SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Abirapro Tablets 500 mg Fim-coated Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Abiraterone Tablets 500 mg.

Excipients with known effect: Each film-coated tablet contains 245mg of Lactose Monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Brownish pink oval shaped, film coated tablets debossed with "G" one side and "121" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abiraterone tablet is indicated in combination with prednisone for the treatment of patients with

- Metastatic castration-resistant prostate cancer (CRPC)
- Metastatic high-risk castration-sensitive prostate cancer (CSPC)

4.2 Posology and method of administration

Recommended Dose for Metastatic CRPC

The recommended dose of abiraterone tablet is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with prednisone 5 mg orally **twice** daily.

Recommended Dose for Metastatic High-risk CSPC

The recommended dose of abiraterone tablet is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with prednisone 5 mg administered orally **once** daily.

Important Administration Instructions

Patients receiving abiraterone should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Abiraterone tablets must be taken as a single dose once daily on an empty stomach. Do not eat food 2 hours before and 1 hour after taking abiraterone. The tablets must be swallowed whole with water. Do not crush or chew tablets.

Dose Modification Guidelines in Hepatic Impairment and Hepatotoxicity

Hepatic Impairment
In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of abiraterone to 250 mg once daily. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5 x upper limit of normal (ULN) or total bilirubin greater than 3 x ULN occur in patients with baseline moderate hepatic impairment, discontinue abiraterone and do not re-treat patients with abiraterone.

Do not use abiraterone in patients with baseline severe hepatic impairment (Child-Pugh Class C).

Hepatotoxicity
For patients who develop hepatotoxicity during treatment with abiraterone (ALT and/or AST greater than 5 x ULN or total bilirubin greater than 3 x ULN), interrupt treatment with abiraterone. Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5 x ULN and total bilirubin less than or equal to 1.5 x ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5 x ULN and total bilirubin less than or equal to 1.5 x ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with abiraterone.

Permanently discontinue abiraterone for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

<u>Dose Modification Guidelines for Strong CYP3A4 Inducers</u>
Avoid concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during abiraterone treatment.

If a strong CYP3A4 inducer must be co-administered, increase the abiraterone dosing frequency to twice a day only during the co-administration period (e.g., from 1,000 mg once daily to 1,000 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions due to Mineralocorticoid Excess

Abiraterone may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition.

Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with abiraterone.

In the combined data from 4 placebo-controlled trials using prednisone 5 mg twice daily in combination with 1,000 mg abiraterone acetate daily, grades 3-4 hypokalemia were detected in 4% of patients on the abiraterone arm and 2% of patients on the placebo arm. Grades 3-4 hypertension were observed in 2% of patients each arm and grades 3-4 fluid retention in 1% of patients each arm.

In LATITUDE (a randomized placebo-controlled, multicenter clinical trial), which used prednisone 5 mg daily in combination with 1,000 mg abiraterone acetate daily, grades 3-4 hypokalemia were detected in 10% of patients on the abiraterone arm and 1% of patients on the placebo arm, grades 3-4 hypertension were observed in 20% of patients on the abiraterone arm and 10% of patients on the placebo arm. Grades 3-4 fluid retention occurred in 1% of patients each arm.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. In postmarketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking abiraterone.

The safety of abiraterone in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in COU-AA-301) or NYHA Class II to IV heart failure (in COU-AA-302 and LATITUDE) has not been established because these patients were excluded from these randomized clinical trials.

<u>Adrenocortical Insufficiency</u>

Adrenal insufficiency occurred in 0.3% of 2230 patients taking abiraterone and in 0.1% of 1763 patients taking placebo in the combined data of the 5 randomized, placebo-controlled clinical studies. Adrenocortical insufficiency was reported in patients receiving abiraterone in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress.

Monitor patients for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency.

Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity

In postmarketing experience, there have been abiraterone-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths.

In the combined data of 5 randomized clinical trials, grade 3-4 ALT or AST increases (at least 5 x ULN) were reported in 6% of 2230 patients who received abiraterone, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to ALT and AST increases or abnormal hepatic function occurred in 1.1% of 2230 patients taking abiraterone. In these clinical trials, no deaths clearly related to abiraterone were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with abiraterone, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced abiraterone dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of

treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt abiraterone treatment and closely monitor liverfunction.

Re-treatment with abiraterone at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5 x ULN and total bilirubin less than or equal to 1.5 x ULN.

Permanently discontinue abiraterone for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

The safety of abiraterone re-treatment of patients who develop AST or ALT greater than orequal to 20 x ULN and/or bilirubin greater than or equal to 10 x ULN is unknown.

Increased Fractures and Mortality in Combination with Radium Ra 223 Dichloride Abiraterone plus prednisone/prednisolone is not recommended for use in combination with radium Ra 223 dichloride outside of clinical trials.

The clinical efficacy and safety of concurrent initiation of abiraterone plus prednisone/prednisolone and radium Ra 223 dichloride was assessed in a randomized, placebo-controlled multicenter study (ERA-223 trial) in 806 patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer with bone metastases. The study was unblinded early based on an Independent Data Monitoring Committeerecommendation.

At the primary analysis, increased incidences of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received abiraterone plus prednisone/prednisolone in combination with radium Ra 223 dichloride compared to patients who received placebo in combination with abiraterone plus prednisone/prednisolone.

