients with end-stage renal disease on a stable hemodialysis schedule (N=8), versus matched control subjects with normal renal function (N=8). Systemic exposure to abiraterone after a single oral 1 g dose did not increase in patients with end-stage renal disease on dialysis.

  Administration of Abiraterone in patients with renal impairment including severe renal impairment does not require dose adjustment (see 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15–30°C).

12 SPECIAL HANDLING INSTRUCTIONS

Based on its mechanism of action, Abiraterone may harm a developing fetus; therefore, women who are pregnant or women who may be pregnant should not handle Abiraterone without protection, e.g., gloves (see section 7.1 Special Populations).

Any unused product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

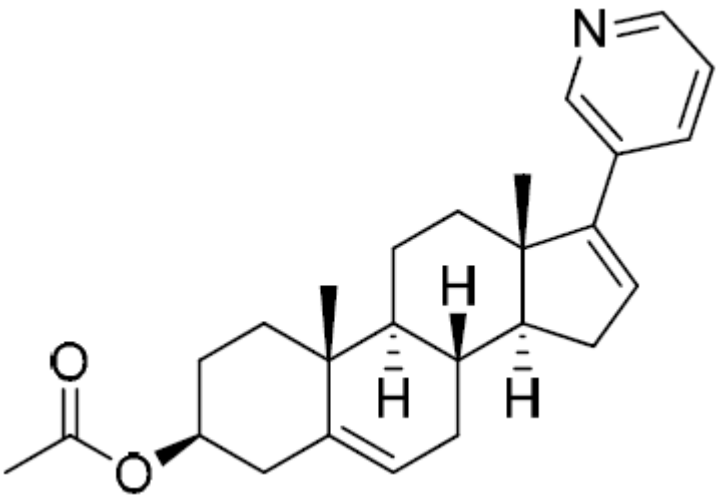
Drug Substance

Proper name: abiraterone acetate

Chemical name: (3β)-17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate

Molecular formula and molecular mass: $C_{26}H_{33}NO_2$ and 391.55 g/mol

Structural formula:



Physicochemical properties: Abiraterone acetate is a white to off-white crystalline powder. Abiraterone acetate is practically insoluble in aqueous media over a wide range of pH values (pH=1.2 to 10.9). The melting point is between 143ºC and 146ºC. The pKa is 3.06.

Solubility profile at different pH conditions at 25ºC

pH	Solubility results
1.2 Solution (Hydrochloric acid buffer)	10mg/100mL (Insoluble)
3.0 Solution (Acid phthalate buffer)	10mg/100mL (Insoluble)
4.6 solution (Neutralized buffer)	10mg/100mL (Insoluble)
6.8 solution (Phosphate buffer)	10mg/100mL (Insoluble)
8.0 solution (Alkaline Borate buffer)	10mg/100mL (Insoluble)
10.0 solution (Alkaline Borate buffer)	10mg/100mL (Insoluble)
4.5 solution (Acetate buffer)	10mg/100mL (Insoluble)
Water	10mg/100mL (Insoluble)

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Indication 1:

Treatment of metastatic prostate cancer (castration-resistant prostate cancer, mCRPC) in patients who:

- are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy
- have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy

Placebo-controlled Phase 3 Study in Asymptomatic or Mildly Symptomatic mCRPC Patients (Study 302)

In this study, the efficacy of abiraterone acetate was established in patients with mCRPC (documented bypositive bone scans and/or metastatic lesions on CT, MRI other than visceral metastasis) who were asymptomatic (as defined by a score of 0-1 on BPI-SF (Brief Pain Inventory Short Form), worst pain over the last 24 hours) or mildly symptomatic (as defined by a score of 2-3 on BPI-SF, worst pain over the last 24 hours) after failure of ADT, who were using a GnRH agonist during study treatment or were previously treated with orchiectomy (N=1088). Patients were randomized 1:1 to receive either abiraterone acetate or placebo. In the active treatment arm, abiraterone acetate was administered orally at a dose of 1 g daily in combination with low dose prednisone 5 mg twice daily (N=546). Control patients received placebo and low dose prednisone 5 mg twice daily (N=542).

Patients were not included in the study if they had moderate or severe pain, opiate use for severe pain, liver or visceral organ metastases, known brain metastasis, clinically significant heart disease (as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or LVEF <50% or New York Heart Association Class II toIV heart failure), prior ketoconazole for the treatment of prostate cancer, a history of adrenal gland or pituitary disorders or prostate tumor showing extensive small cell (neuroendocrine) histology. Spironolactone was a restricted concomitant therapy due to its potential to stimulate disease progression. Patients who had received prior chemotherapy or biologic therapy were excluded from the study.

The co-primary efficacy endpoints for this study were overall survival (OS) 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. Unequivocal clinical progression was characterized as cancer pain requiring initiation of chronic administration of opiate analgesia (oral opiate use for ≥3 weeks; parenteral opiate use for ≥7 days), or immediateneed to initiate cytotoxic chemotherapy or the immediate need to have either radiation therapy or surgical intervention for complications due to tumor progression, or deterioration in ECOG performance status to Grade 3 or higher. Treatments could also be discontinued at the time of confirmed radiographic progression at the discretion of the investigator.

Radiographic progression free survival was assessed with the use of sequential imaging studies as defined by Prostate Cancer Working Group-2 (PCWG2) criteria (for bone lesions) with confirmatory bone scans and modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria (for soft tissue

lesions). Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

Because changes in PSA serum concentration do not always predict clinical benefit, patients were maintained on abiraterone acetate until discontinuation criteria were met as specified for the study.

Table 7 summarizes key demographics and baseline disease characteristics. Demographics and baseline disease characteristics were balanced between the two groups.

Table 7: Key Demographics and Baseline Disease Characteristics (Phase 3 Study in Asymptomatic or Mildly Symptomatic mCRPC Patients: ITT Population)

	Abiraterone acetate + Prednisone (N=546)	Placebo + Prednisone (N=542)	Total (N=1088)
Age (years)			
N	546	542	1088
Mean (SD)	70.5 (8.80)	70.1 (8.72)	70.3 (8.76)
Median	71.0	70.0	70.0
Range	(44, 95)	(44, 90)	(44, 95)
Sex			
n	546	542	1088
Male	546 (100.0%)	542 (100.0%)	1088 (100.0%)
Race			
n	545	540	1085
White	520 (95.4%)	510 (94.4%)	1030 (94.9%)
Black	15 (2.8%)	13 (2.4%)	28 (2.6%)
Asian	4 (0.7%)	9 (1.7%)	13 (1.2%)
Other	6 (1.1%)	6 (1.1%)	12 (1.1%)
Time From Initial Diagnosis to First Dose (years)			
n	542	540	1082
Mean (SD)	6.7 (4.85)	6.5 (4.77)	6.6 (4.81)
Median	5.5	5.1	5.3
Range	(0, 28)	(0, 28)	(0, 28)
Extent of Disease			
n	544	542	1086
Bone	452 (83.1%)	432 (79.7%)	884 (81.4%)
Bone Only	274 (50.4%)	267 (49.3%)	541 (49.8%)
Soft Tissue or Node	267 (49.1%)	271 (50.0%)	538 (49.5%)
ECOG Performance Status Score			
n	546	542	1088
0	416 (76.2%)	414 (76.4%)	830 (76.3%)
1	130 (23.8%)	128 (23.6%)	258 (23.7%)
Baseline PSA (ng/mL)			
n	546	539	1085
Mean (SD)	133.38 (323.639)	127.63 (387.878)	130.52 (356.846)
Median	42.01	37.74	39.51
Range	(0.0, 3927.4)	(0.7, 6606.4)	(0.0, 6606.4)
Baseline Hemoglobin (g/dL)			
n	545	538	1083
Mean (SD)	12.97 (1.22)	12.99 (1.22)	12.98 (1.22)
Median	13.0	13.1	13.1
Range	(7.2,16.6)	(7.0, 15.7)	(7.0, 16.6)

	Abiraterone acetate + Prednisone (N=546)	Placebo + Prednisone (N=542)	Total (N=1088)
Baseline Alkaline Phosphatase (IU/L)			
n	546	539	1085
Mean (SD)	137.4 (166.88)	148.1 (248.11)	142.8 (211.15)
Median	93.0	90.0	91.0
Range	(32, 1927)	(21, 3056)	(21, 3056)
Baseline Lactate Dehydrogenase (IU/L)			
n	543	536	1079
Mean (SD)	199.9 (78.57)	196.8 (59.20)	198.3 (69.61)
Median	187.0	184.0	185.0
Range	(60, 871)	(87, 781)	(60, 871)

Study Results

A median of 15 cycles (60 weeks) were administered in the abiraterone acetate group compared with 9 cycles (36 weeks) in the placebo group. The mean duration of treatment with abiraterone acetate was 18.8 months and 11.3 months for placebo.

At the planned rPFS analysis there were 401 radiographic progression 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 8 and Figure 1, rPFS analyses by subgroup are presented in Figure 2.

