The European Medicines Agency Review of Abiraterone for the Treatment of Metastatic Castration-Resistant Prostate Cancer in Adult Men After Docetaxel Chemotherapy and in Chemotherapy-Naïve Disease: Summary of the Scientific Assessment of the Committee for Medicinal Products for Human Use

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Abiraterone • Prostate cancer • EMA • European Medicines Agency

Learning Objectives

Describe the EU regulatory considerations on the benefits of abiraterone in the treatment of prostate cancer.

Describe the EU regulatory considerations on the risks of abiraterone in the treatment of prostate cancer and their management.

Describe the EU regulatory basis for approving abiraterone for use in the treatment of prostate cancer.

ABSTRACT

On September 5, 2011, abiraterone was approved in the European Union in combination with prednisone or prednisolone for the treatment of metastatic castration-resistant prostate cancer (CRPC) in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. On December 18, 2012, the therapeutic indication was extended to include the use of abiraterone in combination with prednisone or prednisolone for the treatment of metastatic CRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. Abiraterone is a selective, irreversible inhibitor of cytochrome P450 17 α , an enzyme that is key in the production of androgens. Inhibition of androgen biosynthesis deprives prostate cancer cells from important signals for growth, even in cases of resistance to castration. At the time of European Union approval and in a phase III trial in CRPC patients who had failed at least one

docetaxel-based chemotherapy regimen, median overall survival for patients treated with abiraterone was 14.8 months versus 10.9 months for those receiving placebo (hazard ratio, 0.65; 95% confidence interval 0.54–0.77; $p < .0001$). In a subsequent phase III trial in a similar but chemotherapy-naïve patient population, median radiographic progression-free survival was 16.5 months for patients in the abiraterone treatment arm versus 8.3 months for patients in the placebo arm (hazard ratio, 0.53; 95% confidence interval, 0.45–0.62; $p < .0001$). Abiraterone was most commonly associated with adverse reactions resulting from increased or excessive mineralocorticoid activity. These were generally manageable with basic medical interventions. The most common side effects (affecting more than 10% of patients) were urinary tract infection, hypokalemia, hypertension, and peripheral edema. *The Oncologist* 2013;18:1032–1042

Implications for Practice: The regulatory approval of abiraterone (acetate) for use in the European Union implies that this compound, which abrogates the production of male sex hormones, can be used to treat patients with prostate cancer, whose disease

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has ceased to respond to conventional hormonal therapies, either when patients do not have many symptoms so as to require chemotherapy or in more advanced disease when such chemotherapy has been used and has failed. The recommended dose is 1,000 mg (4×250 mg pills) taken once daily, 1 hour before or 2 hours after a meal (i.e., on an empty stomach). Abiraterone must be taken with prednisone or prednisolone (glucocorticoids, the production of which is also inhibited). The most common side effects of abiraterone include increases in blood pressure (hypertension), swelling (edema), and reduced blood potassium (hypokalaemia), all manifestations of increased production of mineralocorticoids. Abiraterone may also affect the liver and the heart.

INTRODUCTION

Prostate cancer is the second most frequent cause of death from cancer in Western societies and affects one in six men [1]. Metastatic prostate cancer cannot be cured by current therapy, and median survival is usually 1–3 years. The initial approach to therapy is generally androgen deprivation therapy (ADT) with medical or surgical castration. However, in prostate cancer progressing after hormone deprivation, cancer cells continue to demonstrate androgen receptor-mediated signaling. Even in metastatic castration-resistant prostate cancer (mCRPC), the tissue (e.g., intratumor) levels of testosterone, dehydroepiandrosterone (DHEA), dihydrotestosterone, and androstenedione all remain sufficient to activate the androgen receptor signaling pathways and to promote prostate tumor growth even in castrate concentrations of testosterone. This is because extratesticular sources (e.g., the adrenals and the tumor itself) produce enough androgens toward this end.

Nearly all men with metastatic prostate cancer eventually develop progressive disease after treatment with ADT. Docetaxel-based chemotherapy has been associated with an improvement in overall survival (OS; vs. mitoxantrone) in men with metastatic hormone-resistant prostate cancer [2]. Recently, cabazitaxel was granted a marketing authorization for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen, as its combination with prednisone improved median OS compared with mitoxantrone [3].

