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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 27, 2011
From	Ke Liu, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 202379
Supplement #	0001-0024
Applicant	Centocor Ortho Biotech, Inc.
Date of Submission	Dec. 20, 2010
PDUFA Goal Date	June 19, 2011
Proprietary Name / Established (USAN) names	Zytiga / Abiraterone
Dosage forms / Strength	Tablets of 250 mg
Proposed Indication	For the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel
Recommended:	Full Approval

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1. Introduction

The proposed indication for this NDA is as follows: abiraterone acetate (Zytiga® Tablets, Centocor Ortho Biotech Inc.) is intended for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel.

The application is based on the results of a randomized, double-blinded, placebo-controlled, multicenter, international clinical trial in 1195 patients with mCRPC previously treated with docetaxel-containing regimens. Patients were randomized 2:1 to receive either abiraterone orally at a dose of 1000 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). Treatment continued 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), unacceptable toxicity, initiation of new treatment, or withdrawal. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded from this trial.

A pre-specified interim analysis was performed when 552 deaths had occurred (69% of 797 deaths required for the planned final analysis) and demonstrated a statistically significant improvement in overall survival in patients on the abiraterone arm compared to patients on the placebo-controlled arm (HR=0.646; 95% CI: 0.543, 0.768; $p < 0.0001$). The median overall survival was 14.8 months in the abiraterone arm versus 10.9 months in the placebo arm. The significance level of this interim analysis ($p < 0.0001$) crossed the pre-specified efficacy boundary of a two-sided alpha of 0.0141. As a result, the trial was unblinded and terminated prior to the planned final analysis. An updated unplanned survival analysis, conducted with 775 deaths (97% of the 797 deaths required for the planned final analysis), showed a median overall survival of 15.8 months in the abiraterone arm versus 11.2 months in the placebo arm (HR 0.74), consistent with the results from the interim analysis.

The most common adverse reactions (> 5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia and upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were increased aspartate aminotransferase (AST) and/or alanine

aminotransferase (ALT), urosepsis and cardiac failure (each in < 1% of patients taking abiraterone).

The most common electrolyte imbalances in patients receiving abiraterone were hypokalemia (28%) and hypophosphatemia (24%).

Adverse reactions associated with mineralocorticoid excess occurred more frequently in the abiraterone arm, including edema (27%), hypokalemia (17%) and hypertension (8.5%). However, Grade 3 or 4 of these adverse reactions occurred in <4% of patients (1.9%, 3.8% and 1.3% respectively). None of these adverse reactions led to treatment discontinuations or deaths.

Adrenocortical insufficiency (AI) was reported in 2 patients receiving abiraterone and none in the placebo arm in the Phase 3 trial. In a combined safety analysis of trials in which abiraterone acetate was administered at the recommended dose of 1000 mg once daily, a total of 5 patients were diagnosed with AI, leading to an estimated AI incidence rate of 0.5%. AI occurred both when patients were taking the recommended dose of corticosteroids and after patients discontinued prednisone. Three of the five cases with AI resolved, one was ongoing at the end of study visit and one case was ongoing at the time of death from disease progression.

Hepatotoxicity associated with abiraterone acetate treatment was also reported. In the integrated safety population, alanine and/or aspartate aminotransferase (ALT/AST) elevations were reported in 7.5% of patients taking abiraterone versus 3.8% of patients taking placebo. Grade 3 or 4 elevations of either ALT or AST were reported in 1.5% of patients taking AA versus 1.0% of patients taking placebo. No hepatic failure or death was observed in abiraterone clinical trials.

Abiraterone C_{max} and AUC_{0-∞} (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasting state.

The recommended dose and schedule for abiraterone acetate is 1000 mg orally once daily in combination with prednisone 5 mg orally twice daily. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before and one hour after the dose of abiraterone is taken.

2. Background

2.1 Castration-Resistant Prostate Cancer (CRPC)

- Prostate cancer

Prostate cancer is the most common malignancy and 2nd most common cause of cancer mortality in men. In 2010, American Cancer Society estimates that 217,730 new cases of prostate cancer will be diagnosed in the United States with 32,050 annual deaths from this disease (1).

Initial primary treatment modalities for subjects with localized prostate cancer include expectant management (watchful waiting), surgery, radiation therapy, brachytherapy, cryotherapy. However, approximately 20 to 40% of men will eventually experience disease recurrence after the initial treatment. Prognostic factors for prostate carcinoma include anatomic stage, histologic grade, prostate-specific antigen (PSA) level, age, and comorbidity (2). One of the most important prognostic factors is the histologic grading of prostate cancer, Gleason score (3). High Gleason score (≥ 8) portends an unfavorable factor for recurrence and overall survival. Standard therapy for prostate cancer patients with disease recurrence, typically presenting with elevated prostate-specific antigen (PSA) but no detectable metastases, is androgen deprivation with either luteinizing hormone-releasing hormone (LHRH) agonist and/or androgen receptor blocker. Despite hormonal therapy, virtually all patients will progress and their disease will spread to distant sites (most commonly regional lymph nodes and/or bones) and will become refractory to hormone therapy. This stage of disease is known as androgen independent prostate cancer (AIPC), hormone refractory prostate cancer (HRPC), or castration-resistant prostate cancer (CRPC). Median survivals of patients with CRPC reported in the literature vary from 10 months to over 25 months depending on prognosis and treatment (4, 5, 6, 7).