Table 8: rPFS of Patients Treated with Either Abiraterone acetate or Placebo in Combination with Prednisone Plus GnRH Agonists or Prior Orchiectomy (ITT Population)

	Abiraterone acetate N=546	Placebo N=542
Progression or death	150 (28%)	251 (46%)
Median rPFS (months) (95% CI)	Not reached (11.66, NE)	8.3 (8.12, 8.54)
Hazard ratio[a] (95% CI)	0.425 (0.347, 0.522)	
p-value[b]	<0.0001	

NE=Not Estimated

a. Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors Abiraterone acetate

b. From a log-rank test of the equality of two survival curves over the time interval, and stratified by baseline ECOG score (0 or 1)

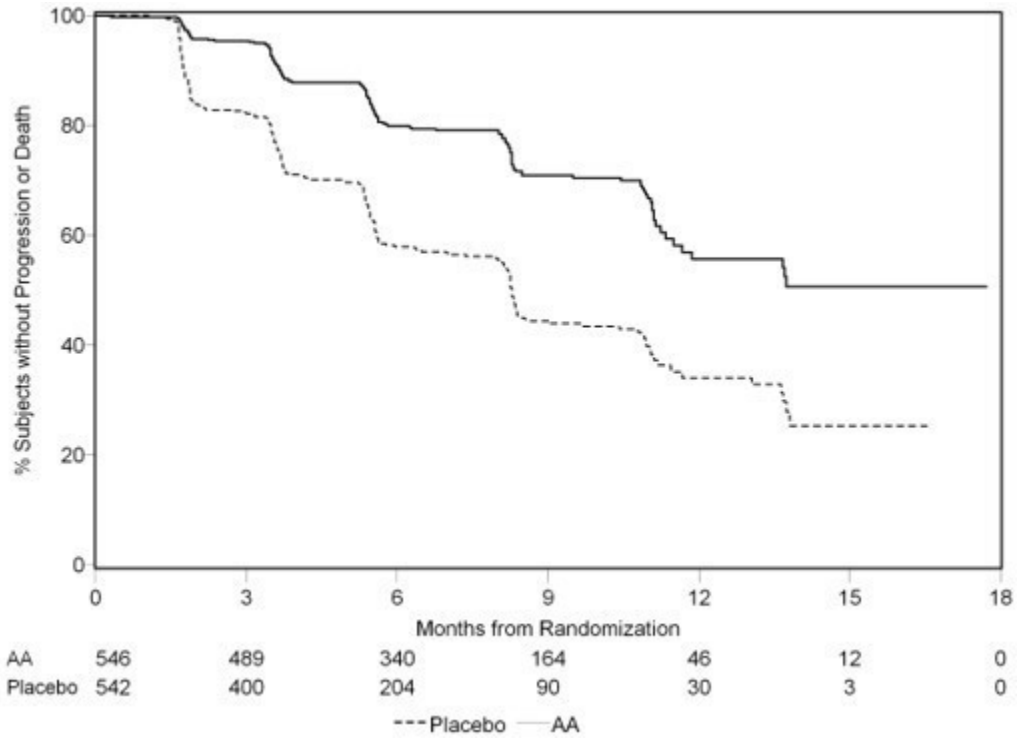
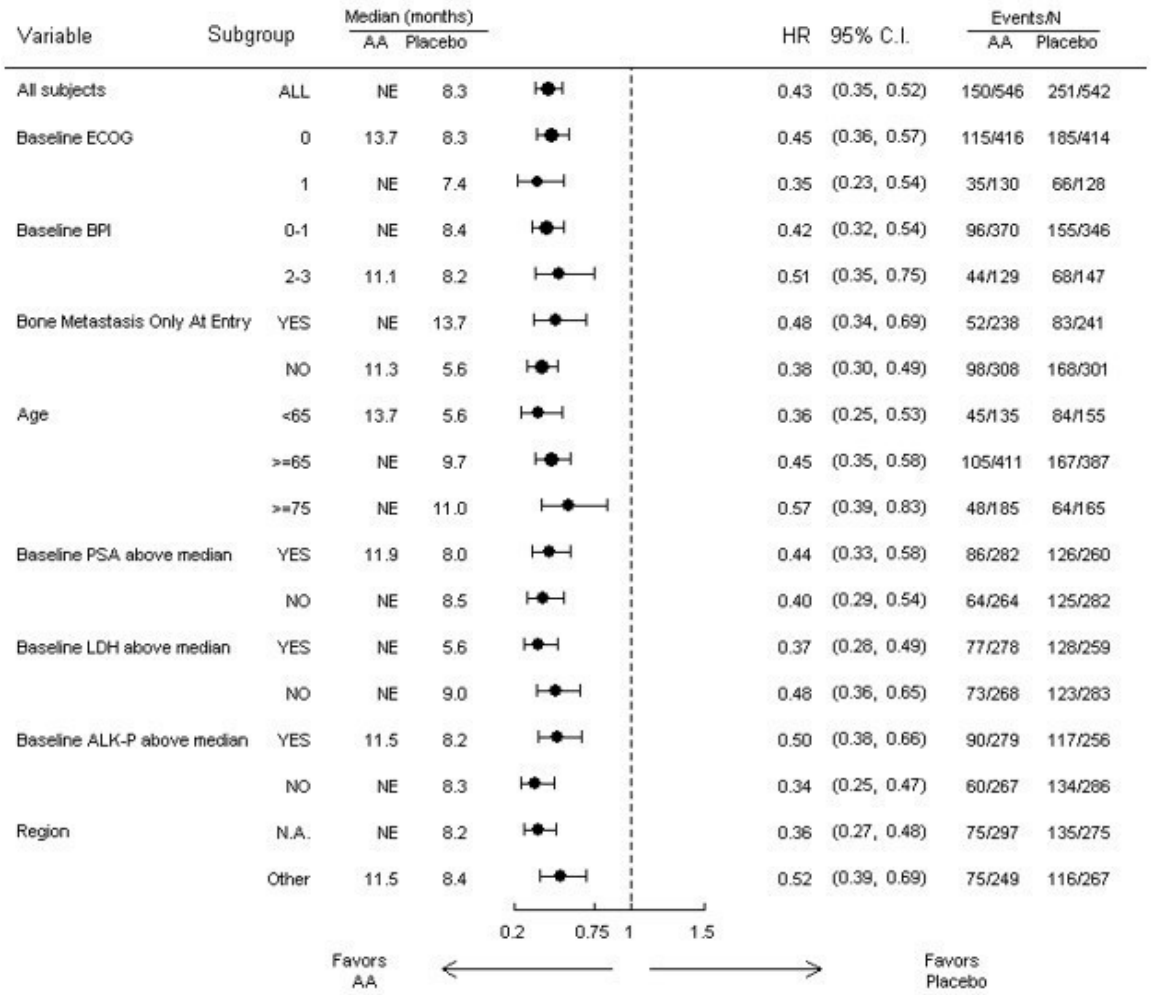


Figure 1: Kaplan Meier Curves of rPFS in Patients Treated with Either Abiraterone acetate or Placebo in Combination with Prednisone plus GnRH Agonists or Prior Orchiectomy



The HR within each subgroup was estimated using a nonstratified Cox proportional hazard model.

AA=abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactate dehydrogenase; N.A.=North America; NE=not estimable; PSA=prostate-specific antigen

Figure 2: rPFS by Subgroup (ITT Population)

A planned interim analysis for OS was conducted after 333 deaths were observed. At this time, the IDMC determined that equipoise no longer existed between the study arms and recommended the trial be unblinded based on the statistically and clinically significant improvements in rPFS, together with improvements in other clinically important secondary endpoints and a positive trend towards improved overall survival. As a result, patients in the placebo group were offered treatment with abiraterone acetate. Overall survival at the IA 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 the results did not meet the pre-specified value forstatistical significance of 0.0008 (Table 9). Overall 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). Sixty-five 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 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 9 and Figure 3). Sixty-seven percent of patients treated with abiraterone acetate and 80% of patients treated with placebo received subsequent therapies that had the potential to prolong OS for thispatient population. Subsequent therapies included abiraterone acetate, 69 (13%) and 238 (44%); docetaxel, 311 (57%) and 331 (61%); cabazitaxel, 100 (18%) and 105 (19%); and enzalutamide 87 (16%) and 54 (10%) for patients receiving abiraterone acetate or placebo, respectively. Survival analyses by subgroup are presented in Figure 4.