The active substance in Zytiga (Janssen Biotech, Inc. Horsham, PA, <http://www.janssenbiotech.com/>) is abiraterone

Abiraterone causes reductions in testosterone levels by specifically inhibiting CYP17. CYP17 inhibition also results in decreased glucocorticoid and increased mineralocorticoid production by the adrenals because of the inhibition of the hydroxylase activity, and this is the cause of the main toxicities with abiraterone.

acetate (Fig. 1), which is rapidly converted in vivo to abiraterone. Abiraterone (acetate) is a selective, irreversible inhibitor of cytochrome P450 17 α (17 α -hydroxylase/C₁₇₋₂₀ lyase; CYP17), an enzyme that is key in the production of androgens. It catalyzes the conversion of precursors of mineralocorticoids (e.g., pregnenolone or progesterone) into DHEA or androstenedione, respectively, two precursors of testosterone. The hydroxylase activity is responsible for the conversion of pregnenolone and progesterone to precursors of glucocorticoids (e.g., 17OH-pregnenolone and 17OH-progesterone),

Figure 1. Chemical structure of abiraterone acetate.

Abbreviations: H, hydrogen; N, nitrogen; O, oxygen.

and the lyase activity is responsible for the further conversion of glucocorticoid precursors to DHEA and androstenedione. Abiraterone causes reductions in testosterone levels by specifically inhibiting CYP17. CYP17 inhibition also results in decreased glucocorticoid and increased mineralocorticoid production by the adrenals because of the inhibition of the hydroxylase activity, and this is the cause of the main toxicities with abiraterone.

The inhibition of androgen production by abiraterone is a novel mechanism of action compared to that of antiandrogens, which inhibit the binding of androgens to their receptor. Enzalutamide, a more recent antiandrogen, has pleiotropic effects on androgen signaling, and it inhibits binding of androgens to the androgen receptor as well as binding of costimulatory molecules and binding to the DNA of androgen-androgen receptor complex (Fig. 2).

The detailed scientific assessment report and the most current product information of Zytiga are available on the European Medicines Agency website (<http://www.ema.europa.eu>).

NONCLINICAL ASPECTS

Abiraterone and, to a lesser extent, abiraterone acetate showed potent and irreversible inhibition of CYP17 in microsomes in vitro [4–8]. Androstenedione, testosterone, and cortisol synthesis was inhibited with half maximal inhibitory concentrations in the nanomolar range. Aldosterone was elevated at these concentrations, probably reflecting the shunting of the accumulated pregnenolone and progesterone substrates into the mineralocorticoid pathway because of inhibition of CYP17.

In mice and rats, abiraterone acetate caused a marked weight reduction of several androgen-sensitive organs (ven-

Figure 2. Mechanism of action of abiraterone and antiandrogens.
Abbreviations: A, androgens; AR, androgen receptor; C, costimulatory molecules.

tral prostate, seminal vesicles, adrenals, testes, and kidneys) in a dose-dependent manner within 2 weeks, similar to the effect of surgical castration. Plasma testosterone levels were markedly decreased in a dose-dependent manner by abiraterone acetate treatment, and the testosterone reductions were maintained despite the compensatory increases in luteinizing hormone levels [7–9].

Castration-resistant prostate cancer (CRPC) may synthesize androgens *de novo* from cholesterol or metabolize adrenal androgens to maintain tissue androgen levels and support growth despite anorchid serum testosterone. It has been shown previously that the CRPC xenograft LuCaP 35V maintains tumoral androgen levels in castrate mice. Montgomery et al. [10] further investigated the effects of abiraterone acetate on the growth of human CRPC xenograft LuCaP 35V in castrated male mice. Treatment with abiraterone acetate reduced androgen production in the tumor xenografts and significantly slowed tumor growth compared with control animals. It also prolonged prostate-specific antigen (PSA) doubling time as well as OS.

In “*per os*” repeat-dose toxicology studies in rats, cynomolgus monkeys, and mice, abiraterone was generally well tolerated. One target organ of toxicity was the liver, as demonstrated by increased liver weight, hepatocellular hypertrophy, bile duct and oval cell hyperplasia, and associated increases in liver function tests. Biliary changes were not consistently observed in all studies, and changes were partially to fully reversible. In rats, cataracts were also seen in a dose-dependent manner in repeat-dose toxicity studies without evidence of reversibility. The mechanism was unclear, although a species-specific effect cannot be excluded because cataract was not observed in monkeys. The mechanism underlying the hepatic changes reported in the rat and monkey repeated-dose studies and the issue of cataract formation in the rat are currently being followed up in carcinogenicity studies.

Abiraterone acetate and abiraterone did not show genotoxic potential in relevant studies, and no carcinogenicity

studies were submitted. However, as mentioned, reproductive organ changes were observed with abiraterone treatment, including reduction in organ weight and morphological and/or histopathological changes. All changes showed complete or partial reversibility. The reproductive organ changes were consistent with the pharmacology of abiraterone acetate and abiraterone. In its current indications, abiraterone is not for use in women, and its use is contraindicated in pregnant or potentially pregnant women. Moreover, pregnant women should use gloves if handling abiraterone tablets, and male patients on abiraterone should use appropriate contraceptive measures.