Embryo-Fetal Toxicity
The safety and efficacy of abiraterone have not been established in females. Based on animal reproductive studies and mechanism of action, abiraterone can cause fetal harm and loss of pregnancy when administered to a pregnant female. In animal reproduction studies, oral administration of abiraterone acetate to pregnant rats during organogenesis caused adverse developmental effects at maternal exposures approximately ≥ 0.03 times the human exposure (AUC) at the recommended dose. Advise males with female partners of reproductive

potential to use effective contraception during treatment with abiraterone and for 3 weeks after the last dose of abiraterone. Abiraterone should not be handled by females who are or may become pregnant.

Hypoglycemia

Severe hypoglycemia has been reported when abiraterone was administered to patients with preexisting diabetes receiving medications containing thiazolidinediones (including pioglitazone) or repaglinide. Monitor blood glucose in patients with diabetes during and after discontinuation of treatment with abiraterone. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Pediatric Use

Safety and effectiveness of abiraterone in pediatric patients have not been established.

Geriatric Use

Of the total number of patients receiving abiraterone in randomized clinical trials, 70% of patients were 65 years and over and 27% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Hepatic Impairment

The pharmacokinetics of abiraterone were examined in subjects with baseline mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of abiraterone increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (N=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold and the fraction of free drug increased 2-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of abiraterone to 250 mg once daily. Do not use abiraterone in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5 x ULN or total bilirubin >3 x ULN occur in patients with baseline moderate hepatic impairment, discontinue abiraterone treatment.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required.

Patients with Renal Impairment
No dosage adjustment is necessary for patients with renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs that Inhibit or Induce CYP3A4 Enzymes
Based on *in vitro* data, abiraterone is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during abiraterone treatment. If a strong CYP3A4 inducer must be co- administered, increase the abiraterone dosing frequency.

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Effects of Abiraterone on Drug Metabolizing Enzymes
Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2D6 substrate drug.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone.

4.6 Fertility, pregnancy and lactation Pregnancy

Risk Summary
The safety and efficacy of abiraterone have not been established in females. Based on findings from animal studies and the mechanism of action, abiraterone can cause fetal harm and potential loss of pregnancy.

There are no human data on the use of abiraterone in pregnant women. In animal reproduction studies, oral administration of abiraterone acetate to pregnant rats during organogenesis caused adverse developmental effects at maternal exposures approximately
≥ 0.03 times the human exposure (AUC) at the recommended dose.

Data

Animal Data
In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral 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 decreased number 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 tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

Lactation
Risk Summary
The safety and efficacy of abiraterone have not been established in females. There is no information available on the presence of abiraterone in human milk, or on the effects on the breastfed child or milk production.

Females and Males of Reproductive Potential
Contraception

Males
Based on findings in animal reproduction studies and its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 weeks after the final dose of abiraterone.

Infertility
Based on animal studies, abiraterone may impair reproductive function and fertility in males of reproductive potential.

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

4.8 Undesirable effects
The following are discussed in more detail in other sections of the labeling:

- Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions due to Mineralocorticoid Excess.
- Adrenocortical Insufficiency.
- Hepatotoxicity.
- Increased Fractures and Mortality in Combination with Radium Ra 223 Dichloride.

Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized placebo-controlled, multicenter clinical trials (COU-AA-301 and COU- AA-302) enrolled patients who had metastatic CRPC in which abiraterone was administered orally at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to patients on the control arm. A third randomized placebo-controlled, multicenter clinical trial (LATITUDE) enrolled patients who had metastatic high-risk CSPC in which abiraterone was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg once daily. Placebos were administered to patients in the control arm. Additionally, two other randomized, placebo-controlled trials were conducted in patients with metastatic CRPC. The safety data pooled from 2230 patients in the 5 randomized controlled trials constitute the basis for the data presented in the Special warnings and precautions for use, Grade 1-4 adverse reactions, and Grade 1-4 laboratory abnormalities. In all trials, a gonadotropin releasing hormone (GnRH) analog or prior orchiectomy was required in both arms.

In the pooled data, median treatment duration was 11 months (0.1, 43) for abiraterone- treated patients and 7.2 months (0.1, 43) for placebo-treated patients. The most common adverse reactions (≥10%) that occurred more commonly (>2%) in the abiraterone arm were fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough, and headache. The most common laboratory abnormalities (>20%) that occurred more commonly (≥2%) in the abiraterone arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, and hypokalemia. Grades 3-4 adverse events were reported for 53% of patients in the abiraterone arm and 46% of patients in the placebo arm.

Treatment discontinuation was reported in 14% of patients in the abiraterone arm and 13% of patients in the placebo arm. The common adverse events (≥1%) resulting in discontinuation of abiraterone and prednisone were hepatotoxicity and cardiac disorders.

Deaths associated with treatment-emergent adverse events were reported for 7.5% of patients in the abiraterone arm and 6.6% of patients in the placebo arm. Of the patients in the abiraterone arm, the most common cause of death was disease progression (3.3%). Other reported causes of death in ≥5 patients included pneumonia, cardio-respiratory arrest, death (no additional information), and general physical health deterioration.

COU-AA-301: Metastatic CRPC Following Chemotherapy

COU-AA-301 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥2.5 x ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT >5 x ULN.

Table 1 shows adverse reactions on the abiraterone arm in COU-AA-301 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with abiraterone with prednisone was 8 months.

Table 1: Adverse Reactions due to abiraterone in COU-AA-301

System/Organ Class Adverse reaction	**Abiraterone with Prednisone (N=791)**		**Placebo with Prednisone (N=394)**	
	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[2]	30	4.2	23	4.1
Muscle discomfort[3]	26	3.0	23	2.3
General disorders				
Edema[4]	27	1.9	18	0.8
Vascular disorders				
Hot flush	19	0.3	17	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	18	0.6	14	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	12	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3

Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0
Cardiac failure[8]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0.
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness.
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness.