Table 9: Overall Survival of Asymptomatic or mildly symptomatic mCRPC Patients Treated with Either Abiraterone acetate or Placebo in Combination with Prednisone Plus GnRH Agonists or Prior Orchiectomy (ITT Population)

	Abiraterone acetate N=546	Placebo N=542
Interim Analysis		
Deaths	147 (27%)	186 (34%)
Median OS (months) (95% CI)	Not reached (NE, NE)	27.2 (25.95, NE)
Hazard ratio[a] (95% CI)	0.752 (0.606, 0.934)	
p-value[b]	0.0097	
Final Survival Analysis		
Deaths	354 (65%)	387 (71%)
Median OS (months) (95% CI)	34.7 (32.7, 36.8)	30.3 (28.7, 33.3)
Hazard ratio[a] (95% CI)	0.806 (0.697, 0.931)	
p-value[b]	0.0033	

NE=Not Estimated

a. Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone acetate

b. From a log-rank test of the equality of two survival curves over the time interval, and stratified by baseline ECOG score (0 or 1)

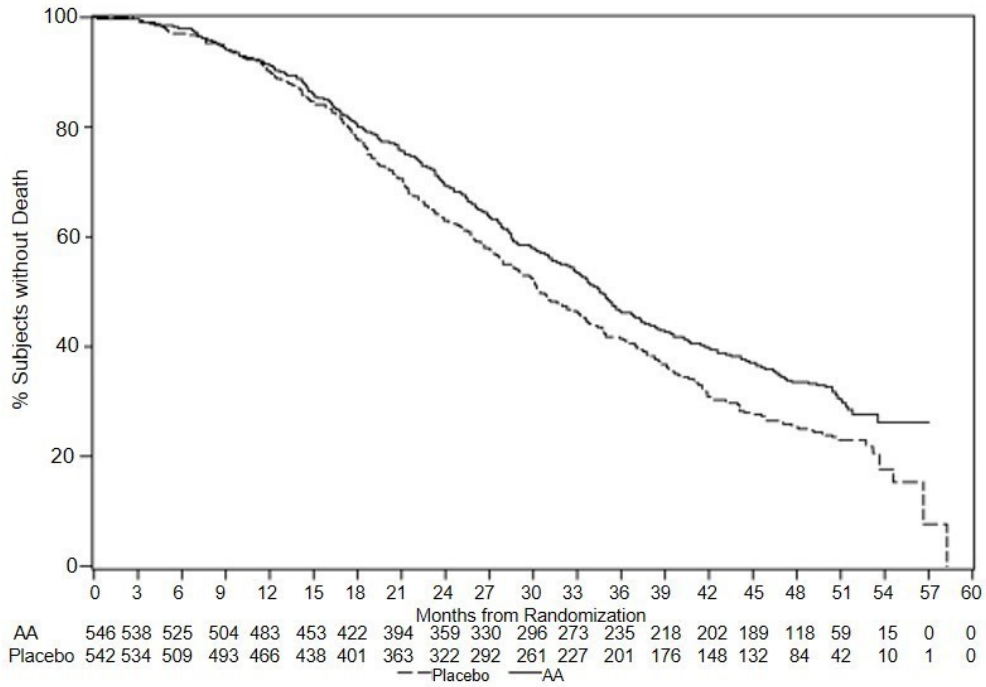
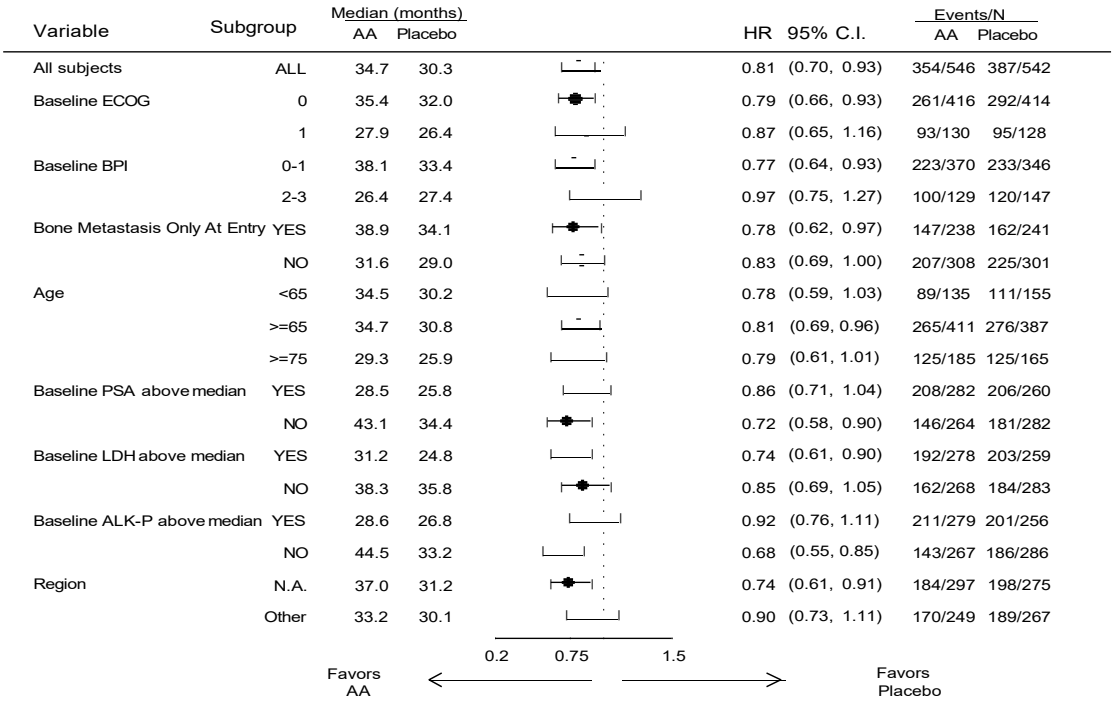


Figure 3: Kaplan Meier Survival Curves of Patients Treated with Either Abiraterone acetate or Placebo in Combination with Prednisone plus GnRH Agonists or Prior Orchiectomy (Final analysis; ITT Population)

Figure 4: Overall Survival by Subgroup (Final Analysis) (ITT Population)



AA= abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group performance score; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not evaluable

Figure 4: Overall Survival by Subgroup (Final Analysis) (ITT Population)

Subgroup analyses showed a consistent but significant rPFS effect and a consistent trend in overall survival effect favoring treatment with abiraterone acetate.

The observed improvements in the co-primary efficacy endpoints of OS and rPFS were supported by clinical benefit favoring Abiraterone acetate vs. placebo treatment in the following prospectively assessed secondary endpoints as follows:

Time to opiate use for cancer pain: The median time to opiate use for prostate cancer pain 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: 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).

PSA Based Endpoints: PSA-based endpoints are not validated surrogate endpoints of clinical benefit in this patient population. Nevertheless, patients receiving abiraterone acetate demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo: 62% versus 24%, p<0.0001. The median time to PSA progression (time interval from randomization to PSA progression, according to PSAWG criteria) was 11.1 months for patients treated with abiraterone acetate and 5.6 months for patients treated with placebo (HR=0.488; 95% CI: [0.420, 0.568], p<0.0001).

Placebo-controlled Phase 3 Study in mCRPC Patients with Prior Docetaxel Treatment (Study 301)

In this study, the efficacy of abiraterone acetate was established in patients with mCRPC who had received prior chemotherapy containing docetaxel. Patients continued to be treated with a GnRH agonist during study treatment or were previously treated with orchiectomy (N=1195).Patients were randomized 2:1 to receive either abiraterone acetate or placebo. In the active treatment arm, abiraterone acetate was administered orally at a dose of 1 g daily in combination with low dose prednisone 5 mg twice daily (N=797). Control patients received placebo and low dose prednisone 5 mg twice daily (N=398).

Patients were not included in the study if they had clinically significant heart disease, (as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe orunstable angina, or LVEF <50% or New York Heart Association Class III or IV heart failure), prior ketoconazole for the treatment of prostate cancer, a history of adrenal gland or pituitary disorders or prostate tumor showing extensive small cell (neuroendocrine) histology. Spironolactone was a restricted concomitant therapy due to its potential to stimulate diseaseprogression.

The primary efficacy endpoint was OS.

PSA serum concentration independently does not always predict clinical benefit. In this study it was also recommended that patients be maintained on their study drugs 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.

Table 10 summarizes key demographics and baseline disease characteristics. Demographics and baseline disease characteristics were balanced between the two groups.

Table 10: Key Demographics and Baseline Disease Characteristics (Phase 3 Study in mCRPC patients with prior Docetaxel treatment: ITT Population)

	Abiraterone acetate + Prednisone (N=797)	Placebo + Prednisone (N=398)	Total (N=1195)
Age (years)			
N	797	397	1194
Mean (SD)	69.1 (8.40)	68.9 (8.61)	69.0 (8.46)
Median	69.0	69.0	69.0
Range	(42, 95)	(39, 90)	(39, 95)

	Abiraterone acetate + Prednisone (N=797)	Placebo + Prednisone (N=398)	Total (N=1195)
Sex			
N	797	398	1195
Male	797 (100.0%)	398 (100.0%)	1195 (100.0%)
Race			
N	796	397	1193
White	743 (93.3%)	368 (92.7%)	1111 (93.1%)
Black	28 (3.5%)	15 (3.8%)	43 (3.6%)
Asian	11 (1.4%)	9 (2.3%)	20 (1.7%)
Other	14 (1.8%)	5 (1.3%)	19 (1.6%)
Time since initial diagnosis to first dose(days)			
N	791	394	1185
Mean (SD)	2610.9 (1630.21)	2510.1 (1712.36)	2577.4 (1657.93)
Median	2303.0	1928.0	2198.0
Range	(175, 9129)	(61, 8996)	(61, 9129)
Evidence of disease progression			
N	797	398	1195
PSA only	238 (29.9%)	125 (31.4%)	363 (30.4%)
Radiographic progression with or without PSA progression	559 (70.1%)	273 (68.6%)	832 (69.6%)
Extent of disease			
Bone	709 (89.2%)	357 (90.4%)	1066 (89.6%)
Soft tissue, not otherwise specified	0	0	0
Node	361 (45.4%)	164 (41.5%)	525 (44.1%)
Viscera, not otherwise specified	1 (0.1%)	0 (0.0%)	1 (0.1%)
Liver	90 (11.3%)	30 (7.6%)	120 (10.1%)
Lungs	103 (13.0%)	45 (11.4%)	148 (12.4%)
Prostate mass	60 (7.5%)	23 (5.8%)	83 (7.0%)
Other viscera	46 (5.8%)	21 (5.3%)	67 (5.6%)
Other tissue	40 (5.0%)	20 (5.1%)	60 (5.0%)
ECOG performance status			
N	797	398	1195
0 or 1	715 (89.7%)	353 (88.7%)	1068 (89.4%)
2	82 (10.3%)	45 (11.3%)	127 (10.6%)
Pain			
N	797	398	1195
Present	357 (44.8%)	179 (45.0%)	536 (44.9%)
Absent	440 (55.2%)	219 (55.0%)	659 (55.1%)
Baseline PSA (ng/mL)			
N	788	393	1181
Mean (SD)	439.18 (888.476)	400.58 (810.549)	426.33 (863.173)
Median	128.80	137.70	131.40
Range	(0.4, 9253.0)	(0.6, 10114.0)	(0.4, 10114.0)

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. As required in the protocol, 100% of patients had received docetaxel therapy prior to treatment with abiraterone acetate. All docetaxel containing regimens were considered as one line of therapy. Liver metastasis was present in 11% of patients treated with abiraterone acetate.