CLINICAL PHARMACOLOGY

Because abiraterone acetate is rapidly hydrolyzed *in vivo* to abiraterone, abiraterone acetate was detected in only a fraction of the total number of collected samples in pharmacokinetic (PK) studies. Consequently, all PK analysis was carried out on abiraterone.

Abiraterone was rapidly absorbed. The absolute bioavailability is not known. The bioavailability from the commercial tablet in the fasted state is unlikely to be higher than 10% because the bioavailability can be increased by 10-fold in the fed state. Abiraterone tablets must not be taken with food so as to avoid exposure higher than clinically indicated. The plasma protein binding of abiraterone at therapeutic concentrations was high (on the order of 98.8%–99.9%).

Hydrolysis of abiraterone acetate to abiraterone is mediated by nonidentified esterases, is not mediated by cytochrome P450 (CYP), and is thought to occur mainly in the liver. Cleavage of the ester within gastrointestinal tissue during the absorption process cannot be excluded. Abiraterone, the active metabolite responsible for the primary pharmacodynamic (PD) effect, is subsequently metabolized extensively. The primary metabolic pathways for abiraterone include sulfation and N-oxidation as well as hydroxylation, dehydration, and glucuronidation pathways. The majority of the drug and

its metabolites are excreted in the feces, with only approximately 5% in the urine.

In vivo, abiraterone is a substrate of CYP3A4, which is inhibited in vitro by abiraterone with moderate potency. In vitro, abiraterone was also shown to inhibit the hepatic drug-metabolizing enzymes CYP1A2 and CYP2D6. The effects of abiraterone acetate on a single dose of the CYP1A2 substrate theophylline showed no increase in systemic exposure to theophylline. The effect of abiraterone acetate on a single dose of the CYP2D6 substrate dextromethorphan showed that systemic exposure to dextromethorphan was increased 2.9-fold.

Treatment with abiraterone acetate resulted in significant suppression of testosterone, DHEA, and androstenedione in healthy male subjects [11]. Moreover, a sequential joint PK-PSA-survival modeling approach was used to describe the relationship between drug exposure and survival following intake of the study drug with PSA PDs as an intermediate marker. The main objective of the PSA-survival modeling was to explore the relationship between PSA dynamics and OS and to link OS to drug exposure through PSA dynamics following treatment. The model suggested that PSA dynamics were indeed an intermediate biomarker of OS in the study population; however, the lack of external validation was considered to limit its validity, and the implications of the model for the interpretation of the results into clinically relevant information were limited.

No dose-limiting toxicities were observed in early dose-finding studies, even at the dose of 2,000 mg per day, so the choice of the dose of 1,000 mg per day taken forward in clinical development was questioned. Yet, no significant differences in concentrations of corticosterone and deoxycorticosterone were observed at doses higher than 750 mg [11], suggesting a maximum inhibition of CYP17 enzyme activity at this dose. PK-PD modeling also showed that 90% of patients in the phase III study described below would have achieved steady-state minimum concentration greater than the estimated half maximal effective concentration value. Therefore, the selection of the 1,000-mg dose was endorsed.

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CLINICAL EFFICACY

One phase III pivotal study (COU-AA-301) and two phase II studies (COU-AA-303/EXT and COU-AA-304) were submitted in support of the use of abiraterone acetate in the initially claimed indication: men with advanced mCRPC whose disease has progressed on or after docetaxel-based chemotherapy. The extension of the approved indication to chemotherapy-

naïve patients was supported by a second phase III pivotal study (COU-AA-302) and two additional phase I/II studies (COU-AA-001/EXT and COU-AA-002).

Post-docetaxel Clinical Setting

The pivotal study COU-AA-301 (EudraCT number 2007-005837-13, ClinicalTrials.gov identifier NCT00638690) was a phase III, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in patients with mCRPC who had progressed on docetaxel-based chemotherapy. The study was conducted at 147 sites in the U.S., Europe, Australia, and Canada [12].

The study enrolled men older than 18 years of age with adenocarcinoma of the prostate and medical or surgical castration who had received one or two different cytotoxic chemotherapy regimens for mCRPC (one of which must have contained docetaxel) and who had investigator-documented prostate cancer progression, defined by successive increases in PSA values and/or radiographic findings, despite ongoing androgen deprivation, with serum testosterone <50 ng/dL (<2.0 nM).

The patients were randomly assigned to receive abiraterone acetate 1,000 mg (administered as four 250-mg tablets) once daily and 5 mg prednisone or prednisolone twice daily or placebo and prednisone or prednisolone in a 2:1 ratio. They were stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) score (0–1 vs. 2), worst pain over the past 24 hours on the Brief Pain Inventory-Short Form (0–3 [absent] vs. 4–10 [present]), prior chemotherapy regimens (1 vs. 2), and type of progression prior to study entry (PSA progression only vs. radiographic progression with or without PSA progression).