[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema.
[5] Includes all fractures with the exception of pathological fracture.
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia.
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the abiraterone arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased.

Table 2 shows laboratory abnormalities of interest from COU-AA-301.

Table 2: Laboratory Abnormalities of Interest in COU-AA-301

Laboratory Abnormality	**Abiraterone with Prednisone (N=791)**		**Placebo with Prednisone (N=394)**	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hypertriglyceridemia	63	0.4	53	0
High AST	31	2.1	36	1.5
Hypokalemia	28	5.3	20	1.0
Hypophosphatemia	24	7.2	16	5.8
High ALT	11	1.4	10	0.8
High Total Bilirubin	6.6	0.1	4.6	0

COU-AA-302: Metastatic CRPC Prior to Chemotherapy
COU-AA-302 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5 x ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the abiraterone arm in COU-AA-302 that occurred in
≥5% of patients with a ≥2% absolute increase in frequency compared to

placebo. The median duration of treatment with abiraterone with prednisone was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the Abiraterone Arm in COU-AA-302

System/Organ Class Adverse reaction	**Abiraterone with Prednisone (N=542)**		**Placebo with Prednisone (N=540)**	
	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
General disorders				
Fatigue	39	2.2	34	1.7
Edema[2]	25	0.4	21	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[3]	30	2.0	25	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23	0.4	19	0.6
Diarrhea	22	0.9	18	0.9
Dyspepsia	11	0.0	5.0	0.2
Vascular disorders				
Hot flush	22	0.2	18	0.0
Hypertension	22	3.9	13	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17	0.0	14	0.2
Psychiatric disorders				
Insomnia	14	0.2	11	0.0
Injury, poisoning and procedural complications				
Contusion	13	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	13	0.0	8.0	0.0
Nasopharyngitis	11	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

[1] Adverse events graded according to CTCAE version 3.0.
[2] Includes terms Edema peripheral, Pitting edema, and Generalized edema.
[3] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness.

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the abiraterone arm compared to placebo in COU-AA-302.

Table 4: Laboratory Abnormalities in >15% of Patients in the Abiraterone Arm ofCOU-AA-302

Laboratory	**Abiraterone with Prednisone (N=542)**	**Placebo with Prednisone (N=540)**

Abnormality	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hematology				
Lymphopenia	38	8.7	32	7.4
Chemistry				
Hyperglycemia[1]	57	6.5	51	5.2
High ALT	42	6.1	29	0.7
High AST	37	3.1	29	1.1
Hypernatremia	33	0.4	25	0.2
Hypokalemia	17	2.8	10	1.7

[1] Based on non-fasting blood draws

LATITUDE: Patients with Metastatic High-risk CSPC

LATITUDE enrolled 1199 patients with newly-diagnosed metastatic, high-risk CSPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT
≥2.5 x ULN or if they had liver metastases. All the patients received GnRH analogs or had prior bilateral orchiectomy during the trial. The median duration of treatment with abiraterone and prednisone was 24 months.

Table 5 shows adverse reactions on the abiraterone arm that occurred in ≥5% of patients with a ≥2% absolute increase in frequency compared to those on the placebos arm.

Table 5: Adverse Reactions in ≥5% of Patients on the Abiraterone Arm in LATITUDE[1]

System/Organ Class Adverse reaction	**Abiraterone with Prednisone (N=597)**		**Placebo (N=602)**	
	All Grades[2] %	Grade 3-4 %	All Grades %	Grade 3-4 %
Vascular disorders				
Hypertension	37	20	13	10

Hot flush	15	0.0	13	0.2
Metabolism and nutrition disorders				
Hypokalemia	20	10	3.7	1.3
Investigations				
Alanine aminotransferase increased[3]	16	5.5	13	1.3
Aspartate aminotransferase increased[3]	15	4.4	11	1.5
Infections and infestations				
Urinary tract infection	7.0	1.0	3.7	0.8
Upper respiratory tract infection	6.7	0.2	4.7	0.2
Nervous system disorders				
Headache	7.5	0.3	5.0	0.2
Respiratory, Thoracic and Mediastinal Disorders				
Cough[4]	6.5	0.0	3.2	0

[1] All patients were receiving an GnRH agonist or had undergone orchiectomy.
[2] Adverse events graded according to CTCAE version 4.0.
[3] Reported as an adverse event or reaction.
[4] Including cough, productive cough, upper airway cough syndrome.

Table 6 shows laboratory abnormalities that occurred in >15% of patients, and more frequently (>5%) in the abiraterone arm compared to placebos.

Table 6: Laboratory Abnormalities in >15% of Patients in the Abiraterone Arm of LATITUDE

Laboratory Abnormality	**Abiraterone with Prednisone (N=597)**		**Placebo (N=602)**	
	All Grades 1-4 (%)	Grade 3-4 (%)	All Grades 1-4 (%)	Grade 3-4 (%)
Hematology Lymphopenia	20	4.1	14	1.8
Chemistry Hypokalemia Elevated ALT Elevated total bilirubin	 30 46 16	 9.6 6.4 0.2	 6.7 45 6.2	 1.3 1.3 0.2

Cardiovascular Adverse Reactions

In the combined data of 5 randomized, placebo-controlled clinical studies, cardiac failure occurred more commonly in patients on the abiraterone arm compared to patients on the placebo arm (2.6% versus 0.9%). Grade 3-4 cardiac failure occurred in 1.3% of patients taking abiraterone and led to 5 treatment discontinuations and 4 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and two deaths due to cardiac failure in the placebo

group.