Study Results

A median of 8 cycles (32 weeks) were administered in the abiraterone acetate group compared with 4 cycles (16 weeks) in the placebo group. The proportion of patients who required dose reductions was low; 4% in the abiraterone acetate group and 1% in the placebo group had dosereductions and 17% and 16%, respectively, required dose interruptions.

In a planned interim 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 11 and Figure 5).

An updated survival analysis was conducted when 775 deaths (97% of the planned number of deaths for final analysis) were observed. Results from this analysis were consistent with thosefrom the interim analysis (Table 11).

Table 11: Overall Survival of Patients Treated with Either Abiraterone acetate or Placebo in Combination with Prednisone Plus GnRH Agonists or Prior Orchiectomy

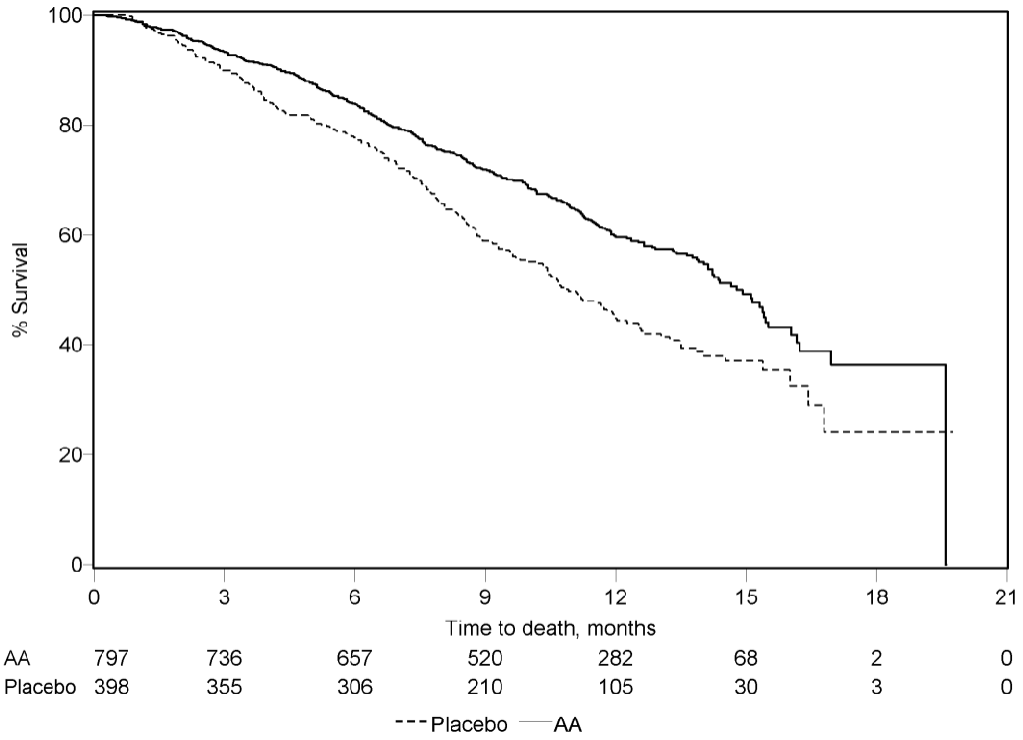
	Abiraterone acetate (N=797)	Placebo (N=398)
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p-value [a]	<0.0001	
Hazard ratio (95% CI) [b]	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)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

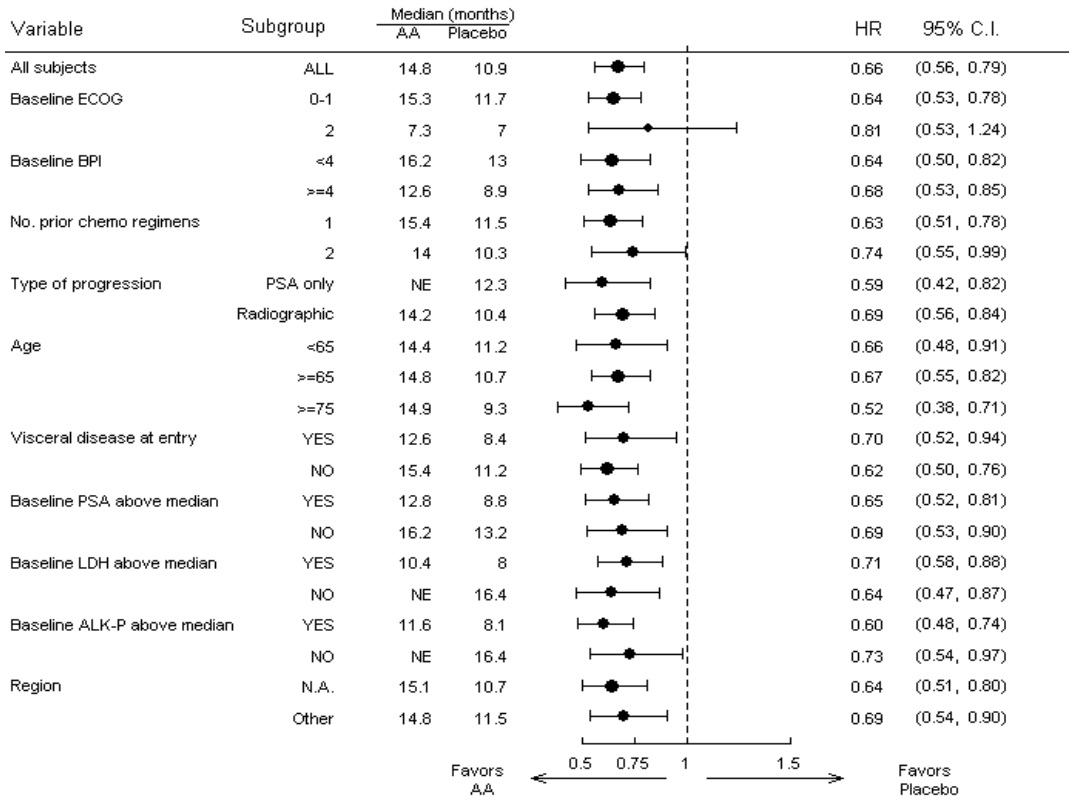
At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with abiraterone acetate remained alive, compared with the proportion of patients treatedwith placebo (see Figure 5).

Figure 5: Kaplan Meier Survival Curves of Patients Treated with either Abiraterone Acetate or Placebo in Combination with Prednisone plus GnRH Agonists or Prior Orchiectomy (planned interim analysis)



AA= abiraterone acetate

Survival analyses by subgroup are presented in Figure 6.



AA= abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group performance score; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not evaluable

Figure 6: Overall Survival by Subgroup

Subgroup analyses showed a consistent favorable survival effect for treatment with abiraterone acetate by presence of pain at baseline, 1 or 2 prior chemotherapy regimens, type of progression, baseline PSA score above median and presence of visceral disease at entry.

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. PSA- based endpoints are not validated surrogate endpoints of clinical benefit in this patient population. Nevertheless, 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% versus 10%, p<0.0001. The median time to PSA progression (time interval from randomization to PSA progression, according to PSAWG criteria) was 10.2 monthsfor 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 rPFS was the time from randomization to the occurrence of either tumor progression in soft tissue according to modified RECIST criteria (with CT or MRI, until an increase above baseline of at least 20% in the longest diameter of target lesions or the appearance of new lesions), or bybone scan (≥ 2 new lesions). A confirmatory bone scan was not mandatory. The median rPFS 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% versus 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 Brief Pain Inventory – Short Form (BPI-SF) worst pain intensity score over the last 24 hourswithout 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 painscore were analyzed (N=512) for pain palliation.

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 observedat two consecutive visits. The time to pain progression at the 25th percentile was 7.4 months inthe abiraterone acetate group, versus 4.7 months in the placebo group.

Skeletal-Related Events
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 vs. 4.9 months. A skeletal-related event was defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.

Indication 2:

Treatment of patients with newly diagnosed hormone-sensitive high-risk metastatic prostate cancer who may have received up to 3 months of prior ADT.