- Treatment options for metastatic CRPC

Once metastatic and androgen-independent, prostate cancer is usually incurable. Currently available therapies are intended for palliation and/or prolonging survival. These therapeutic options include best support care without active cancer treatment, chemotherapy, secondary hormonal treatment or local radiation.

❖ *Chemotherapy*

A number of chemotherapeutic agents have been approved for the treatment of subjects with CRPC, including mitoxantraone, docetaxel and cabazitaxel.

○ Mitoxantrone

Mitoxantrone was approved in 1996 in the United States for use in combination with corticosteroids as initial chemotherapy for hormone refractory prostate cancer based on findings from a randomized multicenter trial comparing mitoxantrone plus prednisone (M+P) 5 mg twice a day to prednisone (P) alone. A total of 161 patients were randomized to this study which had palliative response as a primary endpoint, defined as a 2-point decrease in pain as assessed by a 6-point pain scale completed by patients (or complete loss of pain if initially 1+) without an increase in analgesic medication and maintained for two consecutive evaluations at least 3 weeks apart. Secondary endpoints were a decrease of $>$ or $=$ 50% in use of analgesic medication without an increase in pain, duration of response, and survival. Palliative response was observed in 23 of 80 patients (29%; 95% confidence interval, 19% to 40%) who received mitoxantrone plus prednisone, and in 10 of 81 patients (12%; 95% confidence interval, 6% to 22%) who received prednisone alone ($P = .01$). There was no difference in overall survival. Treatment was generally well tolerated, except for five episodes of possible cardiac toxicity in 130 patients who received mitoxantrone (including those patients from a different trial) (6, 8).

○ Docetaxel

Docetaxel was approved by the United States Food and Drug Administration on May 19, 2004 for use in combination with prednisone for the treatment of metastatic androgen-independent (hormone-refractory) prostate cancer. In a randomized, global study enrolling 1,006 patients, two schedules of docetaxel were compared with mitoxantrone + prednisone as follows: MTZ q 3w (mitoxantrone 12 mg/m² every 21 days + prednisone 5 mg twice a day) for a total of 10 cycles; TXT q 3w (docetaxel 75 mg/m² every 21 days + prednisone 5 mg twice a day) for a total of 10 cycles; and TXT qw (docetaxel 30 mg/m² days 1, 8, 15, 22, and 29 every 6 weeks + prednisone 5 mg twice

a day) for a total of 5 cycles. There was a statistically significant overall survival advantage shown for the TXT q 3w arm over MTZ q 3w (median overall survival 18.9 months versus 16.5 months, $P = 0.0094$). No overall survival advantage was shown for TXT qw compared with MTZ q 3w. The most commonly occurring adverse events included anemia, neutropenia, infection, nausea, sensory neuropathy, fluid retention, alopecia, nail changes, diarrhea, and fatigue (7, 9).

- Cabazitaxel

On June 17, 2010, the U.S. Food and Drug Administration (FDA) approved cabazitaxel (Jevtana® Injection, sanofi-aventis) for use in combination with prednisone for treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.

The approval is based primarily on the results of a randomized, open-label, international trial of 755 patients with mHRPC previously treated with docetaxel-containing regimens. Patients were randomized to receive either cabazitaxel 25 mg/m² intravenously every three weeks in combination with prednisone 10 mg/day or mitoxantrone 12 mg/m² intravenously every three weeks in combination with prednisone 10 mg/day. Patients were treated until disease progression, death, unacceptable toxicity, or completion of 10 cycles of therapy.

Median overall survivals were 15.1 and 12.7 months for cabazitaxel-treated and mitoxantrone-treated patients, respectively [HR 0.70 (95% CI 0.59-0.83), $p < 0.0001$.] Investigator-assessed response rates using RECIST criteria was 14.4 and 4.4% for cabazitaxel-treated and mitoxantrone-treated patients, respectively, $p = 0.0005$. No complete responses were observed on either arm.

The most common ($\geq 10\%$) grade 1-4 adverse reactions included neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia and alopecia. The most common ($\geq 5\%$) grade 3-4 adverse reactions were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue and asthenia.

Deaths due to causes other than disease progression within 30 days of the last dose were reported in 18 (5%) cabazitaxel-treated patients and 3 (<1%) mitoxantrone-treated patients. The most common fatal adverse reactions in cabazitaxel-treated patients were infections (n=5), and renal failure (n=4). One death was due to diarrhea-induced dehydration and electrolyte imbalance (4, 10).

❖ Immunotherapy

○ Sipuleucel T

On April 29, 2010, the U.S. Food and Drug Administration approved sipuleucel-T (PROVENGE®, Dendreon Corporation), an autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

Sipuleucel-T is a cellular immunotherapy consisting of autologous peripheral blood mononuclear cells (PBMC's), obtained by leukapheresis and cultured (activated) with a recombinant human protein (PAP-GM-CSF) consisting of prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor.