In the same combined data, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and three patients with sudden death in the abiraterone arms and five deaths in the placebo arms. There were 7 (0.3%) deaths due to cardiorespiratory arrest in the abiraterone arms and 2 (0.1%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo armsand 3 deaths in the abiraterone arms.

Postmarketing Experience

The following additional adverse reactions have been identified during post approval use ofabiraterone with prednisone. Because these reactions are reported voluntarily from a

population of uncertain size, it is not always possible to reliably estimate their frequency orestablish a causal relationship to drug exposure.

Respiratory, Thoracic and Mediastinal Disorders: non-infectious

pneumonitis. *Musculoskeletal and Connective Tissue Disorders:*

myopathy, including rhabdomyolysis. *Hepatobiliary Disorders:* fulminant

hepatitis, including acute hepatic failure and death.

Cardiac Disorders: QT prolongation and Torsades de Pointes (observed in patients who developed hypokalemia or had underlying cardiovascular conditions).

Immune System Disorders – Hypersensitivity: 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)).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Human experience of overdose with abiraterone is limited.

There is no specific antidote. In the event of an overdose, stop abiraterone, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents
ATC code: L02BX03

Mechanism of action

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals.

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 decreased serum testosterone and other androgens in patients in the placebo- controlled clinical trial. It is not necessary to monitor the effect of abiraterone 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.

Pharmacodynamics

Cardiac Electrophysiology

In a multi-center, open-label, single-arm trial, 33 patients with metastatic CRPC received abiraterone orally at a dose of 1,000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily. Assessments up to Cycle 2 Day 2 showed no large changes in the QTc interval (i.e., >20 ms) from baseline. However, small increases in the QTc interval (i.e., <10 ms) due to abiraterone acetate cannot be excluded due to study design limitations.

Clinical Studies

The efficacy and safety of abiraterone with prednisone was established in three randomized placebo-controlled international clinical studies. All patients in these studies received a GnRH analog or had prior bilateral orchiectomy. Patients with prior ketoconazole treatment for prostate

cancer and a history of adrenal gland or pituitary disorders were excluded from these trials. Concurrent use of spironolactone was not allowed during the study period.

COU-AA-301: Patients with metastatic CRPC who had received prior docetaxel chemotherapy

In COU-AA-301 (NCT00638690), a total of 1195 patients were randomized 2:1 to receive either abiraterone orally at a dose of 1,000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo once daily plus prednisone 5 mg orally twice daily (N=398). Patients randomized to either arm were to continue treatment until disease progression (defined as a 25% increase in PSA over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 39-95) and the racial distribution was 93% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine percent of patients enrolled had an ECOG performance status score of 0-1 and 45% had a Brief Pain Inventory-Short Form score of ≥4 (patient's reported worst pain over the previous 24 hours). Ninety percent of patients had metastases in bone and 30% had visceral involvement. Seventy percent of patients had radiographic evidence of disease progression and 30% had PSA-only progression. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens.

The protocol pre-specified interim analysis was conducted after 552 deaths and showed a statistically significant improvement in overall survival (OS) in patients treated with abiraterone with prednisone compared to patients in the placebo with prednisone arm (Table 7 and Figure 1). 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 those from the interim analysis (Table 7).

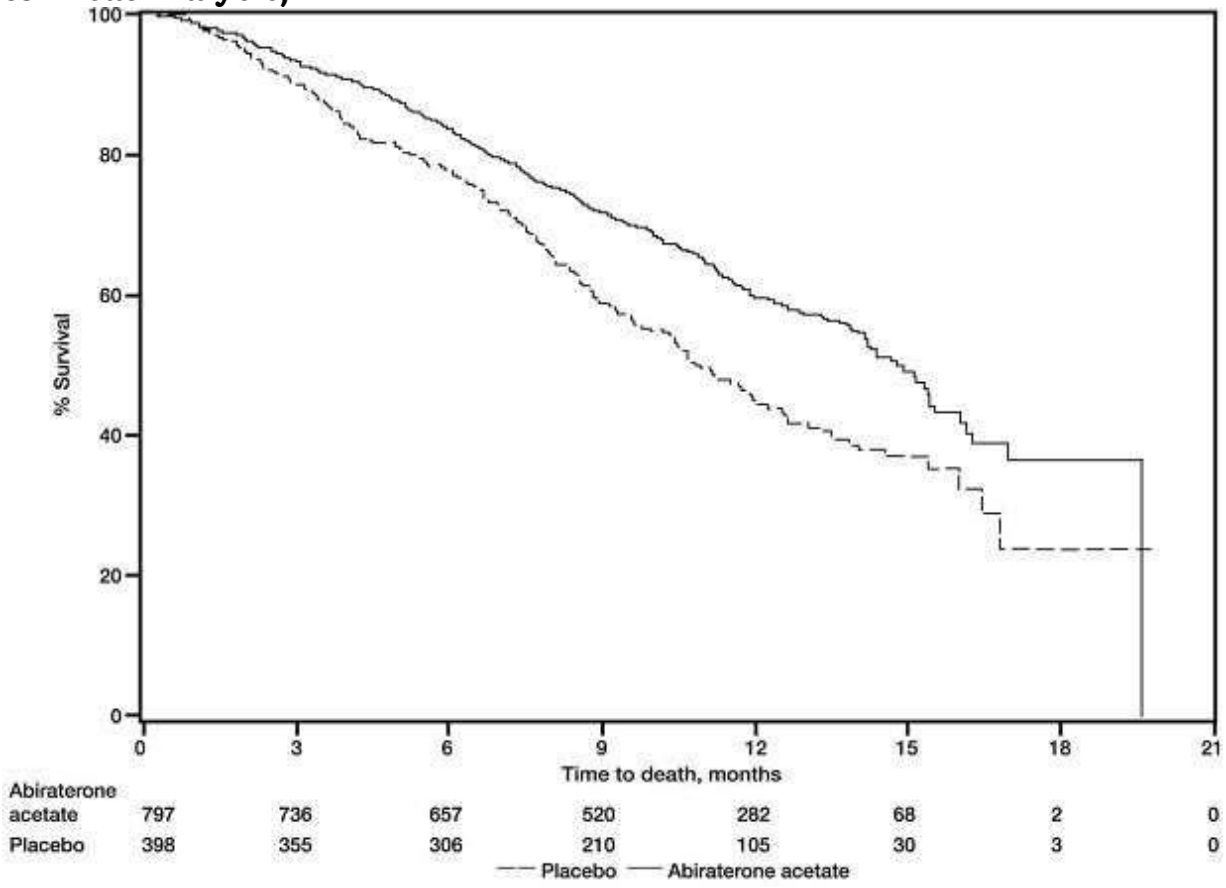
Table 7: Overall Survival of Patients Treated with Either Abiraterone or Placebo in Combination with Prednisone in COU-AA-301 (Intent-to-Treat Analysis)