Placebo-controlled Phase 3 Study in Newly Diagnosed High-Risk Metastatic Prostate Cancer Patients (Study 3011 – LATITUDE)

The study enrolled patients who were diagnosed with metastatic prostate cancer within 3 months of randomization and had high-risk prognostic factors. Patients could have received up to 3 months of prior ADT treatment. 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 arm, abiraterone acetate was administered at a dose of 1 g daily in combination with low dose prednisone or prednisolone 5 mg once daily in addition to ADT (GnRH agonist or orchiectomy),which was the standard of care treatment. Patients in the control arm received ADT and placebos for both abiraterone acetate and prednisone. Patients with uncontrolled hypertension, significantheart disease, or NYHA Class II or worse heart failure were excluded.

Co-primary efficacy endpoints were OS and rPFS. 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).Secondary endpoints included 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 PSAprogression. Treatment continued until disease progression, withdrawal of consent, the occurrence of unacceptable toxicity, or death.

The key demographics and baseline characteristics are shown in Table 12 below.

Table 12: Key Demographics and Baseline Disease Characteristics (Phase 3 Study in Newly Diagnosed High-Risk Metastatic Prostate Cancer Patients: ITT Population)

	Abiraterone acetate + Prednisone + ADT (N=597)	Placebo + ADT (N=602)	Total (N=1199)
Age (years)			
N	597	602	1199
Mean (SD)	67.3 (8.48)	66.8 (8.72)	67.1 (8.60)
Median	68.0	67.0	67.0
Range	(38; 89)	(33; 92)	(33; 92)
Sex			
N	597	602	1199
Male	597 (100.0%)	602 (100.0%)	1199 (100.0%)
Race			
N	597	602	1199
White	409 (68.5%)	423 (70.3%)	832 (69.4%)
Black or African American	15 (2.5%)	10 (1.7%)	25 (2.1%)
Asian	125 (20.9%)	121 (20.1%)	246 (20.5%)
Other	43 (7.2%)	37 (6.1%)	80 (6.7%)
Time from initial diagnosis to first dose (months)			
N	597	602	1199
Mean (SD)	1.8 (0.73)	1.9 (0.75)	1.9 (0.74)
Median	1.8	2.0	1.8
Range	(0; 3)	(0; 4)	(0; 4)
Current Extent of Disease			
N	596	600	1196
Bone	580 (97.3%)	585 (97.5%)	1165 (97.4%)
Liver	32 (5.4%)	30 (5.0%)	62 (5.2%)
Lungs	73 (12.2%)	72 (12.0%)	145 (12.1%)
Node	283 (47.5%)	287 (47.8%)	570 (47.7%)
Prostate mass	151 (25.3%)	154 (25.7%)	305 (25.5%)
Viscera	18 (3.0%)	13 (2.2%)	31 (2.6%)
Soft tissue	9 (1.5%)	15 (2.5%)	24 (2.0%)
Other	2 (0.3%)	0	2 (0.2%)
Subjects with high risk at Screening (IWRS)	597 (100.0%)	601 (99.8%)	1198 (99.9%)
GS≥8 + ≥3 bone lesions	573 (96.0%)	569 (94.7%)	1142 (95.3%)
GS≥8 + Measurable visceral	82 (13.7%)	87 (14.5%)	169 (14.1%)
≥3 bone lesions + Measurable visceral	84 (14.1%)	85 (14.1%)	169 (14.1%)
GS≥8 + ≥3 bone lesions + Measurable visceral	71 (11.9%)	70 (11.6%)	141 (11.8%)
Baseline Pain score (BPI-SF Item3)			
N	570	579	1149
Mean (SD)	2.2 (2.45)	2.2 (2.40)	2.2 (2.42)
ECOG performance status at baseline			
N	597	602	1199
0	326 (54.6%)	331 (55.0%)	657 (54.8%)
1	245 (41.0%)	255 (42.4%)	500 (41.7%)
2	26 (4.4%)	16 (2.7%)	42 (3.5%)
Baseline PSA (ng/mL)			
N	595	600	1195
Mean (SD)	263.24 (791.440)	201.67 (647.807)	232.33 (723.252)

	Abiraterone acetate + Prednisone + ADT (N=597)	Placebo + ADT (N=602)	Total (N=1199)
Median	25.43	23.05	23.85
Range	(0.0; 8775.9)	(0.1; 8889.6)	(0.0; 8889.6)
Baseline Hemoglobin (g/L)			
N	597	602	1199
Mean (SD)	130.52 (16.959)	131.57 (17.430)	131.05 (17.198)
Median	132.00	133.00	132.00
Range	(90.0; 175.0)	(89.0; 174.0)	(89.0; 175.0)
Baseline Lactate Dehydrogenase (U/L)			
N	591	595	1186
Mean (SD)	199.3 (133.11)	193.6 (104.22)	196.4 (119.47)
Median	177.0	176.0	177.0
Range	(73; 2634)	(67; 1444)	(67; 2634)

Study Results

A median of 28 cycles (112 weeks) were administered in the Abiraterone acetate group compared with 15cycles (62 weeks) in the placebo group. The median total treatment duration was 26 months in the Abiraterone acetate group and 14 months in the placebo group.

At the planned rPFS analysis there were 593 events; 239 (40.0%) of patients treated with abiraterone acetate and 354 (58.8%) of patients treated with placebo had radiographic evidence of progression or had died. A statistically significant difference in rPFS between treatment groups was observed (see Table 13 and Figure 7). rPFS analyses by subgroup are presented in Figure 8.

Table 13: Radiographic Progression-Free Survival - Stratified Analysis; ITT Population (Study 3011)

	Abiraterone acetate + Prednisone N=597	Placebo N=602
Event	239 (40.0%)	354 (58.8%)
Median rPFS (95% CI)	33.02 (29.57, NE)	14.78 (14.69, 18.27)
Hazard ratio (95% CI)[a]	0.466 (0.394, 0.550)	
p value[b]	<0.0001	

NE=not estimable. The radiographic progression and death are considered in defining the rPFS event.

a. Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors abiraterone acetate

b. p value is from a log-rank test stratified by ECOG PS score (0/1 or 2) and visceral (absent or present).

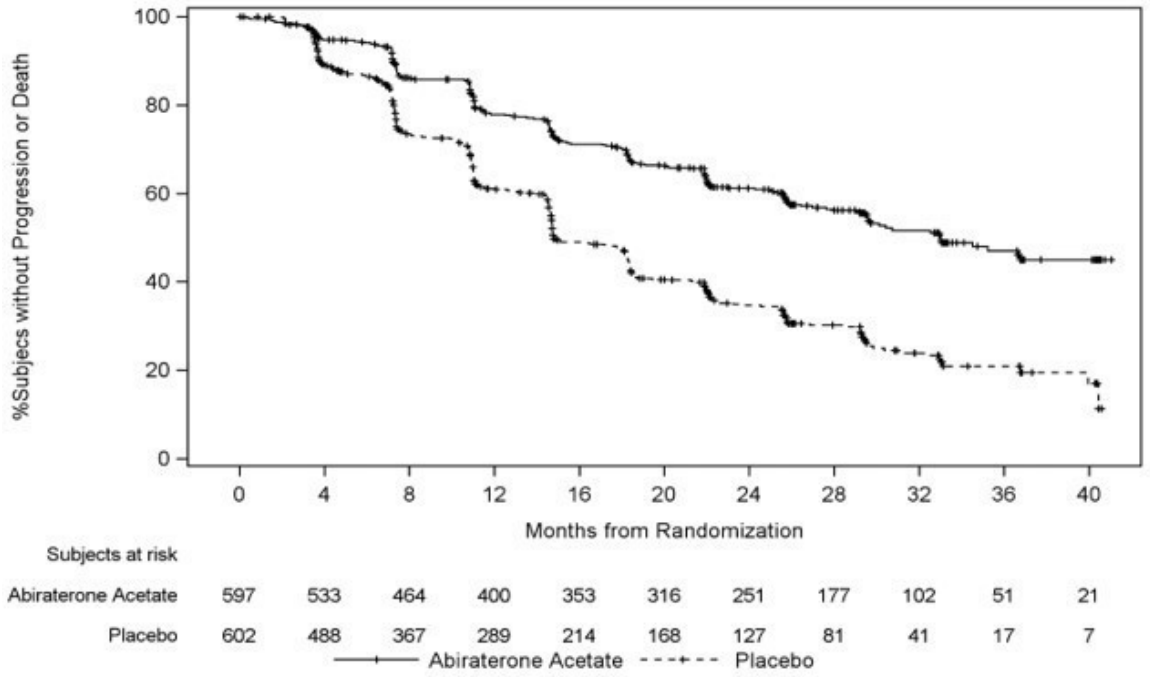
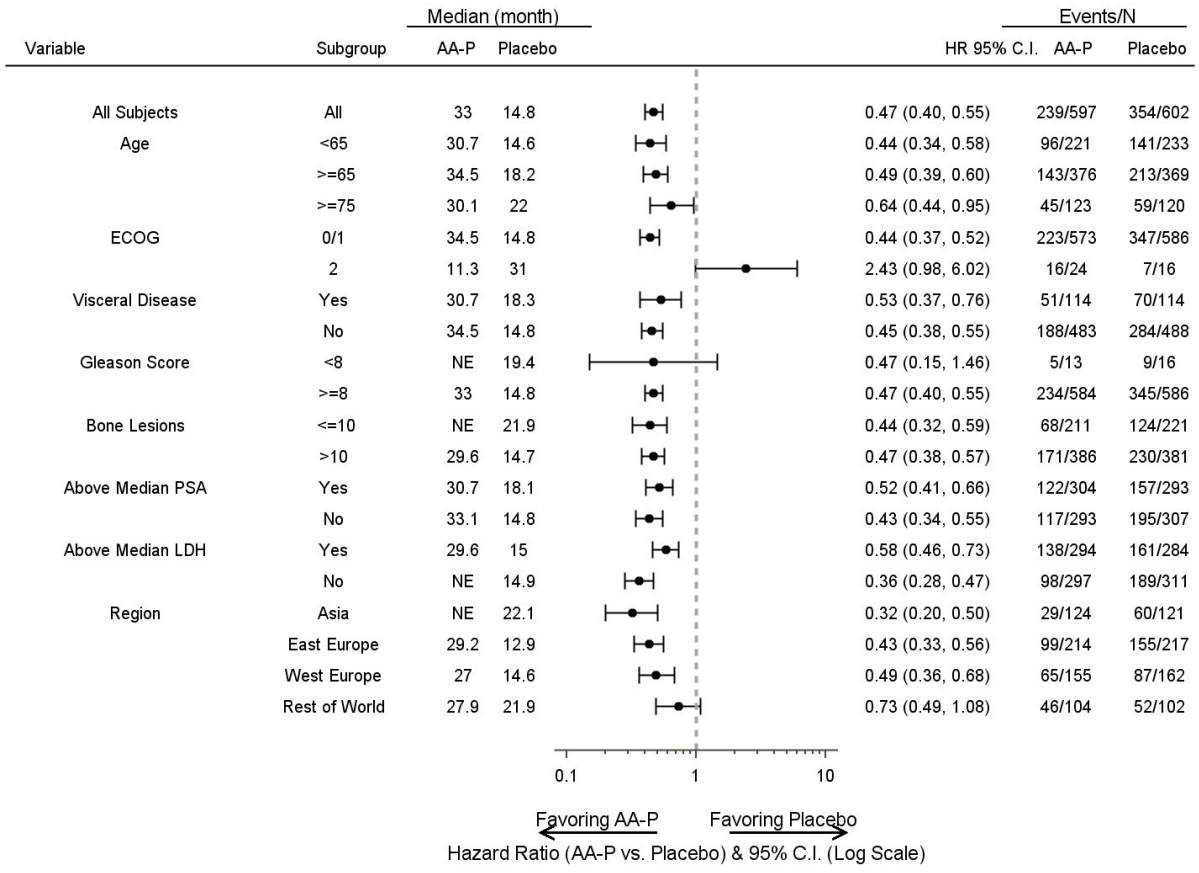