This approval was based on results from a randomized, double-blind, placebo-controlled, multicenter trial. Overall survival (OS) was the primary efficacy endpoint of this trial. Eligible patients had metastatic disease in soft tissue and/or bone with evidence of disease progression determined at either of these sites or by serial measurement of prostate specific antigen (PSA). All patients had prior adequate hormonal therapies with castrate testosterone levels attained. Patients with visceral (liver, lung, or brain) metastases or who reported moderate to severe prostate cancer-related pain and/or use of narcotics for cancer-related pain were excluded. Patients were randomized to receive either the sipuleucel-T treatment or a control (peripheral blood mononuclear cells which were not activated). Patients in both groups underwent three leukapheresis procedures (approximately Weeks 0, 2, and 4), followed 3 days later with an infusion of either sipuleucel-T or the non-activated control. Patients who had disease progression during the trial were

treated at the physician's discretion.

Five hundred twelve patients were randomized (2:1) to either sipuleucel-T (n=341) or control (n=171). Eighty-two percent had received prior combined androgen blockade, 54% local radiotherapy, 35% radical prostatectomies, 18% prior chemotherapy including docetaxel. The median age was 71 years (range 40-89); 90% were Caucasian.

Patients treated with sipuleucel-T had an improvement in median OS when compared to the control (25.8 months versus 21.7 months, $p=0.032$, HR 0.775, 95% CI 0.61, 0.98). There was no difference in time-to-progression or PSA response. Fifty-seven percent of patients in the sipuleucel-T arm and 50.3% in the control arm received docetaxel after disease progression. The mechanism(s) by which sipuleucel-T improved overall survival remains to be determined.

Common adverse reactions reported during a safety evaluation of 601 patients who received sipuleucel-T were chills, fatigue, fever, back pain, nausea, joint ache and headache. The majority of adverse reactions were mild or moderate in severity. Severe adverse events occurred in 23.6% of patients who received sipuleucel-T, compared to 25.1% of the control group. Life-threatening adverse events were observed in 4.0% of patients who received sipuleucel-T, compared to 3.3% of the control group. Fatal adverse events occurred in 3.3% of patients who received sipuleucel-T, compared to 3.6% of the control group. Serious adverse reactions that were reported more frequently in patients receiving sipuleucel-T compared with controls included acute infusion reactions and stroke (5, 11).

Table 1 below summarizes the currently available therapies for patients with mCRPC.

2.2 Endpoints Used for Prior Drug/Biologic Approvals for CRPC

As shown in Table 1, all approvals for mCRPC indication to date have relied on large, randomized, active-controlled or placebo-controlled phase 3 trials. Overall survival has been the standard for last three approvals in this indication. Table 1 also shows that the overall survival of this patient population is inversely related

to the underlying clinical status: asymptomatic patients had longest survival, whereas patients who had already received docetaxel had shortest survival. Treatment with the approved agents as shown led to a 2.4- to 4.1- month increase in median overall survival and 25-30% reduction in the probability of death when compared to control treatments.

This current NDA is based on the demonstration that abiraterone increased overall survival in mCRPC patients after treatment with chemotherapies containing docetaxel. The magnitude of this treatment effect (a 3.9-month increase in median overall survival and a 33% reduction in the probability of death) appears to be comparable with or numerically better than cabazitaxel (2.4-month increase in median overall survival and 30% reduction in the probability of death). However, cross-trial comparisons are inherently difficult because of variations in trial population and differences in the control treatments. For example, in the abiraterone trial, median overall survival was 10.9 months in the control arm (placebo plus prednisone) compared to 12.7 months in the control arm of the docetaxel trial (mitoxantrone plus prednisone).

This difference in median overall survival time in the control arms between these two trials could also be due to the possibility that mitoxantrone had some treatment effect on overall survival in the docetaxel trial. However, abiraterone appears to have a better safety profile (see section 9 below).

Table 1. U.S. FDA Prior Drug/Biologic Approvals for CRPC

Drug/Biologic	Original Approval Date	Primary Endpoint (Basis for Approval)	Trial Population (CRPC)	Trial Size and Treatment			1 ⁰ Endpoint Results		Treatment Effect		
				Total # of Patients	Drug/Biologic	Control	Drug/Biologic	Control	Δ in 1 ⁰ Endpoint Results	Hazard Ratio (95% CI)	P Value
Mitoxantrone (M)	11/13/96	Palliative Pain Response ¹	Symptomatic	161	80 (M + P ²)	81 (P)	29%	12%	17%	Not Applicable	0.011
Median OS (mos ³)											
Docetaxel (D)	05/19/04	OS	KPS ⁴ score ≥ 60%	672	335 (D q3w + P)	337 (M q 3w + P)	18.9	16.5	2.4	0.761 (0.62, 0.94)	0.0094 ⁵
Sipuleucel T (S)	04/29/10	OS	Asymptomatic or minimally symptomatic	512	341 (S)	171 (PBMC ⁶)	25.8	21.7	4.1	0.775 (0.61, 0.98)	0.032
Cabazitaxel (C)	06/17/10	OS	After a docetaxel-containing regimen	755	378 (C + P)	377 (M+ P)	15.1	12.7	2.4	0.70 (0.59, 0.83)	<0.0001
<i>Abiraterone (A)</i>	<i>04/2011</i>	<i>OS</i>	<i>After a docetaxel-containing regimen</i>	<i>1195</i>	<i>797 (A + P)</i>	<i>398 (Placebo + P)</i>	<i>14.8</i>	<i>10.9</i>	<i>3.9</i>	<i>0.646 (0.54, 0.77)</i>	<i><0.0001</i>