	Abiraterone with Prednisone (N=797)	**Placebo with Prednisone (N=398)**
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months)	14.8	10.9
(95% CI)	(14.1, 15.4)	(10.2, 12.0)
p-value[1]	<0.0001	

Hazard ratio (95% CI)[2]	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)[2]	0.740 (0.638, 0.859)	

[1] 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).
[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone with prednisone.

Figure 1: Kaplan-Meier Overall Survival Curves in COU-AA-301 (Intent-to-Treat Analysis)



COU-AA-302: Patients with metastatic CRPC who had not received prior cytotoxic chemotherapy

In COU-AA-302 (NCT00887198), 1088 patients were randomized 1:1 to receive either abiraterone orally at a dose of 1,000 mg once daily (N=546) or Placebo orally once daily (N=542). Both arms were given concomitant prednisone 5 mg twice daily. Patients continued treatment until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to 3 or more) disease progression, unacceptable toxicity or withdrawal. Patients with moderate or severe pain, opiate use for cancer pain, or visceral organ metastases were excluded.

Patient demographics were balanced between the treatment arms. The median age was 70 years. The racial distribution of patients treated with abiraterone was 95% Caucasian, 2.8% Black, 0.7% Asian and 1.1% Other. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

Radiographic progression-free survival was assessed with the use of sequential imaging studies and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Working Group 2 criteria) and/or modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria for progression of soft tissue lesions. Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

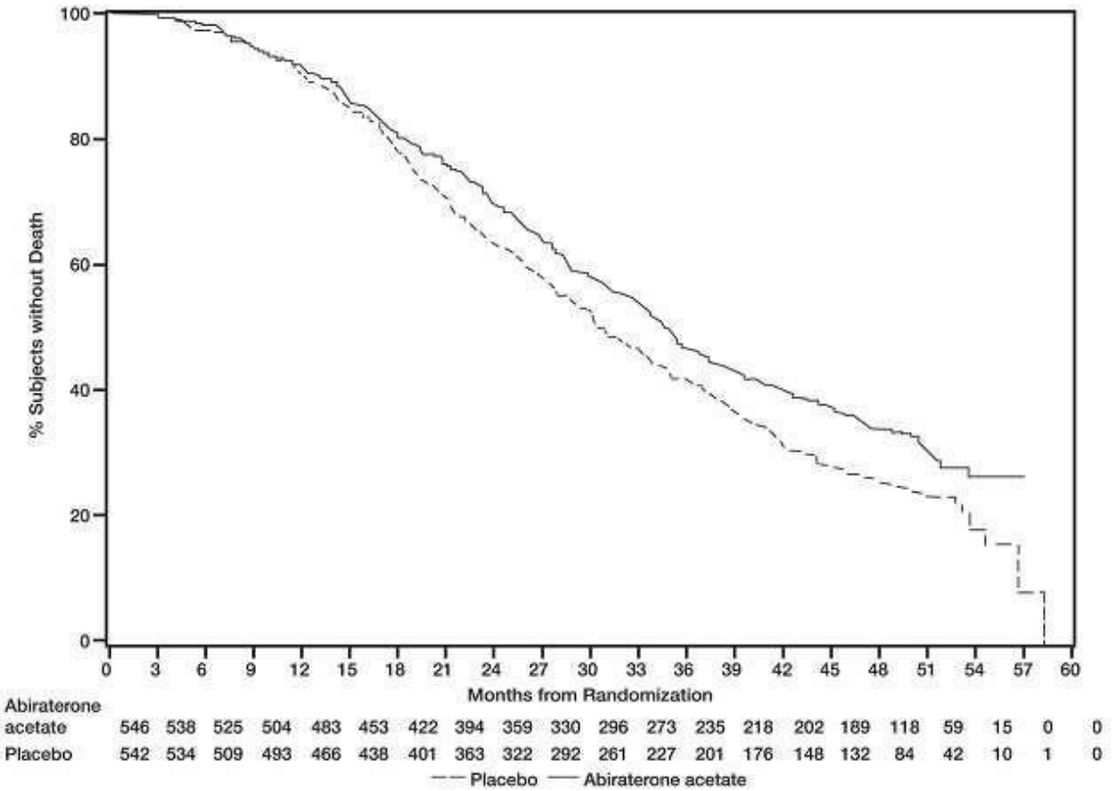
The planned final analysis for OS, conducted after 741 deaths (median follow up of 49 months) demonstrated a statistically significant OS improvement in patients treated with abiraterone with prednisone compared to those treated with placebo with prednisone (Table 8 and Figure 2). Sixty-five percent of patients on the abiraterone arm and 78% of patients on the placebo arm used subsequent therapies that may prolong OS in metastatic CRPC. Abiraterone was used as a subsequent therapy in 13% of patients on the abiraterone arm and 44% of patients on the placebo arm.