Figure 7: Kaplan-Meier Plot of rPFS; ITT Population (Study PCR3011)



AA-P = Abiraterone Acetate +Prednisone

Figure 8: rPFS by Subgroup; ITT population (Study PCR3011)

At the planned first interim analysis (IA-1) for overall survival, four hundred and six deaths had occurred. A statistically significant improvement in OS in favor of abiraterone acetate plus ADT was observed (Table 14). The study was unblinded based on the results of the interim OS analysisand patients in the placebo group were offered treatment with abiraterone acetate. Survival continued tobe followed after this IA.

As of the clinical cut-off for the final analysis, 618 deaths were reported: 275 (46%) in the Abiraterone acetate plus ADT group and 343 (57%) in the placebo group. The median follow-up time for allpatients was 51.8 months. Significant improvement in OS was demonstrated in the abiraterone acetate treated group compared with the placebo group, showing a consistent and robust treatment effect in favor of abiraterone acetate treatment (Table 14, Figure 9). OS analysis by subgroups is shown in Figure 10.

Table 14: Overall Survival, Stratified Analysis; ITT Population (Study PCR3011)

	Abiraterone acetate + Prednisone N=597	Placebo N=602
Interim Analysis		
Event	169 (28.3%)	237 (39.4%)
Median Survival (months) (95% CI)	NE (NE, NE)	34.73 (33.05, NE)
Hazard ratio (95% CI)[a]	0.621 (0.509, 0.756)	
p value[b]	<0.0001	
Final Analysis		
Event	275 (46.1%)	343 (57.0%)
Median Survival (months) (95% CI)	53.32 (48.23, NE)	36.53 (33.54, 39.95)
Hazard ratio (95% CI)[a]	0.661 (0.564, 0.775)	
p value[b]	<0.0001	
a.		

+=censored observation, NE=not estimable.

a. Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors abiraterone acetate.

b. p value is from log-rank test stratified by ECOG PS score (0/1 or 2) and visceral (absent or present).

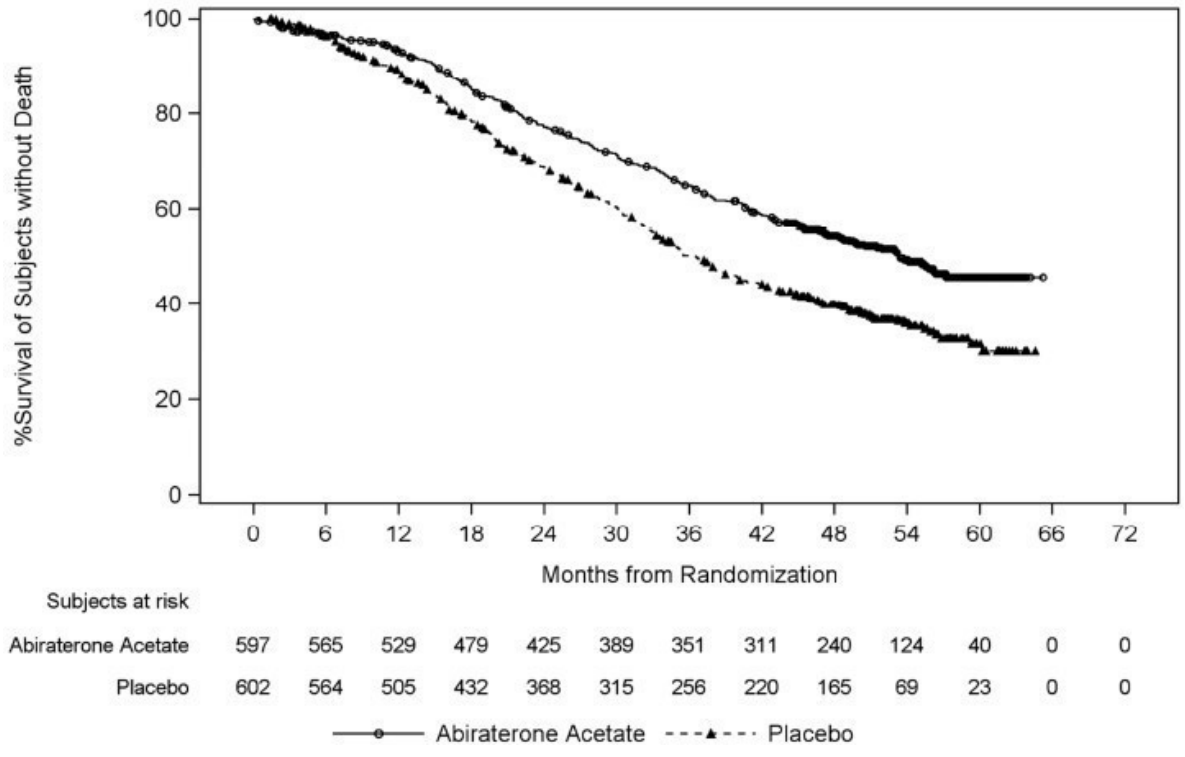
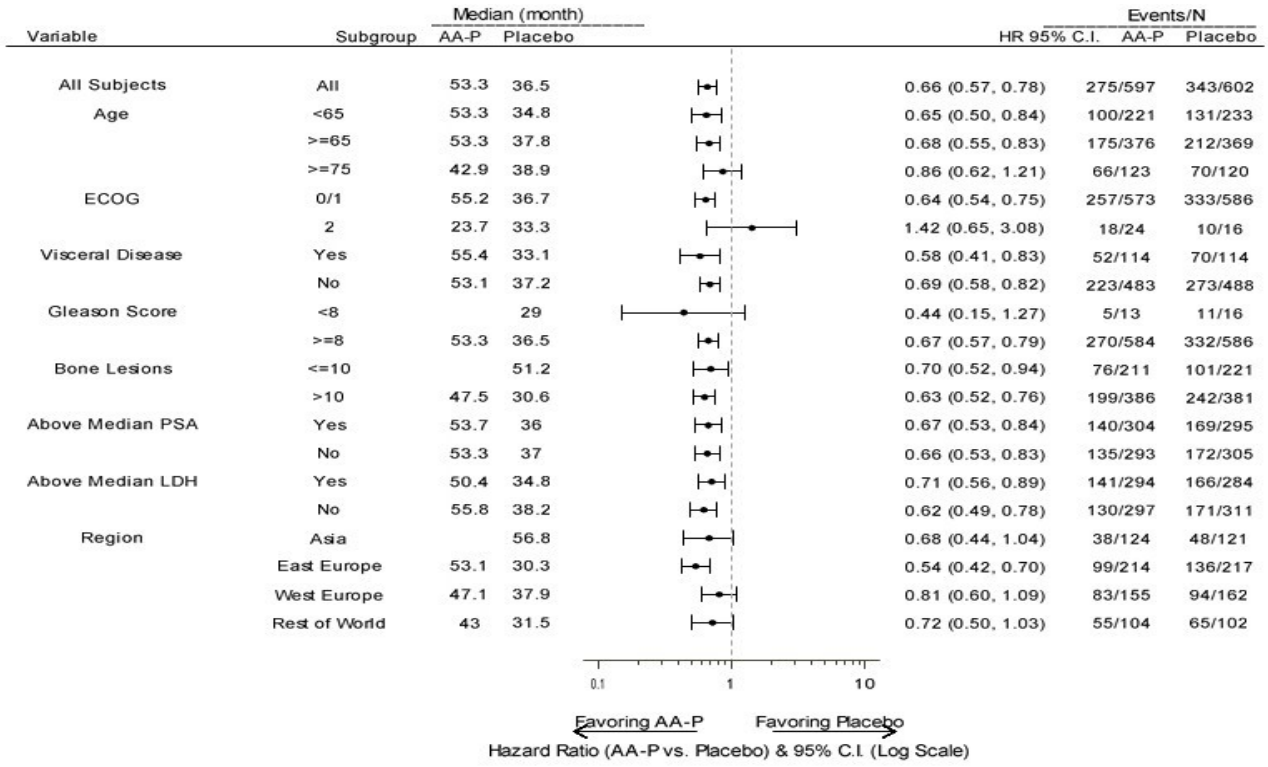