The primary endpoint was OS. One interim analysis and one final analysis for OS were prespecified in the statistical analysis plan. Key secondary endpoints were time to PSA progression (as defined in the Prostate Cancer Clinical Trials Working Group criteria) [13], radiographic progression-free survival (PFS; based on imaging studies as assessed by the investigator) and PSA response rate (proportion of patients achieving a PSA decline of at least 50% according to Prostate Cancer Clinical Trials Working Group criteria).

Overall, 1,195 patients were randomized, 797 to the abiraterone arm and 398 to the placebo arm. All but 10 (6 in the abiraterone arm and 4 in the placebo arm) received the study treatment. In the abiraterone arm, patients received treatment for a mean of 32.5 weeks compared with 23.1 weeks in the placebo arm. Baseline demographic and disease characteristics were well balanced between the two treatment groups (supplemental online Table 1). The mean age of randomized patients was 69 years, and the majority (93%) were white. Overall, 90% had bone metastases at baseline, and 90% had an ECOG PS of 0–1. Seventy percent of patients had received one prior chemotherapy regimen, and 30% had received two.

The primary efficacy results derived from the prespecified interim analysis and forming the basis of the European Union marketing authorization for Zytiga are presented in Table 1 and Figure 3. Final OS results from the study were reported postauthorization [14].

The treatment effect on OS was consistent within all of the subgroups explored (with the exception of patients

Table 1. Results for primary and key secondary endpoints, study COU-AA-301 (post-docetaxel)

Endpoint	Abiraterone	Placebo
No. of patients randomized	797	398
Overall survival, mo		
Median (95% CI)	14.8 (14.1–15.4)	10.9 (10.2–12.0)
Log-rank <i>p</i> value (stratified)	<.0001	
HR (95% CI)	0.646 (0.543–0.768)	
Time to prostate-specific antigen progression, mo		
Median (95% CI)	10.2 (8.4–13.8)	6.6 (4.9–8.4)
Log-rank <i>p</i> value (stratified)	<.0001	
HR (95% CI)	0.580 (0.462–0.728)	
Radiographic progression-free survival, mo		
Median (95% CI)	5.6 (5.6–6.3)	3.6 (2.9–5.5)
Log-rank <i>p</i> value (stratified)	<.0001	
HR (95% CI)	0.673 (0.585–0.776)	
Prostate-specific antigen response rate		
Patients, no. (%)	303 (38.0)	40 (10.1)
Confirmed, no. (%)	232 (29.1)	22 (5.5)
Unconfirmed, no. (%)	71 (8.9)	18 (4.5)
Relative risk (95% CI)	5.266 (3.459–8.018)	
<i>p</i> value (from a chi-square test)	<.0001	

Abbreviations: CI, confidence interval; HR, hazard ratio.

Figure 3. Overall survival, study COU-AA-301 (post-docetaxel, intent-to-treat population).

Abbreviations: AA, abiraterone acetate; ITT, intent to treat.

with ECOG PS 2, for which numbers were low, yet the effect was in the same direction). The proportion of patients with pain palliation was higher in the abiraterone acetate group (44%) than in the placebo group (27%), and a lower proportion of patients treated with abiraterone acetate had pain progression (35% vs. 46% at 18 months; supplemental online Fig. 1) or skeletal-related events (35% vs. 40% at 18

months; supplemental online Fig. 2) compared with patients taking placebo [15].

Chemotherapy-Naïve Clinical Setting

The pivotal study COU-AA-302 (EudraCT number 2008–008004-41, ClinicalTrials.gov identifier NCT00887198) was a phase III, randomized, double-blind, placebo-controlled study

comparing the efficacy and safety of abiraterone acetate plus prednisone with placebo plus prednisone in medically or surgically castrated asymptomatic or mildly symptomatic men with mCRPC who had not received cytotoxic chemotherapy. The study was conducted at 151 sites in the U.S., Europe, and Australia [16].

The study enrolled men older than 18 years of age with metastatic adenocarcinoma of the prostate and medically or surgically castrated who were asymptomatic or mildly symptomatic (ECOG PS of 0 or 1) and who had investigator-documented prostate cancer progression after previous antiandrogen therapy with serum testosterone <50 ng/dL (<2.0 nM). If patients were treated with luteinizing hormone-releasing hormone agonists, the therapy must have been initiated at least 4 weeks prior to study start and continued throughout the study. In contrast, concomitant treatment with antiandrogens was not allowed, and antiandrogens had to be discontinued at least 4 weeks prior to study start.