¹ Response defined as 2-point decrease in a 6-point pain intensity scale, lasting at least 6 weeks without an increase in analgesic use score and no evidence of disease progression

Overall survival: one of secondary endpoints. Median OS in M+P: 11.3 mos, 10.8 mos in prednisone arm. Difference: 0.3 mos, P value; 0.23

² P: Prednisone

³ mos: Months

⁴ KPS: Karnofsky Performance Status

⁵ Threshold for statistical significance = 0.0175 because of the 3-arm trial design

⁶ PBMC: Peripheral Blood Mononuclear Cells

2.3 Major Regulatory Milestones for Abiraterone Acetate

Milestone	Date	Regulatory Issues
Initial IND (71023)	Dec. 2005	Phase 1 studies determined a dosing schedule of 1000 mg QD and Phase 2 studies showed antitumor activity, associated with a PSA response rate of approximately 50% in patients with mCRPC s/p docetaxel treatment.
Special Protocol Assessment	Mar. 2008	Agreement reached for Study COU-AA-301 in patients who have failed docetaxel-based chemotherapy. The study had overall survival as the primary endpoint and was considered as the key study to support regulatory NDA filing.
Enrollment for Study COU-AA-301	May, 2008 to Jul. 2009	Protocol amendments mainly related to safety monitoring and management prior to the interim analysis. See Section 6 for details.
Interim Analysis of Study COU-AA-301	Aug. 2010	The protocol pre-specified interim analysis showed a survival benefit with abiraterone. The IDMC recommended unblinding the study and crossing over of patients initially assigned on placebo. FDA concurred to the proposals.
Pre-NDA Meeting	Nov. 2010	Clarification of the applicant's proposals to provide updated survival analyses with 94% of survival events and to submit safety update information after the NDA submission.
NDA Submission	Dec. 2010	Determined for Priority Review. The projected PDUFA date is on June 19, 2011.

2.4 Mechanism of Action.

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

CYP17 catalyzes two reactions: 1) the conversion of pregnenolone and progesterone by 17 α -hydroxylase activity and 2) the formation of dehydroepiandrosterone (DHEA) and androstenedione by C17, 20 lyase

activity. DHEA and androstenedione are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals.

3. Inspections

FDA's Office of Compliance's overall recommendation for establishment evaluation was acceptable. In the final inspection summary review dated April 15, 2011, the FDA's Division of Scientific Investigations (DSI) recommended that the submitted data be considered reliable in support of the proposed indication

4. CMC/ Biopharmaceutics

One issue related to the dissolution specifications was resolved prior to the action date for this NDA.

The following was excerpted from biopharmaceutics reviewer's memo dated March 8, 2011. "From the Biopharmaceutics perspective, this NDA is acceptable. However, the proposed dissolution specifications need to be revised. A mean of (b) (4) of Zytiga IR tablet dissolved in 30 min, therefore, your (the applicant's) proposed dissolution specifications need to be tightened as follows:

Change from: $Q = (b) (4)$ at 45 min to: $Q = (b) (4)$ at 30 min

Before this NDA can be approved, you (the applicant) need to revise and implement the proposed dissolution specifications." The applicant subsequently implemented this proposed dissolution specification.

The following was excerpted from CMC Division Director's Memo dated April 8, 2011: "Recently, the dissolution specification was approved as $Q = (b) (4)$ in 30 minutes. The following comment was sent to the applicant today (April 8, 2011) via letter: "... FDA recommended that this specification be implemented immediately in the NDA. FDA also confirmed that the recommended specification can be reassessed following approval, at the Applicant's discretion and in conformance with all applicable regulations."

5. Nonclinical Pharmacology/Toxicology

No issues. Pharmacology/toxicology review team's memo indicated the following recommendations: "The non-clinical studies with abiraterone acetate support the safety of its use in metastatic prostate cancer. No additional non-clinical studies are required for abiraterone acetate." Refer to Pharmacology/Toxicology reviewers' review for detail.

6. Clinical Pharmacology

Refer to Clinical Pharmacology reviewers' review for detail

The main review issues related to Clinical Pharmacology included the following and have been resolved prior to the action date for this NDA.

1. Dose reduction in the proposed labeling for the management of hepatotoxicity
2. Use Zytiga in patients with moderately impaired hepatic functions

With respect to dose reduction schema, the clinical pharmacology review team recommended a two-step dose reduction (1000 to 750 to 500 mg) [REDACTED] (b) (4) [REDACTED] to manage hepatotoxicity. The following is excerpted from the Clinical Pharmacology Review:

[REDACTED] (b) (4) [REDACTED] a two-step dose reduction (1000 mg to 750 mg to 500 mg) as used in the pivotal trial is recommended to manage hepatotoxicity. Since efficacy at lower doses or exposures is unknown, reducing the exposures by 50% (1000 to 500 mg) could result in a loss of efficacy. It is important to note that both the 750 and 1000 mg doses had similar biomarker activity in study COU-AA-001 (phase 1/2 dose ranging study). The two-step dose reduction was specified in the protocol for study COU-AA-301 to manage hepatotoxicity and other toxicities. The majority of the patients (21/27) followed the step dose reduction scheme in the pivotal trial. Approximately 60% (16/27) of the patients had their dose reduced to 750 mg and did not need further dose reduction. Five patients had step dose reductions from 1000 to 750 to 500 mg. Six patients had a direct dose reduction from 1000-500 mg of which two patients subsequently resumed dosing at 1000 mg. It is not clear whether the four patients that were reduced directly to 500 mg and stayed at that dose would have tolerated 750 mg. Thus, having an option to be treated at the 750 mg dose may reduce the likelihood of experiencing hepatotoxicity while maintaining efficacy.”