Figure 9: Kaplan-Meier Plot of Overall Survival; ITT Population (Study PCR3011)



AA-P = Abiraterone Acetate +Prednisone

Figure 10: Overall Survival by Subgroup; ITT population (Study PCR3011)

The Secondary endpoint measures at the time of the final analysis were as follows:

Time to skeletal-related event (SRE): Time to skeletal-related event was defined as the earliest of the following: clinical or pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. Skeletal-related events were reported for 22% of patientson abiraterone acetate and 25% on placebo. There was a 24% reduction in the risk of skeletal-related events (HR=0.759; 95% CI: [0.601, 0.960]; p<0.0208). The median time to SRE has not been reached for the abiraterone acetate or placebo study arm.

Time to PSA progression based on PCWG2 criteria: Time to PSA progression was defined as the time interval from the date of randomization to the date of PSA progression, according toProstate Cancer Working Group 2 (PCWG2) criteria. The median time to PSA progression based on PCWG2 criteria was 33.3 months for patients receiving abiraterone acetate and 7.4 months for patients receiving placebo (HR=0.310; 95% CI: [0.266, 0.363]; p<0.0001).

Time to subsequent therapy for prostate cancer: Forty-one percent of patients treated with abiraterone acetate and 59% of patients treated with placebo, received subsequent therapies that had thepotential to prolong OS for this patient population. The median time to subsequent therapy was 54.9 months in the abiraterone acetate plus ADT group and was 21.2 months in the placebo group (HR=0.448; 95% CI: 0.380, 0.528; p<0.0001). Subsequent therapies included docetaxel (24% and 35% of patients treated with

abiraterone acetate and placebo, respectively), enzalutamide (9% and 16%), cabazitaxel (4% and 8%), radium-223 dichloride (4% and 7%), and abiraterone acetate (3% and 14%).

Time to initiation of chemotherapy: Time to initiation of chemotherapy was defined as the time interval from the date of randomization to the date of initiation of chemotherapy for prostate cancer. The median time to initiation of chemotherapy was not reached for patients receiving abiraterone acetate and was 57.6 months for patients receiving placebo (HR=0.508; 95% CI: [0.412, 0.627]; p<0.0001).

Time to pain progression: Time to pain progression was defined as the time interval from randomization to the first date a subject experienced a ≥30% increase from baseline in the Brief Pain Inventory – Short Form (BPI-SF) worst pain intensity (Item 3) observed at 2 consecutive evaluations ≥4 weeks apart. Pain progression was reported in 41% of patients on abiraterone acetate and49% of patients on placebo. The median time to pain progression was 47.4 months for patients receiving abiraterone acetate and 16.6 months for patients receiving placebo (HR=0.721; 95% CI: [0.607,0.857], p<0.0002).

14.3 Comparative Bioavailability Studies

A double blind, balanced, randomised, two-treatment, two-period, two-sequence, single dose (1 x 500 mg), crossover, bioequivalence study comparing Abiraterone (JAMP Pharma Corporation) and PrZYTIGA® (Janssen Inc.) was conducted in 56 healthy adult male human subjects under fasting conditions.

Abiraterone (1 x 500 mg) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng*h/mL)	320.59 361.11 (46.7)	330.98 378.00 (54.1)	96.86	87.96 - 106.67
C_{max} (ng/mL)	52.68 61.59 (54.4)	61.90 75.08 (72.6)	85.10	75.75 - 95.61
AUC_I (ng*h/mL)	330.58 370.9 (46.1)	342.17 388.42 (53.0)	96.61	87.95 - 106.13
T_{max}§ (h)	1.67 (0.67 – 5.00)	1.67 (0.67 – 5.00)		
$T_{½}$€ (h)	14.56 (23.2)	15.74 (22.3)		

*Abiraterone (abiraterone acetate) tablet 500 mg (JAMP Pharma Corporation)
† PrZYTIGA® (abiraterone acetate) tablet 500 mg (Janssen Inc.) purchased in Canada
§ Expressed as the median (range)
€ Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In 13- and 26-week repeated dose studies in rats and 13- and 39-week repeated dose studies in monkeys, a reduction in circulating testosterone levels occurred withabiraterone at approximately one half the human clinical exposure based on AUC. As a result,morphological and/or histopathological changes were observed in the reproductive organs. These included aspermia/hypospermia, atrophy/weight reductions in the male genital tract organs and testes. In addition, adrenal gland hypertrophy, Leydig cell hyperplasia, pituitary gland hyperplasia and mammary gland hyperplasia were observed. The changes in the reproductive organs and androgen- sensitive organs are consistent with the pharmacology ofabiraterone. All treatment-related changes were partially or fully reversed after a four-week recovery period.

After chronic treatment from 13 weeks onward, hepatocellular hypertrophy was observed in rats only at exposure levels of abiraterone 0.72-fold the human clinical exposure based on AUC. Bile duct/oval cell hyperplasia, associated with increased serum alkaline phosphatase and/or total bilirubin levels, was seen in the liver of rats (at exposure levels of abiraterone 3.2-fold the human clinical exposure based on AUC) and monkeys (at exposure levels of abiraterone 1.2-fold the human clinical exposure based on AUC). After a four-week recovery period, serum parameters reversed, whereas bile duct/oval cell hyperplasia persisted.

A dose dependent increase in cataracts was observed after 26 weeks of treatment in rats atexposure levels of abiraterone 1.1 times the human clinical exposure based on AUC. Thesechanges were irreversible after a four-week recovery period. Cataracts were not observed inmonkeys after 13 or 39 weeks of treatment at exposure levels 2-fold greater than the clinical exposure based on AUC.

Carcinogenicity: 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. The clinical relevance of thisfinding is not known. Abiraterone acetate was not carcinogenic in female rats.

Genotoxicity: Abiraterone acetate and abiraterone were devoid of genotoxic potential in the standard panel of genotoxicity tests, including an *in vitro* bacterial reverse mutation assay (the Ames test), an *in vitro* mammalian chromosome aberration test (using human lymphocytes) andan *in vivo* rat micronucleus assay.

Reproductive and Developmental Toxicology: In fertility studies in rats, reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility were observed in males dosed for 4 weeks at ≥ 30 mg/kg/day. Mating of untreated females with males that received 30 mg/kg/day abiraterone acetate resulted in a reduced number of corpora lutea, implantations and live embryos and an increased incidence ofpre-implantation loss. Effects on male rats were reversible after 16 weeks from the last abiraterone acetate administration. Female rats dosed for 2 weeks until day 7 of pregnancy at ≥ 30 mg/kg/day had an increased incidence of irregular or extended estrous cycles and pre-implantation loss (300 mg/kg/day). There were no differences in mating, fertility, and litter parameters in female rats that received abiraterone acetate. Effects on

female rats were reversible after 4 weeks from the last abiraterone acetate administration. The dose of 30 mg/kg/day in rats is approximately 0.3 times the recommended dose of 1000 mg/day based on body surface area.

In developmental toxicity study in rats, although abiraterone acetate did not have teratogenic potential, abiraterone acetate caused developmental toxicity when administered at doses of 10,30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions and decreasednumber of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses (10, 30, or 100 mg/kg) tested in rats resulted in systemicexposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

Abiraterone is contraindicated in pregnancy (see 2 CONTRAINDICATIONS and 7.1 Special Populations).

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrZYTIGA® (abiraterone acetate tablets, uncoated 250 mg tablets and film-coated 500 mg tablets), Product Monograph, Submission Control # 254299, Janssen Inc. (November 15, 2021).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] Abiraterone

Abiraterone acetate tablets, USP

Read this carefully before you start taking **Abiraterone** and each time you get a refill. This leaflet isa summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Abiraterone**.