Table 8: Overall Survival of Patients Treated with Either Abiraterone or Placebo in Combination with Prednisone in COU-AA-302 (Intent-to-Treat Analysis)

	Abiraterone with Prednisone (N= 546)	**Placebo with Prednisone (N= 542)**
Overall Survival		
Deaths	354 (65%)	387 (71%)
Median survival (months) (95% CI)	34.7 (32.7, 36.8)	30.3 (28.7, 33.3)
p-value[1]	0.0033	
Hazard ratio[2] (95% CI)	0.81 (0.70, 0.93)	

[1] p-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).
[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone with prednisone.

Figure 2: Kaplan Meier Overall Survival Curves in COU-AA-302



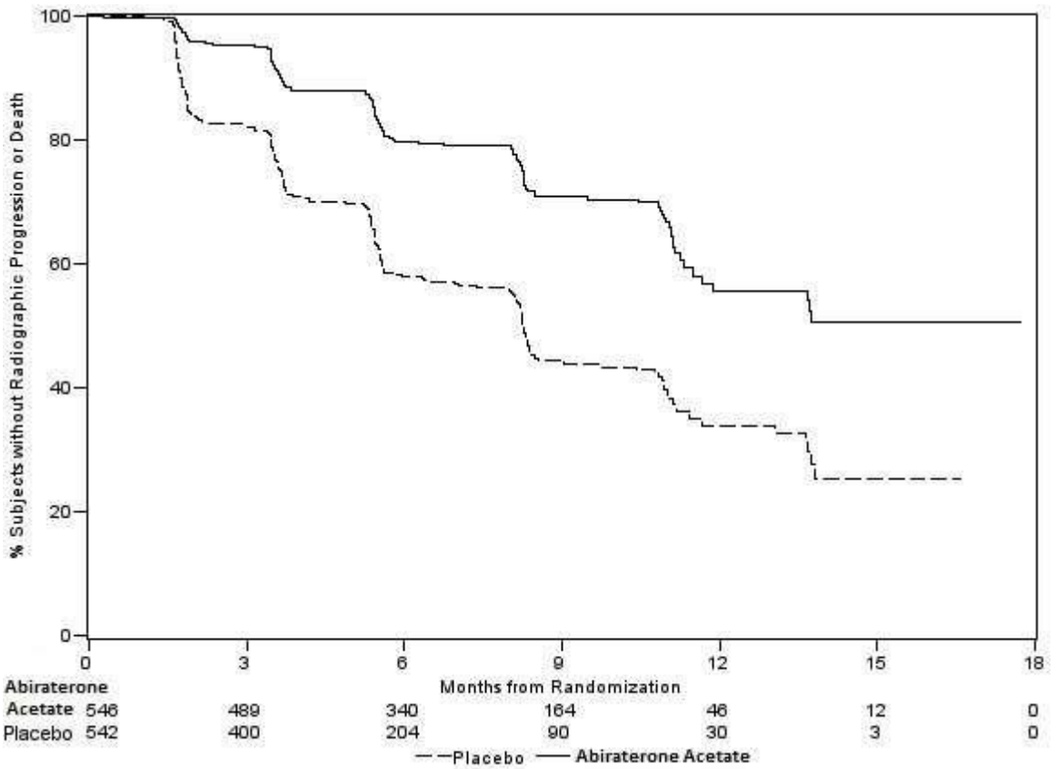
At the pre-specified rPFS analysis, 150 (28%) patients treated with abiraterone with prednisone and 251 (46%) patients treated with placebo with prednisone had radiographic progression. A significant difference in rPFS between treatment groups was observed (Table 9 and Figure 3).

Table 9: Radiographic Progression-free Survival of Patients Treated with Either Abiraterone or Placebo in Combination with Prednisone in COU-AA-302 (Intent-to-Treat Analysis)

	Abiraterone with Prednisone (N= 546)	**Placebo with Prednisone (N= 542)**
Radiographic Progression-free Survival		
Progression or death	150 (28%)	251 (46%)
Median rPFS (months) (95% CI)	NR (11.66, NR)	8.28 (8.12, 8.54)
p-value[1]	<0.0001	
Hazard ratio[2] (95% CI)	0.425 (0.347, 0.522)	

NR=Not reached.
[1] p-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).
[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone with prednisone.

Figure 3: Kaplan Meier Curves of Radiographic Progression-free Survival in COU- AA-302 (Intent-to-Treat Analysis)



The primary efficacy analyses are supported by the following prospectively defined endpoints. The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients in the abiraterone arm and 16.8 months for patients in the placebo arm (HR=0.580;95% CI: [0.487, 0.691], p < 0.0001).

The median time to opiate use for prostate cancer pain was not reached for patients receiving abiraterone and was 23.7 months for patients receiving placebo (HR=0.686; 95% CI: [0.566, 0.833], p=0.0001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the abiraterone arm.