[REDACTED] (b) (4) [REDACTED] (b) (4) [REDACTED] However, the clinical pharmacology team's detailed review indicated the following: “In the dedicated hepatic impairment study (COU-AA-011), systemic exposure of abiraterone acetate in the mild hepatic impairment cohort (Child-Pugh Classification A) was comparable to that in the normal hepatic function cohort. Based

on geometric mean estimates, the C_{max} was 2.7-fold higher and AUC was 3.6-fold higher in the moderate hepatic impairment cohort (Child-Pugh Classification B) compared to the normal hepatic function cohort. The mean T_{1/2} was approximately 4.6 to 5.5 hours longer for the mild and moderate hepatic impairment cohorts compared to the normal hepatic function cohort.” The team recommended that abiraterone acetate can be administered in patients with moderate hepatic impairment as follows: “In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of abiraterone acetate to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. 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 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue abiraterone acetate and do not re-treat patients with abiraterone acetate.”

7. Clinical Microbiology

Not applicable.

8. Clinical/Statistical- Efficacy

This NDA is based on the efficacy and safety results of abiraterone from a randomized, double-blind, placebo-controlled, multicenter phase 3 trial (COU-AA-301) in patients with mCRPC who had received prior chemotherapy containing docetaxel, recruited from 147 study centers in 13 countries. A total of 1195 patients were stratified and randomized 2:1 to receive either abiraterone orally at a dose of 1000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo orally 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), unacceptable toxicity, initiation of new treatment, or withdrawal. The primary endpoint was overall survival.

All patients had received prior docetaxel-based chemotherapy. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens. At enrollment, 89% of patients had an ECOG performance

status score of 0-1, 45% had a Brief Pain Inventory score of ≥ 4 (patient's reported worst pain over the previous 24 hours), 30% had visceral metastases, 70% had radiographic evidence of disease progression while 30% had PSA-only disease progression. These characteristics as well as other baseline characteristics examined were well balanced between the two arms.

8.1 Main Efficacy Results

The clinical reviewer's main efficacy findings are shown below. Refer to the Clinical Reviewer's review for details.

Patient demographic and baseline characteristics were well balanced among the treatment arms (Table).

The primary endpoint was overall survival. The trial was designed to detect a 20% improvement in survival in abiraterone acetate-treated arm compared to the placebo arm and a pre-specified interim analysis was planned to be conducted at the time when 67% of the required 797 death events occurred. The interim analysis was conducted at the time of 552 deaths (not 67% but rather 69% actually) observed with the data cutoff of January 22, 2010.

The results of the pre-specified interim analysis showed a statistically significant improvement in overall survival in patients in the abiraterone arm compared to patients in the placebo arm.

Table summarizes the results and

Figure 1 shows the Kaplan-Meier overall survival curves from this interim analysis. Compared to placebo, treatment with abiraterone acetate had a 35% decreased risk of death in patients with progressive mCRPC who had received prior docetaxel-based chemotherapy (HR=0.646; 95% CI: 0.543, 0.768; $p<0.0001$). The median overall survival for patients in the abiraterone acetate arm was 14.8 months compared to a median overall survival of 10.9 months for patients in the placebo arm.

Table 2: Trial COU-AA-301 Patient Disease Characteristics at Baseline (ITT Population)

	AA (N=797)	Placebo (N=398)
Disease Metastasis Site		
Bone	709 (89%)	357 (90%)
Lymph Node	361 (45%)	164 (41%)
Viscera (Liver, Lung, Other)	239 (30%)	96 (24%)
Disease Progression Type		
PSA only	238 (30%)	125 (31%)
Radiographic Progression*	559 (70%)	273 (69%)
PSA at entry (ng/mL)		
Median (range)	128.8 (0.4, 9253.0)	137.7 (0.6, 10114.0)
Gleason Score at Initial Prostate Cancer Diagnosis	(N=697)	(N=350)
≤7	342 (49%)	161 (46%)
≥8	356 (51%)	189 (54%)
Pain at entry**	357 (45%)	179 (45%)
ECOG Score at Enrollment		
0	274 (34%)	135 (34%)
1	441 (55%)	218 (55%)
2	82 (10%)	45 (11%)
*May have concurrent PSA progression as well.		
**Baseline BPI-SF pain score of ≥4 (worst pain over last 24 hours)		

Table 3: Primary Endpoint Analysis Results (Pre-specified Interim Analysis in ITT)