The patients were randomly assigned to receive abiraterone acetate 1,000 mg (administered as four 250-mg tablets) once daily and 5 mg prednisone or prednisolone twice daily or placebo and prednisone or prednisolone in a 1:1 ratio. They were stratified by ECOG PS score (0 versus 1).

The study had two primary endpoints: radiographic PFS (rPFS; PFS based on imaging studies assessed by independent radiographic review; bone scans were conducted every 8 weeks for the first 24 weeks and confirmatory bone scans of new lesions were performed and assessed based on adapted Prostate Cancer Working Group 2 criteria and modified Response Evaluation Criteria In Solid Tumors) and OS. Key secondary endpoints included time to initiation of cytotoxic chemotherapy, time to opiate use for cancer pain, time to ECOG PS deterioration by at least one grade, and time to PSA progression. One analysis for rPFS and three interim analyses plus one final analysis for OS were prespecified in the statistical analysis plan.

A total of 1,088 patients were randomized, 546 to the abiraterone arm and 542 to the placebo arm. Only four patients in the abiraterone arm and two in the placebo arm did not receive the study treatment. In the abiraterone arm, patients received treatment for a mean of 14.3 months compared with 10.4 months in the placebo arm. Baseline demographic and disease characteristics were well balanced between the two treatment groups (supplemental online Table 2). The mean age of randomized patients was 70 years, and the majority (95%) were white. Eighty-one percent of patients had bone metastases at baseline.

The primary analysis for rPFS was conducted at the time of the first interim analysis for OS. An updated rPFS analysis was conducted at the time of the second interim analysis for OS, at which time the independent data monitoring committee recommended that the study be unblinded and that patients in the placebo arm be allowed to cross over to the abiraterone arm on the basis of overwhelming efficacy. At the time of the third interim analysis for OS, 145 patients (26.8%) in the placebo group had received abiraterone as subsequent therapy.

The most updated efficacy results derived from the updated rPFS analysis (and updated analysis for key secondary endpoints) and the third interim OS analysis are presented in Table 2 and Figure 4.

The treatment effect on PFS was consistent among all of the subgroups explored. For OS, results in subgroups were in the same direction, although the upper boundary of the 95% confidence interval crossed 1 in half of the subgroups examined. PSA response rate and objective response rate were higher in the abiraterone arm compared with the placebo arm, and patient-reported outcome measures also showed differences in favor of abiraterone (data not shown).

CLINICAL SAFETY

The safety of abiraterone acetate administered as monotherapy with or without prednisone or prednisolone was evaluated in 2,955 subjects included in 21 clinical studies. This included 1,680 patients with mCRPC who were treated with abiraterone acetate 1,000 mg administered as a continuous daily dose with or without prednisone 5 mg twice daily (i.e., at the intended clinical dose, in 12 early clinical studies and 934 patients treated with placebo and prednisone in the pivotal trials COU-AA-301 and COU-AA-302). Patients received abiraterone for a mean of 34.0 weeks (median: 31.9 weeks) in study COU-AA-301 and 14.31 months (median: 13.80 months) in study COU-AA-302.

In the two pivotal trials, 99% of patients that received abiraterone experienced adverse events (AEs) and 77% (in study COU-AA-301) to 78% (in study COU-AA-302) of patients experienced adverse drug reactions (drug-related AEs).

Adverse drug reactions in the integrated safety population are summarized in Table 3. The most common adverse drug reactions observed with abiraterone acetate were peripheral edema, hypokalemia, urinary tract infection, and hypertension. Adrenal insufficiency occurred at a rate <1%.

Consistent with the pharmacological mechanism of action of abiraterone, mineralocorticoid-related toxicities, such as fluid retention and edema, hypokalemia, and hypertension, were observed more frequently in patients treated with abiraterone acetate compared with those treated with placebo in both pivotal studies. Adjustment for the longer exposure time to study treatment in the abiraterone arm only partially relieved the differences.

In study COU-AA-301, hepatotoxicity AEs were observed in 10% of patients in the abiraterone acetate group and 8% of patients in the placebo group, and increases in alanine aminotransferase (ALT) were observed in 3% of abiraterone patients and 1% of placebo patients. In study COU-AA-302, hepatotoxicity AEs were observed in 18% of patients in the abiraterone group and 11% in the placebo group. The most frequently reported preferred terms were aspartate transaminase and ALT increases. ALT increases were 12% in the abiraterone group compared with 5% in the placebo group, and aspartate transaminase increases were 11% versus 5%, respectively. Hy's Law criteria were applied across all studies in patients with mCRPC to assess the incidence of severe hepatotoxicity, and two patients were identified as potentially having met Hy's Law criteria.