LATITUDE: Patients with metastatic high-risk CSPC

In LATITUDE (NCT01715285), 1199 patients with metastatic high-risk CSPC were randomized 1:1 to receive either abiraterone orally at a dose of 1,000 mg once daily with prednisone 5 mg once daily (N=597) or placebos orally once daily (N=602). High-risk disease was defined as having at least two of three risk factors at baseline: a total Gleason score of ≥8, presence of ≥3 lesions on bone scan, and evidence of measurable visceral metastases. Patients with significant cardiac, adrenal, or hepatic dysfunction were excluded. Patients continued treatment until radiographic or clinical disease progression, unacceptable toxicity, withdrawal or death. Clinical progression was defined as the need for cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to ≥3.

Patient demographics were balanced between the treatment arms. The median age was 67 years among all randomized subjects. The racial distribution of patients treated with abiraterone was 69% Caucasian, 2.5% Black, 21% Asian, and 8.1% Other. The ECOG performance status was 0 for 55%, 1 for 42%, and 2 for 3.5% of patients. Baseline pain

assessment was 0-1 (asymptomatic) in 50% of patients, 2-3 (mildly symptomatic) in 23% of patients, and ≥4 in 28% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

A major efficacy outcome was overall survival. The pre-specified interim analysis after 406 deaths showed a statistically significant improvement in OS in patients on abiraterone with prednisone compared to those on placebos. Twenty-one percent of patients on the abiraterone arm and 41% of patients on the placebos arm received subsequent therapies that may prolong OS in metastatic CRPC. An updated survival analysis was conducted when 618 deaths were observed. The median follow-up time was 52 months. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 10 and Figure 4). At the updated analysis, 29% of patients on the abiraterone arm and 45% of patients on the placebos arm received subsequent therapies that may prolong OS in metastatic CRPC.

Table 10: Overall Survival of Patients Treated with Either Abiraterone or Placebos in LATITUDE (Intent-to-Treat Analysis)

	Abiraterone with Prednisone (N= 597)	**Placebo with Prednisone (N=602)**
Overall Survival[1]		
Deaths (%)	169 (28%)	237 (39%)
Median survival (months) (95% CI)	NE (NE, NE)	34.7 (33.1, NE)
p-value[2]	<0.0001	
Hazard ratio (95% CI)[3]	0.62 (0.51, 0.76)	
Updated Overall Survival		
Deaths (%)	275 (46%)	343 (57%)
Median survival (months) (95% CI)	53.3 (48.2, NE)	36.5 (33.5, 40.0)
Hazard ratio (95% CI)[3]	0.66 (0.56, 0.78)	

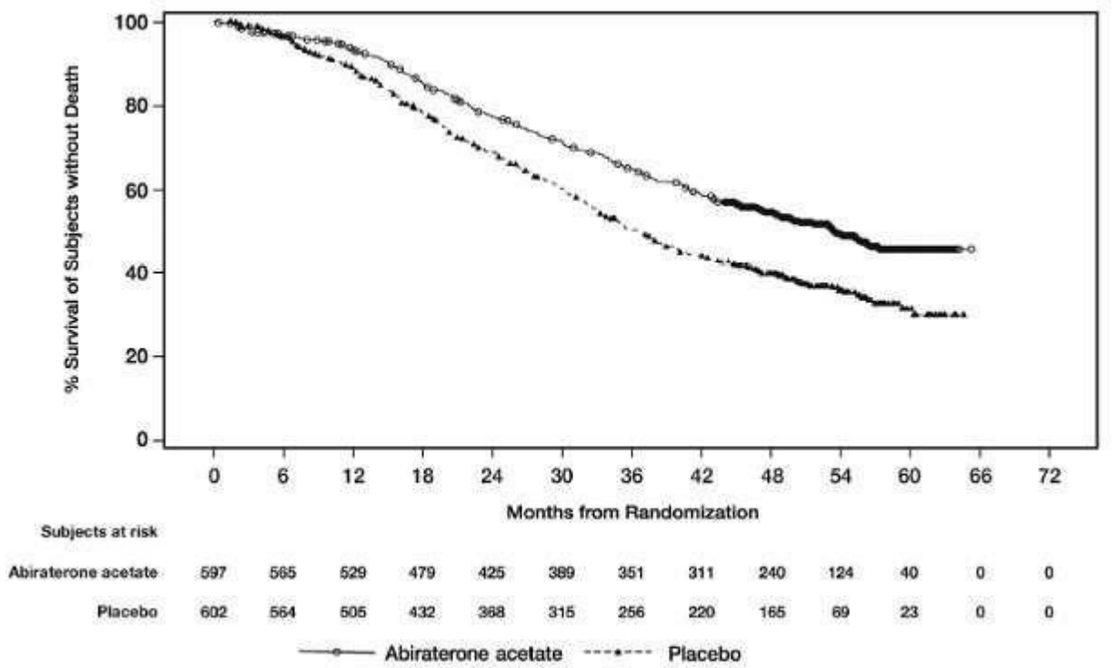
NE=Not estimable

[1] This is based on the pre-specified interim analysis

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

[3] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone with prednisone.

Figure 4: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population in LATITUDE Updated Analysis



The major efficacy outcome was supported by a statistically significant delay in time to initiation of chemotherapy for patients in the abiraterone arm compared to those in the placebos arm. The median time to initiation of chemotherapy was not reached for patients on abiraterone with prednisone and was 38.9 months for patients on placebos (HR = 0.44; 95% CI: [0.35, 0.56], $p < 0.0001$).

5.2 Pharmacokinetic properties

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone have been studied in healthy subjects and in patients with metastatic CRPC. *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (<0.2 ng/mL) in >99% of the analyzed samples.

Absorption

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate.

At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of C_{max} were 226 ± 178 ng/mL and of AUC were 993 ± 639 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg. However, the exposure was not significantly increased when the dose was doubled from 1,000 to 2,000 mg (8% increase in the mean AUC).