	AA (N=797)	Placebo (N=398)
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p value ^a	< 0.0001	
Hazard ratio (95% CI) ^b	0.646 (0.543, 0.768)	
<i>^aP-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).</i>		

Figure 1: Kaplan-Meier Overall Survival Curves ((Pre-specified Interim Analysis in ITT)

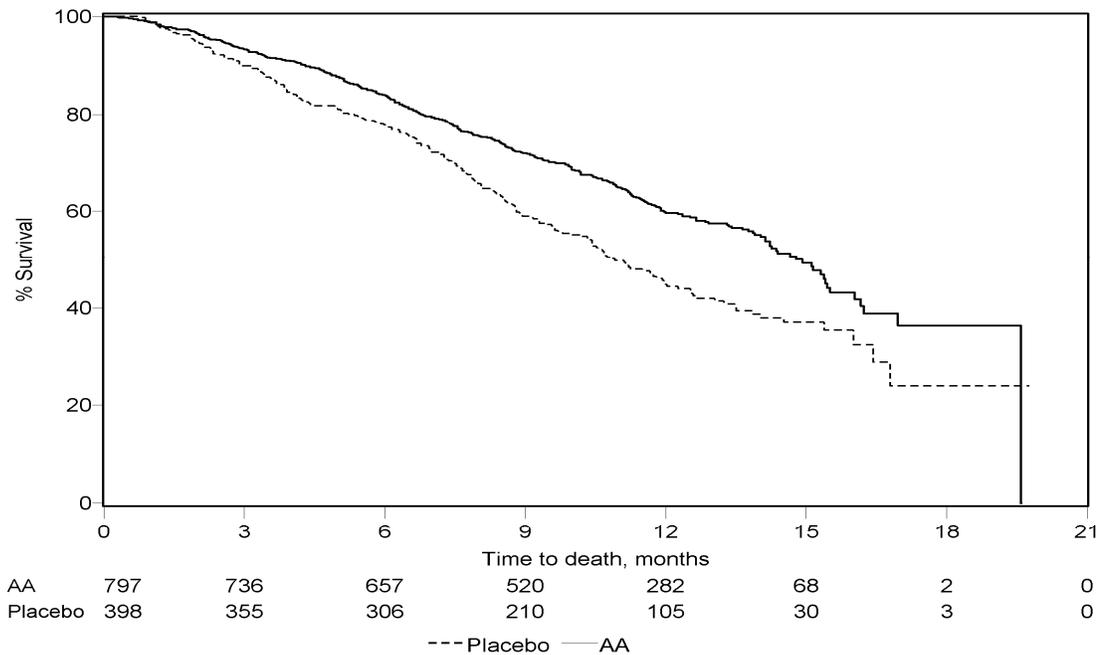


Table 4: Updated Primary Endpoint Analysis Results in ITT

	AA (N=797)	Placebo (N=398)
Deaths (%)	501 (63%)	274 (69%)
Median survival (months)	15.8	11.2
(95% CI)	(14.8, 17.0)	(10.4, 13.1)
Hazard ratio (95% CI) ^a	0.740 (0.638, 0.859)	

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

The trial was unblinded in August 2010 with the IDMC recommendation based on the interim analysis results. As of September 20, 2010, a total of 775 deaths were observed and an unplanned analysis was performed with the updated number of events. The results of the updated analysis, as summarized in

Key secondary endpoint results of the phase 3 trial appeared to support the improvement in overall survival: Median time to PSA progression (10.2 vs. 6.6 months), median radiographic PFS as assessed by investigators (5.6 vs. 3.6 months), and confirmed PSA responses (declines of $\geq 50\%$ from baseline, 29% vs. 6%) all

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avored abiraterone acetate treatment and corroborated the reported antitumor activity in the same patient population in two previous Phase 2 trials conducted by the applicant. In addition, objective tumor response rate, an exploratory endpoint assessed by investigators according to the RECIST criteria, was higher in the abiraterone acetate arm (14%) than in the placebo arm (3%). However, limitation of these secondary endpoint and exploratory results included lack of validation for PSA measurements, and absence of central independent review for imaging results in assessing tumor progression or responses. Due to these reasons, these secondary and exploratory endpoint results were not displayed in the product labeling.

, were consistent with those from the interim analysis, with a median overall survival of 15.8 months in patients on the abiraterone acetate arm compared to a median overall survival of 11.2 months in patients on the placebo arm.

The improvement in median overall survival with abiraterone acetate treatment became 4.6 months in the updated analysis, but the hazard ratio increased to 0.74 (95% C.I. 0.638, 0.859) from 0.65 at the interim analysis (95% C.I. 0.543, 0.768). Since the 775 deaths accounted for 97% of the required number of events for final analysis, the results from the updated analysis would most likely represent results of the final analysis if it were conducted.

Key secondary endpoint results of the phase 3 trial appeared to support the improvement in overall survival: Median time to PSA progression (10.2 vs. 6.6 months), median radiographic PFS as assessed by investigators (5.6 vs. 3.6 months), and confirmed PSA responses (declines of $\geq 50\%$ from baseline, 29% vs. 6%) all favored abiraterone acetate treatment and corroborated the reported antitumor activity in the same patient population in two previous Phase 2 trials conducted by the applicant. In addition, objective tumor response rate, an exploratory endpoint assessed by investigators according to the RECIST criteria, was higher in the abiraterone acetate arm (14%) than in the placebo arm (3%). However, limitation of these secondary endpoint and exploratory results included lack of validation for PSA measurements, and absence of central independent review for imaging results in assessing tumor progression or responses. Due to these reasons, these secondary and exploratory endpoint results were not displayed in the product labeling.