In study COU-AA-301, the incidence of cardiac events was slightly higher in the abiraterone acetate group compared with the placebo group (13% vs. 11%, respectively); however, the rates of cardiac-related death were low and balanced in the two groups (1% of patients in each group). In addition, death from myocardial infarction was infrequent in the two groups (one patient each). In study COU-AA-302, cardiac dis-

Table 2. Results for coprimary and key secondary endpoints, study COU-AA-302 (chemotherapy-naïve)

Endpoint	Abiraterone	Placebo
No. of patients randomized	546	542
Radiographic progression-free survival, mo		
Median (95% CI)	16.46 (13.80–16.79)	8.25 (8.05–9.43)
Log-rank <i>p</i> value (stratified)	<.0001	
HR (95% CI)	0.530 (0.451, 0.623)	
Overall survival, mo		
Median (95% CI)	35.29 (31.24–35.29)	30.13 (27.30–34.10)
Log-rank <i>p</i> value (stratified)	.0151	
HR (95% CI)	0.792 (0.655–0.956)	
Time to opiate use for cancer pain, mo		
Median (95% CI)	NE (28.25, NE)	23.66 (20.24, NE)
Log-rank <i>p</i> value (stratified)	.0001	
HR (95% CI)	0.686 (0.566–0.833)	
Time to initiation of chemotherapy, mo		
Median (95% CI)	25.17 (23.26, NE)	16.82 (14.55–19.38)
Log-rank <i>p</i> value (stratified)	<.0001	
HR (95% CI)	0.580 (0.487–0.691)	
Time to Eastern cooperative Oncology Group performance status deterioration, mo		
Median (95% CI)	12.29 (11.33–14.29)	10.87 (9.49–11.76)
Log-rank <i>p</i> value (stratified)	.0053	
HR (95% CI)	0.821 (0.714–0.943)	
Time to prostate-specific antigen progression, mo		
Median (95% CI)	11.07 (8.51–11.24)	5.55 (5.39–5.59)
Log-rank <i>p</i> value (stratified)	<.0001	
HR (95% CI)	0.488 (0.420–0.568)	

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable.

orders were reported in 19% of patients in the abiraterone group and 16% of patients in the placebo group. The following incidences of cardiac disorder AEs by subcategory were reported for abiraterone versus placebo, respectively: arrhythmias, 14% versus 12%; ischemic heart disease, 4% versus 3%; cardiac disorders for other causes, 3% in each treatment group; and cardiac failure, 2.0% versus 0.4%. Exposure-standardized rates of all cardiac disorders were lower for the abiraterone group compared with the placebo group. In contrast, the proportion of patients with corrected QT interval prolongation of either >30 ms or >60 ms was higher in the abiraterone group compared with the placebo group, and this was also the case for postbaseline Fridericia's formula-corrected QT interval values of >450 ms (27% for abiraterone vs. 20% for placebo). Consequently, abiraterone should be used with caution in patients with a history of cardiovascular disease. Such disease should be adequately evaluated and controlled prior to treatment initiation as well as monitored and controlled during treatment.

In study COU-AA-302, abiraterone treatment increased the incidence versus placebo of grade 3 or 4 AEs (4% vs. 42%), serious AEs (33% vs. 26%; most notably, infections, pneumonia, urinary tract infection, dehydration, and cardiac disorders), AEs leading to treatment discontinuation (10% vs. 9%), and AEs other than disease progression with an outcome of

death (4% vs. 2%; most notably, because of infection). In contrast, in study COU-AA-301, there was no increase over placebo in any of these AE categories.

RISK MANAGEMENT PLAN

Important identified risks are hypertension, hypokalemia, fluid retention and edema, hepatotoxicity, cardiac disorders, and osteoporosis and osteoporosis-related fractures. Important potential risks are anemia, sexual dysfunction, decreased libido and impotence, cataracts, drug-drug interactions (related to CYP2D6 inhibition), and increase in abiraterone exposure with food. Consequently, abiraterone tablets should be taken at least 2 hours after eating, and no food should be eaten for at least 1 hour after taking the tablets. The mechanism of cataract formation in the rat will be further investigated in nonclinical studies, as mentioned previously, and a phase II clinical study will aim to determine the short-term safety of abiraterone acetate in fasting and fed states in patients with mCRPC.

Information was missing with regard to use in patients with active or symptomatic viral hepatitis, with moderate or severe hepatic impairment and chronic liver disease, with severe renal impairment, with severe heart disease, in nonwhite patients, and with regard to drug-drug interaction related to CYP2C8. Toward addressing these and in addition to routine

pharmacovigilance, a single-dose PK trial in noncancer subjects with severe hepatic impairment (Child-Pugh class C) and a drug-drug interaction clinical study using a CYP2C8 probe substrate will be conducted. In addition, an integrated analysis of concluded and ongoing trials will be performed to address the lack of experience in nonwhite patients. Moreover, targeted follow-up through guided questionnaires for events of arrhythmia and cardiac failure will be conducted to collect clinical information related to this safety concern.