Serious Warnings and Precautions

- Abiraterone may cause **hypertension** (high blood pressure), **hypokalemia** (low blood potassium) and **peripheral edema** (swelling of the legs or hands caused by fluid retention). These will need to be treated before starting Abiraterone. Your healthcare professional will do tests to check these problems monthly.
- Tell your healthcare professional if you have a history of heart failure, heart attack, or other heart problems. This will help avoid side effects and ensure proper use of Abiraterone.
- If you have moderate to serious liver problems, you should not take Abiraterone.
- Abiraterone may cause **liver failure**, sometimes causing death.

What is Abiraterone used for?

Abiraterone, is used with another drug called prednisone to treat adults with prostate cancer that has spread to other parts of the body. These adults must have:

- Mild or no symptoms after treatment with androgen deprivation therapy (ADT) that does not work.
  or
- had cancer treatment with a drug called docetaxel after treatment of ADT that does not work.

Abiraterone, is also used with another drug called prednisone and androgen deprivation therapy (ADT) to treat adults with prostate cancer that has spread to other parts of the body. These adults must have:

- newly confirmed case of hormone-sensitive high-risk prostate cancer and may have been treated with ADT for up to 3 months.

How does Abiraterone work?

Abiraterone works to stop your body from making a type of hormone called androgens. Androgens promote cancer cell growth. Therefore, Abiraterone can help slow the growth of prostate cancer.

What are the ingredients in Abiraterone?

Medicinal ingredient: Abiraterone acetate

Nonmedicinal ingredients:
Abiraterone 250 mg film-coated tablets: Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone (K 30), sodium lauryl sulphate. Tablet film coating: iron oxide red, iron oxide yellow, polyvinyl alcohol-partially hydrolyzed, propylene glycol, talc, titanium dioxide.

Abiraterone 500 mg film-coated tablets: Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone (K 30), sodium lauryl sulphate. Tablet film coating: iron oxide red, ferrosoferric oxide, polyvinyl alcohol-partially hydrolyzed, propylene glycol, talc, titanium dioxide.

Abiraterone comes in the following dosage forms:

Film-coated tablets, 250 mg and 500 mg.

Do not use Abiraterone if:

- You are allergic to abiraterone acetate or any of the other ingredients of Abiraterone orthe container.
- You are pregnant or might be pregnant.
- You are breastfeeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Abiraterone. Talk about any health conditions or problems you may have,including if you:

- have or have had high blood pressure, low blood potassium and irregular heartbeats
- have diabetes
- have or have had heart failure, heart attack, artery blood clots or other heart problems
- have liver problems
- have or have had adrenal (hormonal) problems
- will have surgery or had surgery
- have or have had severe trauma or infections

Other warnings you should know about:

Abiraterone **must be taken on an empty stomach** since food can increase the blood level of Abiraterone and this may be harmful. Do not eat any solid or liquid food two hours before taking Abiraterone and at least one hour after taking Abiraterone.

Liver Problems: Abiraterone can cause liver failure which can lead to death. Talk to your healthcare professional if you have yellowing of the skin or eyes, dark urine, or serious nauseaor vomiting. These could be signs or symptoms of liver problems. You will have regular blood tests done before starting Abiraterone, every two weeks for the first three months while taking Abiraterone, and every month after. These blood tests will tell your healthcare professional how your liver is working.

Low blood sugar (hypoglycemia):
Abiraterone may affect your blood sugar levels if you have diabetes. Your blood sugar might drop if you take Abiraterone plus prednisone / prednisolone with drugs for diabetes, like pioglitazone or repaglinide. Your healthcare professional will check your blood sugar levels.

Muscle problems: Abiraterone might cause muscle problems including break down of damaged muscle (**rhabdomyolysis**). This can cause kidney failure.

See the "**Serious side effects and what to do about them**" table, below, for more information on these and other serious side effects.

Check-ups and testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will:

- Check your blood pressure
- Do blood tests and physical exams

Fertility and Sexual Health:

Male patients

- During your treatment with Abiraterone, use a condom along with another effective birth control method each time you have sex with a woman who is pregnant, may be pregnant or could get pregnant. Continue using condoms until 1 week after your last dose.
- If, during your treatment with Abiraterone, your sexual partner becomes pregnant or thinks she may be pregnant, tell your healthcare professional right away.

Male patients – fertility

- Treatment with Abiraterone may affect your ability to father a child. If you have questions about this, talk to your healthcare professional.

Females

- Abiraterone is not for use in women.
- Abiraterone may harm an unborn baby.
- Women who are pregnant or may be pregnant should not handle Abiraterone tablets without protective gloves.

Abiraterone should not be used in patients under 18 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Abiraterone:

- medicines typically used to treat epilepsy (seizures) such as phenytoin, carbamazepine, phenobarbital
- medicines to treat bacterial infections such as rifampicin, rifabutin
- an herbal treatment for depression called St. John's wort

- medicines used to treat diabetes, such as pioglitazone, repaglinide
- a medicine used to relieve coughs such as dextromethorphan.

How to take Abiraterone:

- Take exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- **Take on an empty stomach**. Do not eat any solid or liquid food two hours before taking Abiraterone and at least one hour after taking Abiraterone. Taking Abiraterone with food may harm you.
- Swallow tablets whole with water. Do not break the Abiraterone tablets.
- Take Abiraterone for as long as your healthcare professional prescribes it. Do not stop taking this medicine unless your healthcare professional tells you to.
- Your healthcare professional will monitor your health. They may interrupt, reduce or stop your dose. This may occur based on your current health if you take certain other medications or if you have certain side effects.
- Take the prednisone exactly as your doctor has told you.

Usual dose:

Recommended adult dose: 1000 mg per day. To make this dose, take two 500 mg tablets or four 250 mg tablets once per day.

You will also receive treatment with another medicine, prednisone. Your healthcare professional will tell you how much of this medicine you will take and how to take it.

Overdose:

If you think you, or a person you are caring for, have taken too much Abiraterone, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you miss a dose of Abiraterone or prednisone, skip the missed dose. Take your next dose at the usual time on the next day.

If you miss more than one dose of Abiraterone or prednisone, talk to your healthcare professional right away.

What are possible side effects from using Abiraterone?

These are not all the possible side effects you may have when taking Abiraterone. If you experience any side effects not listed here, tell your healthcare professional.

- Joint swelling or pain, muscle pain
- Hot flushes
- Cough
- Diarrhea

- Fatigue
- Constipation
- Vomiting
- Insomnia
- High blood pressure
- Stomach upset / Indigestion
- Flu-like symptoms
- Weight gain
- Frequent urination
- Blood in urine
- Bone fractures including ribs
- Rash and skin wounds
- Falls
- Bruising
- Headache
- Depression

Your healthcare professional will do blood tests, check your blood pressure and monitor your health during your treatment. These will tell your healthcare professional how Abiraterone is affecting your blood, blood sugar, adrenal system and liver.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness.		✓	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations.			✓
Hypokalemia (low level of potassium in the blood): muscle weakness, muscle twitches or a pounding heartbeat, cramping, constipation, fatigue, tingling or numbness.			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Peripheral edema (swelling of legs or hands caused by fluid retention): swollen hands, legs, ankles or feet			✓
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Burning or pain during urination, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine.		✓	
COMMON			
Angina (not enough oxygen to the heart muscle): discomfort in the shoulder, arm, back, throat, jaw or teeth; pain or pressure in the chest.		✓	
Arrhythmias, including QT prolongation and Torsades de Pointes (irregular heart beat disorders): feeling faint, lightheaded, chest pain, a racing heartbeat, a slow heartbeat, shortness of breath, sweating, weakness seizures, or a fluttering in your chest.		✓	
Heart failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise.			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Pneumonia (infection in the lungs): chest pain when you breathe or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, nausea, vomiting or diarrhea, shortness of breath.		✓	
Tachycardia (rapid heart rate)		✓	
UNCOMMON			
Adrenal effects: body aches, fatigue, low blood pressure, light-headedness, loss of body hair, skin discolouration, unexplained weight loss.		✓	
VERY RARE			
Hypoglycemia (low blood sugar): thirst, frequent urination, hunger, nausea and dizziness, fast heartbeat, tingling, trembling,nervousness, sweating, low energy.		✓	
UNKNOWN			
Allergic alveolitis (lung allergic reaction): shortness of breath, cough, fatigue, chills, sweating.		✓	
Dyspnea (shortness of breath)		✓	
Rhabdomyolysis (breakdown of damaged muscle): muscle weakness, muscle pain, muscle spasms, red-brown coloured urine.		✓	
Liver Failure (serious disturbance of liver function): yellowing of the skin or eyes, darkening of the urine, or severe nausea or vomiting, confusion, fatigue.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Severe allergic reactions includes, but are not limited to difficulty swallowing or breathing, swollen face or lips, tongue or throat, or an itchy rash called urticaria.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect- canada/adverse-reaction-reporting.html) for more information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage yourside effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15−30ºC. Keep out of reach and sight of children.

Do not use Abiraterone after the expiry date which is stated on the label. The expiry date refers to the last day of the month.

Do not throw away any drugs via wastewater or household waste. Ask your pharmacist how to throw away drugs you no longer use.

If you want more information about Abiraterone:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.jamppharma.com), or by calling 1-866-399-9091.

This leaflet was prepared by:

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Last revised: NOV 02, 2022