8.2 Main Efficacy Review Issues

No major efficacy review issues were identified.

Both clinical and statistical review teams recommended regular approval (full approval) for the proposed indication.

9. Safety

Refer to the clinical review for details.

9.1 Main Safety Findings

In this NDA, the applicant submitted safety data of 1,185 patients from the pivotal randomized, placebo-controlled trial COU-AA-301 as well as pooled data from 279 patients with castrate-resistant prostate cancer (CRPC) in 6 phase 1 and 2 trials. The total number of patients and drug exposure are adequate for the purpose of the safety review. Overall, 1000 mg of abiraterone acetate (AA) given once daily with prednisone appeared to offer a reasonable safety profile when compared to placebo plus prednisone. Several categories of unique adverse events reasonably likely to be related to abiraterone acetate (adverse reactions) have been identified and include an increased incidence of mineralocorticoid excess (hypokalemia, fluid retention, hypertension); hepatic enzyme elevations; cardiac events including arrhythmia, heart failure and chest pain; urinary tract infection; and muscle and joint discomfort. A summary of safety results is listed below.

- The exposure to abiraterone acetate in this population is adequate. A median of 8 cycles (32 weeks) were received by patients taking AA in the pivotal trial COU-AA-301 versus 4 cycles (16 weeks) of those in placebo. Patients in the AA group across trials also received a median of 8 cycles. There was high treatment compliance (90%). Additionally, in the two phase 1 and 2 dose-escalation trials (COU-AA-001 and -002), doses were tolerated up to 2000 mg orally once daily without reaching maximum tolerated dose (MTD).
- In the pivotal trial, nearly all patients reported at least one treatment-emergent adverse event (TEAE) on study (99% for AA, 99.5% for placebo). However, abiraterone acetate did not increase the overall incidence of Grade 3-4 TEAEs, serious adverse events (SAE) or TEAEs leading to discontinuation or death when compared to placebo. In pivotal study COU-AA-301, dose interruptions were seen in a similar number of AA and placebo patients (17% and 16%). Dose reductions occurred in 4% of AA and 1% of placebo. The most frequent adverse reactions leading to dose reductions in the abiraterone arm were heart failure, aminotransferase (AST/ALT) elevation and urosepsis (all <1%).
- The most frequent adverse events (AEs) reported for AA were fatigue, nausea, back pain, arthralgia and constipation (44%, 30%, 30%, 27% and 26%, respectively). All

were seen more commonly in the placebo arm with the exception of fatigue (44% vs 43%) and arthralgia (27% vs 23%) which were higher in the abiraterone arm.

- The most frequently reported adverse reactions (>10%) for abiraterone acetate included joint swelling and discomfort (30%), edema (27%), muscle discomfort (26%), hot flush (19%), diarrhea (18%), urinary tract infection (12%) and cough (11%). Laboratory dataset review revealed that hypokalemia occurred in 28% of patients taking AA compared to 20% of those taking placebo.

- Toxicities related to mineralocorticoid excess were seen more frequently in patients receiving AA versus placebo. These toxicities were higher in the pooled safety group of patients in earlier phase trials who were not uniformly given low-dose glucocorticoids to reduce the incidence of these toxicities. Importantly, no treatment discontinuation due to hypertension, hypokalemia or peripheral edema was reported in trial COU-AA-301.

- Elevations in alanine and/or aspartate aminotransferase (ALT and/or AST) were reported in 7.5% of patients taking abiraterone versus 3.8% of patients taking placebo in the integrated safety population. Grade 3 or 4 elevations of either ALT or AST were reported in 1.5% of patients taking AA versus 1.0% of patients taking placebo. No hepatic failure or death was observed in abiraterone clinical trials. Two patients experienced AST/ALT and bilirubin elevations meeting Hy's law by laboratory criteria; however, interpretation of this finding is difficult because both patients had pre-existing liver conditions (hepatic metastases and gallstones) and elevated alkaline phosphatase. Elevated hepatic enzymes led to dose modifications, reductions, or discontinuations in less than 1% of patients. There were no deaths associated with liver toxicity.

- AEs of grouped term arrhythmias, cardiac failure and chest pain or discomfort occurred more frequently in the AA arm. Cardiac SAEs were reported in 3% AA patients versus 1% placebo patients. Abiraterone acetate should be used with caution in patients with heart failure. Cardiac death rates were low and balanced between the two groups in COU-AA-301.

- Review of the 4-month safety update did not reveal any new safety signals.

9.2 Main Safety Review Issues

- Discrepancy in the causality attribution of adverse events contained in the data listings submitted to abiraterone acetate IND vs. those submitted to the NDA.