DISCUSSION AND BENEFIT-RISK ASSESSMENT

EU marketing authorization decisions are based on the demonstration of a positive benefit-risk balance, in that the benefits from the use of the new drug are considered to outweigh the risks associated with it in a well-defined patient population and indication. The benefit-risk balance is discussed separately for the initial therapeutic indication and extension in the following settings.

Post-docetaxel Clinical Setting

A single pivotal trial (study COU-AA-301) was submitted in support of the efficacy of abiraterone acetate in combination with concomitant glucocorticoid therapy in patients with advanced mCRPC in a population that had previously progressed on one or two chemotherapy regimens (one of which must have contained docetaxel). Median OS was prolonged by 3.9 months (14.8 months in the abiraterone group and 10.9 months in the placebo group). Treatment effect on OS was robust after adjustment for stratification factors in multivariate analysis and was consistently favorable across all subgroups (ECOG PS, pain score, number of prior lines of chemotherapy, type of progression, age, visceral disease, baseline PSA, lactate dehydrogenase or alkaline phosphatase, and geographical region). The effect was further substantiated by results in the prespecified secondary efficacy endpoints and was in agreement with effects observed in supportive earlier clinical studies.

Patients who had received prior ketoconazole therapy were excluded from the pivotal study, and lower rates of response might be expected in patients treated with ketoconazole for prostate cancer. This is because ketoconazole is also a weak inhibitor of CYP17 [17].

The most common adverse drug reactions with abiraterone were peripheral edema, hypokalemia, urinary tract infection, and hypertension (Table 3). In addition to the expected adverse drug reactions because of increased mineralocorticoid activity, the following key safety risks have been identified: The incidence of cardiac events was slightly higher in the abiraterone acetate and prednisone group, with no differences in the rates of cardiac-related death (<1% of patients in each group), and there is a risk for increased urinary infections. Finally, there was a higher incidence of hepatotoxic events in relation to treatment with abiraterone. Increments in hepatic enzymes occurring during treatment were managed with careful laboratory monitoring, treatment interruptions, and retreatment only after return of liver function tests to baseline or grade 1. Although no patients treated with abiraterone acetate were confirmed to have met all Hy's Law criteria, two relevant cases of drug-induced liver injury were identified. The role of abiraterone in hepatotoxicity is not fully understood.

Treatment with abiraterone showed an improvement in the median OS in a population with few therapeutic alternatives at the time of study design. Results in key secondary endpoints supported the observed improvement of OS and measures of functional status, and symptom-related endpoints also tended to favor abiraterone-treated patients over placebo controls.

Treatment with abiraterone showed an improvement in the median OS in a population with few therapeutic alternatives at the time of study design. Results in key secondary endpoints supported the observed improvement of OS and measures of functional status, and symptom-related endpoints also tended to favor abiraterone-treated patients over placebo controls. The results were considered to be mature, robust, consistent, and of clinical relevance. The fact that this medicine is administered orally is considered an additional advantage for this clinical setting.

The safety profile was considered acceptable and generally manageable, with basic medical interventions (oral potassium supplements, diuretics, and antihypertensive medication). Toxicities were generally mild (most grade 1–2) and resulted in infrequent drug discontinuations. In this regard, it should be noted that the safety profile of abiraterone acetate is distinct from that typically induced by conventional cytotoxic agents frequently associated with AEs that are potentially dose limiting, debilitating, cumulative, or life threatening. AEs such as hypertension or hypokalemia were generally asymptomatic, and although fluid retention and edema or urinary tract infections may be more disturbing to the patient, abiraterone did not induce toxicities such as myelosuppression, diarrhea, mucositis, or asthenia. Such toxicities may not only be associated with higher risks of severe medical complications, including death, but often have a major impact on the patient's quality of life, which is particularly relevant in the context of noncurative therapy for an end-stage disease.

The benefits from abiraterone in the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen were considered to clearly outweigh the risks associated with its use in this patient population. In conclusion, abiraterone was initially approved in the European Union for this indication.

Chemotherapy-Naïve Clinical Setting

The extension of the therapeutic indication in combination with glucocorticoids to asymptomatic or mildly symptomatic patients after failure of ADT and in whom chemotherapy is not yet clinically indicated was supported by a single pivotal phase III trial (study COU-AA-302). Such extensions of the therapeutic indication have to be accompanied by relevant quality, nonclinical (as appropriate), and clinical data. Although prior experience with the drug reduces uncertainty and facilitates authorization decisions in these cases, the drug's favorable benefit-risk balance has to be separately and independently demonstrated in the patient population that is ultimately targeted by the new indication.