Effect of Food

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. In healthy subjects abiraterone C_{max} and $AUC_{0-\infty}$ were approximately 7-and 5-fold higher, respectively, when a single dose of abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17-and 10-fold higher,

respectively, when a single dose of abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal compared to overnight fasting. Abiraterone $AUC_{0-\infty}$ was approximately 7- fold or 1.6-fold higher, respectively, when a single dose of abiraterone acetate was administered 2 hours after or 1 hour before a medium fat meal (25% fat, 491 calories) compared to overnight fasting.

Systemic exposures of abiraterone in patients with metastatic CRPC, after repeated dosing of abiraterone acetate were similar when abiraterone acetate was taken with low-fat meals for 7 days and increased approximately 2-fold when taken with high-fat meals for 7 days compared to when taken at least 2 hours after a meal and at least 1 hour before a meal for 7 days.

Given the normal variation in the content and composition of meals, taking abiraterone with meals has the potential to result in increased and highly variable exposures.

Distribution

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 19,669
± 13,358 L.

Elimination

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours.

Metabolism

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate.

Excretion

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).

Specific Populations

Patients with Hepatic Impairment

The pharmacokinetics of abiraterone was examined in subjects with baseline mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. Systemic exposure to abiraterone after a single oral 1,000 mg dose given under fasting conditions increased approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (N=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function. In addition, the mean protein binding was found to be lower in the severe hepatic impairment group compared to the normal hepatic function group, which resulted in a two-fold increase in the fraction of free drug in patients with severe hepatic impairment.

Patients with Renal Impairment
The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). In the ESRD cohort of the trial, a single 1,000 mg abiraterone dose was given under fasting conditions 1 hour after dialysis, and samples for pharmacokinetic analysis were collected up to 96 hours post dose. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function.

Drug Interaction Studies
Clinical Studies

Effect of Other Drugs on Abiraterone

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

Strong CYP3A4 inhibitors: Co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Effect of Abiraterone on Other Drugs

CYP2D6 substrates: The C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8-and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold.

CYP1A2 substrates: When abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) was given with a single dose of 100 mg theophylline (CYP1A2 substrate), no increase in systemic exposure of theophylline was observed.

CYP2C8 substrates: The AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given to healthy subjects with a single dose of 1,000 mg abiraterone acetate.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Abiraterone is a substrate of CYP3A4 and has the

potential to inhibit CYP1A2, CYP2D6, CYP2C8 and to a lesser extent CYP2C9, CYP2C19 and CYP3A4/5.

Transporter Systems: In vitro studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp. *In vitro*, abiraterone and its major metabolites were shown to inhibit the hepatic uptake transporter OATP1B1. There are no clinical data available to confirm transporter based interaction.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, and Impairment of Fertility

A two-year carcinogenicity study was conducted in rats at oral abiraterone acetate doses of 5, 15, and 50 mg/kg/day for males and 15, 50, and 150 mg/kg/day for females. Abiraterone acetate increased the combined incidence of interstitial cell adenomas and carcinomas in the testes at all dose levels tested. This finding is considered to be related to the pharmacological activity of abiraterone. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Abiraterone acetate was not carcinogenic in female rats at exposure levels up to 0.8 times the human clinical exposure based on AUC. Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse.

Abiraterone acetate and abiraterone was not mutagenic in an *in vitro* microbial mutagenesis (Ames) assay or clastogenic in an *in vitro* cytogenetic assay using primary human lymphocytes or an *in vivo* rat micronucleus assay.

In repeat-dose toxicity studies in male rats (13-and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥50 mg/kg/day in rats and ≥250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone. These effects were observed in rats at systemic exposures similar to humans and in monkeys at exposures approximately 0.6 times the AUC in humans.

In a fertility study in male rats, reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility were observed in animals dosed for 4 weeks at ≥30 mg/kg/day orally. Mating of untreated females with males that received 30 mg/kg/day oral abiraterone acetate resulted in a reduced number of corpora lutea, implantations and live embryos and an increased incidence of pre-implantation loss. Effects on male rats were reversible after 16 weeks from the last abiraterone acetate administration.

In a fertility study in female rats, animals dosed orally 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 1,000 mg/day based on body surface area.

In 13-and 26-week studies in rats and 13-and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one

half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate.

Animal Toxicology and/or Pharmacology

A dose-dependent increase in cataracts was observed in rats after daily oral abiraterone acetate administration for 26 weeks starting at ≥50 mg/kg/day (similar to the human clinical exposure based on AUC). In a 39-week monkey study with daily oral abiraterone acetate administration, no cataracts were observed at higher doses (2 times greater than the clinical exposure based on AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Microcrystalline cellulose,
Croscarmellose sodium,
Colloidal silicon dioxide,
Magnesium stearate,
Povidone K-30,
Sodium lauryl sulfate,
Opadry
Purified Water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C
Store in its original packaging.

6.5 Nature and contents of container

60 tablets packed in 150cc HDPE container with 38mm CRP cap with induction seal packed in a carton along with the leaflet.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed off in accordance with localrequirements.

7. MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Limited
B/2, Mahalaxmi Chambers22, Bhulabhai Desai Road Mumbai- 400 026, India
Manufactured at –
Glenmark Pharmaceuticals Ltd.
Plot No. B-25,5 Star M.I.D.C Area, Shendra,
Aurangabad - 431154, Maharashtra

8. MARKETING AUTHORISATION NUMBER(S) –
H2024/CTD9452/21520

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION--
28TH March 2024

10. DATE OF REVISION OF THE TEXT
November 2024