One issue that was resolved prior to the action date was a discrepancy in the causality attribution of adverse events contained in the data listings submitted to abiraterone acetate IND when compared to NDA. DSI had requested the applicant submit adverse event data listings to the IND to facilitate the selection of clinical sites for inspection. In response to this request, the applicant submitted adverse event data listings to the abiraterone acetate IND before the NDA submission. However, as part of the NDA review, DSI's clinical site inspections identified that the column headings "Causality (Abiraterone) and Causality (Prednisone/Prednisolone)" in the data listings of the IND submission did not match those with the source documents at the clinical sites inspected and those in the NDA submission. It appeared that the headings of these two columns were reversed in the IND submission when compared to the NDA submission.

FDA sent the following information request to the applicant:

- "1) Provide an explanation for the observed issues above as they raise concerns about the integrity of the data submitted in support of NDA 202379;
- 2) Provide an assessment of the extent and scope of this issue for all sites, as well as corrective actions to ensure that the data listings submitted to the NDA are accurate reflections of the source data and Case Report Forms;
- 3) Provide assurance that the root cause that resulted in the issues identified is not systemic in nature and that it does not impact other critical data submitted in support of this NDA;
- 4) Once you have determined the extent of the discrepancies you will need to amend your NDA as necessary so that the data and study reports are correct."

The applicant responded that the reversal of the column headings "Causality (Abiraterone) and Causality (Prednisone/Prednisolone)" in the data listings of the IND submission was caused by a computer programming error. This error was identified after the data listings were submitted to the IND but corrected before the NDA submission. The applicant resubmitted all data listings with the corrected column headings of causality to the IND file. The safety reviewer verified that the resubmitted corrected IND AE data listings matched those in the NDA submission. The DSI reviewer also confirmed that the discrepancy between AE data listings and the source documents at the sites could be explained by this programming error for the IND datalisting. Therefore, the data integrity and the safety results were not affected.

10. Advisory Committee Meeting

During this NDA review, DDOP chose not to present the application to the oncology drug advisory committee (ODAC) for the following reasons:

- 1) The trial COU-AA-301 was adequate and well controlled;
- 2) The primary endpoint of the trial, overall survival, is the golden standard for drug approval and has been used in previous drug/biologic approvals for the same/similar indication for which this applicant is seeking;
- 3) Review teams' reviews indicated that the results of trial COU-AA-301 were robust and the magnitude of the abiraterone's treatment effect in the intended patient population was both statistically significant and clinically meaningful with a highly favorable benefit-risk file.
- 4) There were no controversial issues of significance that would warrant the discussion and advice from the ODAC.

11. Pediatrics

This NDA received a waiver for Pediatric Equity Research Act (PREA) requirement since prostate cancer does not occur in pediatric patients.

12. Other Relevant Regulatory Issues

None.

13. Labeling

The following table summarizes the major revisions to the labeling the applicant submitted to the original NDA. Refer to the finalized labeling for detailed information.

(b) (4)

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14. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend a regular approval (full approval) for abiraterone acetate for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel.

- Risk Benefit Assessment

My recommendation is based on the following:

The efficacy and safety findings from Trial COU-AA-301, an adequate and well-controlled trial, provide substantial evidence for the effectiveness of abiraterone acetate in the intended patient population (a 3.9-month improvement in median overall survival compared to placebo) with an acceptable toxicity profile. Distinct from myelosuppression-related toxicities (e.g., severe neutropenia and/or febrile neutropenia) commonly observed with cytotoxic chemotherapy in the treatment of patients with mCRPC, abiraterone acetate has unique toxicities including mineralocorticoid excess-associated adverse reactions, adrenocortical insufficiency, and hepatotoxicity. These unique safety issues have been discussed and addressed during this NDA review and in the labeling of the product. Given the totality of data, abiraterone acetate offers a highly favorable risk-benefit profile for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel.

- Post-Marketing Requirement

The following post-marketing requirements related to clinical pharmacology discipline are recommended:

1. Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate. The proposed protocol must be submitted for review prior to trial initiation.
2. Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inducer (e.g., rifampin) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate. The proposed protocol must be submitted for review prior to trial initiation.

3. Conduct a trial to determine the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate in individuals with severe hepatic impairment. The proposed protocol should contain the rationale for dose selection, and must be submitted for review prior to trial initiation. In the design of the trial, consider development of lower dosage strengths to allow for administration of a safe dose in patients with severe hepatic impairment.
4. Perform an *in vitro* screen to determine if abiraterone is an inhibitor of human CYP2C8. Based on results from the *in vitro* screen, a clinical drug-drug interaction trial may be needed.

15. References

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(4) de Bono, J. S., et al. "Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial." *Lancet* 376 (9747) (2010): 1147-54.

(5) Kantoff, P. W., et al. "Sipuleucel-T immunotherapy for castration-resistant prostate cancer." *The New England Journal of Medicine* 363 (5) (2010): 411-22.

(6) Tannock, I. F., et al. "Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points." *Journal of Clinical Oncology* 14 (6) (1996): 1756-64.

(7) Tannock, I. F., et al. "Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer." *The New England Journal of Medicine* 351 (15) (2004): 1502-12.

(8) http://www.accessdata.fda.gov/drugsatfda_docs/nda/96/019297_s014ap.pdf

(9) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/20-449s028_Taxotere_Medr.PDF

(10) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201023s000MedR.pdf

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04/27/2011