Figure 4. Overall survival, study COU-AA-302 (chemotherapy-naïve).

Table 3. Adverse drug reactions observed in abiraterone acetate-treated patients

Reaction	Frequency
Infections and infestations	Very common: urinary tract infection
Endocrine disorders	Uncommon: adrenal insufficiency
Metabolism and nutrition disorders	Very common: hypokalemia Common: hypertriglyceridemia
Cardiac disorders	Common: cardiac failure, ^a angina pectoris, arrhythmia, atrial fibrillation, tachycardia
Vascular disorders	Very common: hypertension
Gastrointestinal disorders	Common: dyspepsia
Hepatobiliary disorders	Common: alanine aminotransferase increased, aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Common: rash
Renal and urinary disorders	Common: hematuria
General disorders and administration site conditions	Very common: edema peripheral
Injury, poisoning, and procedural complications	Common: fractures ^b

^aCardiac failure also includes congestive heart failure, left ventricular dysfunction, and ejection fraction decreased.

^bFractures includes all fractures with the exception of pathological fracture.

In the COU-AA-302 study, treatment with abiraterone decreased the risk of radiographic progression or death by 58% compared with placebo, and the reduction in risk of progression was maintained after an additional year of follow-up. The results were consistently favorable across analyses, demonstrating the robustness of the primary analysis. Treatment with abiraterone resulted in a 25% decrease in the risk of death, although the *p* value did not reach the nominal significance level. The early crossover of patients in the placebo arm, as a consequence of early trial termination resulting from the

documentation of a clear benefit for abiraterone-treated patients in the second interim analysis, may have hampered the ability of the trial to detect a true effect on survival. A favorable OS trend in the treatment effect was observed across all subgroups examined.

The results from the secondary endpoints support the benefit observed for the coprimary endpoints of rPFS and OS. In particular, opiate use was documented for fewer patients, and the median time to initiation of cytotoxic chemotherapy was significantly longer. For patient-related outcome data,

delays in median time to average pain intensity progression and in the degradation in the total score on the Functional Assessment of Cancer Therapy-Prostate scale were observed, indicating that quality of life was generally preserved in patients treated with abiraterone.

Treatment with abiraterone was tolerable for the majority of patients. The safety profile was generally consistent with previous experience, despite an increase versus placebo in all categories of AEs (overall, grade 3–4, AEs leading to discontinuation, and serious AEs) and significantly longer exposure to the drug than in study COU-AA-301. AEs were manageable and no major safety concerns were raised. Potential QT interval prolongation and safety in patients with New York Heart Association class II–IV failure are the most prominent risks with the use of abiraterone. These risks are managed adequately with warnings in the product information, electrocardiographic monitoring in ongoing clinical studies, and targeted follow-up for events of arrhythmia and cardiac failure, as mentioned.

The prognosis for mCRPC patients is still poor (median survival of approximately 1–2 years). After patients become castration resistant and provided that they remain asymptomatic or have mild symptoms so that chemotherapy is not yet indicated, different hormonal therapies can be used; however, globally, there is neither clear consensus nor clear proof of efficacy in terms of survival with available treatments. Such patients who are not in immediate need of chemotherapy may still benefit from alternative therapies. The results of study COU-AA-302 demonstrated a clinically relevant benefit to patients who require additional therapeutic options. The magnitude of the effect is significant, particularly in terms of the observed delay in progression, the delay in the median time to initiation of cytotoxic chemotherapy, and the reduction in the requirement for opiate use. A favorable OS trend was observed and quality of life was preserved in patients treated with abiraterone compared with those treated with placebo. Treatment with abiraterone was tolerable for the majority of subjects, and the AE profile was consistent with previous experience.

The favorable effects were considered to more than exceed the unfavorable effects and uncertainties, and the benefit-risk profile was considered to be positive. The most influential factors for a positive opinion were the magnitude of the delay of progression and the clinically relevant advantage of the delay in time to initiation of chemotherapy and re-

duced opiate use. Furthermore, quality of life was generally preserved in patients treated with abiraterone compared with those treated with placebo. In line with previous experience, treatment with abiraterone was generally tolerable. In conclusion, abiraterone was also approved for use in the new population of asymptomatic or mildly symptomatic patients having failed ADT and for whom chemotherapy is not yet clinically indicated. The recommended dose is 1,000 mg (four 250-mg tablets) given once daily together with prednisone or prednisolone.

The most current information on this medicinal product is available on the European Medicines Agency website (<http://www.ema.europa.eu>).

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